

ZnO nanoparticle as catalyst for efficient green one-pot synthesis of coumarins through Knoevenagel condensation

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Abstract. Green chemistry protocols with the reusability of the nano particle as catalyst in the synthesis of coumarins is described. The zinc oxide (ZnO) nanoparticles functions as highly effective catalyst for the reactions of various *o*-hydroxy benzaldehydes with 1,3-dicarbonyl compounds under microwave and thermal conditions to afford the corresponding coumarins in moderate to good yields. The catalyst is inexpensive, stable, can be easily recycled and reused for several cycles with consistent activity.

Keywords. Knoevenagel condensation; *o*-hydroxy benzaldehyde; zinc oxide (ZnO); catalyst; green chemistry.

1. Introduction

Intensive studies have been recently focused on the development of catalytic systems owing to their importance in synthetic organic chemistry. One of the most attractive synthetic strategies favoured by organic chemists is the use of heterogeneous catalyst in increasing the efficiency of a wide range of organic synthesis.

Heterogeneous catalysis is being used in the fine-chemicals industry because of the need for more environmentally friendly production technology. This tendency is assisted by the availability of novel catalytic materials and modern techniques of creating and investigating specific active sites on catalyst surfaces.^{1,2} In the field of fine chemical production, important steps in the synthesis of relatively large and complex molecules include carbon–carbon bond forming reactions such as Knoevenagel condensations or Michael additions.

The Knoevenagel condensation, is one of the most useful and widely employed methods for carbon–carbon formation in organic synthesis, with numerous applications in the synthesis of fine chemicals,³ hetero Diels–Alder reactions,⁴ and carbocyclic as well as heterocyclic compounds of biological significance.⁵ The reactions are usually catalysed by bases⁶ such as piperidine, pyridine, ammonia or sodium ethoxide in organic solvents. In recent years, metal oxides constitute the largest family of catalyst in heterogeneous catalysis^{7–10}

due to their acid-base and redox properties. Recently, bulk Zinc oxide has been employed as a heterogeneous catalyst for various organic transformations.¹¹ The recent literature survey reveals that nano ZnO¹² as heterogeneous catalyst has received considerable attention because of its inexpensive, non-toxic catalyst and has environmental advantages i.e., minimum execution time, low corrosion, waste minimization, recycling of the catalyst, easy transport and disposal of the catalyst. In recent years, in biological field the potential utility of ZnO nanoparticle in the treatment of cancer have been reported by many researchers. Owing to numerous advantages associated with this eco-friendly nature, it has been explored as a powerful catalyst for several organic transformations.¹³

Further, coumarin and their derivatives have attracted considerable interest in recent times because of their promising biological activities as antibacterial, anticoagulant, pesticidal, fungicidal and antimicrobial.^{14–18} Moreover, coumarins are structural units of several natural products and feature widely in pharmacologically active compounds.^{19,20} Thus, synthesis of this heterocyclic nucleus is of much current importance. Coumarins have been synthesized by several routes including Pechmann,²¹ Perkin,²² Knoevenagel,²³ Reformatsky²⁴ and Wittig reactions.²⁵

Previously, Philip Kisanga and co-workers²⁶ had reported a new method for the preparation of some

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substituted coumarins by Knoevenagel condensation of aromatic aldehydes with dicarbonyl compounds under solvent-free condition using a promoter $P(RNCH_2CH_2)_3N$ (where $R=Me, i-Pr$) as a catalyst and also Dipak Prajapati and co-worker²⁸ reported new method for preparation of some coumarin derivatives by Knoevenagel condensation of aromatic aldehydes with active methylene compounds under solvent-free conditions using molecular iodine as catalyst, but it needed a long reaction time and had to have a high reaction temperature.

Hence, in continuation of our quest in organic synthesis by different methods with the use of nano catalyst, we report an easy and rapid catalytic application of zinc oxide nanoparticle for one-pot synthesis of coumarins via Knoevenagel condensation under MW irradiation conditions.

2. Experimental

Microwave irradiation was carried out in a microwave single-mode reactor (Biotage, Initiator). The melting

point was determined by open capillaries are uncorrected. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm). The IR spectra were recorded on a Shimadzu model impact 400D FT-IR spectrophotometer using KBr pellets. 1H NMR were recorded on a Bruker AC-300F 400 MHz spectrometer in $CDCl_3$ using TMS as an internal standard with 1H resonant frequency of 400 MHz.

Zn dust (Qualigens Fine Chemicals, AR grade, 325 mesh, 99.90% purity), *o*-hydroxy benzaldehydes and 1,3-dicarbonyl compounds were commercially, procured from HiMedia Laboratories Pvt. Ltd., and used without any further purification.

2.1 Catalyst preparation

Zinc oxide nanoparticle used in the experiments was produced according to the procedure²⁹ with modification in following manner. Zinc powder 0.019 g (0.3 mmol) in dust form was sonicated for 2 h with

Table 1. Knoevenagel condensation of 2-hydroxy aldehydes with various β -dicarbonyl compounds in the presence of ZnO under microwave (MW 300 W, 120°C) and thermal (Δ , 100°C) conditions.

Entry	Product	Time (min)		Yield (%) ^a		Observed M.P. (°C)	Literature M.P. (°C)
		MW	Δ	MW	Δ		
1	3a	5	36	92	85	95	93–94 ²⁶
2	3b	6	43	90	83	122–124	121–123 ²⁶
3	3c	4	52	86	73	232–234	233–234 ²⁷
4	3d	5	45	92	88	89–91	88–90 ²⁶
5	3e	5	54	90	85	175	173–174 ²⁶
6	3f	6	60	92	86	122–124	120–125 ²⁶
7	3g	5	51	93	87	114–116	115–116 ²⁶
8	3h	5	53	87	78	79	77–78 ²⁶
9	3i	7	72	88	76	152–154	151–153 ²⁶
10	3j	7	52	90	87	227–230	228–229 ²⁶
11	3k	5	37	62	45	172–174	174–175 ²⁷
12	3l	7	48	85	78	168	166–167 ²⁷
13	3m	9	54	92	85	206	204 ³³
14	3n	6	48	95	87	233–235	231–233 ³³
15	3o	8	52	93	82	179–181	178–179 ³³
16	3p	6	51	93	85	220–222	220 ³³
17	4a	6	34	92	81	186–188	187–188 ²⁶
18	4b	5	57	91	87	297	298–299 ²⁶

^aIsolated yield

Reaction attempted in a single-mode microwave reactor (Biotage Initiator)

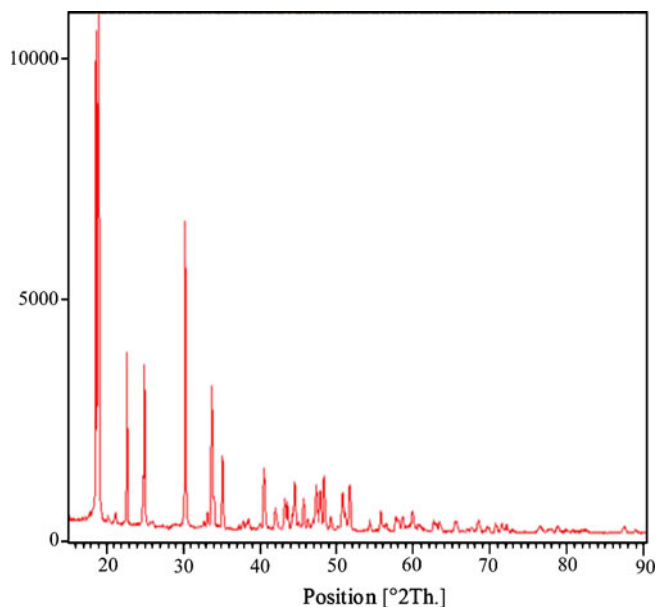


Figure 1. XRD pattern of the ZnO nanoparticle.

4 mL of *n*-butanol. To the above solution, 1.2 mL of triethanolamine (TEA) was added slowly. It was then sonicated for ten more minutes. Finally, the mixture was irradiated in a closed vessel mono-mode microwave reactor at 140°C and 10.9 bar for 6 min. The obtained white solid suspension was centrifuged, washed several times with distilled water and vacuum dried. It was then calcined at 900°C for 1 h and can be stored for extended period of time. The sample was then characterized using scanning electron microscopy (SEM), and X-ray powder diffraction (XRD) techniques.

2.2 General experimental procedure for the synthesis of coumarins

A 2–5 mL microwave reactor vial was charged with *o*-hydroxy benzaldehyde (2 mmol), 1,3-dicarbonyl com-

pound (2 mmol) and nano zinc oxide (10 mol%) was added. The vial was sealed with an aluminum cap fitted with a pressure and temperature-calibrated Teflon seal. The vial was inserted into the cavity of the microwave reactor, and the reaction mixture was irradiated with monomode irradiation at 120°C and 9.6 bar for the time indicated in (table 1). The reaction progress was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and solidified within an hour. The resulting solidified mixture was diluted with ethyl acetate (5 mL) and the catalyst was separated. The filtrate obtained was washed twice with water and evaporation of the solvent under reduced pressure. It yielded the crude product, which was further purified by recrystallization. The same procedure was used for synthesis of derivatives. All synthesized coumarin derivatives were characterized using analytical techniques such as IR and ¹H NMR. Also the identity of these compounds was established by comparison of their melting point with those of reported samples (table 1).^{26,27,33}

3. Results and discussion

In general, the nanoparticle is considered to be more reactive because it offers higher surface area and low coordinating sites. The surface area of the catalyst increases tremendously when size decreases to nano levels which are responsible for the higher catalytic activity. Studies on interaction of alcohols with Zn metal has revealed that C–O bond of the alcohol is readily cleaved on zinc metal surface giving hydrocarbons and the oxide species on the metal surface.³⁰

The structure directing additive is a common approach to control morphology, as shown by the effect of ethylene diamine in hydrothermal ZnO nanorod synthesis. Di- and tri-organic amines as well as long chain

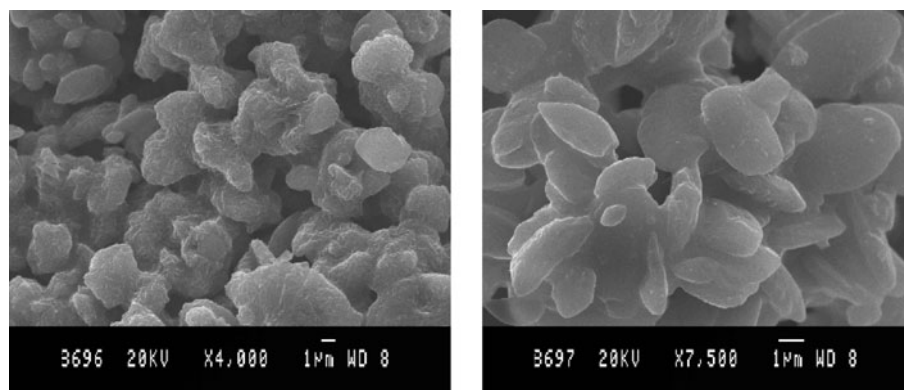
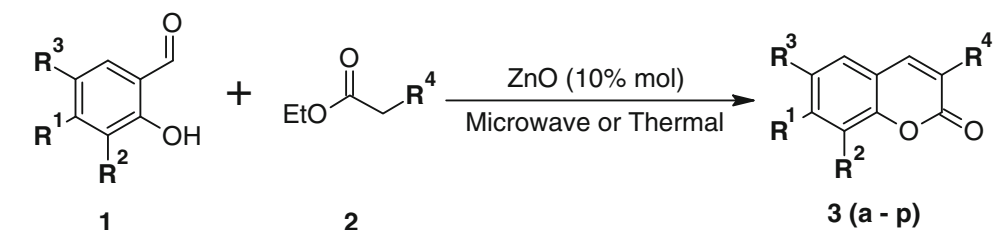
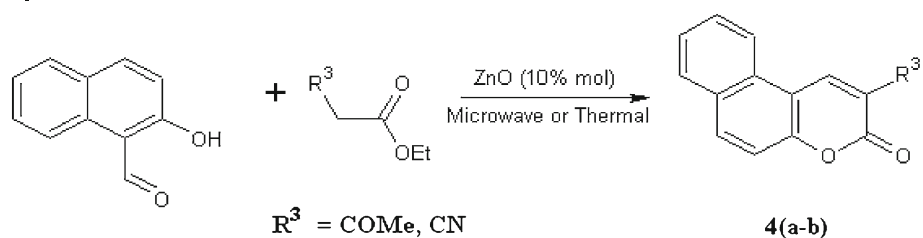


Figure 2. Scanning electron microscopy (SEM) image of synthesized ZnO nanoparticle.



	R ¹	R ²	R ³	R ⁴
3a	H	H	H	CO ₂ Et
3b	H	H	H	COMe
3c	OH	OH	H	CO ₂ Et
3d	H	OMe	H	CO ₂ Et
3e	H	OMe	H	COMe
3f	OMe	H	H	CO ₂ Et
3g	OMe	H	H	COMe
3h	Et ₂ N	H	H	CO ₂ Et
3i	Et ₂ N	H	H	COMe
3j	Et ₂ N	H	H	CN
3k	H	OH	H	CO ₂ Et
3l	OH	H	H	CO ₂ Et
3m	H	H	Cl	COMe
3n	H	H	Br	COMe
3o	H	H	NO ₂	COMe
3p	H	H	OH	COMe



Scheme 1. Synthesis of coumarins by Knoevenagel condensation under microwave and thermal condition.

Table 2. Optimization of the ZnO nanoparticles catalysed model reaction for synthesis of ethyl 2-oxo-2*H*-chromene-3-carboxylate (**3a**).

Entry	Catalyst (mol %)	Yields(%) ^a
1	No catalyst	-
2	ZnO nano (5%)	55
3	ZnO nano (10%)	90 ^b
4	ZnO nano (20%)	65
5	ZnO nano (10%)	85 ^c
6	ZnO nano (10%)	52 ^d
7	ZnO bulk (10%)	26

^aIsolated yield^bReaction was carried out at 120°C^cReaction was carried out at 100°C^dReaction was carried out at 140°C

glycols are reported to promote rod-like morphologies, as has increasing the base content during synthesis.³¹ Thus, triethanol amine used as size stabilizer and found effective in directing the morphology of ZnO nanoparticle.

The obtained particles were characterized by X-ray powder diffraction (XRD) (figure 1). The XRD pattern of the newly prepared zinc oxide nanoparticles showed the presence of peaks, which corresponds to hexagonal wurtzite structure.³² The size of the particles has been computed from the width of first peak using Debye Scherrer formula

$$D = K \lambda / \beta \cos \theta,$$

here K is constant, λ is the wavelength of X-rays employed radiation (1.54056 Å), β is corrected full width at half maximum and θ is Bragg angle. The 2 θ value to be 19.0104. The crystallite size of the powder particles is calculated as about 30 nm.

The morphology of the sample was investigated with scanning electron microscopy (SEM) figure 2

which shows ZnO to be in nanostructure. This may be the results of the presence of small amount of triethanolamine, which acts as stabilizer. These nanoparticles are generally in random and not uniform, very similar to those described in the literature.³⁰

Although numerous methods to achieve coumarins by Knoevenagel condensation are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. Thus, we have been interested in the development of method for Knoevenagel condensation that would avoid the use of added acids and bases, are easy to perform and are economical for application to large scale preparations. The experimental reaction is presented in scheme 1.

To obtain the optimal reaction conditions, the synthesis of ethyl 2-oxo-2*H*-chromene-3-carboxylate (**3a**) was used as a model reaction. A mixture of *o*-hydroxy benzaldehyde (2 mmol), ZnO (10 mol %) and diethyl malonate (2.5 mmol) was irradiated in microwave oven or heated in an oil bath in different solvents (4 mL). A control experiment was conducted in the absence of zinc oxide nanoparticle catalyst; for ethyl 2-oxo-2*H*-chromene-3-carboxylate (**3a**) the reaction did not proceed and the substrate remained unchanged, while good results were obtained in the presence of ZnO nanoparticles (table 2).

On the optimized of amount of catalyst, we found that 10 mol% of ZnO nanoparticles could effectively catalyze the reaction for synthesis of the desired product. With the inclusion of 5 mol% of ZnO nanoparticles the reaction took longer time. Using more than 20 mol% ZnO nanoparticles has less effect on the yield and time of the reaction. It is remarkable that the reaction carried out by changing the size of the particles from nanoparticles to bulk resulted in a drop in the catalytic activity. It is interesting to note that the ZnO nanoparticle catalyst catalyses the reaction in excellent yield within a shorter reaction time than the bulk (table 2).

Table 3. Comparative synthesis of compound **3a** using solution versus the solvent-free conditions under microwave (MW, 300 W, max. 120°C) and thermal (Δ , 100°C) conditions.

Entry	Solvents	Time (min)		Yield (%) ^a	
		MW	Δ	MW	Δ
1	No solvent	6	36	90	85
2	DMF	20	180	15	11
3	Acetonitrile	18	190	20	18
4	Dioxane	14	120	16	12
5	Methanol	10	96	72	66
6	Ethanol	8	56	84	79

^aIsolated yield

In order to select the appropriate microwave power, the model reaction was examined at different microwave powers (100–400W) with controlled temperature (max. 140°C) in the presence of ZnO nanoparticles. The reaction was also examined at 60–140°C in thermal conditions. Higher yield and shorter reaction time were attained at 120°C.

To compare the efficiency of the solvent-free versus solution conditions, the reaction was examined in several solvents under microwave and thermal conditions. Thus, a mixture of 2-hydroxy benzaldehyde (2 mmol), ZnO (0.4 mmol) and β -dicarbonyl compound (2.5 mmol) was irradiated in microwave oven (300 W, max. 120°C) or heated in an oil bath (100°C) in different solvents. The results are depicted in table 3. As it is clear from table 3, lower yields and longer reaction times were observed in solution conditions. Therefore, the solvent-free method is more efficient.

To investigate the versatility and capability of our method, the reactions of *o*-hydroxy benzaldehyde was examined with diethyl malonate compounds under both microwave and thermal conditions (table 1). As table 3 indicates, the reactions proceeded efficiently and the desired products were obtained in good to excellent yields.

In order to investigate the scope of this reaction, a variety of different substituted *o*-hydroxy benzaldehyde and different 1,3-dicarbonyl compounds were subjected to this reaction (table 1, entries 1–18). A variety of substituted *o*-hydroxy benzaldehyde possessing a wide

range of electron-donating and electron-withdrawing functional groups afforded the corresponding products in good yields.

3.1 Regeneration of catalyst

To examine the reusability, the catalyst recovered by filtration from the reaction mixture *o*-hydroxy benzaldehyde and diethyl malonate after dilution with ethyl acetate was reused as such for subsequent experiments (up to four cycles) under similar reaction conditions. The observed fact that yields of the product remained comparable in these experiments (figure 3), established the recyclability and reusability of the catalyst without significant loss of activity.

4. Conclusions

From the experimental results, we found that the mono-mode microwave-assisted method has been successfully used for fast synthesis of nano-ZnO catalyst. The use of triethanolamine has a significant influence on the morphology of ZnO. We have developed an efficient, facile and environmentally acceptable synthetic methodology for the synthesis of coumarin derivatives using nano-ZnO catalyst under solvent-free condition. The advantages of this environmentally benign and safe protocol include a simple reaction setup, very mild reaction conditions, high product yields, short reaction times, and the possibility for reusing the catalyst, chemoselectivity and solvent-free conditions.

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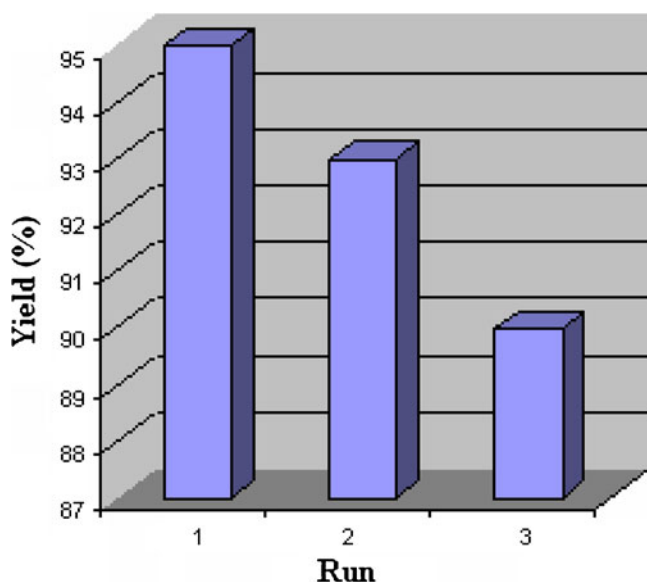


Figure 3. Recyclability of ZnO nano catalyst.

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