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A new strategy for the synthesis of 3-Acyl-coumarin using nano ZnO as an efficient catalyst

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ABSTRACT

3-Acyl-coumarins were obtained in high yields from ortho-hydroxybenzaldehydes and ethyl acetoacetate or ethyl benzoylacetate in acetonitrile in the presence of a catalytic amount of nano-ZnO.

Keywords: 3-Acyl-coumarins, nano catalyst, ethyl acetoacetate, one-pot

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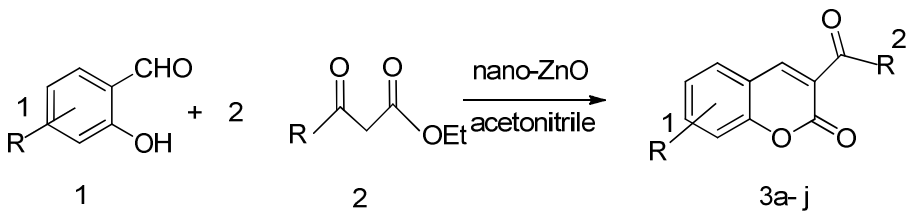
INTRODUCTION

Coumarin and its derivatives form an elite class of compounds, occupying an important position in the realm of natural products and synthetic organic chemistry.[1] 3-Acyl-coumarins are important initial compounds for the synthesis of coumarins, which has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. Their applications range from additives in food, perfumes, cosmetics, pharmaceuticals to the preparation of insecticides,[1]optical brighteners[2] and dispersed fluorescent and tunable laser dyes.[3] Also, coumarins have varied bioactivities, for example, inhibition of platelet aggregation,[4] anticancer[5] and inhibition of steroid 5α-reductase.[6] Their properties turn coumarins very interesting targets to organic chemists, and several strategies for their synthesis were already developed. The last decade witnessed a series of publications on the development of synthetic protocols for this important heterocyclic scaffold. Thus, it is clearly evident that the need for the development of new and flexible protocols is required.

Coumarins can be synthesized by various methods such as Pechmann,[7] Perkin,[8] Knoevenagel,[9] Reformatsky[10] and Witting[11] reactions. In 1898, Knoevenagel described the solution phase synthesis of coumarins by the condensation of malonic acid with *ortho*-hydroxyarylaldehydes.[9a] In our attempts to develop new catalyst systems, herein, we describe the use of this Knoevenagel condensation reaction to prepare 3-Acyl-coumarins in a mild and facile manner in the presence of a catalytic amount of nano-ZnO in high yields (Scheme 1).



Scheme 1

MATERIALS AND MEHTODS

Chemical and apparatus

All products are known compounds and were characterized by mp, IR, ^{1}HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Preparation of catalyst

Bulk zinc oxide was prepared by simple precipitation method wherein aqueous ammonia solution (30 %) was added dropwise to zinc nitrate solution under vigorous stirring (till pH of solution reached (7. 5–8). The white precipitate of Zn(OH)2 was filtered and washed several times with distilled water till the washings were neutral. The precipitate was then dried overnight at 100 °C in an oven and calcined at 600 °C for 3h. Nano zinc oxide catalyst was prepared by the gel combustion method as described by Riahi-Noori et al.[24] An appropriate molar ratio of citric acid and zinc nitrate (2:1) were mixed in a minimum amount of distilled water. The aqueous solution was homogenized and further concentrated on a hot plate to a viscous liquid, which was further heated at 100 °C for complete removal of water to obtain a dry mass. This mass was then further heated gradually till its combustion occurred giving a white fluffy powder. The powder obtained was annealed at 600 °C for 3h to give Nano ZnO. The oxide was further characterized by various analytical techniques to confirm its structural properties. External morphology and particle size of the catalyst was determined by TEM image (Fig. 1). It is clear from TEM image that the zinc oxide has polymorphic geometry and the size of the particles is in the range of 50-70 nm.

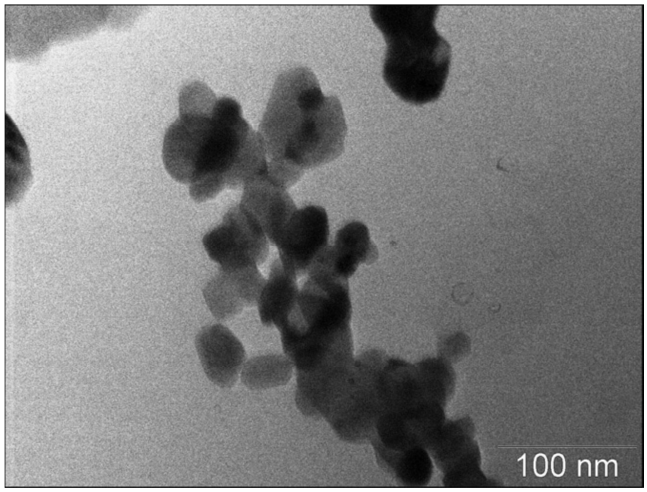


Fig 1. TEM image of Nano ZnO at 100 nm.

General procedure for the synthesis of 3-acyl-coumarins

A mixture of *ortho*-hydroxybenzaldehyde (1 mmol) and Ethyl acetoacetate or Ethyl benzoylacetate (1 mmol) and nano-ZnO (0.02 g) in acetonitrile (5 mL) was stirred at room temperature for 1.5 h. The progress of the reaction was monitored by TLC using EtOAc: hexane (1:2) as eluent. After completion of the reaction, the catalyst was filtered and the solvent was evaporated. The residue was recrystallized from ethanol to give the pure product. mp. 123 (Lit. 121/122 [20])

3a: IR (KBr): 1712, 1657, 1623, 1567, 1455, 1240, 1220, 980, 756 cm^{-1}; ^{1}HNMR ($CDCl_3$, 500 MHz): δ=2.76 (s, 3H, CH_3), 7.35~7.39 (m, 2H, Ar-H), 7.60~7.68 (m, 2H, Ar-H), 8.43 (s, 1H, CH).

3e: IR (KBr): 1746, 1670, 1611, 1500, 1357, 1200, 980, 831, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$, 500 MHz): δ=2.77 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 6.76 (d, J=2.30 Hz, 1H, Ar-H), 6.88 (q, J=3.70 Hz, 1H, Ar-H), 7.46 (d, J=8.70 Hz, 1H, Ar-H), 8.41 (s,1H, CH).

RESULTS AND DISCUSSION

In this paper, we decided to investigate the Knoevenagel condensation reaction to prepare 3-acyl-coumarins, then we set out for the synthesis of coumarins via condensation of *ortho*-hydroxybenzaldehydes with ethyl acetoacetate or ethyl benzoylacetate using nano-ZnO as an efficient catalyst at room temperature (Scheme 1). To investigate the generality of this process, various salicylic aldehydes were reacted under similar conditions, allowing the easy synthesis of 3-acyl-coumarins in good yields (Table 1). This one-pot procedure is convenient and straightforward with simple product isolation. From Table 1, it can be observed that the reactions proceeded faster than the conventional methods and the yields were comparable.

Table 1 Synthesis of 3-acyl-coumarins in the presence of nano-ZnO as a catalyst

Entry	R^1	R^2	Product	Yield(%)[a]
1	H	CH_3	3a	98
2	3-hydroxy	CH_3	3b	98
3	4-hydroxy	CH_3	3c	98
4	5-bromo	CH_3	3d	96
5	4-methoxy	CH_3	3e	98
6	H	Ph	3f	95
7	3-hydroxy	Ph	3g	96
8	4-hydroxy	Ph	3h	96
9	5-bromo	Ph	3i	93
10	4-methoxy	Ph	3j	95

To show the merits and advantages of using nano-ZnO as a catalyst, our method is compared with reported reactions (Table 2). The reaction results without catalyst decrease and the reaction time increases. This method is suitable for *ortho*-hydroxy benzaldehydes but the *ortho*-hydroxyaryl ketones were recovered and unchanged after the reaction.

Table 2 Comparison of various catalysts for the synthesis of 3-acetyl-coumarin (3a)

Entry	Catalyst	Time	Yield(%)	Reference
1	nano-ZnO	1.5h	98	This article
2	$H_{14}[NaP_5W_{30}O_{110}]$	2h	98	12
3	Piperidinium acetate	2h	89	13
4	none	10h	90	14
5	Piperidine	2h	50	15
6	[bmIm]OH	15min	88	16

We performed the effect of various solvents on the synthesis of 3a. This reaction was carried out in various solvents and the best results in terms of yield and time obtained in acetonitrile (Table 2). The effect of temperature was studied by carrying out the reactions at different temperatures. The yields of reactions increased as the reaction temperature was raised. From these results, it was decided that refluxing temperature would be the best temperature for all reactions.

Table 2. Synthesis of 3a in the presence of different solvents using nano-ZnO as a catalyst

Entry	Solvent	Time(h)	Yield(%)[a]
1	THF	2	68
2	CH_3OH	2	93
3	CH_3CN	2	98
4	$CHCl_3$	2	75
5	Solvent-free	2	90
6	C_2H_5OH	2	90

[a]*Yields were analyzed by GC*

Reusability of nano-ZnO

Next, we investigated the reusability and recycling of nano-ZnO. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with methanol and subjected to a second run

of the reaction process. To assure that catalysts were not dissolved in acetonitrile, the catalysts were weighted after filteration and before using and reusing for the next reaction. The results show that these catalysts are not soluble in acetonitrile. In Table 3, the comparison of efficiency of nano- ZnO in synthesis of 3a after five times is reported. As it is shown in Table 1 the first reaction using recovered nano-ZnO afforded similar yield to those obtained in the first run. In the second, third, fourth and fifth runs, the yield were gradually decreased.

Table 3. Reuse of the nano-ZnO for synthesis of 3-acetyl counarin (3a)

Entry	Time(h)	Yield/%[a]
1	1.5	98
2	2	95
3	3	92
4	4	83
5	4.5	80

(a) Isolated yields

CONCLUSION

In conclusion, we have developed a simple and efficient synthesis of 3-acyl-coumarins via Knoevenagel condensations in high yields and selectivities from *ortho*-hydroxy benzaldehydes using nano-ZnO as a catalyst under mild conditions at room temperature. Moreover the fast reaction time, simple experimental procedure, recyclability of the catalyst and high yields of the products are the advantages. We believe our procedure will find important applications to the synthesis of coumarins.

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