# A NEW STRATEGY FOR THE SYNTHESIS OF 3-ACYLCOUMARIN USING NANO ZINC OXIDE AS AN EFFICIENT CATALYST

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3-Acylcoumarins 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.

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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 have 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] 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 there is a need for the development of new and flexible protocols for the synthesis of coumarins.

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-acylcoumarins, in high yields, in a mild and facile manner, in the presence of a catalytic amount of nano-ZnO.

## Experimental

### Chemicals and apparatus

All products are known compounds and were characterized by m.p., IR, $^1$H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. $^1$H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. IR spectra were recorded on KBr disk using 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 spectral and physical data.

### Preparation of the catalyst

Bulk zinc oxide was prepared by simple precipitation method wherein aqueous ammonia solution (30 %) was added drop-wise 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 3 h. Nano zinc oxide catalyst was prepared by the gel combustion method as described by Riahi-Noori et al.[12] 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 characterized by various analytical techniques to confirm its structural properties. External morphology and particle size of the catalyst was determined by TEM image (Figure 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.

### General synthetic procedure

A mixture of the appropriate benzaldehyde (1 mmol) and ethyl acetoacetate or ethyl benzoylacetate (1 mmol) and nano-ZnO (0.02 g) in MeCN (5 mL) was stirred at room temperature for 1.5 h. The progress of the reaction was monitored by TLC (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 EtOH to give the pure product (Scheme 1).

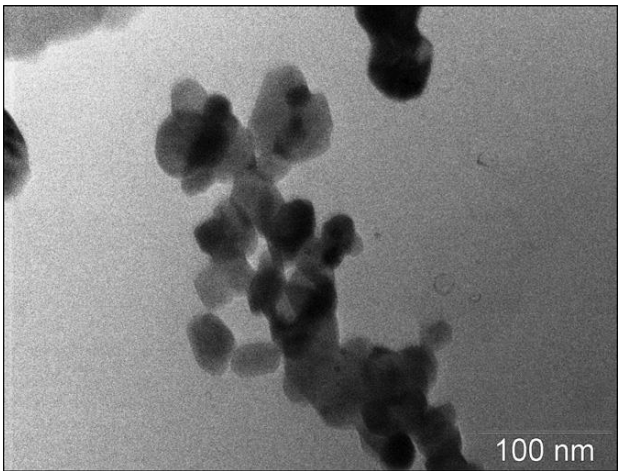
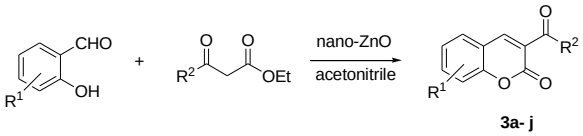



**Figure 1.** TEM image of nano zinc oxide at 100 nm.




**Scheme 1.** Synthesis of 3-acylcoumarins.

**3a**: m.p. 123 °C (Lit. 121/122 [13]). IR (KBr): 1712, 1657, 1623, 1567, 1455, 1240, 1220, 980, 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 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 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 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 study, we have investigated the Knoevenagel condensation reaction to prepare 3-acylcoumarins and 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. To investigate the generality of this process, various salicylic aldehydes were reacted under similar conditions, allowing the easy synthesis of 3-acylcoumarins 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.

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.

## Conclusion

In conclusion, we have developed a simple and efficient synthesis of 3-acylcoumarins via Knoevenagel condensations in high yields and selectivities from *ortho*-hydroxybenzaldehydes 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 is the main advantages. We believe our procedure will find important applications to the synthesis of coumarins.

**Table 1.** Synthesis of 3-acylcoumarins in the presence of nano-ZnO as a catalyst.

| Entry | $R^1$ | $R^2$ | Product | Yield (%) |
|---|---|---|---|---|
| 1 | H | $CH_3$ | 3a | 98 |
| 2 | 3-OH | $CH_3$ | 3b | 98 |
| 3 | 4-OH | $CH_3$ | 3c | 98 |
| 4 | 5-Br | $CH_3$ | 3d | 96 |
| 5 | 4-OMe | $CH_3$ | 3e | 98 |
| 6 | H | Ph | 3f | 95 |
| 7 | 3-OH | Ph | 3g | 96 |
| 8 | 4-OH | Ph | 3h | 96 |
| 9 | 5-Br | Ph | 3i | 93 |
| 10 | 4-OMe | Ph | 3j | 95 |

**Table 2.** Comparative efficiency of various catalysts for the synthesis of 3-acetylcoumarin (**3a**).

| Catalyst | Time | Yield (%) | Refer. |
|---|---|---|---|
| nano-ZnO | 1.5 h | 98 | This article |
| $H_{14}[NaP_5W_{30}O_{110}]$ | 2 h | 98 | 14 |
| Piperidinium acetate | 2 h | 89 | 15 |
| none | 10 h | 90 | 16 |
| Piperidine | 2 h | 50 | 17 |
| [bmIm]OH | 15 min | 88 | 18 |

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