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Nano-TiO_2: An Efficient and Useful Catalyst for the Synthesis of 3-acetyl-Coumarin Derivatives.

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ABSTRACT

3-acetyl-coumarins were obtained in high yields from ortho-hydroxybenzaldehydes and ethylacetoacetate or ethylbenzoylacetate in acetonitrile in the presence of a catalytic amount of nano-TiO_2.

Keywords: coumarins, catalyst, one-pot, salicylic aldehydes.

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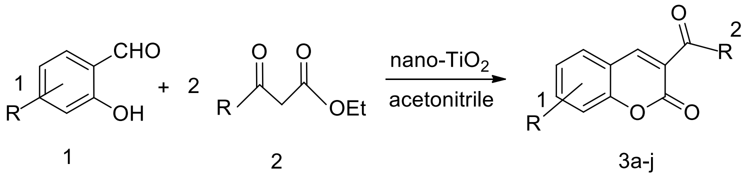
INTRODUCTION

Coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry. [1] 3-acetyl-coumarins are important initial compounds for the synthesis of coumarins and the synthesis of coumarins and their derivatives 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 and in 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, [10] Herein, we describe the use of this Knoevenagel condensation reaction to prepare 3-acetyl-coumarins in a mild and facile manner in the presence of a catalytic amount of nano-TiO_2 in high yields. (Scheme 1)



Scheme 1

RESULTS AND DISCUSSION

It is known that, the specific surface area and surface-to-volume ratio increase dramatically as the size of a material decreases. The high surface area brought about by nanoparticle size is beneficial to many TiO_2-based devices, as it facilitates reaction/interaction between the devices and the interacting media. [11] TiO_2 nanoparticle has been widely investigated in the past decades due to its multiple potential catalytic activity for esterification,[12] degradation of methyl parathion,[13] photodecomposition of methylene-blue,[14] rhodamine B degradation,[15] synthesis of b-acetamido ketones,[16] 2-alkylbenzimidazoles and indazole,[17] β-amino ketones,[18] bis(indolyl)methanes,[19] 2-indolyl-1-nitroalkane,[20] selective oxidation of sulfides,[21] Friedel–Crafts alkylation of indoles,[22] and photocatalytic synthesis of quinaldines.[23]

The investigation on nano-TiO_2 catalytic activity for the synthesis of many organic molecules is current work in our laboratory. The dimensions of applied TiO_2 nanoparticles were determined with SEM and are 38 nm (Fig. 1).

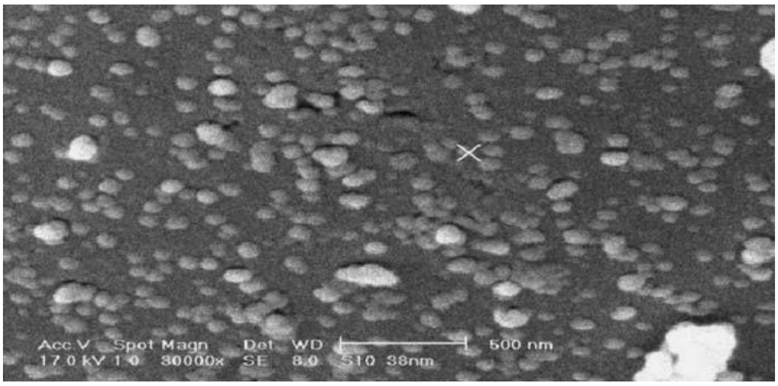


Figure 1: SEM photograph of nano-TiO2.

In this investigation, we decided to investigate the Knoevenagel condensation reaction to prepare 3-acetyl-coumarins then, we set out for the synthesis of coumarins via condensation of ortho-hydroxybenzaldehydes and ethylacetoacetate or ethylbenzoylacetate using nano-TiO_2 as an inexpensive and non-polluting catalyst at room temperature (Scheme 1). The experimental procedure with this catalyst is very simple and the catalyst can be removed easily by filtration. Hence, there will not be any unnecessary acidic waste streams to create environmentally hazardous pollution. To investigate the generality of this process, various salicylic aldehydes were reacted under similar conditions, allowing the easy synthesis of 3-acetyl-coumarins in good yields (Table 1). This one-pot procedure is convenient and straightforward with simple product isolation. From Table 1, it is observed that the reactions proceeded faster than the conventional methods and the yields are comparable.

Table 1: Synthesis of 3-acetyl-coumarins in the presence of nano-TiO_2 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-TiO_2 as a catalyst, our method is compared with reported reactions (Table 2). The reaction results without catalyst decrease and the reaction times increase. This method is suitable for ortho-hydroxybenzaldehydes but The orthohydroxyaryl ketones were recovered unchanged after the reaction.

Table 2: COMPARISON of various catalyst for the synthesis of 3-acetyl coumarin (3a)

Entry	Catalyst	Time	Yield(%)	References
1	nano-TiO_2	1.5h	98	This article
2	$H_{14}[NaP_5W_{30}O_{110}]$	2h	98	24
3	Piperidinium acetate	2h	89	25
4	Without catalyst	10h	90	26
5	Piperidine	2h	50	27
6	[bmIm]OH	15min	88	28

EXPERIMENTAL

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.

General procedure for the synthesis of 3-acetyl-coumarins

A mixture of ortho-hydroxybenzaldehydes (1mmol) and Ethylacetoacetate or Ethyl benzoylacetate (1 mmol) and nano-TiO_2 (0.01g) 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 eluents. 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. M.p. 123 (lit. 121-122 [28])

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).

Synthesis of nano-TiO_2

A 500 mL three-necked flask containing 5 mL of titanium tetrachloride was equipped with a condenser, a gas trap and a water steam producer. The titanium tetrachloride was heated to 130 ˚C. By adding water steam to hot titanium tetrachloride for 15 min, a milky solution was formed. After washing the condenser, the milky solution was filtered to obtain a white solid. By heating of the white solid in oven at 400 ˚C for 7 h, the TiO_2 nanoparticle as a white crystalline powder was formed.

Reusability of nano-TiO_2

Next, we investigated the reusability and recycling of nano-TiO_2. 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-TiO_2 in synthesis of 3a after five times is reported. As it is shown in Table 1 the first reaction using recovered nano-TiO_2 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-TiO_2 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

Isolated yields

CONCLUSION

In conclusion, we have developed a simple and efficient synthesis of 3-acetyl-coumarins via Knoevenagel condensations in high yields and selectivities from ortho-hydroxybenzaldehydes using nano-TiO_2 as a solid acid catalyst under mild conditions at room temperature. Moreover the low cost of the catalyst, low toxicity of the catalyst, fast reaction times, simple experimental procedure, recyclablity of the catalyst and high yields of the products are the advantages. We believe our procedure will find important applications in the synthesis of coumarins.

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