

**NANO CRYSTALLINE ZnO CATALYZED ONE POT THREE-COMPONENT
SYNTHESIS OF 7-ALKYL-6*H*,7*H*-NAPHTHO[1',2':5,6]PYRANO[3,2-*c*]
CHROMEN-6-ONES UNDER SOLVENT-FREE CONDITIONS**

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ABSTRACT. In the present paper, an efficient one-pot synthesis of 7-alkyl-6*H*,7*H*-naphtho[1',2':5,6]pyrano[3,2-*c*]chromen-6-ones is described by three-component reaction of β -naphthol, aromatic aldehydes and 4-hydroxycoumarin using ZnO nanoparticles under solvent-free conditions. The present method provides a novel and efficient procedure for the synthesis of chromene derivatives with some advantageous such as short reaction times, easy workup, high yields, wide range of products, reusability of the catalyst, little catalyst loading and green conditions in the presence of ZnO nanoparticles (7 mol%) at 110 °C.

KEY WORDS: ZnO nanoparticles, Three-component reactions, Solvent-free, Chromene, Heterogeneous catalysts

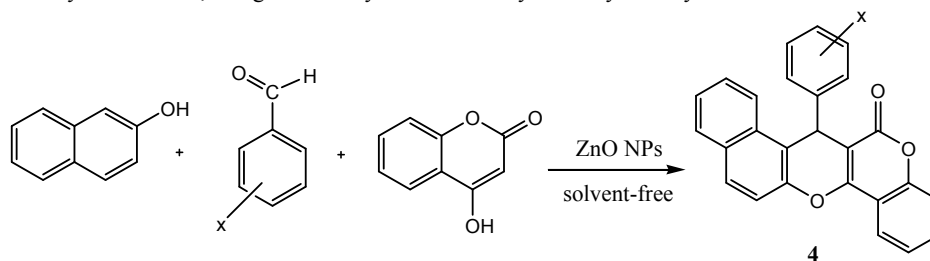
INTRODUCTION

Chromenes are important class of heterocyclic compounds with a broad range of pronounced biological properties such as antioxidant [1, 2], inhibitors of bacterial growth [3], anti-HRV serotype 1B within micro or submicromolar range with a high therapeutic index [4], cytotoxic [5], disrupt tumor vasculature and anticancer [6], antimicrobial [7], antihypertensive [8], and anti-tumor [9] activities. Also some of them have displayed a remarkable assay in the treatment of important diseases including Alzheimer's [10], high blood pressure [11], and as inhibitors of HIV virus [12]. Moreover; chromenes can also be utilized as cosmetics and pigments [13] and served as potential biodegradable agrochemicals [14]. A diversity of chromenes have been known for more than 50 years and isolated from a variety of plants [15]. The synthesis and applications of chromene derivatives has been reported by Hepworth [16] while naturally occurring chromenes have been reviewed by Rodriguez and Proksch [17]. In recent years, chromene derivatives have been synthesized by diverse catalysts such as [DBU][Ac] [18], ([Sipim]HSO₄) [19], SBPPSP [20], SiO₂PrSO₃H[21], Zr(HSO₄)₄ [22], ferric hydrogensulfate [23], nanosized magnesium oxide [24], H₁₄[NaP₅W₃₀O₁₁₀] [25], cetyl trimethyl ammonium chloride (CTACl) [26] and inorganic-organic hybrid magnetic nanocatalyst [27]. Recent advances in nanoscience and nanotechnology have led to new research interests in using nanometer-sized particles as an alternative matrix for catalytic reactions [28]. Ideally, introducing neat processes and utilizing eco-friendly and green catalysts, which can be simply recycled at the end of the reaction has received significant attention in recent years. Nanoparticle metal oxides have these advantages and widely used as effective catalysts in many organic reactions due to their high surface-to-volume ratio and easy recovery and simple recycling without losing their activity [29-31]. Recently, zinc oxide (ZnO) nanoparticles (NPs) have been reported as catalysts [32], antibacterial substances [33], sensors [34], luminescent materials [35] and photocatalysts [36]. ZnO has been successfully used as a Lewis acid catalyst, in organic reactions such as: Mannich reaction [37], Knoevenagel condensation [38], and also the synthesis of 1*H*-Tetrazoles [39], 4*H*-pyrane [40], benzimidazole [41] and N-amino-2-pyridones [42].

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Multi-component reactions (MCRs) have become attractive protocols to synthesize diverse and complex heterocyclic compounds of small molecules. MCRs often shorten reaction periods, giving higher chemical yields than multiple-step syntheses, and so can reduce the use of energy and operating cost [43-44].

In the background of our interest on sustainable approaches in the preparation of heterocyclic compounds and in continuing our attempts towards the advancement of effective and environmentally friendly nanocatalysts in organic synthesis [45-46], in this work we have reported one pot synthesis of 7-alkyl-6*H*,7*H*-naphtho[1',2':5,6] pyrano [3,2-*c*]chromen-6-ones by three component condensation of β -naphthol, aromatic aldehydes and 4-hydroxycoumarin in the presence of ZnO NPs as a highly efficient catalyst (Scheme 1). The present methodology offers advantages such as reduced reaction times, high yields, operational simplicity, reduced toxicity of ZnO NPs, along with catalyst recoverability and recyclability.



Scheme 1. The preparation of substituted chromenes.

EXPERIMENTAL

General

Chemicals were purchased from Merck and Sigma-Aldrich and were used without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 50, 60 and 80 W, was used for the ultrasonic irradiation. All melting points are uncorrected and were determined in capillary tubes on Boetius melting point microscope. ^1H NMR spectra were obtained on Bruker Avance DRX 400 MHz spectrometer with CDCl_3 as solvent using tetramethylsilane (TMS) as an internal standard, the chemical shift values are in δ . The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. Powder X-ray diffraction (XRD) of ZnO NPs was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu $K\alpha$ radiation ($\lambda = 1.5406 \text{ \AA}$). Microscopic morphology of products was visualized by SEM (LEO 1455VP). The compositional analysis was done by energy dispersive analysis of X-ray (EDAX, Kevex, Delta Class I).

Preparation of ZnO nanoparticles

To a solution of anhydrous ZnCl_2 in deionized water was added NaOH to keep a pH of 12. Then, the mixture was ultrasonically irradiated for 30 min. The white as-synthesized fouling was divorced by centrifugation and washed with deionized water to take impurities for several times and then dried at 120°C for 24 h. Eventually, the formed nanoparticles were calcined at 600°C for 12 h to gain a fine white powder.

General procedure for the preparation of 7-alkyl-6H,7H-naphtho[1',2':5,6]pyrano[3,2-c]chromen-6-one derivatives (4a-4l)

A mixture of β -naphthol (1.0 mmol), aldehyde (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol) was heated in a tube at 110 °C (in an oil bath) in the presence of catalytic amount of nano crystalline ZnO (7 mol%) under magnetic stirring (Scheme 1). After completion of the reaction (TLC), the reaction mixture was washed with water (15 mL). The residue dissolved in dichloromethane and then filtered to separate the nano ZnO catalyst. Upon concentrating the extract under reduced pressure, crude product was obtained which was finally purified by recrystallization from ethanol. The isolated compounds were characterized by mp, IR, ^1H NMR, ^{13}C NMR and elemental analysis (C, H and N).

The selected spectral data

7-(4-Boromophenyl)-6H,7H-naphtho[1',2':5,6]pyrano[3,2-c]chromen-6-one (4h). White powder, m.p. 281–282 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 8.18 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.84–7.89 (m, 2H), 7.66 (t, J = 8.0 Hz, 1H), 7.45–7.52 (m, 4H), 7.40 (t, J = 7.6 Hz, 1H), 7.30–7.36 (m, 4H), 6.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 175.50, 159.62, 152.51, 149.14, 146.78, 134.26, 132.23, 131.43, 130.31, 129.50, 128.75, 127.71, 125.82, 125.02, 123.66, 122.44, 118.55, 117.84, 116.79, 115.87, 109.50, 98.46, 35.69; IR (KBr, ν_{max} /cm $^{-1}$): 3058, 3027, 1692, 1634, 1554, 1482, 1361, 1259, 1027, 966, 875, 776; anal. calcd. for C $_{26}$ H $_{15}$ BrO $_3$: C, 68.59; H, 3.32; found: C, 68.55; H, 3.28.

7-(4-Hydroxyphenyl)-6H,7H-naphtho[1',2':5,6]pyrano [3,2-c]chromen-6-one (4j). White powder, m.p. 299–300 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.29 (s, 1H, OH), 8.17 (d, J = 8.0 Hz, 1H), 8.08 (t, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 3H), 7.97 (d, J = 8.0 Hz, 3H), 7.81 (t, J = 8.0 Hz, 1H), 7.69–7.73 (m, 3H), 7.61 (d, J = 9.2 Hz, 1H), 5.88 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 175.03, 162.41, 156.28, 152.32, 151.98, 149.08, 140.63, 140.11, 135.27, 131.52, 131.01, 130.87, 128.57, 128.13, 127.29, 126.88, 123.72, 123.03, 122.82, 118.91, 116.12, 112.53, 98.76, 35.46; IR (KBr, ν_{max} /cm $^{-1}$): 3293, 3023, 1712, 1648, 1562, 1467, 1311, 1226, 1051, 918, 835, 756, 690; anal. calcd. for C $_{26}$ H $_{16}$ O $_4$: C, 79.58; H, 4.11; found: C, 79.54; H, 4.17.

RESULTS AND DISCUSSION

Initially, the catalyst structure was identified by SEM, XRD, and EDX analysis. In order to study the morphology and particle size of ZnO nanoparticles, SEM image of ZnO nanoparticles is shown in Figure 1. These results show that spherical ZnO NPs were obtained from ultrasonically irradiation with particle size between 20-30 nm.

The XRD pattern of ZnO nanoparticles is shown in Figure 2. All reflection peaks in Figure 2 can be easily indexed to pure hexagonal phase of ZnO with P63mc group (JCDPS No. 36-1451). The crystallite size diameter (D) of the ZnO nanoparticles has been calculated by Debye–Scherrer equation ($D = K \lambda / \beta \cos\theta$) and crystallite size of zinc oxide has been found to be 24 nm. The chemical purity of the samples as well as their stoichiometry was tested by EDAX studies. The EDAX spectra given in Figure 3 were shown the presence of zinc and oxygen are the only elementary components.

In the following, the reaction of β -naphthol, 4-nitrobenzaldehyde, and 4-hydroxycoumarin was employed as the model reaction. In order to evaluate the catalytic activities, the model reaction was performed in the presence of various catalysts including FeCl $_3$, CuI, AgI, MgO, ZnO, ZnO NPs. Table 1 shows that ZnO NPs are superior to any of the other catalysts, owing to their strong catalytic performance. It is noteworthy to mention that the quantity of the catalyst

can be a vital role for the formation of the desired product. So, the optimization of amount of the catalyst was performed and results summarized in Table 2, the best amount of ZnO NPs was considered 7 mol%. Also in order to find the best temperature to get maximum yield in short duration, the reaction was carried out in different temperatures and it found that the maximum yield of the product afforded at 110 °C.

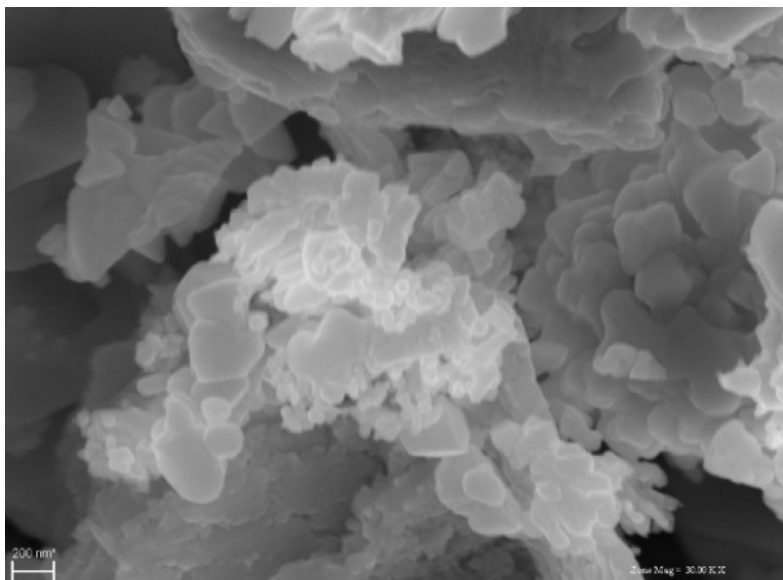


Figure 1. SEM image of ZnO nanoparticles.

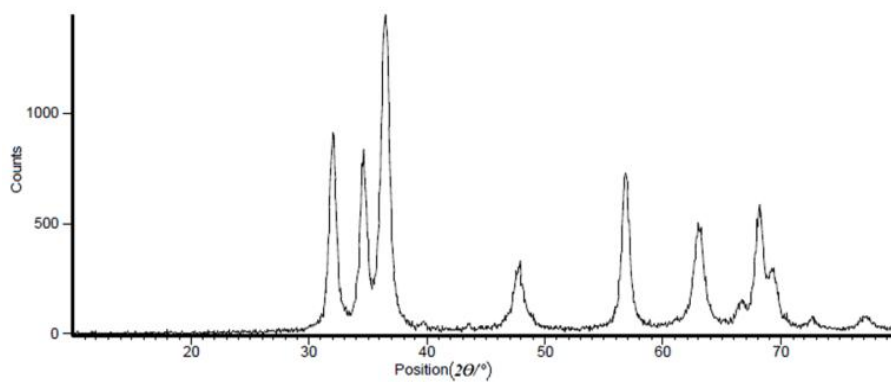


Figure 2. The XRD pattern of zinc oxide nanoparticle.

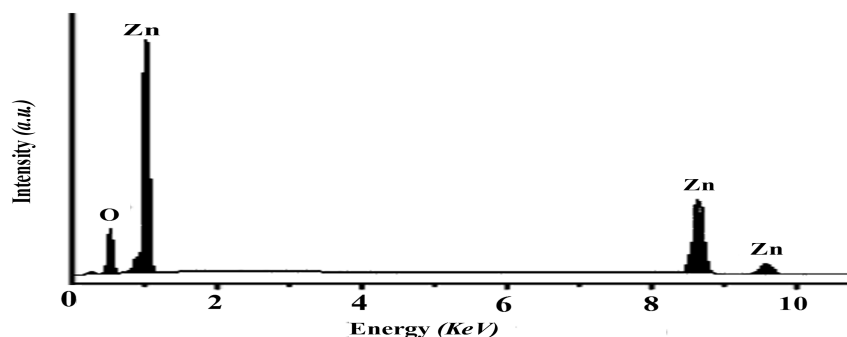


Figure 3. EDX spectrum of ZnO nanoparticles.

Table 1. The model reaction was carried out in various catalysts^a.

Entry	Catalyst	Time (min)	Temperature (°C)	Yields (%) ^b
1	FeCl ₃	100	120	60
2	CuI	100	130	70
3	AgI	100	130	68
4	MgO	100	120	72
6	ZnO	100	120	79
7	ZnO (NPs)	40	110	93
8	ZnO (NPs)	50	25	48
9	ZnO (NPs)	50	60	65
10	ZnO (NPs)	50	90	83

^aReaction conditions: β -naphthol (1 mmol), 4-NO₂-benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), catalyst (7 mol%), solvent-free. ^bIsolated yields.

Table 2. Synthesis of 7-Alkyl-6H,7H-naphtho [1',2':5,6] pyrano [3,2-c]chromen-6-ones in the presence of various amounts of ZnO NPs^a.

Entry	ZnO (NPs) (mol %)	Time (min)	Yields (%) ^b
1	0	60	0
2	3	70	70
3	5	60	80
4	7	40	93
5	10	40	93

^aReaction conditions: β -naphthol (1 mmol), 4-nitro-benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), Solvent-free at 110°C. ^bIsolated yield.

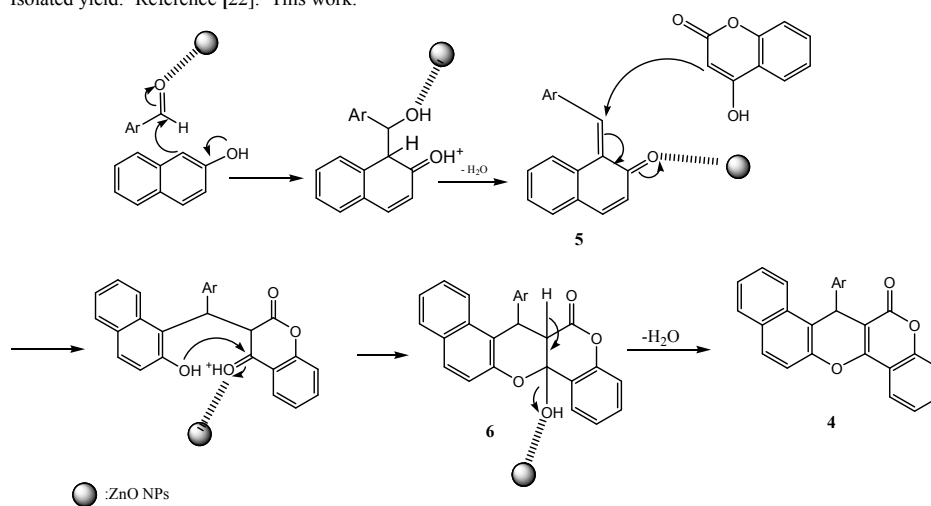
With the optimized conditions in hand, to delineate this approach, the scope and generality of this protocol was examined by employing various aldehydes. The data of Table 3 show aryl aldehydes with electron-withdrawing group such as NO₂, Cl, F and Br react with β -naphthol very smoothly to produce 7-alkyl-6H,7H-naphtho [1',2':5,6] pyrano [3,2-c]chromen-6-ones in relatively short reaction times. In addition, sterically hindered aldehydes reacted more slowly in comparison with unhindered aldehydes. As seen from Table 3, aromatic aldehydes having electron-withdrawing groups were better than electron donating groups in transforming uniformly into the corresponding 7-alkyl-6H,7H-naphtho [1',2':5,6] pyrano [3,2-c]chromen-6-ones in high to excellent yields within 40 min.

The plausible mechanism of the reaction is shown in Scheme 2. The reaction proceeds via initial formation of ortho-quinone methide (**5**). The oxonium species (**6**) is then formed on reaction with 2-hydroxynaphthalene-1,4-dione, which then undergoes dehydration to afford the desired product (**4**).

Table 3. One-pot synthesis of chromenecatalyzed by zinc oxide nanoparticles.

Entry	Ar	Product	Time (min)	Yield (%) ^a	Lit. m.p. (°C) ^b
1	Ph	4a	50	70	281-282
2	4-Cl-C ₆ H ₄	4b	40	91	267-268
3	4-F-C ₆ H ₄	4c	40	92	253-254
4	4-Me-C ₆ H ₄	4d	60	85	230-231
5	4-NO ₂ -C ₆ H ₄	4e	40	93	257-258
6	3-NO ₂ -C ₆ H ₄	4f	60	70	249-250
7	2,4-Cl ₂ -C ₆ H ₃	4g	45	85	267-268
8	4-Br-C ₆ H ₄	4h	40	89	281-282 ^c
9	4-OMe-C ₆ H ₄	4i	50	89	214-215
10	4-OH-C ₆ H ₄	4j	50	90	299-300 ^c
11	3,4-Cl ₂ -C ₆ H ₃	4k	60	86	256-257
12	2,5-MeO ₂ -C ₆ H ₃	4l	60	81	191-192

^aIsolated yield. ^bReference [22]. ^cThis work.



Scheme 2. The mechanism of synthesis of 7-alkyl-6H,7H-naphtho [1',2':5,6] pyrano [3,2-c]chromen-6-ones using ZnO nanoparticles.

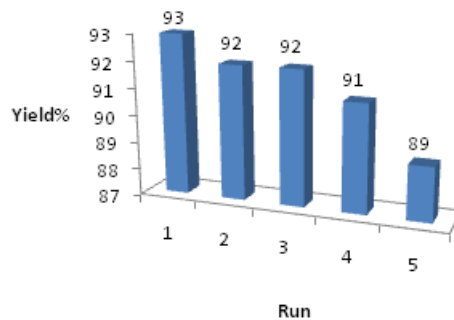


Figure 4. Recoverability of ZnO nanoparticles.

The role of nano-ZnO catalyst in reaction was the activation of carbonyl groups. This catalytic activity can be correlated to the high surface-to-volume ratio of ZnO nanoparticles. The reusability of the catalyst was studied through the model reaction. After completion of the reaction, the mixture was centrifuged and the ZnO NPs was filtered. Then, nanoparticles were washed three to four times with dichloromethane and methanol and dried at 150 °C for 4 h. The recovered catalyst was used for five times with a slightly decreased activity (Figure 4).

CONCLUSION

In conclusion, we have developed a straight forward and efficient approach to synthesis of pyrano[3,2-c]chromenes by three-component reaction of β -naphthol, aromatic aldehydes and 4-hydroxycoumarin using ZnO nanoparticles under solvent-free conditions. The advantages offered by this method include, short reaction times, excellent yields, a simple procedure, easy workup and the employment of a cost-effective catalyst.

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