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ORIGINAL PAPER

A flexible one-pot synthesis of 8,10-dimethyl-12-aryl-9*H*-naphto[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-9,11-diones catalyzed by ZnO nanoparticles under solvent-free conditions

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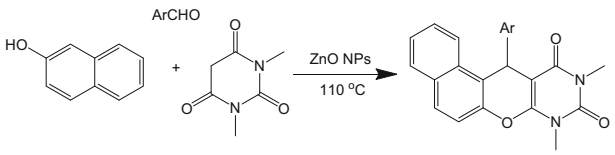
Abstract A new, convenient, and green procedure for the synthesis of naphthopyranopyrimidine-diones is described using a one-pot multi-component reaction of β-naphthol, 1,3-dimethylbarbituric acid, and various aryl aldehydes in the presence of ZnO nanoparticles, an effective and recyclable heterogeneous catalyst, under solvent-free conditions. This method provides excellent advantages, such as waste-free, simple work-up procedure, and excellent yield with high selectivity. The stability of the catalyst was investigated by determining its activity after recycling for six times without significant loss of its catalytic activity.

Graphical abstract



Keywords ZnO nanoparticles · Solvent-free · Multi-component reactions · Heterogeneous catalysts

Introduction

Nanocrystalline metal oxides are considered as efficient catalysts in many organic reactions due to their large surface-to-volume ratio, which provides a greater number of active sites per unit area in comparison with their heterogeneous counter sites [1, 2]. One of the extensively used materials for many chemical applications, such as gas sensors [3], photoactivity, flame-retardancy [4], solar cells [5], semiconductors [6], miniaturized lasers, light sources, piezoelectric elements for self-powered nano systems, transparent electrodes [7–9], and cosmetic and sunscreen to protect against UV-induced skin damage [10, 11] is nanocrystalline zinc oxide. During the last decade, ZnO nanoparticles (NPs) were used as an active catalyst in the synthesis of β-phosphonomalonates [12], benzimidazoles [13], as well as Mannich reactions [14].

In recent years, design and synthesis of pharmacologically active molecules is one of the principal challenges in medicinal chemistry. So, numerous efforts have been directed towards the development of new and green methods for the synthesis of heterocyclic compounds because of their potential importance in the pharmaceutical and agricultural field. Among others, naphthopyranopyrimidine and its derivatives have attracted interest due to the fact that structural motifs of these compounds are very useful in medicinal and biological chemistry [15, 16]. Also these compounds exhibit promising physiological [17], anticonvulsant behavior [18], hypotensive effect [19], analgesic [20], fungicidal [21, 22], antibacterial [23–26], antitumor [27, 28], hypolipidemic [29], molluscicidal [30], and antifungal activities [31–33]. Lately, the biological activity of these molecules for the treatment of sleep, anxiety, and addiction disorders has been reported [34].

Recently, multi-component reactions (MCRs) have attracted much attention due to their wide domain of applications in pharmaceutical chemistry, synthetic and practical efficiency, reduction of isolation and purification steps, minimization of costs, energy, time, and waste production [35–37]. Multi-component reactions are also one-

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pot reactions in which three or more substrates together react in a single vessel to form the desired product [38].

Besides, solvent-free reactions lead to environmentally benign procedures that save resources and energy. "Green chemistry" suggests these kinds of reactions due to great attention in economical and synthesis point of view. In addition, solvent-free reactions possess some benefits over traditional reactions in organic solvents, for instance they not only reduce the burden of organic solvent disposal, but also enhance the rate of many organic reactions.

The synthesis of 8,10-dimethyl-12-aryl-12*H*-naphto[1′,2′:5,6]pyrano [2,3-*d*]pyrimidine-9,11-diones and its derivatives via previous methods has been reported so far using formic acid [39], indium(III) chloride [40], and iodine catalysts [41]. The majority of these methods have low yields, consumption of huge amount of catalyst or long reaction times. As well toxicity and non-recoverability of the catalyst are drawbacks of these methods. Accordingly, for solving these problems there was a need to develop flexible and green protocol for the synthesis of these compounds.

To the best of our knowledge, this is the first report on the synthesis of 8,10-dimethyl-12-aryl-9*H*-naphto[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-9,11-dione derivatives **4** (Scheme 1) in the presence of ZnO NPs as catalyst under solvent-free conditions via three component reaction. The products can be simply separated from the catalyst by filtration, and in particular, the catalyst can be recycled for several times without noticeable decrease of the catalyst activity.

Considering the above factors, we report a one-pot synthesis of **4a**–**4k** in high to excellent yields using mixture of an aromatic aldehyde **1** and *β*-naphthol (**2**) with 1,3-dimethylbarbituric acid (**3**) by ZnO NPs under solvent-free condition (Scheme 1).

Results and discussion

In the beginning treatment of 4-nitrobenzaldehyde (**1**), (**2**), and (**3**) was chosen as the standard reaction to test various catalysts to yield **4b**. Accordingly, the catalytic behaviors of some catalysts are compared in Table 1.

Initially, we found that in absence of any catalyst the reaction could not be achieved at all (Table 1, entry 1). These results in Table 1 clearly indicate that among the various catalysts, such as $FeCl_3$, CH_3COOH, HCl, CuI, and AgBr the yields of reaction are moderate. The best yield was observed when the reaction was carried out with ZnO (Table 1, entry 8). Notably, ZnO NPs (Table 1, entry 9) is an advantageous catalyst characterized with high reaction rate and yield.

Expectedly, the yield of reaction is influenced by different factors, such as the nature of aldehydes, solvent system, amount of catalyst, and temperature. A set of experiments in the presence of different amounts of ZnO NPs was performed to derive the optimal reaction conditions. As shown in Table 1, entries 9–12, the yields of product were improved when the amount of ZnO NPs was increased from 1 to 3 mol% (Table 1, entries 9 and 10). Also when mole percent was further increased to 5 mol% (Table 1, entry 11) the yield was stable and no evident influence was observed on this reaction. Thus, 3 mol% was chosen for future experiments.

Scanning electron microscopy (SEM) was used to characterize morphology of the nanocatalyst and its particle diameter. The SEM image (Fig. 1) shows ZnO NPs as white particles with diameters in the range of 10–15 nm. In addition, the size and morphology of zinc oxide nanoparticles were analyzed by transmission electron microscopy (TEM) (Fig. 2). The results show that the catalyst contains spherical particles with a crystallite size between 10 and 15 nm.

Moreover, the crystalline structure of ZnO NPs was verified by its X-ray diffraction pattern (XRD). The peaks in Fig. 3b show a pure hexagonal phase, and by means of the Debye–Scherrer formula ($d = K\lambda/\beta \cos\theta$) where K is the dimensionless shape factor, which typically has a value of about 0.9, λ is the X-ray wavelength (1.5406 Å for Cu Kα), β is the full-width at half maximum or half-width in radian, and θ is the Bragg angle. The diameter (d) of crystalline size of ZnO NPs was thus computed to be

Scheme 1

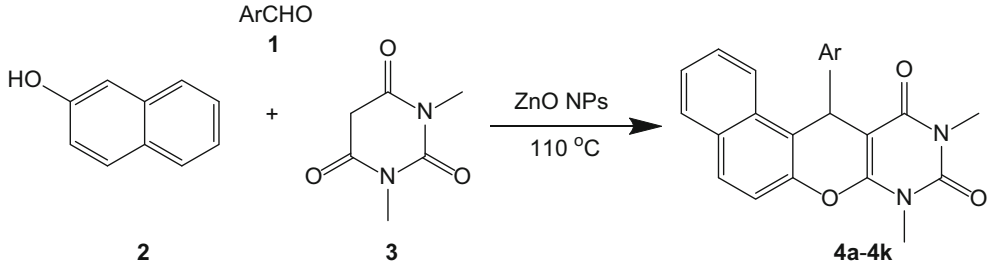


Table 1 Synthesis of naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidines using various catalysts under solvent-free condition at 110°C

Entry	Catalyst	Mol/%	Time/min	Yield[a]/%
1	None	0	360	0
2	$FeCl_3$	10	180	21
3	$N(Et)_3$	10	360	0
4	CH_3COOH	10	180	15
5	HCl	10	150	30
6	CuI	10	130	55
7	AgBr	10	100	42
8	ZnO	10	40	50
9	ZnO NPs	1	20	80
10	ZnO NPs	3	20	92
11	ZnO NPs	5	20	92

Reaction conditions: aromatic 4-nitrobenzaldehyde (**1**, 1.1 mmol), *β*-naphthol (**2**, 1 mmol), and 1,3-dimethylbarbituric acid (**3**, 1 mmol)

[a] Isolated yields

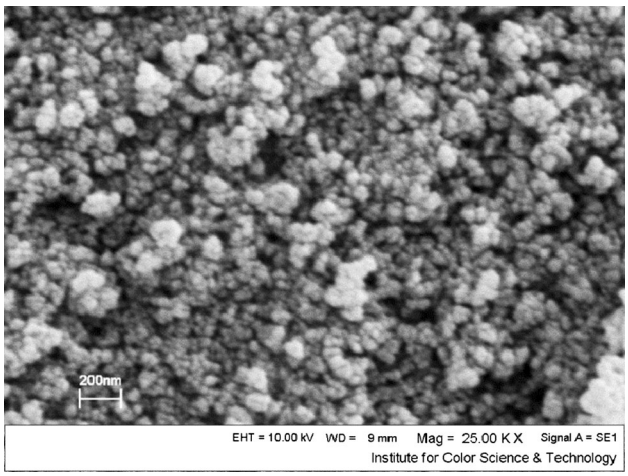


Fig. 1 SEM image of ZnO nanoparticle

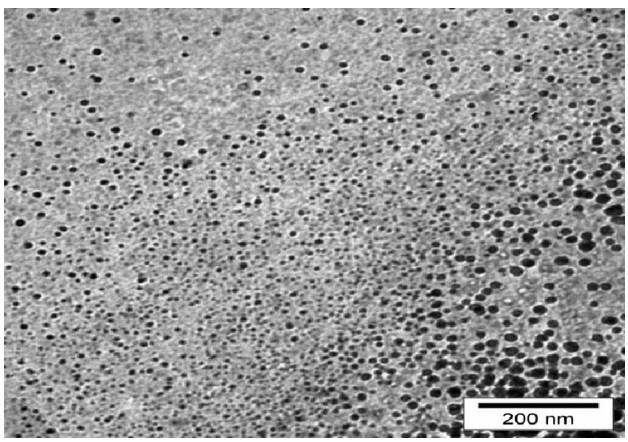


Fig. 2 TEM image of ZnO nanoparticles

10 nm. The stoichiometry of the sample and its chemical purity was checked by EDAX studies that are shown in Fig. 3 revealing that zinc and oxygen are the only elementary components of ZnO NPs.

To find the optimum solvent, the reaction was investigated under solvent-free conditions and using water, THF, EtOH, AcOH, ethylene glycol, DMF, and acetonitrile as solvents. The outcomes of this screening are presented in Table 2. The desired product was not formed in water and CH_3CN. In the case of ethanol and AcOH only low yield was obtained. When ethylene glycol, THF, and DMF were selected, the product **4b** was obtained in relatively good yield, whereas under solvent-free conditions the product **4b** was achieved with the best yield and the lowest reaction time.

Keeping these results in mind, this reaction was carried out under solvent-free conditions at temperatures between 50 and 120 °C to choosing the best reaction temperature. The results are summarized in Table 3. Thus, the reaction did not occur at temperatures less than 100 °C. As shown in Table 3 the best yield of **4b** was obtained at 110 °C (Table 3, entries 2 and 3).

With optimized conditions in hand we explored scope and limitations of the method. Thus, the reaction was carried out with a wide diversity of aromatic aldehydes (either electron-donating or electron-withdrawing group) for providing **4a**–**4k**. In all experiments, higher yields were obtained with electron-withdrawing groups. The results are summarized in Table 4.

A proposed reaction mechanism is demonstrated in Scheme 2. This mechanism consists of reaction sequences of addition, condensation, cyclization, and dehydration. The catalyst ZnO NPs interacts as the Lewis acid with the carbonyl group to improve cyclization. At first

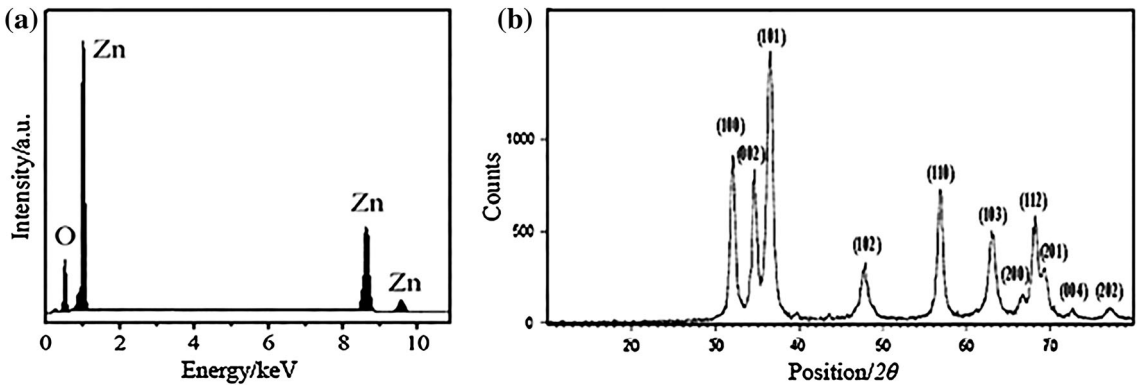


Fig. 3 EDX (**a**) and XRD pattern (**b**) of ZnO nanoparticles

Table 2 Solvent optimization for the synthesis of **4b** in presence of ZnO NPs (3 mol%)

Entry	Solvent	Time/min	Yield[a]/%
1	H_2O	480	Trace
2	THF	180	67
3	EtOH	480	21
4	AcOH	480	28
5	Ethylene glycol	180	63
6	DMF	90	77
7	CH_3CN	480	Trace
8	Solvent-free	20	92

[a] Isolated yields

Table 3 Temperature optimization for the synthesis of **4b**

Entry	Temp/°C	Yield[a]/%
1	50	0
2	100	70
3	110	92
4	115	85

[a] Isolated yields

condensation between **1** and **2** provides intermediate **6**. This is by a Michael addition with **3** gives intermediate **8**. Then cyclization of **8** gives **9** and subsequent dehydration resulted in the desired product **4**.

Then the same reaction using the recovered catalyst was done six times consequently to check the reusability of catalyst. It was found that the yield up to six times use did not substantially decrease the activity of the catalyst (Fig. 4).

Conclusion

In conclusion, the main aim of our research was based on a method for the synthesis of new 8,10-dimethyl-12-aryl-9*H*-naphto[1′,2′:5,6] pyrano[2,3-*d*]pyrimidine-9,11-dione derivatives in the presence of catalytic ZnO NPs under solvent-free conditions which provided in addition to several known compounds also a novel one of perhaps biological activity. The present method has many advantages, such as short reaction times, easy workup and excellent yields. High selectivity, mild reaction conditions, and a waste-free procedure are also benefits of this method. Especially ZnO nanoparticles are a green, recyclable heterogeneous and non-toxic catalyst that could be used for this purpose in the future and might be applied to obtain analogous targets.

Table 4 One-pot synthesis of naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidines under solvent-free condition at 110 °C

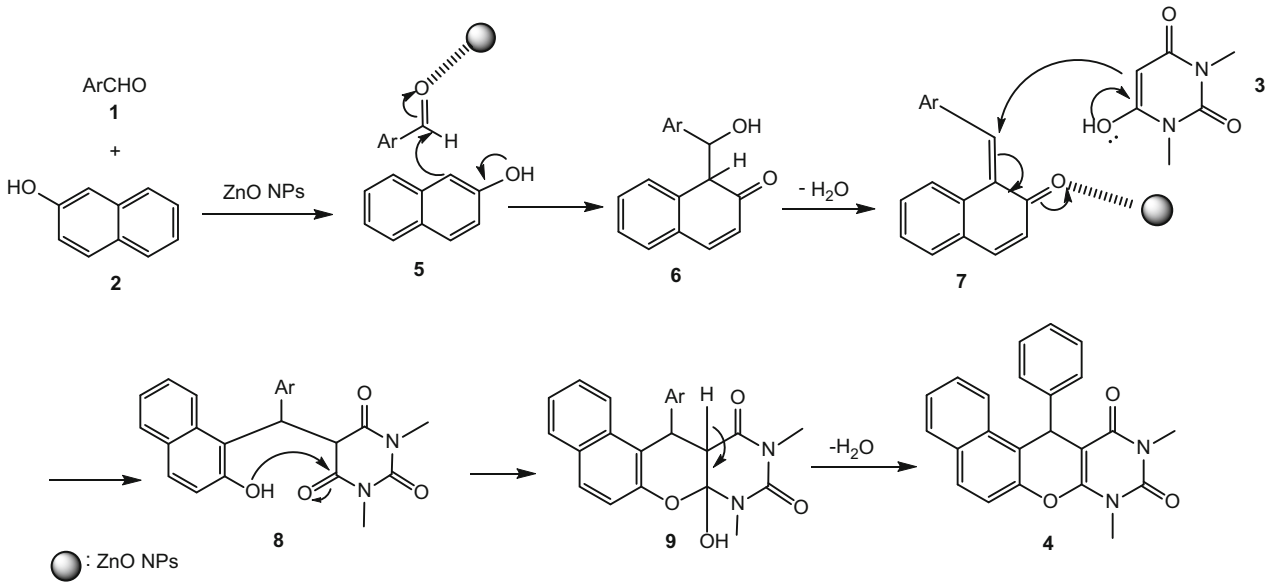
Entry	Product	R	Time/min	Yield[a]/%	M.p./°C (Ref)
1	**4a**	4-Br	25	85	243–245 [41]
2	**4b**	4-NO_2	20	92	290–292 [41]
3	**4c**	H	20	75	223–225 [41]
4	**4d**	4-Cl	25	87	274–276 [41]
5	**4e**	4-F	25	90	306–307 [41]
6	**4f**	4-Me	40	75	200–202 [41]
7	**4g**	2,4-di-Cl	20	95	219–221 [41]
8	**4h**	3-NO_2	25	82	310–312 [43]
9	**4i**	3-Cl	35	81	221–223 [41]
10	**4j**	4-OMe	30	80	257–259 [43]
11	**4k**	2-OMe	30	78	296–297

[a] Isolated yields

Experimental

Chemicals of commercial reagent grade and without further purification were obtained from Sigma-Aldrich and Merck. All of melting points were determined in capillary tubes on Boetius melting point microscope. ^{13}C NMR and ^{1}H NMR spectra were measured on Bruker 400 MHz

Scheme 2



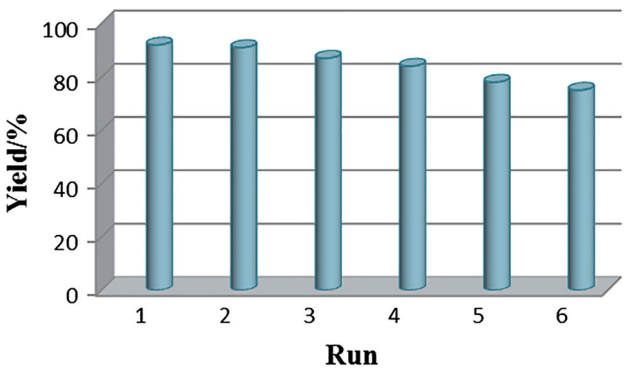


Fig. 4 Recoverability of Zno nanoparticles

spectrometer with $CDCl_3$ as solvent using TMS as internal standard, the chemical shift magnitudes are in δ. FT-IR spectrum were recorded on a Magna-IR, spectrometer 550 Nicolet in KBr pellets in the range of 400–4,000 cm^{-1}. The elemental analyses (C, H, N) were obtained by means of a Carlo ERBA Model EA 1108 analyzer; the results were in good agreement with the calculated values. Scanning electron microscopy (SEM) images were obtained on a Philips EM208 instrument. The TEM image was obtained on Philips EM208 transmission electron microscope with an accelerating voltage of 100 kV. The energy-dispersive X-ray spectroscopy (EDAX) measurements were performed on the PV9100 instrument. Powder X-ray diffraction (XRD) was performed on a Philips diffractometer of X'pert Company. The ZnO NPs were prepared according to Ref. [42].

General procedure for the synthesis of 8,10-dimethyl-12-aryl-9H-naphto[1′,2′:5,6]pyrano[2,3-d]pyrimidine-9,11-dione derivatives

A mixture of 1.1 mmol aromatic aldehyde, 0.144 g **2** (1 mmol), 0.156 g **3** (1 mmol), and 0.01 g ZnO NPs (10 mol%) in a round bottom flask was heated in an oil bath at 110 °C for 20–35 min. During the reflux the reaction was monitored by TLC (eluent: *n*-hexane: ethyl acetate, 1:1). After completion of the reaction the mixture was cooled to room temperature, then the reaction mixture was dissolved in dichloromethane and stirred for 5 min. The suspended solution was filtered and then heterogeneous nanocatalyst was recovered. Then solvent was evaporated and the solid was recrystallized from methanol to afford the pure product **4**.

Recycling and reusing of the catalyst

After completion of the reaction, the CH_2Cl_2-insoluble catalyst could be recycled by an easy filtration. The recovered catalyst from the experiment was washed two to three times with water and acetone (3 × 5 cm^3) and dried at 60 °C for 24 h.

12-(2-Methoxyphenyl)-8,12-dihydro-8,10-dimethyl-9H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine-9,11(10H)-dione (**4k**, $C_{24}H_{20}N_2O_4$)

White solid; *m.p.*: 295–297 °C; *IR* (KBr): $\bar{\nu}$ = 3,058, 2,952, 1,710, 1,652, 1,596, 1,482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 2H),

7.78–7.74 (m, 2H), 7.48–7.36 (m, 2H), 7.29–7.10 (m, 4H), 5.93 (s, 1H), 3.87 (s, 3H), 3.64 (s, 3H), 3.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.1, 29.0, 35.1, 57.50, 90.3, 115.5, 116.1, 123.2, 123.7, 125.4, 127.6, 128.4, 128.7, 129.0, 130.1, 130.3, 131.5, 143.2, 146.4, 147.0, 150.2, 150.8, 152.3, 161.3$ ppm; MS (EI): $m/z = 400$.

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