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$PbWO_4$ nanoparticles: A robust and reusable heterogeneous catalyst for the synthesis of benzopyranopyridines under ultrasonic irradiation

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ABSTRACT

An efficient four-component synthesis of benzopyranopyridines is described by one-pot condensation of salicylaldehydes, thiols and 2 equiv of malononitrile with nano-$PbWO_4$ as a robust and reusable heterogeneous catalyst under ultrasonic irradiation. Lead tungstate ($PbWO_4$) nanostructures have been synthesized *via* a sonochemical method based on the reaction between lead (II) nitrate and sodium tungstate dihydrate in an aqueous solution. Some advantages of this protocol include use of simple and readily available starting materials, rapid assembly of medicinally privileged heterocyclic molecules, reusability of the catalyst, low amount of the catalyst and application of the sonochemical methodology as an efficient technique and innocuous means of activation in synthetic chemistry.

***Keywords**: Benzopyranopyridine, Salicylaldehydes, Ultrasonic irradiation, Heterogeneous catalysts, Nano-$PbWO_4$, Thiols.*

1. Introduction

Benzopyranopyridines are attractive targets in organic and medicinal chemistry owing to their potency and wide spectrum of biological activities including dopamine D_4 receptor antagonists [1], anti-inflammatory and analgesic [2], anti-allergic [3], treatment of bronchial asthma [4], MK-2 inhibitors [5], antibacterial [6]. They can also serve as synthetic intermediates for many kinds of pharmaceuticals or drug precursors [7-9]. Therefore, the development of simple methods for the synthesis of benzopyranopyridines is a major challenge and an interesting field in chemistry. The synthesis of benzopyranopyridine derivatives has been reported in the presence of diverse catalysts such as K_2CO_3 [10], Et_3N [11,12], NaOH [13] and ZrP_2O_7 nanoparticles [14]. However, some of the reported methods tolerate disadvantages including long reaction times, harsh reaction conditions, low yield, tedious work-up, and use of toxic and non-reusable catalysts. Therefore, to avoid these limitations, the exploration of an efficient catalyst with high catalytic activity and short reaction times under ultrasonic irradiation for the preparation of benzopyranopyridine is still favored. Expansion of new catalytic transformations with simple separation and recyclability of the catalyst is an essential task in chemical synthesis. Among various nanoparticles, $PbWO_4$ nanoparticles have received considerable attention because of their unique properties and potential applications in diverse fields [15,16]. Recently, $PbWO_4$ nanostructures have been prepared using the hydrothermal approach [17,18], the solvothermal method [19], the microwave–assisted method [20], the wet chemical process [21] and the sonochemical route [22,23]. The ultrasound approach is a very attractive process used for synthesizing these nanosized materials. Ultrasound irradiation has been utilized to accelerate the chemical reactions proceeding through the formation, growth, and implosive collapse of bubbles in the solution. These extreme conditions can drive a diversity of chemical reactions to fabricate nanosized materials. Nanocatalysts have been emerged as an alternative approach for the improvement of many significant organic reactions under ultrasonic irradiations. The chemical synthesis productivity can be enhanced by nanosized catalysts due to the small size and high surface to volume ratios [24,25].

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Herein, we reported the use of $PbWO_4$ nanostructures as an efficient catalyst for the preparation of benzopyranopyridines by one-pot condensation of salicylaldehydes, thiols and 2 equiv of malononitrile under ultrasonic irradiation (Scheme 1).

2. Experimental

2.1. Materials and apparatus

All organic materials were purchased commercially from Sigma–Aldrich and Merck 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 200 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. All melting points were uncorrected and were determined in capillary tube on Boetius melting point microscope. FT-IR spectra were recorded with KBr pellets using a Magna-IR, spectrometer 550 Nicolet. NMR spectra were recorded on a Bruker 400 MHz spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. CHN compositions were measured by Carlo ERBA Model EA 1108 analyser. Nano-$PbWO_4$ was prepared according to the procedure reported in the literature [16]. X-ray diffraction (XRD) patterns were recorded by a Philips-X'PertPro, X-ray diffractometer using Ni-filtered Cu Kα radiation at scan range of $10<2\theta<80$. Scanning electron microscopy (SEM) images were obtained on LEO-1455VP equipped with an energy dispersive X-ray spectroscopy. DLS was performed using a Malvern Zetasizer Nano-S (Malvern Instruments. The magnetic measurement of samples was carried out in a vibrating sample magnetometer (VSM) (Meghnatis Daghigh Kavir Co.; Kashan Kavir; Iran) at room temperature in an applied magnetic field sweeping between ±10,000 Oe. The mass spectra were recorded on a Joel D-30 instrument at an ionization potential of 70 eV.

2.2. Synthesis of $PbWO_4$ nanostructures

Appropriate amounts of lead nitrate ($Pb(NO_3)_2$) and sodium tungstate dihydrat ($Na_2WO_4.2H_2O$) were used as the Pb and W sources. In a typical synthesis procedure, 0.2 gr of sodium tungstate dihydrate and 0.18 gr of lead nitrate were dissolved in 30 ml of distilled water separately. Then, $Pb(NO_3)_2$ solution was added dropwise to the solution of $Na_2WO_4.2H_2O$ and was heated to 45°C. Afterwards, the above-mentioned solution was loaded into a beaker and the reaction was carried out in an ultrasonic digestion system at 50 W for 30 min. The product was filtered and washed with distilled water and ethanol several times. Finally, the final product obtained was dried at 60°C and calcined at 550°C for 180 min.

2.3. General procedure for the preparation of benzopyranopyridines

A mixture of a selected salicylaldehyde (1.5 mmol), malononitrile (3 mmol) and a desired thiol (1.5 mmol) and 0.7 mol% nano-$PbWO_4$ in 10 mL of anhydrous ethanol was sonicated at 60 W power. The reaction was monitored by TLC. After completed reaction, the formed precipitate was isolated by filtration. The product was dissolved in DMF (5 mL) and the catalyst was filtered. Then, 5 mL water was added to the filtrate which resulted in the crystallization of the product. The resulting crystalline structure was filtered and dried with a vacuum pump. The structures of the products were fully established on the basis of their ^{1}HNMR, ^{13}CNMR, FT-IR, CHN and MS spectra (See Supplementary data).

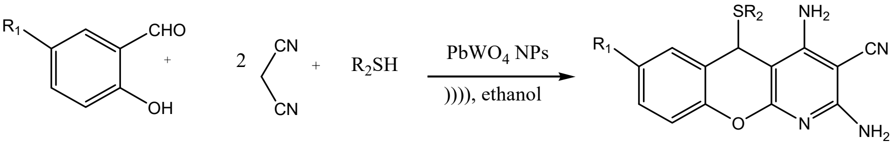
3. Results and Discussion

3.1. Structural analysis of $PbWO_4$ nanostructures

The crystalline structure and phase purity of prepared nano-$PbWO_4$ have been determined using XRD. The XRD pattern of prepared nano-$PbWO_4$ is shown in Fig. 1. Based on Fig. 1, the diffraction peaks observed can be indexed to pure Tetragonal phase of $PbWO_4$ (a= 5.4616 A° b= 5.4616 A°, c= 12.0460 A°) with space group of I41/a and JCPDS No. 08-0476. No diffraction peaks from other species could be detected, which indicates that the obtained $PbWO_4$ nanoparticle is pure. From XRD data, the crystallite diameter (D_c) of $PbWO_4$ nanoparticles was calculated to be 85-95 nm using the Scherer equation:

$$D_c = K\lambda/\beta\cos\theta \qquad \text{(Scherer equation)}$$

Where β is the breadth of the observed diffraction line at its half intensity maximum, K is the so-called shape factor, which usually takes a value of about 0.9, and λ is the wavelength of X-ray source used in XRD.



Scheme 1. Synthesis of benzopyranopyridines using nano-$PbWO_4$.

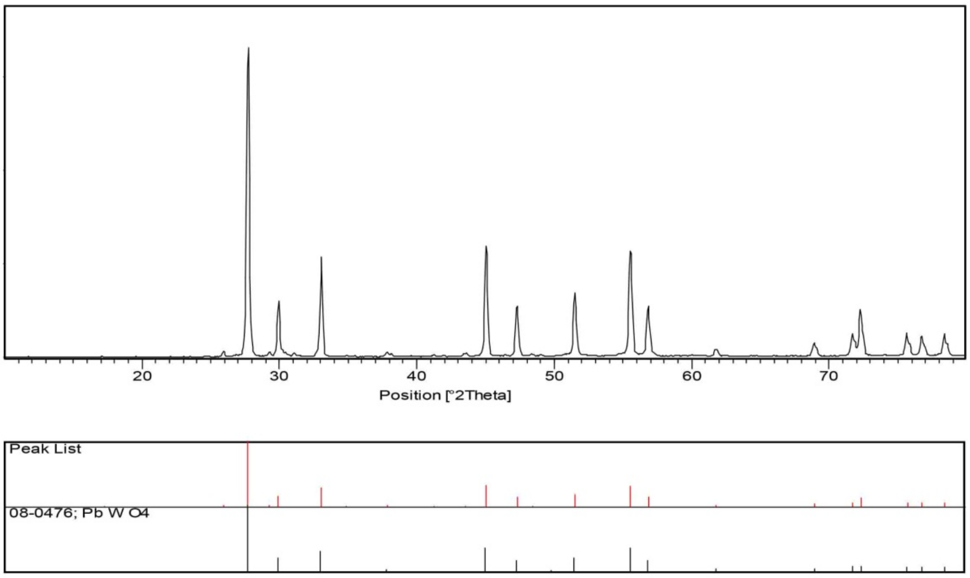


Fig. 1. XRD pattern of $PbWO_4$ nanostructures.

The morphology of the $PbWO_4$ nanoparticle was investigated using SEM (Fig. 2). The SEM image shows particles with diameters in the range of nanometers.

Room temperature specific magnetization (M) versus applied magnetic field (H) curve measurements for $PbWO_4$ nanoparticles are illustrated in Fig. 3. The synthesized $PbWO_4$ indicates a magnetization of ~ 0.005 emug^{-1}.

EDS (energy dispersive X-ray) spectrum of $PbWO_4$ nanostructures (Fig. 4) shows that the elemental compositions are lead, oxygen and tungsten.

In order to investigate the size distribution of nanostructures, DLS (dynamic light scattering) graph of the nanostructures were presented in Fig. 5. This size distribution is centered at a value of 94 nm.

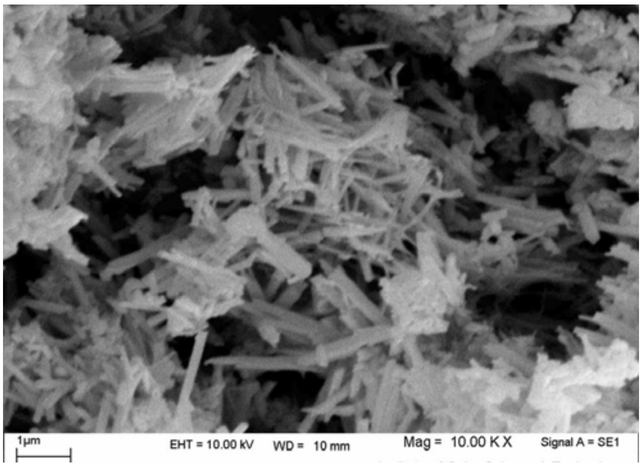


Fig. 2. SEM images of $PbWO_4$ nanostructures.

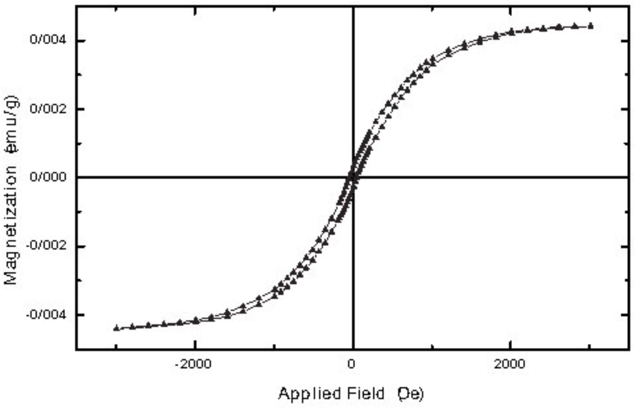


Fig 3. VSM curve of $PbWO_4$ nanostructures.

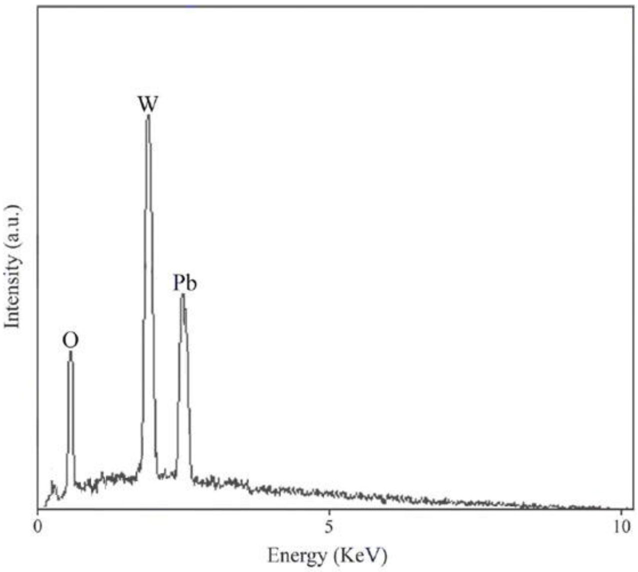


Fig.4. EDS spectrum of $PbWO_4$ nanostructures.

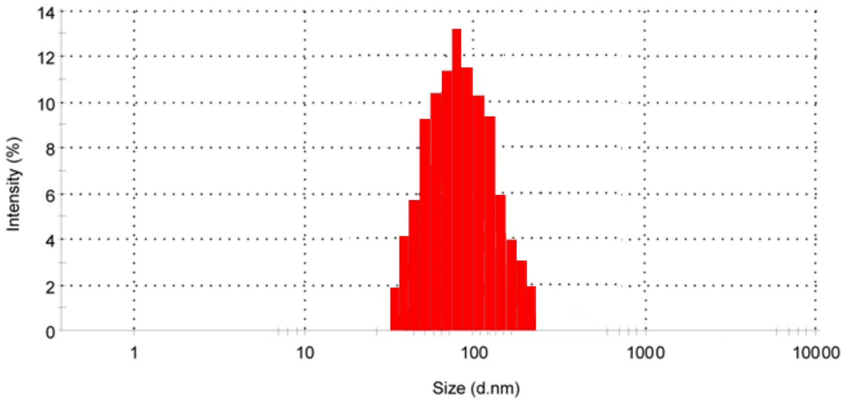


Fig. 5. DLS data of $PbWO_4$ nanostructures

3.2. Catalytic behaviors of nano-$PbWO_4$ for the synthesis of benzopyranopyridines

Initially, we focused on the systematic evaluation of different catalysts for the model reaction of salicyladehyde (1.5 mmol), malononitrile (3 mmol) and thiophenol (1.5 mmol) in different solvents. We employed various conditions and found that the reaction gave satisfying results in the presence of nano-$PbWO_4$ under ultrasonic irradiation in ethanol. The reaction was carried out with different amounts of nano-$PbWO_4$ as the catalyst. As show in Table 1, 0.70 mol % of nano-$PbWO_4$ as the catalyst was suitable and when the amount of the catalyst was enhanced to 0.90 mol %, but the yield was not developed. The model reaction was carried out in the presence of various catalysts such as DBU, nano-PbO, nano-WO_3, and nano-$PbWO_4$.

In continuation of this work, the role of ultrasonic irradiation on the reaction were examined. The results demonstrated that the sonication undoubtedly affected the reaction system. It could decrease the reaction time and enhance the yield of the products (Table 1). When the reaction was carried out under reflux conditions, it gave low yields of the products and took longer reaction times, while the same reaction was carried out under ultrasonic irradiation to give excellent yields of products in short reaction times. As we know, more energy was provided to the reaction system to accelerate cavitation effect with ultrasonic power increasing. The increase in the acoustic power could increase the number of active cavitation bubbles and also the size of the individual bubbles. Both increases can be expected to result in an increase in the maximum collapse temperature and the respective reaction could be accelerated. Therefore, it was observed that the reaction in the presence of 0.70 mol % of nano-$PbWO_4$ and under ultrasonic irradiation with the power of 60W gave the best result as the obtained product with 91% isolated yield during 15 minutes.

The recycling of nano-$PbWO_4$ catalyst was also checked. The possibility of recycling of the catalyst is an important process from different aspects such as environmental concerns, and commercial applicable processes. In the recycling procedure of nano-$PbWO_4$, DMF was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by filtering. The reusability of the catalyst was tested for seven runs, providing almost similar yields of the desired product. The yields for these runs were 91, 91, 91, 90, 90, 89 and 89%, respectively.

The reaction works well for salicylaldehydes and different thiols. All the reactions reached completion within 15–20 min to afford good yields of products. The yields of recrystallized benzopyranopyridines are given in Table 2.

3.3. The proposed reaction mechanism

A possible mechanism for the formation of benzopyranopyridines is shown in Scheme 2. Initially, salicylaldehyde reacts with 1 equiv. of malononitrile to form intermediate $\mathbf{I_1}$ and subsequent intramolecular addition of the hydroxyl group to the C≡N gave the cyclic intermediate $\mathbf{I_2}$. This compound undergoes addition with thiophenol to afford phenylsulfanylchromene $\mathbf{I_3}$. The intermediate $\mathbf{I_3}$ treats with another equivalent of malononitrile to form intermediate $\mathbf{I_4}$, followed by intramolecular cyclization to form intermediate $\mathbf{I_5}$. Finally, the chromenopyridine was formed by the tautomerization of the imino group to the amino group. This proposed mechanism was supported by literatures [11-14]. In this mechanism the nano-$PbWO_4$ act as Lewis solid acid and activate the C=O and C≡N groups for better reaction with nucleophiles. So, we were encouraged to use nano-$PbWO_4$ in the following optimization of the reaction conditions (Scheme 2).

Table 1. Optimization of reaction conditions using different catalysts.[a]

Entry	Solvent (condition)	Catalyst (mol)%	Time (min)	Yield (%)[b]
1	EtOH (reflux)	-	300	9
2	EtOH (reflux)	DBU (10)	250	40
3	EtOH (reflux)	nano-MgO (15)	250	47
4	EtOH (reflux)	*p*-TSA (10)	300	25
5	EtOH (reflux)	nano-PbO (3)	100	56
6	CH_3CN (reflux)	nano- PbO (3)	100	49
7	EtOH (reflux)	nano-WO_3 (2)	100	60
8	H_2O (reflux)	nano-$PbWO_4$ (0.7)	55	62
9	DMF (reflux)	nano- $PbWO_4$ (0.7)	55	70
10	CH_3CN (reflux)	nano- $PbWO_4$ (0.7)	55	78
11	EtOH (reflux)	nano- $PbWO_4$ (0.5)	55	80
12	EtOH (reflux)	nano- $PbWO_4$ (0.7)	55	84
13	EtOH (reflux)	nano- $PbWO_4$ (0.9)	55	86
14	EtOH (30 W)[c]	nano- $PbWO_4$ (0.7)	30	63
15	EtOH (40 W)[c]	nano- $PbWO_4$ (0.7)	30	74
16	EtOH (50 W)[c]	nano- $PbWO_4$ (0.7)	25	83
17	EtOH (60 W)[c]	nano- $PbWO_4$ (0.5)	15	87
18	**EtOH (60 W)[c]**	**nano- $PbWO_4$ (0.7)**	**15**	**91**
19	EtOH (60 W)[c]	nano- $PbWO_4$ (0.9)	15	91
20	EtOH (70 W)[c]	nano- $PbWO_4$ (0.7)	15	91
21	EtOH (60 W)[c]	-	15	42
22	EtOH (60 W)[c]	nano-PbO (3)	25	64

[a] Salicyladehyde (1.5 mmol), malononitrile (3 mmol) and benzenethiol (1.5 mmol).

[b] Isolated yields.

[c] Ultrasonic irradiation.

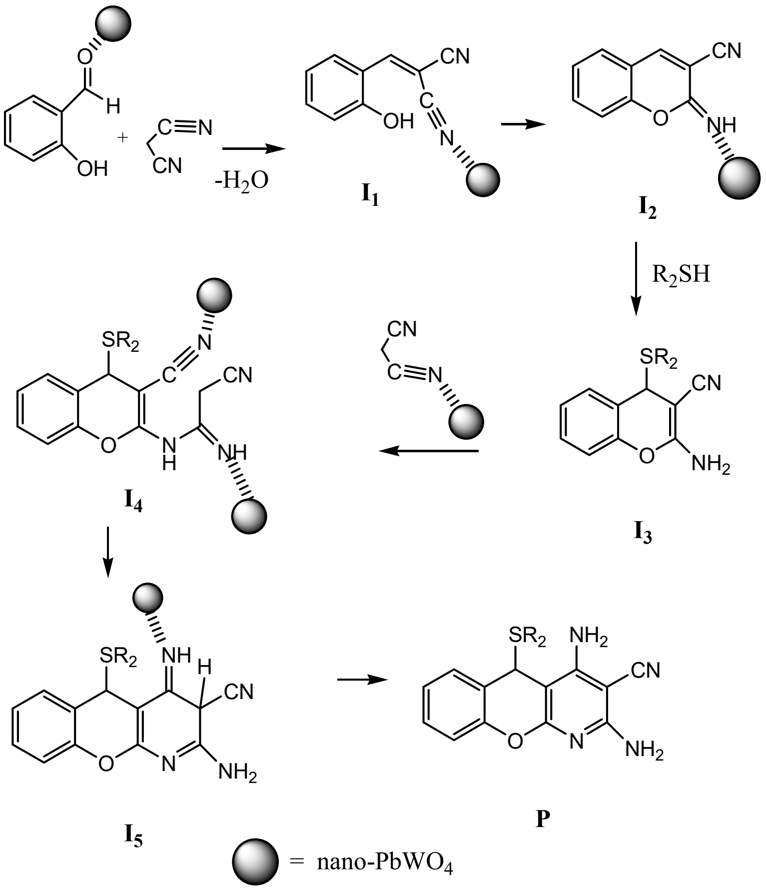
4. Conclusion

In conclusion, we have developed a simple and highly efficient protocol for the synthesis of benzopyranopyridines using $PbWO_4$ nanostructures as an efficient catalyst under ultrasonic irradiation. The high catalytic activity and ease of recovery from the reaction mixture through filtration or centrifugation methods, rapid assembly of medicinally privileged heterocyclic molecules, cleaner reaction profiles and several reuse times without significant losses in performance are additional eco-friendly attributes of this catalytic system. We hope this method will find extensive applications in the field of combinatorial chemistry, drug discovery, sonochemistry, and very useful area of organic synthesis.

Table 2. Synthesis of benzopyranopyridines using nano-$PbWO_4$ under ultrasonic irradiation.

Entry	(R_1) Aldehyde	(R_2) thiol	Product	Time (min)	Yield (%)[a]	m.p. (°C)	Ref.
1	H	C_6H_5	**5a**	15	91	221-223	[10]
2	H	4-Me-C_6H_4	**5b**	15	94	222-224	[10]
3	H	Ar-CH_2-C_6H_5	**5c**	20	85	173-175	[12]
4	H	2-furyl-methyl	**5d**	20	83	194-197	[12]
5	Br	C_6H_5	**5e**	15	93	215-217	[14]
6	Br	4-Me-C_6H_4	**5f**	15	95	213-215	[14]
7	Br	C_6H_5-CH_2	**5g**	20	87	206-208	[14]
8	Br	2-furyl-methyl	**5h**	20	85	225-227	[14]
9	Me	4-Cl-C_6H_4	**5i**	20	84	280-282	-

[a] Isolated yields.



Scheme 2. Schematic mechanism for the catalytic activity of nano-$PbWO_4$ in the synthesis of titled compound.

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