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12-Tungstophosphoric acid ($H_3PW_{12}O_{40}$): An efficient and reusable catalyst for one-pot synthesis of pyrano[2,3-*d*]pyrimidines

Sedighe Gholipour[a], Abolghasem Davoodnia*[a] and Mahboobeh Nakhaei-Moghaddam[b]

[a]*Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran*
[b]*Department of Biology, Mashhad Branch, Islamic Azad University, Mashhad, Iran*

ABSTRACT

12-Tungstophosphoric acid ($H_3PW_{12}O_{40}$) was found to be highly efficient, eco-friendly and recyclable catalyst for the three-component cyclocondensation of 1,3-dimethylbarbituric acid, aryl aldehydes, and malononitrile, giving rise to pyrano[2,3-d]pyrimidines. The reactions occur in ethanol as solvent and furnish the corresponding products in high yields. The catalyst is inexpensive and readily available and can be recovered conveniently and reused efficiently such that a considerable catalytic activity still could be achieved after fourth run. Other advantages of this protocol are short reaction times and a simple procedure with an easy work-up.

Keywords: pyrano[2,3-*d*]pyrimidines, 1,3-dimethylbarbituric acid, $H_3PW_{12}O_{40}$.

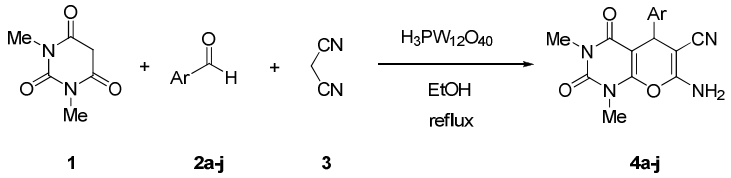
INTRODUCTION

Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity. MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [1-6]. Thus, the developing of new MCRs and improving known MCRs are an area of considerable current interest. One such reaction is the synthesis of pyrano[2,3-*d*]pyrimidines.

4H-Pyrans and pyrimidinones are very important organic compounds with a wide range of biological activities. These compounds are reported to possess significant antibacterial, anticoagulant, anticancer, spasmolytic, diuretic, antianaphylactic, antihypertensive and anti-inflammatory activities [7-13]. On the other hand, pyrano[2,3-*d*]pyrimidines have received considerable attention over the past years due to their wide range of the diverse pharmacological action such as antitumor, cardiotonic, hepatoprotective, antihypertensive and antibronchitic activity [14-18]. These compounds are generally synthesized *via* a one-pot three-component cyclocondensation of 1,3-dimethylbarbituric acid, aryl aldehydes, and malononitrile in the presence of several catalysts such as 1,8-diazabicyclo[5.4.0]undec-7-ene [19], MgO [20], PEG-stabilized Ni nanoparticles [21], $ZnFe_2O_4$ nanoparticles [22], KF [23] and Mn/ZrO_2 [24]. Synthesis of these compounds using microwave irradiation [25] and electrocatalytic procedure in the presence of sodium bromide as electrolyte [26] have been also reported. However, most of these methodologies suffer from disadvantages such as unsatisfactory yields, long reaction times and the use of relatively expensive catalysts. These finding prompted us towards further investigation in search for a new catalyst, which will carry out the synthesis of these compounds under simpler experimental set up and eco-friendly conditions.

As a result of our interest in the synthesis of heterocyclic compounds [27-32], and as part of our research on the development of environmentally friendly methods for synthesis of organic compounds using reusable catalysts [33-42], we report here our results from efficient synthesis of pyrano[2,3-*d*]pyrimidines **4a-j** by one-pot, three-

component reaction of 1,3-dimethylbarbituric acid **1**, aryl aldehydes **2a-j**, and malononitrile **3**, using 12-tungstophosphoric acid, $H_3PW_{12}O_{40}$, as a novel inorganic catalyst (Scheme 1).



Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidines catalyzed by $H_3PW_{12}O_{40}$

MATERIALS AND METHODS

All chemicals were available commercially and used without additional purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. The ^{1}H NMR (400 MHz) spectra were recorded with a Bruker 400 spectrometer.

General Procedure for the Synthesis of Pyrano[2,3-*d*]pyrimidines 4a-j Catalyzed by $H_3PW_{12}O_{40}$

A mixture of 1,3-dimethylbarbituric acid **1** (1 mmol), an aryl aldehyde **2a-j** (1 mmol), malononitrile **3** (1 mmol), and $H_3PW_{12}O_{40}$ (5 mol % based on aryl aldehyde) in ethanol (5 ml) was heated under reflux for 35-75 min. During the procedure, the reaction was monitored by TLC. Upon completion of the transformation, the reaction mixture was cooled to room temperature. This resulted in the precipitation of the product, which was collected by filtration, washed repeatedly with cold water and recrystallized from ethanol to give products **4a-j** in high yields.

RESULTS AND DISCUSSION

To optimize the catalytic system, the reaction of 1,3-dimethylbarbituric acid **1** (1 mmol), 4-chlorobenzaldehyde **2b** (1 mmol), and malononitrile **3** (1 mmol), for the synthesis of compound **4b** was used as a model reaction. In order to get the effective reaction conditions the reaction was optimized in terms of various parameters like effect of solvent, catalyst amount, and influence of temperature. The results are summarized in Table 1. Trace amounts of the product **4b** were formed in the absence of the catalyst in refluxing H_2O or EtOH and also under solvent-free conditions at high temperature (Entries 1-3) indicating that the catalyst is necessary for the reaction. As can be seen, among the tested solvents such as H_2O, EtOH, MeOH, CH_2Cl_2, and also solvent-free conditions and various amounts of the catalyst, the reaction was more facile and proceeded to give the highest yield, using 5 mol% of $H_3PW_{12}O_{40}$ in EtOH at reflux temperature (Entry 5). No significant improvement in yield or reaction time was observed using a higher amount of the catalyst. All subsequent reactions were carried out in these optimized conditions.

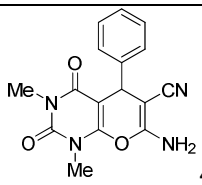
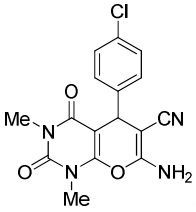
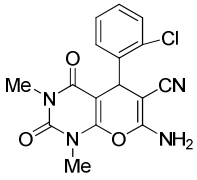
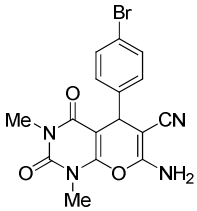
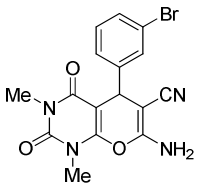
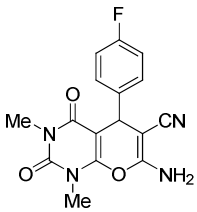
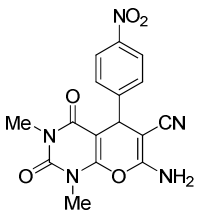
Table 1 Optimization of reaction conditions for the synthesis of compound 4b catalyzed by $H_3PW_{12}O_{40}$*

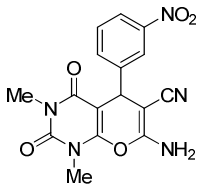
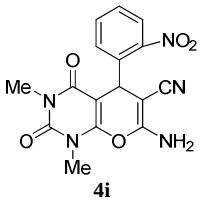
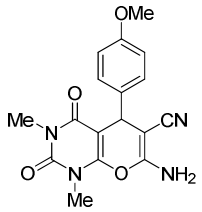
Entry	Catalyst (mol%)	Solvent	T/°C	Time/min	Isolated Yield/%
1	None	H_2O	Reflux	180	Trace
2	None	EtOH	Reflux	180	Trace
3	None	Solvent-free	110	180	Trace
4	2.5	EtOH	Reflux	60	70
5	5	EtOH	Reflux	40	90
6	10	EtOH	Reflux	45	89
7	5	EtOH	50	80	71
8	5	EtOH	r.t.	120	28
9	2.5	H_2O	Reflux	80	38
10	5	H_2O	Reflux	120	55
11	10	H_2O	Reflux	120	53
12	2.5	MeOH	Reflux	80	61
13	5	MeOH	Reflux	60	80
14	10	MeOH	Reflux	60	80
15	2.5	CH_2Cl_2	Reflux	80	57
16	5	CH_2Cl_2	Reflux	60	75
17	10	CH_2Cl_2	Reflux	60	72
18	2.5	solvent-free	130	100	65
19	5	solvent-free	100	80	60
20	5	solvent-free	130	80	70
21	10	solvent-free	130	90	65

Reaction conditions: 1,3-dimethylbarbituric acid **1 (1 mmol), 4-chlorobenzaldehyde **2b** (1 mmol), and malononitrile (1 mmol).*

To show the generality of this model reaction, a range of pyrano[2,3-*d*]pyrimidines were prepared by the reaction of 1,3-dimethylbarbituric acid, malononitrile and different aromatic aldehydes under optimized reaction conditions. The results presented in Table 2 show that the protocol is useful for different aromatic aldehydes, giving high yields of the products. Under the same conditions, however, this reaction almost could not be observed when the aliphatic aldehydes were used as starting materials.

Table 2. Synthesis of pyrano[2,3-*d*]pyrimidines 4a-j using $H_3PW_{12}O_{40}$ as catalyst[a]

Entry	Ar	Product[b]	Time (min)	Isolated Yield (%)	mp °C	
					Found	Reported
1	C_6H_5	 **4a**	40	92	219	219-220 [24]
2	4-ClC_6H_4	 **4b**	40	90	206-208	200 [21]
3	2-ClC_6H_4	 **4c**	60	88	235-237	243-244 [22]
4	4-BrC_6H_4	 **4d**	40	92	230-232	235 [22]
5	3-BrC_6H_4	 **4e**	55	87	213-214	209 [22]
6	4-FC_6H_4	 **4f**	35	93	230-231	227-228 [22]
7	4-$O_2NC_6H_4$	 **4g**	35	93	218-220	217-219 [22]

8	3-$O_2NC_6H_4$	 **4h**	45	89	198-200	204 [22]
9	2-$O_2NC_6H_4$	 **4i**	60	88	202-204	206 [21]
10	4-$MeOC_6H_4$	 **4j**	75	80	222-224	225-226 [24]

[a] *Reaction conditions: 1,3-dimethylbarbituric acid **1** (1 mmol), an aryl aldehyde **2a-j** (1 mmol), malononitrile **3** (1 mmol), $H_3PW_{12}O_{40}$ (5 mol% based on aryl aldehyde), EtOH (5 ml), reflux.*

[b] *All the products were characterized by IR spectral data and comparision of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ^{1}H NMR spectral data.*

We also used our optimized reaction conditions to evaluate the reusability of the catalyst $H_3PW_{12}O_{40}$. After completion of the reaction, the reaction mixture was cooled to room temperature, the product was collected by filtration, and washed repeatedly with cold water. The combined filtrate was evaporated to dryness under reduced pressure. The solid catalyst was collected, dried at 60 °C under vacuum for 2 h and reused for the same experiment. We found that the catalyst could be used at least four times with only a slight reduction in activity (Fig. 1).

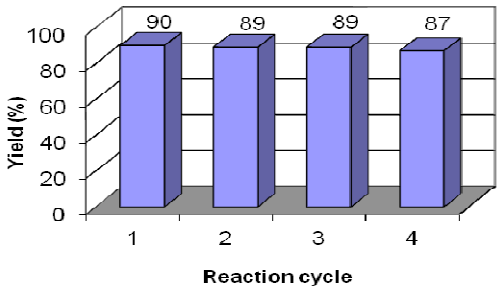


Fig. 1. Reusability of $H_3PW_{12}O_{40}$ for the synthesis of compound 4b

CONCLUSION

In conclusion, we have developed a simple new catalytic method for the synthesis of pyrano[2,3-*d*]pyrimidines by one-pot, three-component reaction of 1,3-dimethylbarbituric acid, aryl aldehydes, and malononitrile in the presence of a catalytic amount of $H_3PW_{12}O_{40}$ as an efficient, reusable, and green inorganic catalyst in refluxing ethanol. Some attractive features of this protocol are good yields, simple procedure, short reaction times, easy work-up, high catalytic activity and recyclability and reusability of the catalyst. The catalyst can be used at least four times without substantial reduction in its catalytic activity.

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