

Short communication

A catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2(1H)-one using 12-tungstophosphoric acid

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Abstract

A simple, efficient and cost-effective method for the synthesis of 3,4-dihydropyrimidin-2(1H)-one by a one-pot three-component cyclocondensation reaction of a 1,3-dicarbonyl compound, an aldehyde and urea or thiourea using 12-tungstophosphoric acid as a recyclable catalyst is reported.

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1. Introduction

Pyrimidinones and their derivatives [1] are medicinally important [2–4] as calcium channel blockers, antihypertensive and anti-inflammatory agents. Additionally, their particular structure has been found in natural marine alkaloid Batzelladine A and B which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, so disclosing a new field towards the development of AIDS therapy [5]. The original procedure for the preparation of this type of compounds was reported by Biginelli [6] in 1983, involving one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions [6].

One major drawback of this so called Biginelli reaction, however is the low to moderate yield that is often encountered when substituted aromatic (20–60%) or aliphatic aldehydes (10%) is used [7].

Recently, several improved procedures [8,9] have been reported using Lewis acids as well as protic acids as promoted several example of these methods involve the use of LiClO₄ [9], Lewis acids such as ytterbium triflate [10],

bismuth triflate [11], cupric chloride [12], manganese triacetate [13], cerium(III) chloride [14], copper(II) triflate [15], ferric chloride [16], nickel chloride [16], BF₃ etherate/copper(II) acetate [17], zirconium(IV) chloride [18] and polymer-supported ytterbium(III) reagent [19] as well as Bronsted acids such as *p*-toluenesulfonic acid [20], silica sulfuric acid [21] and KHSO₄. [22] Montmorillonit KSF [23] and natural HEU-type zeolite [24] was also claimed to act as solid acid catalyst in the Biginelli reaction. Due to the importance of Biginelli reaction products, the discovery and introduction of better and milder conditions using new catalysts has been under attention. Along of this line, using heteropolyacids (HPAs), which are low in toxicity, highly stable towards humidity, being recyclable and air stable have found more attention. Herein, we report the use of tungstophosphoric acid as a reusable and heterogeneous catalyst for the Biginelli reaction (Scheme 1).

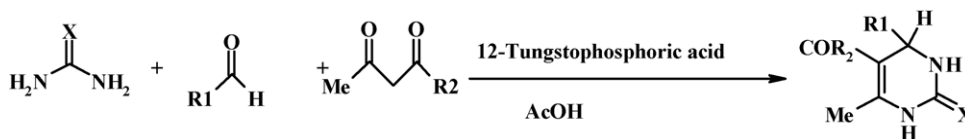
2. Experimental

2.1. General procedure for the synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-one

A mixture of aldehyde (10 mmol), 1,3-dicarbonyl compound (15 mmol), urea or thiourea (15 mmol) and 12-

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Scheme 1.

Table 1
Biginelli reaction using 2 mol% 12-tungstophosphoric acid

Entry	R1	R2	X	Time (h)	Yield (%) ^a	m.p. (°C)	
						Found	Reported (Lit.)
1	Ph-	OEt	O	6–7	75	204	205–206 [17]
2	4-Me-Ph	OEt	O	6–7	70	214	214–215 [17]
3	4-MeO-Ph	OEt	O	6–7	75	203	201–203 [17]
4	4-Cl-Ph	OEt	O	6–7	70	216	214–215 [17]
5	4-Br-Ph	OEt	O	6–7	65	215	213–215 [25]
6	2-NO ₂ -Ph	OEt	O	6–7	72	220	218–220 [26]
7	3-NO ₂ -Ph	OEt	O	6–7	74	230	227–229 [20]
8	4-NO ₂ -Ph	OEt	O	6–7	73	211	209–211 [17]
9	Thiophenyl-	OEt	O	6–7	75	210	209–210 [27]
10	2-Furyl-	OEt	O	6–7	65	205	203–205 [18]
11	Ph-	OEt	S	6–7	55	206	205–206 [10]
12	4-MeO-Ph	OEt	S	6–7	50	153	152–153 [28]
13	Ph-	OMe	O	6–7	70	211	207–210 [17]
14	4-Cl-Ph	OMe	O	6–7	75	206–207	204–207 [16]
15	3-NO ₂ -Ph	OMe	O	6–7	75	279	278–279 [29]
16	Ph-	Me	O	6–7	40	233	234–235 [30]
17	4-Cl-Ph	Me	O	6–7	40	216	215–216 [30]

^a Yields refer to the isolated pure products.

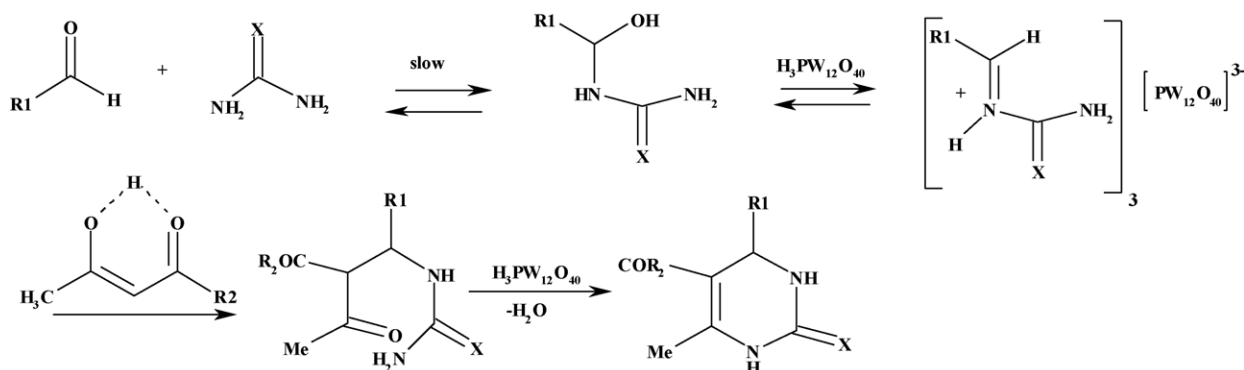
tungstophosphoric acid (2 mol%) was refluxed in glacial acetic acid (30 mL) for 6–7 h. the mixture was cooled to room temperature and the catalyst was then removed by filtration and the solution poured on to ice-water (60 mL). The resulting solid product was filtered and recrystallized from ethanol to give the pure products.

After removing the reaction product by filtration and washing the solid catalyst with diethyl ether, it could be reused and subjected to a second run of the Biginelli reaction. The results of the first experiment and subsequent experiments were almost consistent in yields.

All products are known compounds and were characterized by mp, IR and ¹H NMR spectra [10,16–18,20,25–30].

3. Results and discussion

Due to the ever-mounting environmental concern in the field of chemistry, it is advisable to use easily recovered and recycled catalysts, especially expensive or toxic metallic ones for the next use [31]. In this respect, only few of the aforementioned catalysts meet this criterion of green chemistry. For example, the recovery of ytterbium triflate from water seems cumbersome since water must be removed through heating and then drying under vacuum at 100 °C for 2 h. [10] In the case of polymer-supported Yb(III) resin, the activity of recycled resin is much lower than that of the original one thus limiting the recyclability [19]. Therefore, there is still



Scheme 2.

room for further search for recyclable catalysts to be used in the Biginelli type that can convert a variety of aldehydes to pyrimidinones in high yields under mild reaction conditions.

Heteropolyacids as catalyst for fine organic synthetic processes have been developed for industrial related to fine chemicals such as the flavors, pharmaceuticals and food industries [32]. Heteropolyacids are more active catalysts than conventional inorganic and organic acids for reaction in solution [33,34]. They are used as industrial catalyst for several liquid-phase reactions, [35–37] including alcohol dehydration, [38] alkylation, [39] and esterification [40]. Among heteropolyacids tungstic acids are the most widely used catalysts owing to their high acid strengths, thermal stabilities and low reducibilities. Tungstophosphoric acid is a cheap, heterogeneous and available catalyst. The observed catalytic activity of $H_3PW_{12}O_{40}$ with Hammett acidity function $H_0 < -13.16$ reflects the stronger acidity strength of this compound in comparison with, for example, H_2SO_4 $H_0 = -12$ [41]. Recently, an acidity scale for Bronsted acids including $H_3PW_{12}O_{40}$ was reported in literature [42]. The reported results show the acidity strength follows the order: $H_3PW_{12}O_{40} > p\text{-CH}_3\text{-C}_6\text{H}_4\text{-SO}_3\text{H} \sim H_2SO_4$.

In the present communication, the Biginelli reaction (Scheme 1) was carried out with catalytic amount of 12-tungstophosphoric acid, urea, ethylaceto acetate and aldehydes were converted to the corresponding pyrimidinones in a three component one-pot Biginelli-type reaction. The products were obtained in good yields in refluxing acetic acid (Table 1). The suggested mechanism is illustrated in Scheme 2.

4. Conclusions

We here reported a catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2(H)-one using $H_3PW_{12}O_{40}$ as an efficient, reusable and eco friendly heterogeneous inorganic catalyst.

It is noteworthy to mention that the catalyst is reusable. Even after five runs for the Biginelli reaction, the catalytic activity of $H_3PW_{12}O_{40}$ was almost the same as that of the freshly used catalyst. $H_3PW_{12}O_{40}$ is non-corrosive and environmentally benign and presents fewer disposal problems.

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