

Silica Gel-Supported Polyphosphoric Acid (PPA-SiO₂) Catalyzed One-Pot Multi-Component Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and -thiones: An Efficient Method for the Biginelli Reaction

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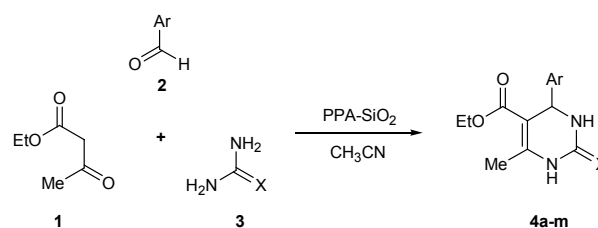
A green and efficient method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones through one-pot three-component reaction of ethyl acetoacetate, an aryl aldehyde, and urea or thiourea in acetonitrile using silica gel-supported polyphosphoric acid (PPA-SiO₂) as catalyst is described. Compared to the classical Biginelli reaction conditions, the present methodology offers several advantages such as high yields, relatively short reaction times, mild reaction condition and a recyclable catalyst with a very easy work up.

Key Words: Biginelli reaction, Heterogeneous catalysis, PPA-SiO₂, Multi-component reactions

Introduction

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate.¹⁻³ MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Therefore, the discovery for new MCRs and improving the already known MCRs are of considerable interest.

Dihydropyrimidinones and -thiones have attracted considerable interest recently because of their wide range of biological activities such as antibacterial, antitumor, anticancer, and anti-inflammatory properties.⁴⁻⁶ Also, Functionalized dihydropyrimidinones have been used as potent calcium channel blockers⁷ and antihypertensive agents.⁸ The first procedure for the synthesis of dihydropyrimidinones reported by Biginelli in 1893, involves acid catalyzed one-pot three-component condensation of β -dicarbonyl compounds with an aromatic aldehyde and urea derivatives.⁹ A major drawback to Biginelli's original reactions, however, was poor to moderate yields.¹⁰ There are several improved methods for the synthesis of dihydropyrimidinones and -thiones using various Brønsted acid and Lewis acid catalysts such as alcoholic HCl,¹¹ dry acetic acid,¹² boric acid,¹³ *p*-TsOH,¹⁴ silica sulfuric acid,¹⁵ La(OTf)₃,¹⁶ Sr(OTf)₂,¹⁷ Fe(ClO₄)₃,¹⁸ InBr₃,¹⁹ InCl₃,²⁰ and Bi(OTf)₃.²¹ However, many of these methods are associated with expensive and highly acidic catalysts, long reaction times, unsatisfactory yields, and difficult product isolation. Therefore, the development of simple, efficient, clean, high-yielding, and environmentally friendly approaches using new catalysts for the synthesis of these compounds is an important task for organic chemists.



Scheme 1. Biginelli reaction catalyzed by PPA-SiO₂

Recently, solid-supported reagents, such as silica gel-supported acids, have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling.²²⁻²⁴ Although, the catalytic applications of silica supported reagents for organic synthesis have been established, to the best of our knowledge, there is no report in the literature on the use of PPA-SiO₂ in Biginelli reaction.

Due to our interest in the synthesis of heterocyclic compounds,²⁵⁻²⁹ and in continuation of our previous works on the applications of reusable catalysts in organic reactions,³⁰⁻³⁹ herein we reported the PPA-SiO₂ catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones (Scheme 1).

Experimental

All chemicals were commercially available and used without further purification. The PPA-SiO₂ was prepared according to the literature.⁴⁰ Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ¹H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer.

General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones and -thiones 4a-m Using PPA-SiO₂ as Catalyst.

A mixture of ethyl acetoacetate **1** (5 mmol), aryl aldehyde **2** (5 mmol), urea or thiourea **3** (6 mmol), and PPA-SiO₂ (0.3 g) as catalyst in acetonitrile (15 mL) was heated under reflux for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered under hot condition. After cooling the filtrate, the precipitated solid was filtered and recrystallized from ethyl acetate/*n*-hexane to give compounds **4a-m** in good to excellent yields. The structures of the products were confirmed by ¹H NMR, IR spectra and comparison with authentic samples prepared by reported methods.^{15,17,18}

Recycling and Reusing of the Catalyst. The catalyst was recovered by filtration, dried at 100 °C under vacuum for 2 h and reused in another reaction. The catalyst could be reused at least three times with only slight reduction in the catalytic activity of the catalyst.

Results and Discussion

For our investigations, PPA-SiO₂ was prepared according to the literature procedure.⁴⁰ Initially, in order to optimize the reaction conditions, the synthesis of compound **4b** was used as a model reaction. Therefore, a mixture of ethyl acetoacetate (5 mmol), 4-chlorobenzaldehyde (5 mmol), and thiourea (6

Table 1. Synthesis of compound **4b** in the presence of PPA-SiO₂ as catalyst in different solvents^a

Entry	Catalyst (g)	Solvent	T (°C)	Time (min)	Yield (%) ^b
1	None	CH ₃ CN	reflux	180	None
2	0.1	CH ₃ CN	reflux	60	53
3	0.2	CH ₃ CN	reflux	60	56
4	0.25	CH ₃ CN	reflux	60	79
5	0.3	CH ₃ CN	reflux	60	92
6	0.3	CH ₃ CN	reflux	45	92
7	0.4	CH ₃ CN	reflux	60	93
8	0.1	CHCl ₃	reflux	60	35
9	0.2	CHCl ₃	reflux	60	46
10	0.3	CHCl ₃	reflux	60	60
11	0.4	CHCl ₃	reflux	60	62
12	0.1	EtOH	reflux	60	41
13	0.2	EtOH	reflux	60	52
14	0.3	EtOH	reflux	60	73
15	0.4	EtOH	reflux	60	72
16	0.1	CH ₂ Cl ₂	reflux	60	44
17	0.2	CH ₂ Cl ₂	reflux	60	59
18	0.3	CH ₂ Cl ₂	reflux	45	83
19	0.3	CH ₂ Cl ₂	reflux	60	88
20	0.4	CH ₂ Cl ₂	reflux	60	88
21	0.1	Solvent-free	100	60	37
22	0.2	Solvent-free	100	60	42
23	0.3	Solvent-free	100	60	50
24	0.4	Solvent-free	100	60	51

^a5 mmol ethyl acetoacetate, 5 mmol 4-chlorobenzaldehyde, 6 mmol thiourea. ^bThe yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

mmol) in the presence of PPA-SiO₂ was heated in different solvents and under solvent-free conditions (Table 1). As can be seen from Table 1, the shortest time and best yield was achieved in acetonitrile (entry 6). The efficiency of the reaction is mainly effected by the amount of the catalyst. No product could be detected in the absence of this catalyst even after 3 hours (entry 1), while good results were obtained in the presence of PPA-SiO₂. The optimal amount of the catalyst was 0.3 g (entry 6), the higher amount of the catalyst did not increase the yield noticeably (entry 7).

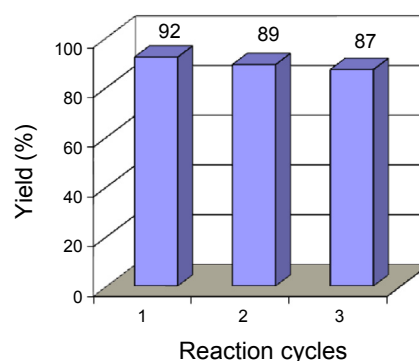
In order to evaluate the generality of this model reaction we then prepared a range of 3,4-dihydropyrimidin-2(1H)-ones and -thiones under the optimized reaction conditions. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in good to excellent yields in relatively short reaction times. The kind of aldehyde has no significant effect on the reaction. The results are shown in Table 2.

Reusability of the catalyst was also investigated. For this purpose, the same model reaction was again studied under the optimized conditions. After completion of the reaction, the ca-

Table 2. PPA-SiO₂ catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones **4a-m**^a

Entry	Ar	X	Comp.	Time (min)	Yields (%) ^b	mp (°C)	
						Found	Reported
1	C ₆ H ₅	S	4a	30	85	206-208	209-211 ¹⁸
2	4-ClC ₆ H ₄	S	4b	45	92	185-187	191-195 ¹⁸
3	3-HOC ₆ H ₄	S	4c	45	84	181-183	183-184 ¹⁵
4	4-HOC ₆ H ₄	S	4d	45	91	198-200	202-203 ¹⁷
5	4-CH ₃ OC ₆ H ₄	S	4e	60	73	154-156	155-156 ¹⁸
6	C ₆ H ₅	O	4f	60	88	210-211	201-204 ¹⁸
7	4-ClC ₆ H ₄	O	4g	45	76	214-216	214-217 ¹⁸
8	3-HOC ₆ H ₄	O	4h	45	77	169-171	167-170 ¹⁵
9	4-HOC ₆ H ₄	O	4i	30	71	231-233	237-238 ¹⁷
10	4-CH ₃ OC ₆ H ₄	O	4j	45	94	214-216	202-204 ¹⁸
11	4-CH ₃ C ₆ H ₄	O	4k	45	87	219-220	215-217 ¹⁸
12	3-NO ₂ C ₆ H ₄	O	4l	45	79	215-217	225-228 ¹⁸
13	4-NO ₂ C ₆ H ₄	O	4m	45	83	208-210	205-209 ¹⁸

^a5 mmol ethyl acetoacetate, 5 mmol aryl aldehyde, 6 mmol urea or thiourea, and 0.3 g PPA-SiO₂ in acetonitrile under reflux. ^bThe yields were calculated based on aryl aldehyde and refer to the pure isolated product.

**Figure 1.** Reusability of PPA-SiO₂ for model reaction.

talyst was filtered under hot condition, dried and reused for the same reaction process. As shown in Fig. 1, the catalyst could be reused at least three times with only slight reduction in the catalytic activity of the catalyst.

Conclusion

In conclusion, we have developed an efficient, mild, and green method for the synthesis of dihydropyrimidin-2(1*H*)-ones and -thiones through one-pot three-component reaction of ethyl acetoacetate, an aryl aldehyde, and urea or thiourea in acetonitrile using PPA-SiO₂ as catalyst. The catalyst can be reused after a simple work-up, with only slight reduction in the catalytic activity. Good to excellent yields, relatively short reaction times, simple operation and easy work-up are some advantages of this protocol. We believe this applicability of PPA-SiO₂ with mentioned advantages makes our method superior over other reported methods to synthesis dihydropyrimidin-2(1*H*)-ones and -thiones.

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