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# Melamine trisulfonic acid: A new, efficient and recyclable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones in the absence of solvent

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#### Abstract

Melamine trisulfonic acid (MTSA) can be used as an efficient and recyclable catalyst for the promotion of the synthesis of 3,4dihydropyrimidin-2(1H)-ones/thiones (DHPMs) in the absence of solvent. All reactions were performed at 80 °C in good to high yields.

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In recent years, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones has attracted the attention of many organic chemists. This attention can be attributed to their wide range therapeutical and pharmacological properties, such as antiviral, antitumor, antibacterial, and anti-inflammatory properties [1]. Also, some of them have been successfully used as calcium channel blockers, antihypertensive agents, and  $\alpha_{Ia}$ -antagonists [2]. In addition, several alkaloids containing the dihydropyrimidine core unit, exhibiting interesting biological properties, have been isolated from marine sources [3–5]. Among these the crambine [3] and batzelladine alkaloids [4] were found to be potent HIVgp-120-CD4 inhibitor.

In 1893, Biginelli reported the first synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, *via* a one-pot three component condensation of an aldehyde, a  $\beta$ -ketoester and urea [6]. In spite of the importance of the reported method, it suffers from long reaction times, acidic reaction conditions, low yields of the products particularly in the case of substituted aldehydes and loss of sensitive functional groups during the reaction. This problem has led to the development of multi-step synthetic approaches for the synthesis of DHPMs. These methods however afford better yields of the desired products, but lack the simplicity of the original one-step synthesis [7].

In order to improve the efficiency of Biginelli reaction, a variety of catalysts have been reported which of them  $H_4PMo_{11}VO_{40}$  [8], Dowex-50W [9],  $H_3PW_{12}O_{40}/SiO_2$  [10],  $MgBr_2$  [11], polymer-supported 4-aminoformoyl-diphenylammonium triflate [12], NaHSO<sub>4</sub>/SiO<sub>2</sub> [13], FeCl<sub>3</sub> [14], ZrCl<sub>4</sub> [15], Cu(OTf)<sub>2</sub> [16], Bi(OTf)<sub>3</sub> [17],

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yutterbium triflate [18], NH<sub>2</sub>SO<sub>3</sub>H [19], 12-molbdophosphoric acid [20], natural HEU type zeolite [21], Sr(OTf)<sub>2</sub> [22], covalently anchored sulfonic acid onto silica [23], ZrOCl<sub>2</sub>·8H<sub>2</sub>O [24], silica triflate [25], Fe(HSO<sub>4</sub>)<sub>3</sub> [26], TCICA [27], PPh<sub>3</sub> [28], CaF<sub>2</sub> [29], [bmim]BF<sub>4</sub>-immobilized Cu(II) acetylacetonate [30], and [bmim][FeCl<sub>4</sub>] [31] are examples. However, in spite of their potential utility, the practical application of most of these reagents suffers from disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction times, high temperatures, unsatisfactory yields and tedious manipulations to isolate the products. Therefore, the discovery of an inexpensive, facile and efficient reagent for the preparation of DHPMs under mild conditions is an active ongoing research topic.

# 1. Experimental

Table 1

Chemicals were purchased form Fluka, Merck and Aldrich Chemical Companies. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by thin-layer chromatography (TLC) on a silica-gel polygram SILG/UV 254 plates. The IR spectra were recorded on a PerkinElmer 781 Spectrophotometer. In all the cases the <sup>1</sup>H NMR spectra were recorded with Bruker Avance 300 MHz instrument. Chemical shifts are reported in parts per million in CDCl<sub>3</sub> with tetramethylsilane as an internal standard. <sup>13</sup>C NMR data were collected on Bruker Avance 75 MHz instrument.

### 1.1. General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones/thiones

A mixture of aldehyde (1 mmol),  $\beta$ -ketoester (1 mmol), urea or thiourea (1 mmol) and MTSA (0.05 mmol, 0.02 g) was heated in an oil bath (80 °C) for the appropriate time (Table 1). The reaction was monitored by TLC. On completion, 5 mL of ethyl acetate was added to the mixture and filtered. The catalyst was washed with ethyl acetate and dried; the recovered catalyst can be used for two reactions again. The solvent was evaporated from the organic

Entry	$R^1$	$R^2$	X	Time (min)	Yield (%)	M.P. (°C)	
						Found	Reported
1	Ph	Et	0	8 (9, 9) <sup>c</sup>	92 (90, 87) <sup>c</sup>	204-206	202-204 [28]
2	2-Cl-Ph	Et	0	14	91	213-216	216-218 [19]
3	4-Cl–Ph	Et	0	10	89	209-211	210-212 [21]
4	3-NO <sub>2</sub> -Ph	Et	0	22	90	227-228	226-227 [19]
5	4-NO <sub>2</sub> –Ph	Et	0	13	86	209-211	212-214 [22]
6	4-Me–Ph	Et	0	8 (8, 10) <sup>c</sup>	92 (90, 90) <sup>c</sup>	212-214	215-216 [28]
7	4-MeO–Ph	Et	0	5	93	200-202	202-204 [28]
8	2-Furyl	Et	0	12	90	209-211	208-210 [22]
9	Ph	Et	S	13	90	205-206	208-209 [22]
10	2-Cl-Ph	Et	S	18	87	167-169	168–169 [34]
11	4-Cl–Ph	Et	S	16	91	181-183	192–194 [12]
12	3-Cl-Ph	Et	S	14	88	191–194	192–196 [34]
13	3-NO <sub>2</sub> -Ph	Et	S	24	86	205-207	206-207 [22]
14	Ph	Me	0	9	90	210-213	209-212 [22]
15	4-Cl–Ph	Me	0	11	94	204-206	204-207 [22]
16	4-MeO–Ph	Me	0	7	92	190-192	192-194 [21]
17	2-Furyl	Me	0	14	85	209-210	202-204 [21]
18	Ph	Me	S	9	92	220-222	221-222 [35]
19	$CH_3(CH_2)_3$	Et	0	45	0	-	-
20	PhCH <sub>2</sub> CH <sub>2</sub>	Et	0	30	0	_	-
21	$4-Cl-Ph + PhCH_2CH_2$	Et	0	12	$100^{d} + 0^{d}$	_	-

Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones in the absence of solvent.<sup>a,b</sup>

<sup>a</sup> Products were characterized by their physical constants, comparison with authentic samples, IR and NMR spectroscopy.

<sup>c</sup> Results obtained using recycled catalyst.

<sup>d</sup> Conversion.

<sup>&</sup>lt;sup>b</sup> Isolated yield.



layer and the solid residue was washed with cold water, dried and recrystallized from ethanol to afford the corresponding DHPMs in good to high yields.

#### 2. Results and discussion

Recently, we have reported the preparation of melamine trisulfonic acid (MTSA) and its application in the promotion of the chemoselective methoxymethylation of alcohols and acetylation of alcohols, phenols and amines [32,33]. In continuation of these studies, herein, we wish to report the applicability of this reagent in the promotion of the preparation of DHPMs *via* three-component Biginelli reaction (Scheme 1).

At first, for the optimization of the reaction conditions, the condensation of benzaldehyde, ethyl acetoacetate and urea was investigated under solvent-free conditions. The best result was achieved by caring out the reaction of benzaldehyde, ethyl acetoacetate and urea (with 1:1: mol ratio) in the presence of 0.05 mmol of MTSA at 80 °C for 8 min under solvent-free conditions (Table 1, entry 1). Other aromatic aldehydes, containing both electron-donating and electron-withdrawing groups, and heteroaromatic aldehydes were also reacted under the same reaction conditions to produce the corresponding DHPMs in good to high yields (Table 1). Methyl acetoacetate and thiourea were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones. Aliphatic aldehydes remain intact under the same reaction conditions (Table 1, entries 19 and 20). Therefore, the method can be useful for the chemoselective Biginelli condensation of aromatic aldehydes in the presence of aliphatic ones (Table 1, entry 21).

Our investigation showed that MTSA is reusable for three times (Table 1, entries 1 and 6). The same IR spectra of the reagent were obtained before and after its use in the reactions, which demonstrate the stability of its comparison.

A plausible mechanism of the reaction is shown in Scheme 2 based on the literature [22], our observations and obtained results.

The priority of this method to some of the previously reported ones, is shown by the comparison of the obtained results in Table 2 [21-23,28].

In conclusion, we have described a novel and efficient method for the preparation of DHPMs catalyzed by MTSA, as a newly prepared melamine based reagent, under solvent-free conditions. High yields of the products, short reaction times, ease of the preparation and recyclability of the reagent, solvent-free nature of the reaction, chemoselectivity of the reaction and easy work-up are among the other advantages of this method which make this procedure a useful addition to the available methods.



Scheme 2.

Table 2

Entry	$R^1$	$R^2$	X	Time (h)/yield (%)				
				(I)	(II)	(III)	(IV)	(V)
1	Ph	Et	0	0.13/92	5/75	4/97	8/90	10/70
2	4-MeO-Ph	Et	0	0.1/93	5/75	_	7/92	10/58
3	Ph	Et	0	0.15/90	5/76	4/93	-	-

Comparison of some of the results obtained by the present method (I) with some of those reported by natural HEU (II) [21],  $Sr(OTf)_2$  (III), covalrntly anchored sulfonic acid onto silica (IV) [23], and PPh<sub>3</sub> (V) [28].

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