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Simple and Efficient Method for One Pot Multicomponent Synthesis of 3,4-Dihydropyrimidin-2-(1H)-One Derivatives Catalyzed by Organocatalyst: Benzoic Acid

The Biginelli reaction is one the useful multicomponent reactions and a very appropriate reaction for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones derivatives. These 3,4-dihydropyrimidin-2(1H)-ones have biological and pharmacological properties which make them a very important class of medicinal chemistry. Although they are an important class of medicinal chemistry, the syntheses of these compounds have been catalyzed by large number of strong Bronsted acids and Lewis acids under thermal conditions. Small organic molecules, organocatalysts, have been used as catalysts for the Biginelli reaction in a small number as compared to Bronsted acids and Lewis acid. Benzoic acid, which is a small organic molecule, although an acid, has never been tested for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones. Benzoic acid is an inexpensive, non-toxic molecule, it has been successfully tested here as a catalyst for the one-pot three component synthesis of 3,4-dihydropyrimidin-2-(1H)-one derivatives via Biginelli reaction between β-keto ester, a variety of aromatic aldehydes and urea or thiourea under thermal conditions using 20 mol% benzoic acid in acetonitrile solvent refluxed for 12 h to give good to high yields. This synthetic method includes inexpensive, non-toxic, easily available benzoic acid as a catalyst and is carried out in a simple operational procedure.

Keywords: organocatalyst, benzoic acid, Biginelli, 3,4-dihydropyrimidin-2-(1H)-one, β-keto ester, aldehydes, urea, thiourea.

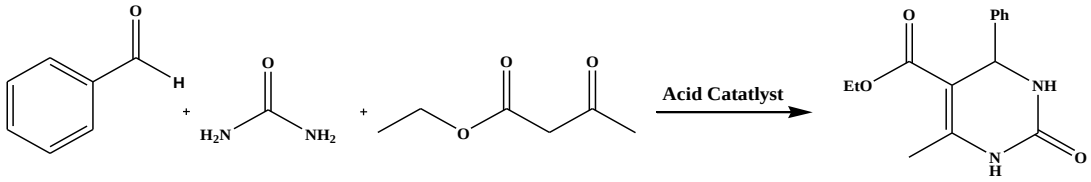
Introduction

The Biginelli reaction is one of the multicomponent reactions. It is a very suitable reaction for preparation of the 3,4-dihydropyrimidin-2(1H)-ones. 3,4-Dihydropyrimidinones (DHPMs) are a very important class since the recent discovery of their biological and pharmacological properties, namely antiviral, antitumour, antibacterial, anti-inflammatory and antihypertensive ones. Dihydropyrimidinone cores are also found in many natural products, highlighting important efforts aimed at the synthesis of these heterocycles [1–6]. These DHPMs have become a crucial basis for several calcium channel blockers, antihypertensives, α_{1a}-adrenergic antagonists and neuropeptide Y (NPY) antagonists [7].

Conventionally, Biginelli reactions were performed under strong acidic conditions with heating, and the yields were low to moderate (Scheme 1) [8].

Traditionally, there are several suitable reaction conditions with strong Bronsted acid along with the use of Lewis acid in condensation to more efficiently synthesize these DHPMs molecules; e.g. H_2SO_4 [7], $BF_3{\cdot}Et_2O/CuCl$ [9], $BiCl_3$ [10], $CeCl_3{\cdot}7H_2O$ [11], $Cu(OTf)_2$ [12], $TiCl_4$ [13], LiBr [14], Gallium (III) halides [15], Metal triflimide [16], *p*-toluenesulfonic acid [17], polystyrenesulfonic acid (PSSA) [18], $Cu(OTf)_2$ [19],

$ZrCl_4$ [20], $FeCl_3 \cdot 6H_2O$ [21], $RuCl_3$ [22], $Bi(NO_3)_3 \cdot 5H_2O$–TBAF [23], SmI_2 [24]. In addition to these, the Biginelli reaction has also been reported by using nanomaterials [25–27], nano-composite [28], zeolites [29–31], polymers [32], ultrasonic irradiation [33, 34], microwaves [35–38] and ball milling [39].



Scheme 1

The use of small organic molecules known as Organocatalysts [40–44] is a very rapidly developing area of synthetic organic chemistry that is replacing the use of metal-based Lewis acids. Organocatalysis offers many advantages for synthetic organic chemistry. In contrast to many transition metal catalysts, most organocatalysts are resistant to air and water, easily handled experimentally, relatively nontoxic, and readily separated from the crude reaction mixture [45]. Given the growing interest in developing green processes and procedures in organic synthesis [46], organocatalysts are considered to be a more eco-friendly and user-friendly alternative to traditional counterparts. Because of these many advantages of organocatalysts, few organocatlysts have been explored in the synthesis of DHPM derivatives such as bakers' yeast [47], hydrazine type [48], oxalic acid [49, 50], citric acid [51], boric acid [52], phenylboronic acid [53], L-proline [54] and Lactic acid [55].

In continuation of our work on new methodologies using organocatalysts [44, 56] in the synthetic organic chemistry we wish to report the efficient use of benzoic acid and a very simple effective approach for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones derivatives via the Biginelli reaction under thermal conditions having good to high yield.

In addition to those listed above, numerous methods for the synthesis of 3,4-dihydropyrimidin-2-(1H)-one derivatives by the Biginelli reaction are available in the literature. However, few organocatalysts are available for the synthesis of DHPMs. Benzoic acid is cheap, non-toxic and readily available in every laboratory. To our knowledge, so far the potential of benzoic acid as a mild organocatalyst has not been much tested in organic synthesis. We decided to explore the potential of benzoic acid as an organocatalyst for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones and their thione analogs as well as their derivatives by the Biginelli reaction under thermal conditions.

Experimental

The following reagents were used in this work without additional purification; benzaldehyde, 4-chlorobenzaldehyde, 3-nitrobenzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, 4-hydroxybenzaldehyde, ethylacetoacetate, methylacetoacetate, benzoic acid, urea, thiourea, acetonitrile, ethanol (loba Chemie), 4-methylbenzaldehyde, 3-methoxybenzaldehyde (Sigma-Aldrich).

The general procedure for the Biginelli reaction is as follows: a solution of the appropriate aldehyde **1** (1.0 mmol), urea or thiourea **2** (1.5 mmol), β-keto ester **3** (1.0 mmol), benzoic acid (20 mol%, 0.2 mmol) in acetonitrile (10 mL) is heated to reflux for 12 h. Then it is cooled to room temperature and poured into ice-water about 50mL. The solid products are filtered, washed with ice water, dried and recrystallized from ethanol to give pure product **4 (a-m)**.

4a. 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin- 2(1H)-one, Melting point: Found 206–208 °C (200–202 °C) [57] ^{1}H NMR (DMSO-d6): δ = 9.18 (s, 1H), 7.73 (s, 1H), 7.20–7.30 (m, 5H), 5.14 (s, 1H), 3.98 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d6): δ = 166.3, 152.1, 147.2, 144.2, 128.1, 127.2, 126.5, 99.0, 58.1, 53.9, 17.9, 14.0. Mass m/z $[M+1]^+$ = 261.11.

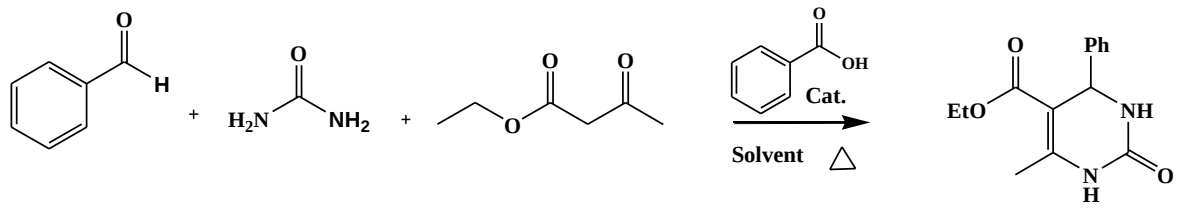
4b. 4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, Melting point: Found 214–216 °C (210–212 °C) [58]. ^{1}H NMR (DMSO-d6): δ = 9.20 (s, 1H), 7.76 (s, 1H), 7.40 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H) 5.16 (s, 1H), 3.95 (q, J = 7.1Hz, 2H), 2.19 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (DMSO-d6): δ = 167.1, 151.4, 146.4, 141.9, 130.1, 126.2, 125.5, 98.0, 56.1, 53.6, 19.7, 13.4. Mass m/z $[M+1]^+$ = 295.07.

Results and Discussion

We started our study with the reaction of benzaldehyde, ethyl acetoacetate and urea using benzoic acid as a catalyst under thermal conditions (Scheme 2) as a model reaction and the results are summarized in Table 1.

Initially, the reaction was carried out without a catalyst for an appropriate time and no progress was observed in acetonitrile solvent (Table 1, entry 01). Catalyst 1 mole % was added and the reaction was carried out up to 18 h, the obtained yield was very low (Table 1, entry 05).

The reaction gradually progressed with increasing the amount of catalyst while maintaining the reaction time (Table 1, entries 06 & 07). Due to the gradual development of the reaction, the amount of catalyst was increased to 7.5 mol % to see the reaction development, reducing the reaction time to 15 hours, a yield of 60 % was obtained (Table 1, entry 08). To obtain high and excellent yields, we continued to vary the amount of catalyst (Table 1, entries 09 & 16). The best reaction conditions were obtained using 20 mol% catalyst and the reaction was completed after 12 hours with a yield of 92 % (Table 1, entry 17). To our curiosity, we continued the reaction again up to 15 hours and also increased the amount of catalyst, but there was no any significant improvement in either case (Table 1, entry 18 & 19). In addition to acetonitrile, we also optimized the reaction conditions using different solvents as shown in Table 1. Without using a catalyst none of the reactions progressed to give any product (Table 1, entries 02, 03 & 04). Instead of introducing lower amount of catalyst for solvents water, THF and ethanol, we purposefully used 10 mol% and 20 mol% catalyst for our study. Yields were obtained relatively lower as compared with acetonitrile using 10 mol% catalyst for 15 hours (Table 1, entries 10, 11 & 12). Also, approximately the same results were observed using 20 mol% catalyst for 12 hours (Table 1, entries 13, 14 & 15) as compared with acetonitrile solvent (Table 1, entry 17).



Scheme 2

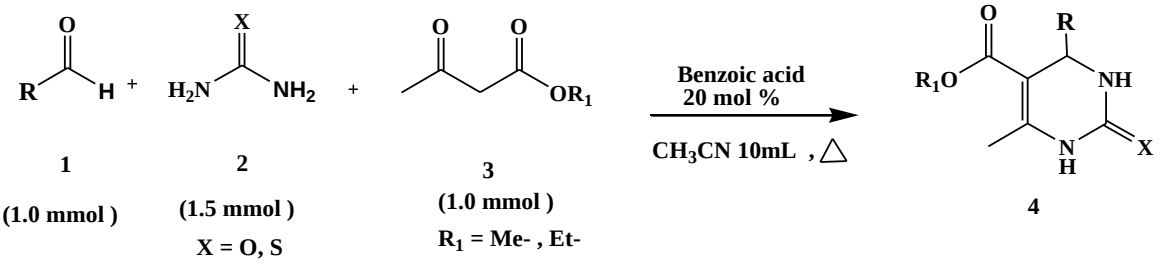
Table 1

Optimization of the reaction conditions in the synthesis of DHPM[a]

Entry	Solvent	Catalyst (mole %)	Time (h)	Yield[b] (%)
01	CH_3CN	None	18	0
02	H_2O	None	18	0
03	THF	None	18	0
04	EtOH	None	18	0
05	CH_3CN	1	18	20
06	CH_3CN	2	18	30
07	CH_3CN	5	18	46
08	CH_3CN	7.5	15	60
09	CH_3CN	10	15	72
10	H_2O	10	15	20
11	THF	10	15	35
12	EtOH	10	15	30
13	H_2O	20	15	32
14	THF	20	12	65
15	EtOH	20	12	54
16	CH_3CN	15	15	85
17	CH_3CN	20	12	92
18	CH_3CN	20	15	94
19	CH_3CN	25	15	96

[a]Reaction conditions: Benzaldehyde (1.0 mmol), Urea (1.5 mmol), Ethyl acetoacetate (1.0 mmol), catalyst, solvent (10 ml) refluxed for the appropriate time.
[b]Isolated yields.

After obtaining the best reaction conditions; 1.0 mmol of benzaldehyde, 1.0 mmol of ethyl acetoacetate, 1.5 mmol of urea, 20 mol% benzoic acid as a catalyst in 10 ml of acetonitrile refluxed for 12 hrs, in order to explore the scope and generality of the present reaction conditions, various aldehydes and an urea analog, i.e. thiourea were taken for the Biginelli reaction using our optimized reaction conditions (Scheme 3). The results obtained are summarized in Table 2.



Scheme 3

In addition to the parent benzaldehyde, aldehydes with electron-donating groups such as methyl-, methoxy- and chloro-type groups, also electron withdrawing group such as nitro- were treated with ethyl acetoacetate and urea, resulting in the formation of the corresponding DHPM derivative in 84–92 % yield (Table 2, entries 01–05). The urea analog, i.e., thiourea, was also tested in the same reaction with benzaldehydes bearing chloro-, hydroxyl-, nitro- and methoxy-groups yielding the corresponding product in 82–90 % yield (Table 2 entries 06–10). Reaction with methylacetoacetate showed results similar to the reaction with ethylacetoacetate and gave the corresponding DHPM (Table 2, entries 11–12) in high yield. This reaction was also suitable for aldehydes with α-hydrogen, such as *n*-valeraldehyde (Table 2, entry 13), to give the corresponding DHPM product in good yield, and a significant reduction in yield was observed compared with aromatic aldehydes.

Table 2

Scope of Aldehydes with urea/thiourea and β-keto esters in the synthesis of DHPM derivatives[a]

Entry	Aldehyde 1 (R)	Urea/thiourea 2 (X)	β-keto ester 3 (R_1)	Product 4	Yield[b] %
01	C_6H_5	O	Et	**4a**	92
02	4-ClC_6H_4	O	Et	**4b**	90
03	4-$CH_3C_6H_4$	O	Et	**4c**	84
04	4-$OCH_3C_6H_4$	O	Et	**4d**	87
05	4-$NO_2C_6H_4$	O	Et	**4e**	90
06	C_6H_5	S	Et	**4f**	84
07	4-OHC_6H_4	S	Et	**4g**	82
08	3-$NO_2C_6H_4$	S	Et	**4h**	87
09	3-$OCH_3C_6H_4$	S	Et	**4i**	90
10	4-ClC_6H_4	S	Et	**4j**	86
11	C_6H_5	O	Me	**4k**	86
12	4-ClC_6H_4	O	Me	**4l**	82
13	n-Bu	O	Et	**4m**	72

[a]Reaction conditions: Aldehyde (1.0 mmol), Urea/thiourea (1.5 mmol), β-keto esters (1.0 mmol), benzoic acid 20 mol%, in acetonitrile (10 ml) refluxed for the 12 h.
[b]Isolated yields.

Conclusions

In conclusion, we have developed a simple and efficient method for one-pot three-component synthesis of 3,4-dihydropyrimidinone derivatives from aldehydes with β-keto esters and urea or thiourea using benzoic acid as an organocatalyst by refluxing in acetonitrile in high yields of 72–92 %. This method using benzoic acid as an organocatalyst is very useful to explore diversified aldehydes for synthesizing derivatives of 3,4-dihydropyrimidinones as well as thione analogues, which can play crucial role in the field of medicinal chemistry.

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