

Article

# Green High-Yielding One-Pot Approach to Biginelli Reaction under Catalyst-Free and Solvent-Free Ball Milling Conditions

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Academic Editor: Rajender S. Varma

Received: 4 November 2016; Accepted: 7 December 2016; Published: 14 December 2016

**Abstract:** A simple, green, and efficient approach was used to synthesize 3,4-dihydropyrimidines derivatives. We showed that the application of the planetary ball milling method with a ball-to-reagent weight ratio of 8 for the Biginelli reaction provides 3,4-dihydropyrimidines derivatives with excellent yields (>98%) in a short reaction time from the one-pot, three-component condensation of aldehydes, ethyl acetoacetate, and urea (or thiourea).

**Keywords:** Biginelli reaction; ball milling; catalyst-free; solvent-free; dihydropyrimine derivatives

## 1. Introduction

The development of new efficient methods to synthesize organic heterocycles that are both economical and eco-friendly presents a great challenge for the scientific community.

Solvent-free reactions are highly significant from both economical and synthetic points of view. These kinds of reactions ensure an essential facet of green chemistry to reduce the risks to humans and the environment.

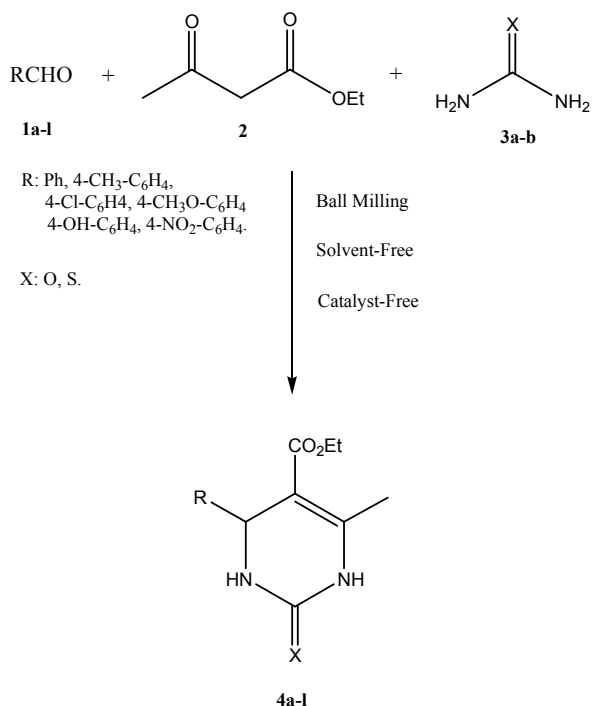
Multicomponent reactions (MCRs) have gained importance because of their efficiency and effectiveness as a method for one-pot synthesis of a wide range of heterocycles [1–6]. The optimal MCR is sufficiently flexible. Thus, it can be conducted to generate adducts with a variety of functional groups that may then be selectively paired to enable different cyclization manifolds, thereby leading to a diverse collection of products.

Among the MCRs, the Biginelli reaction [7] is used for the direct synthesis of 3,4-dihydropyrimidine derivatives. The 3,4-dihydropyrimidine and its derivatives are highly significant because they generally show diverse medicinal properties, such as calcium channel blockers, antihypertensive and anti-inflammatory agents, and  $\alpha$  1-a antagonists [8–11]. Furthermore, 3,4-dihydropyrimidine derivatives have emerged as important target molecules because of their pharmacological and therapeutic properties, such as antimitotic, antiviral, antitumor, anticarcinogenic, antibacterial, and fungicidal activities [12–19].

Several improvements were made towards good reaction conditions, and they involved the use of catalysts/reagents, transition metal-based reagents, ionic liquids, polymer-immobilized reagents, microwaves, and ultrasound irradiation; these improvements have been recently reported for the synthesis of the aforementioned compounds [20–33].

Despite all of the improved methods, organic synthesis methods still have many drawbacks, such as the use of organic solvents, long reaction times, high costs, low yields, nonsustainable catalysts, and purification issues [34–40].

In this study, we propose a new and highly efficient approach to the one-pot synthesis of Biginelli 3,4-dihydropyrimidine derivatives under planetary ball milling solvent-free and catalyst-free conditions (Scheme 1).



**Scheme 1.** The 3,4-dihydropyrimidine derivatives synthesis under the ball milling technique.

## 2. Experimental Section

### 2.1. Materials and Techniques

The ball mill used in this study was a Planetary Micro Mill PULVERISETTE 7 (Fritsch, Idar-Oberstein, Germany) classic line with 45 mL tempered steel vials and 10 mm tempered steel grinding balls. The melting points were determined with a Stuart SMP10 melting point apparatus (Bibby Scientific, Staffordshire, UK). All of the compounds used in this study were purchased from Aldrich (St. Louis, MO, USA). IR spectra were obtained with an FT-IR-Tensor 27 spectrometer in KBr pellets (Bruker, Ettlingen, Germany). <sup>1</sup>H and <sup>13</sup>C-NMR spectra were determined with a Bruker 400 NMR spectrometer (Bruker Biospin, Rheinstetten, Germany) in DMSO-*d*<sub>6</sub> with TMS as the internal standard. Chemical shifts were expressed as δ ppm units. The elemental analysis was performed on a PerkinElmer 2400 CHN Elemental Analyzer (Wellesley, MA, USA). The progress of all reactions was monitored through TLC on silica gel 60 with 1:1 hexane/ethyl acetate.

### 2.2. General Procedure for Synthesis of 3,4-Dihydropyrimidine Compound 4a

An equimolar amount (0.02 mol) of benzaldehyde (1a), ethyl acetoacetate (2), and urea (3a) (total mass 5.92 g) was placed into tempered steel vials with 47.36 g of tempered steel balls (22 balls of 10 mm in diameter). The vials were closed and then placed in a Planetary Micro Mill Pulverisette 7, which is set to 750 rpm. The 3,4-dihydropyrimidine compound 4a was obtained in pure form after 30 min of milling without further purification.

### 3. Results and Discussion

Recently, Mal et al. [41] showed that the 3,4-dihydropyrimidines can be accessed in two steps under ball milling through a combination of a catalytic amount of potassium bromide (KBr), oxone and TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy).

In this paper, we present an efficient one-pot, three-component solvent-free and catalyst-free approach to synthesize 3,4-dihydropyrimidine derivatives by direct condensation of equimolar quantities of benzaldehyde derivatives, ethyl acetoacetate, and urea/thiourea in a simple planetary ball mill at 750 rpm without adding any solvent or catalyst (Scheme 1). The progress of the reactions was monitored every 10 min of the milling cycle through thin-layer chromatography (TLC).

We examined different ball ratios (Table 1) to improve the efficiency of the ball milling approach for the Biginelli reaction. Equimolar quantities (0.02 mol) of benzaldehyde (1a), ethyl acetoacetate (2), and urea (3a) (with a total mass of 5.92 g) were introduced in the planetary ball milling, and several milling times and ball weights were tested [42].

**Table 1.** Milling parameters and the conversion rate for the synthesis of 3,4-dihydropyrimidines derivatives.

Entry *	BRR (Balls-to-Reagents Weight Ratio)	Time (min)	Conversion (%)
1	1:1	720	00
2	2:1	720	00
3	3:1	720	20
4	4:1	720	40
5	5:1	300	70
6	6:1	360	100
7	7:1	180	100
8	8:1	30	100

\* 0.02 mol of benzaldehyde, ethyl acetoacetate, and urea (5.92 g).

Accordingly, our investigation showed that the reaction does not change even after 12 h of milling when the ratio (ball weight/reagent weight) is equal to 1. The increasing value of the ball weight causes the conversion rate to increase to the optimal value for the ball weight-to-reagent weight ratio, which is equal to 8 (47.36 g of balls) (Table 1). The protocol also provides simple access to 3,4-dihydropyrimidine derivatives (4a–j) (Table 2).

This approach exhibits the advantages of high yield, short reaction time (30 min), and easy workup. It is also environmentally benign. All of the synthesized products have been characterized through NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ), IR, and elemental analysis.

**Table 2.** Synthesis of 3,4-dihydropyrimidine derivatives using planetary ball milling technique.

Entry	R	X	Product	Yield (%)	M.P. (°C)	
					Found	Reported References
1	C <sub>6</sub> H <sub>5</sub> -	O	4a	>98	200–202	(202–204) [40]
2	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	O	4b	>98	214–216	(215–217) [39]
3	4-Cl-C <sub>6</sub> H <sub>4</sub> -	O	4c	>98	208–210	(207–210) [40]
4	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> -	O	4d	>98	204–207	(203–205) [40]
5	4-OH-C <sub>6</sub> H <sub>4</sub> -	O	4e	>98	221–223	(224–227) [40]
6	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -	O	4f	>98	208–210	(206–208) [39]
7	C <sub>6</sub> H <sub>5</sub> -	S	4g	>98	209–211	(206–208) [39]
8	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	S	4h	>98	187–189	(186–188) [39]
9	4-Cl-C <sub>6</sub> H <sub>4</sub> -	S	4i	>98	182–184	(181–183) [39]
10	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> -	S	4j	>98	155–157	(151–153) [39]
11	4-OH-C <sub>6</sub> H <sub>4</sub> -	S	4k	>98	206–208	(200–202) [40]
12	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -	S	4l	>98	197–199	(191–193) [39]

#### 4. Conclusions

We developed a simple, green, and quick method for the one-pot Biginelli reaction. This technique is highly efficient. The important advantage of the present procedure, in addition to its simplicity, is its ability to obtain the synthesized 3,4-dihydropyrimidine derivatives in a short reaction time, in pure form, and with excellent yields.

**Supplementary Materials:** Experimental details and spectroscopic data are available online at [www.mdpi.com/2076-3417/6/12/431/s1](http://www.mdpi.com/2076-3417/6/12/431/s1), Figure S1: <sup>1</sup>H-NMR spectrum of compound **4a**, Figure S2: <sup>13</sup>C-NMR spectrum of compound **4a**, Figure S3: <sup>1</sup>H-NMR spectrum of compound **4g**, Figure S4: <sup>13</sup>C-NMR spectrum of compound **4g**.

**Acknowledgments:** The authors extend their appreciation to the Deanship of Academic Research at Al Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, Kingdom of Saudi Arabia, for funding the work through research project Number 341205, 1434 H.

**Author Contributions:** M.O.M. and O.M.L. conceived and designed the experiments; M.O.M. performed the experiments; A.G.A. and O.M.L. analyzed the data; A.G.A. contributed reagents/materials/analysis tools; M.O.M. wrote the paper.

**Conflicts of Interest:** The authors declare no conflict of interest.

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