

## A Simple and New Method for the Synthesis of Dihydropyrimidinones by Biginelli Reaction

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Borax/phosphorous oxychloride (BPO) is found to be a new efficient catalyst for three component coupling of  $\beta$ -dicarbonyl compounds, aldehydes and urea (or thiourea) to afford the corresponding dihydropyrimidinones or their sulfur analogues. The reaction proceeds efficiently under solvent-free conditions with excellent yields.

**Key Words:** Dihydropyrimidinones, Biginelli reaction, Multicomponent reactions, Borax.

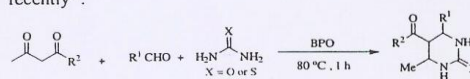
### INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry<sup>1,2</sup>. The strategies of multicomponent reactions offer significant advantages over conventional linear-type syntheses for their high degree of atom economy, convergence, ease of execution and broad applications characters. Multicomponent reactions are particularly useful to generate diverse chemical libraries of 'druglike' molecules for biological screening<sup>3,4</sup>. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. The three-component Biginelli reaction is attractive, since the resulting dihydropyrimidinone (DHPM) scaffold displays a wide range of biological activity as antiviral, antitumor, antibacterial, antiinflammatory<sup>5,6</sup> calcium channel blockers, anti-hypertensive agents<sup>7</sup> and as  $\alpha_1$  and enoceptor-selective antagonists<sup>8</sup>. Several marine alkaloids containing the dihydropyrimidinone core unit have shown interesting biological properties. In particular, batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors<sup>9</sup>. The original Biginelli protocol for the preparation of dihydropyrimidinones consisted of heating a mixture of the three components included  $\beta$ -ketoester, aldehyde and urea in ethanol containing a catalytic amount of HCl<sup>10</sup>.

Many reagents have been reported in the literature for this reaction including,  $\text{InCl}_3$ <sup>11</sup>,  $p\text{-TsOH}$ <sup>12</sup>,  $\text{Bi}(\text{OTf})_3$ <sup>13</sup>,  $\text{BF}_3\cdot\text{OEt}_2$ <sup>14</sup>, ionic liquids (BMIm. $\text{PF}_6$  and BMIm. $\text{BF}_4$ )<sup>15</sup>,  $\text{I}_2$ <sup>16</sup>, NBS<sup>17</sup>, polyaniline-bismoclit complex<sup>18</sup>, heteropoly acid<sup>19</sup>, sulfated zirconia<sup>20</sup>,  $\text{Sr}(\text{NO}_3)_2$ <sup>21</sup>, iron(III) trifluoroacetate<sup>22</sup>, trichloroisocyanuric acid<sup>23</sup>,  $\text{SbCl}_5$ <sup>24</sup> PS-PEG bound sulfonic

acid<sup>25</sup> and mesoporous aluminosilicate<sup>26</sup>, are also used. Many of these protocols involve expensive reagents, strongly acidic conditions, long reaction times, unsatisfactory yields and incompatibility with other functional groups.

Surface-mediated solid phase reactions are of growing interest<sup>27</sup>, because of their ease of set-up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts. This paper reports a new study on the Biginelli reaction catalyzed by  $\text{Na}_2\text{B}_4\text{O}_7/\text{POCl}_3$  (BPO). It is found that borax (anhydrous)-supported  $\text{POCl}_3$  under solvent-free conditions was capable of producing high yields of dihydropyrimidinone from Biginelli reaction (Scheme-I). The work on borax/phosphorous oxychloride (BPO) is reported recently<sup>28</sup>.



Scheme-I

### EXPERIMENTAL

**Preparation of BPO:** A mixture of  $\text{POCl}_3$  (3 g) and anhydrous borax (2 g) were combined in a mortar and pestle by grinding them together until a fine, homogeneous powder was obtained (15-20 min).

**General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones:** 0.15 g BPO was added to a 25 mL round-bottomed flask containing aldehyde (2 mmol),  $\beta$ -ketoester or  $\beta$ -diketone (2 mmol) and urea or thiourea (3 mmol). The reaction mixture was heated with stirring at 80  $^\circ\text{C}$