

## Multicomponent Biginelli's Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Promoted by SnCl<sub>2</sub>·2H<sub>2</sub>O

Dennis Russowsky<sup>\*a</sup>, Fabrício A. Lopes<sup>a</sup>, Victor S. S. da Silva<sup>a</sup>, Karen F. S. Canto<sup>a</sup>, Marcelo G. Montes D'Oca<sup>b</sup> and Marla N. Godoi<sup>b</sup>

<sup>a</sup>Instituto de Química, Universidade Federal do Rio Grande do Sul, 91501-970 Porto Alegre - RS, Brazil

<sup>b</sup>Departamento de Química, Fundação Universidade do Rio Grande 96201-900, Rio Grande - RS, Brazil

Neste trabalho é descrita a habilidade do SnCl<sub>2</sub>·2H<sub>2</sub>O como catalisador na reação de Biginelli tricomponente. Uma variedade de aldeídos aromáticos mono- e dissustituídos foi utilizada na condensação com acetoacetato de etila e uréia ou tiouréia. A reação foi efetuada em etanol ou acetonitrila como solventes em meio neutro e os resultados representam um melhoramento com relação ao procedimento clássico de Biginelli e uma vantagem com relação ao uso de FeCl<sub>3</sub>·6H<sub>2</sub>O, NiCl<sub>2</sub>·6H<sub>2</sub>O e CoCl<sub>2</sub>·6H<sub>2</sub>O que são utilizados juntamente com HCl como co-catalisador. A síntese das 3,4-diidropirimidinonas foi conseguida em bons rendimentos.

The ability of SnCl<sub>2</sub>·2H<sub>2</sub>O as catalyst to promote the Biginelli three-component condensation reaction from a diversity of aromatic aldehydes, ethyl acetoacetate and urea or thiourea is described. The reaction was carried out in acetonitrile or ethanol as solvents in neutral media and represents an improvement of the classical Biginelli protocol and an advantage in comparison with FeCl<sub>3</sub>·6H<sub>2</sub>O, NiCl<sub>2</sub>·6H<sub>2</sub>O and CoCl<sub>2</sub>·6H<sub>2</sub>O which were used with HCl as co-catalyst. The synthesis of 3,4-dihydropyrimidinones was achieved in good to excellent yields.

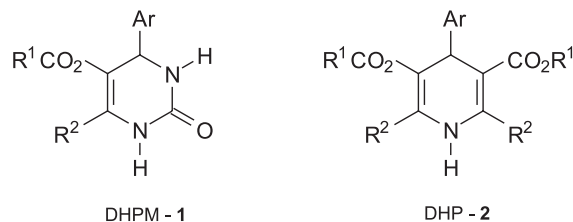
**Keywords:** Biginelli reaction, multicomponent reaction, dihydropyrimidinones, tin(II) chloride hydrate, Lewis acid

### Introduction

The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry.<sup>1</sup> The diversity, efficiency and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process.<sup>2</sup>

The 3,4-dihydropyrimidin-2(1H)-ones (DHPMs-**1**, Figure 1) have recently emerged as important target molecules due to their therapeutic and pharmacological properties<sup>3</sup> such as antiviral,<sup>4</sup> antimitotic,<sup>5</sup> anticarcinogenic,<sup>6</sup> antihypertensive<sup>7</sup> and noteworthy, as calcium channel modulators.<sup>8</sup> Additionally, their particular structure has been found in natural marine alkaloid batzelladine A and B which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, so disclosing a new field towards the development of AIDS therapy.<sup>9</sup> Also,

due to the close related structure of DHPMs with the known dihydropyridine calcium channel modulators of the Hantzsch-type (DHPs - **2**, Figure 1), an intensive research has been devoted to synthesize the dihydropyrimidinone nucleus and this subject was recently reviewed.<sup>10</sup>



**Figure 1.** The Biginelli (**1**) and Hantzsch (**2**) compounds

The original one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones was firstly reported by Pietro Biginelli in 1893 performing the three-component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Brønsted acid catalysis.<sup>11</sup> However, this reaction suffers from the harsh conditions, high reaction times and frequently low yields. Among the diversity of available methodologies in the

\* e-mail: dennis@iq.ufrgs.br

literature that use lithium salts,<sup>12</sup> TMSI,<sup>13</sup> reactions performed under ionic liquids,<sup>14</sup> solid phase,<sup>15</sup> polymer-supported,<sup>16</sup> heterogeneous catalysis by silicas<sup>17</sup> and montmorillonites<sup>18</sup> or activation by ultrasound<sup>19</sup> and microwave<sup>20</sup> energies as synthetic protocols to prepare DHPMs, special attention has been dedicated to Lewis acids catalysis.

Recently,  $\text{BF}_3 \cdot \text{OEt}_2$  complex was shown to be an excellent promoter of the three-component reaction<sup>21</sup> but anhydrous conditions were required. High yields of DHPMs were obtained using metals halides, such as  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  and  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ,<sup>22</sup>  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ,<sup>23</sup>  $\text{BiCl}_3$ ,<sup>24</sup> In(III)-halides,<sup>25</sup> and  $\text{ZrCl}_4$ ,<sup>26</sup> or lanthanide halides such as  $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ ,<sup>27</sup> and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ <sup>28</sup> as Lewis acid catalysts. Metal triflates, such as  $\text{Zn}(\text{OTf})_2$ ,<sup>29</sup>  $\text{Cu}(\text{OTf})_2$ ,<sup>30</sup>  $\text{Bi}(\text{OTf})_3$ ,<sup>31</sup> and  $\text{Sc}(\text{OTf})_3$ <sup>32</sup> or lanthanide triflates as  $\text{Yb}(\text{OTf})_3$ ,<sup>32</sup> and  $\text{La}(\text{OTf})_3$ ,<sup>33</sup> were also reported.

## Results and Discussion

In connection with our research on the use of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in multicomponent Mannich reaction,<sup>34</sup> we would like to disclose here our preliminary results employing this catalyst as a new and mild Lewis acid which, to our best knowledge, has not yet been reported promote the multicomponent Biginelli reaction (Scheme 1, Table 1). It should be noted, that  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  was used as the sole promoter agent in neutral media while for the others previously reported hydrates of metallic halides such as Fe(III), Ni(II) and Co(II) a catalytic amount of conc. HCl was needed as a Brönsted acid co-catalyst.

To evaluate the ability of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  as catalyst in this reaction, we performed the three component condensation reaction of benzaldehyde (**3a**), ethyl acetoacetate (**4**) and urea (**5a**) in EtOH and  $\text{CH}_3\text{CN}$  as solvents. To establish the optimal conditions, we carried out a set of experiments varying the reaction time, amounts of the catalysts and the quantities of urea.

The best condition to prepare the dihydropyrimidinone **6a** were achieved when 20 mol% of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ , 1 equivalent of both aldehyde **3a** and ethyl acetoacetate (**4**)

and 1.2 equivalents of urea (**5a**) were mixed under reflux for 6 hours, affording the desired product in good yield (>90%, Entry 1, Table 1). This condition was applied to a series of substituted aromatic aldehydes **3b-m** with urea (**5a**) affording the desired products **6b-m**.

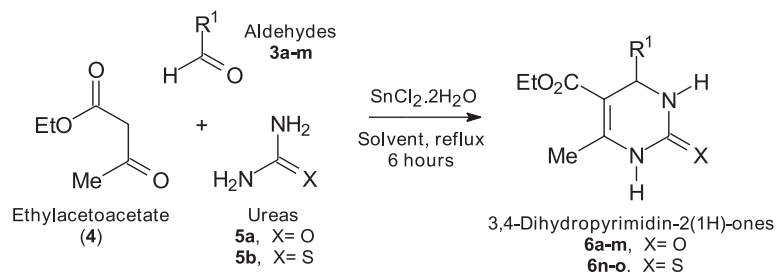
The ability of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  to promote the Biginelli reaction in EtOH was comparable to those performed in  $\text{CH}_3\text{CN}$ , affording good yields in all cases (Entries 2-26). The reactions of aldehydes **3a** and **3d** with thiourea (**5b**) also afforded the desired products in good yields for both the solvents (entries 27-30). Apparently, for the employed reaction conditions (reflux for 6 hours) the nature of the substituents does not affect significantly the yield of the reactions. The product **6c**, which has an electron-donating substituent attached at C-4 position of the aromatic ring was produced in 98% yield while the dihydropyrimidinone **6l** with an electron-withdrawing group yielded 96% (see entries 6 and 24, respectively).

The <sup>1</sup>H NMR and <sup>13</sup>C NMR data of compounds **6a-o** were compatible with the proposed structures as well as the melting points were in accordance with those reported in the literature.

A general procedure for the synthesis of 3,4-dihydropyrimidinones is described as follow: a 50 cm<sup>3</sup> round-bottom flask was charged with 3.6 mmol of urea or thiourea, 3.0 mmol of the aldehyde, 3.0 mmol of ethyl acetoacetate, 0.6 mmol of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  and 4.0 cm<sup>3</sup> of ethanol (or acetonitrile). The mixture was heated to reflux for 6 hours period under magnetic stirrer. The solution was cooled to room temperature and 10 cm<sup>3</sup> of cold water was added, the mixture was additionally stirred for 15 minutes. The resulting solid was filtered under suction, washed with cold ethanol (3 cm<sup>3</sup>) and recrystallized from hot ethanol to afford the product.

In some cases (compounds **6c**, **6d** and **6g**, entries 5, 7 and 13, respectively), the crude isolated solid compound was dried under vacuum pump and shown essentially the same purity as the recrystallized sample.

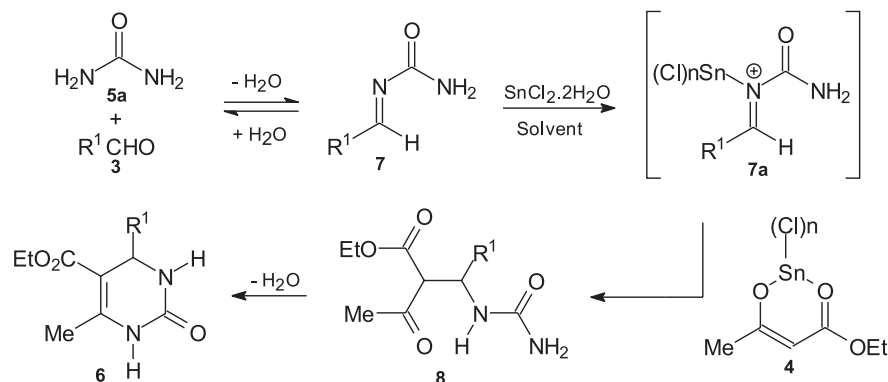
Although different mechanistic pathways have been previously proposed,<sup>35, 36</sup> we believe that the reaction may



**Scheme 1.** The multicomponent Biginelli reaction.

proceed through an initially *N*-acylimine **7** formed from aldehyde **3** and urea **5** (Scheme 2).

The coordination of the lone-pair of the nitrogen atom in the *N*-acylimine **7** with the Lewis acid could lead to the



**Scheme 2.** The suggested pathway to the Biginelli reaction.

**Table 1.** Synthesis of 3,4-dihydropyrimidin-2(1H)-ones **6a-o**

Entry	R <sup>1</sup> - <b>3</b>	X - <b>5</b>	Solvent	Product <b>6</b>	% Yield	mp (°C) <sup>a</sup>
1		O	EtOH	<b>6a</b>	92	204-205 <sup>38</sup>
2		O	CH <sub>3</sub> CN	<b>6a</b>	98	
3		O	EtOH	<b>6b</b>	82	257-259
4		O	CH <sub>3</sub> CN	<b>6b</b>	98	
5		O	EtOH	<b>6c</b>	81	202-205 <sup>22</sup>
6		O	CH <sub>3</sub> CN	<b>6c</b>	98	
7		O	EtOH	<b>6d</b>	93	192-193 <sup>22</sup>
8		O	CH <sub>3</sub> CN	<b>6d</b>	95	
9		O	EtOH	<b>6e</b>	96	188-189 <sup>22</sup>
10		O	CH <sub>3</sub> CN	<b>6e</b>	75	
11		O	EtOH	<b>6f</b>	96	199-201 <sup>30</sup>
12		O	CH <sub>3</sub> CN	<b>6f</b>	63	
13		O	EtOH	<b>6g</b>	95	196-198 <sup>22</sup>
14		O	CH <sub>3</sub> CN	<b>6g</b>	96	
15		O	EtOH	<b>6h</b>	60	233-235 <sup>22</sup>
16		O	CH <sub>3</sub> CN	<b>6h</b>	65	
17		O	EtOH	<b>6i</b>	90	213-215
18		O	CH <sub>3</sub> CN	<b>6i</b>	90	
19		O	EtOH	<b>6j</b>	94	257-258 <sup>22</sup>
20		O	CH <sub>3</sub> CN	<b>6j</b>	90	
21		O	EtOH	<b>6k</b>	96	223-224 <sup>30</sup>
22		O	CH <sub>3</sub> CN	<b>6k</b>	73	
23		O	EtOH	<b>6l</b>	94	209-210 <sup>33</sup>
24		O	CH <sub>3</sub> CN	<b>6l</b>	96	
25		O	EtOH	<b>6m</b>	84	209-210 <sup>13</sup>
26		O	CH <sub>3</sub> CN	<b>6m</b>	95	
27		S	EtOH	<b>6n</b>	85	205-206 <sup>32</sup>
28		S	CH <sub>3</sub> CN	<b>6n</b>	70	
29		S	EtOH	<b>6o</b>	65	152-153 <sup>33</sup>
30		S	CH <sub>3</sub> CN	<b>6o</b>	68	

<sup>a</sup> Literature reported mp values.

*in situ* formation of an *N*-carbamoyliminium ion **7a**, which is sufficiently electrophilic to react with the enol form of ethyl acetoacetate **4** affording the open chain intermediate **8**. Further intramolecular cyclization, with loss of H<sub>2</sub>O, produce the 2,3-dihydropyrimidin-2-(1*H*)-ones **6**.

Spectroscopic evidences for such mechanism from <sup>1</sup>H NMR and <sup>13</sup>C NMR studies were reported by Kappe, supporting the intervenience of a *N*-carbamoyliminium ion as a possible intermediate.<sup>37</sup>

## Conclusion

In summary, we have demonstrated the ability of SnCl<sub>2</sub>·2H<sub>2</sub>O as a new and mild Lewis acid promoter in the multicomponent Biginelli reaction. Besides its simplicity, neutral reaction conditions and use of commercial solvents without previous purifications or drying, this method was effective with a variety of substituted aromatic aldehydes independently of the nature of the substituents in the aromatic ring, representing an improvement to the classical Biginelli's methodology.

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