

## An efficient and recyclable L-proline triflate ionic liquid catalyst for one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones via the multi-component Biginelli reaction

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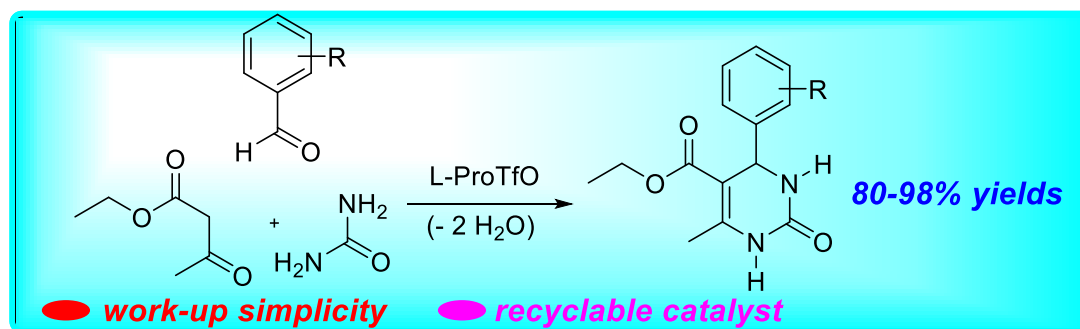
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### Abstract

A simple, efficient, and environmentally-friendly process has been developed for the synthesis of L-proline triflate ionic liquid (L-ProTfO) from L-proline and triflic acid using ultrasound irradiation. The combination of L-proline triflate ionic liquid technology with microwave energy represents an attractive and rapid alternative to the conventional acid-base-catalyzed thermal process. The current method has several advantages, including high yield, short reaction time, and work-up simplicity. In addition, the L-proline triflate ionic liquid could be recycled and reused four times without a noticeable decrease in catalytic activity.



**Keywords:** Biginelli reaction, ultrasonic irradiation, microwave irradiation, L-proline triflate, solvent-free conditions

## Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) and their derivatives have attracted increasing interest due to their diverse therapeutic and pharmacological activities, such as calcium-channel blocking, antihypertensive, antifungal, antibacterial, antiviral, anti-inflammatory, and anticancer properties.<sup>1-3</sup> Some of them have been successfully used as calcium-channel blockers, antihypertensive agents, and  $\alpha_{1a}$ -antagonists.<sup>4, 5</sup> Several alkaloids isolated from marine sources whose molecular structures contain the dihydropyrimidinone unit also exhibit interesting biological activities.<sup>1</sup> The Biginelli reaction involves a three-component, one-pot condensation of benzaldehyde,  $\beta$ -keto ester, and urea under strongly acidic conditions.<sup>1</sup> However, some methods often require harsh conditions, long reaction times, expensive catalysts, and volatile organic solvent.<sup>5-13</sup> The search for new, efficient, and green catalysts is still being actively pursued.

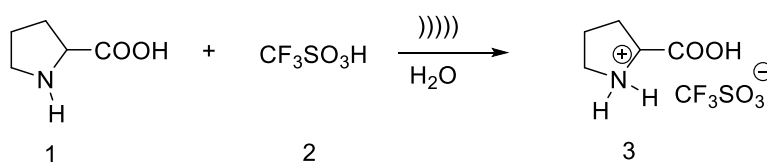
Ionic liquids (ILs) have attracted interest as powerful alternatives to volatile organic solvents and catalysts due to their negligible vapor pressure, thermal stability, designability, nonflammability, wide range of solubility and ease of recycling.<sup>14-18</sup> Some ionic liquids have been used as catalysts for the synthesis of dihydropyrimidinones.<sup>19-22</sup> Low yields and long reaction times, however, have limited the applicability of these ionic liquids. The use of acidic-ionic liquids in the Biginelli reaction under microwave irradiation has been studied sparsely in the literature.<sup>23-26</sup> The preparation of these acidic-ionic liquids usually required a two-step procedure *via* zwitterions, and the purification of ionic liquids was not easily achieved.

The utility of microwave irradiation (MW) and ultrasound activation to assist organic reactions has been studied extensively. The prominent features of these techniques are significant rate enhancement, short reaction time, energy savings, high yields with high selectivity. A large number of papers have previously reported the application of MW and ultrasound irradiation in the synthesis of heterocyclic compounds.<sup>27-33</sup>

In the present study, an easily synthesizable and cost-effective L-proline triflate ionic liquid was prepared from L-proline and triflic acid using ultrasonic irradiation technology. This ionic liquid was used as an efficient and green catalyst for the Biginelli reaction under solvent-free conditions. The Biginelli reaction was carried out using both conventional heating methods and microwave energy for comparison.

## Results and Discussion

In our current work, an efficient pathway for the synthesis of L-ProTfO, an  $\alpha$ -amino acid-based IL from L-proline (**1**) and triflic acid (**2**), has been developed under ultrasonic irradiation (Scheme 1).<sup>34</sup> For the first time, L-ProTfO has been used as an efficient and green catalyst for the Biginelli reaction under solvent-free conditions.



**Scheme 1.** Synthesis of L-proline triflate using ultrasonic irradiation.

As seen from Table 1, the reaction between L-proline and triflic acid is exothermic; it was performed at ambient temperature (30 °C). The control experiment without sonication resulted in a slightly lower yield

while also requiring a longer time (Table 1: entries 3, 6). The most significant effect of ultrasound irradiation is that, by passing its waves through a liquid medium, which causes the generation of energy provided by cavitation, resulting in the formation, and subsequent collapse, of the bubble which liberates considerable energy in a short period of time. This is also a green protocol for the efficient synthesis of L-proline triflate because this process used water as the only solvent, thereby avoiding toxic organic solvents, and used a green method, ultrasonic irradiation.

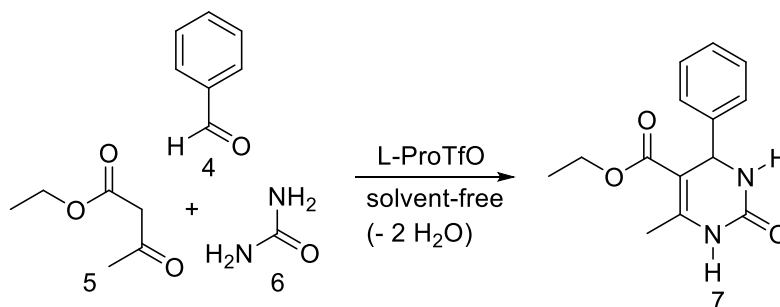
**Table 1.** Preparation results of L-proline triflate under ultrasonic irradiation

Entry	Temperature (°C)	Time (min)	Yield (%) <sup>a</sup>
1	30	2	80
2	30	3	90
3	30	4	99
4	30	5	99
5	30	6	99
6 <sup>b</sup>	30	60	98

<sup>a</sup> Isolated yield.

<sup>b</sup> Without ultrasonic irradiation.

L-proline triflate was used to catalyze the Biginelli reaction to prepare 3,4-dihydropyrimidin-2(1H)-one (DHPM) under conventional heating and microwave irradiation for the first time (Scheme 2).



**Scheme 2.** The Biginelli synthesis of DHPM.

Initially, we began our investigation by using benzaldehyde (4), ethyl acetoacetate (5), and urea (6) for the model reaction. As shown in Table 2, when the reaction was carried out at 70 °C in the presence of L-proline triflate (10 mol%), the yields increased from 57% to 72% when the reaction time was increased from 1.0 to 1.5 h. When the reaction time was prolonged beyond 1.5 h, however, the product yield did not increase (Table 2, entries 1-4). The molar ratio of reagents and reaction temperatures were also investigated. The best yield obtained was 88% yield (Table 2, entry 9).

**Table 2.** Synthesis of DHPM under solvent-free conventional heating

Entry	Cmpds 4:5:6 (molar ratio)	L-ProTfO (mol%)	Temperature (°C)	Time (h)	Yield (%) <sup>a</sup>
1	1:1:1	10	70	1.0	57
2	1:1:1	10	70	1.5	72
3	1:1:1	10	70	2.0	72
4	1:1:1	10	70	2.5	71
5	1:1:1	10	60	1.5	60
6	1:1:1	10	80	1.5	75
7	1:1:1	10	90	1.5	70
8	1:1:1.5	10	80	1.5	78
9	1:1:2.0	10	80	1.5	88
10	1:1:2.5	10	80	1.5	80
11	1:1:2.0	5	80	1.5	65
12	1:1:2.0	15	80	1.5	80
13	1:1:2.0	20	80	1.5	75

<sup>a</sup>Isolated yield.

Next, we focused on trying to lower the reaction time using microwave irradiation instead of conventional heating. As seen from Table 3, in comparison with conventional heating, microwave irradiation is a more efficient and environmentally-friendly tool because of the shorter reaction times and resulting energy savings. The best yield was 90% following only 10 min (Table 3, Entry 9). Under the same reaction conditions, the conventional heating method resulted in extremely poor yield (Table 3, entry 14).

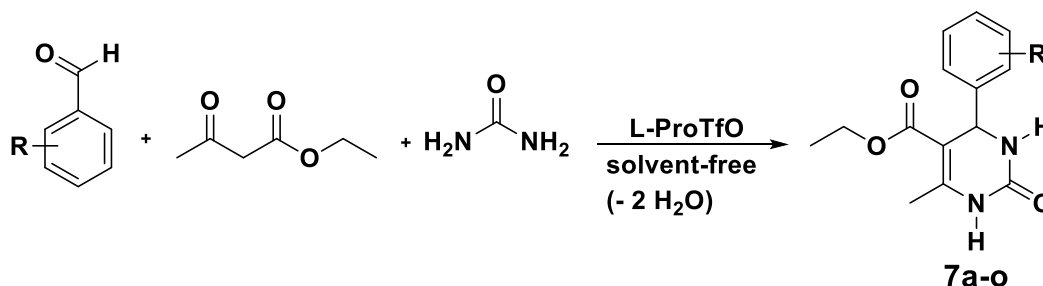
**Table 3.** Synthesis of DHPM under solvent-free microwave irradiation

Entry	Cmpds 4:5:6 (molar ratio)	L-ProTfO (mol%)	Temperature (°C)	Time (min)	Yield (%) <sup>a</sup>
1	1:1:1	10	70	5	59
2	1:1:1	10	70	10	74
3	1:1:1	10	70	15	74
4	1:1:1	10	70	20	72
5	1:1:1	10	60	10	64
6	1:1:1	10	80	10	77
7	1:1:1	10	90	10	70
8	1:1:1.5	10	80	10	80
9	1:1:2.0	10	80	10	90
10	1:1:2.5	10	80	10	83
11	1:1:2.0	5	80	10	70
12	1:1:2.0	15	80	10	82
13	1:1:2.0	20	80	10	77
14 <sup>b</sup>	1:1:2.0	10	80	10	20

<sup>a</sup>Isolated yield.<sup>b</sup>Conventional heating.

With the optimized conditions in hand, a variety of aldehydes were investigated. The results are summarized in Table 4. Both electron-withdrawing and electron-donating groups on the aldehyde aryl ring were investigated and found to be reactive. *Ortho*- and *para*- electron-donating groups on the aldehyde aryl ring produced the desired products, *o*-Cl (**7e**), *p*-Cl (**7g**), *o*-Br (**7h**), *p*-Br (**7j**), *o*-Me (**7l**), *o*-MeO (**7m**), and *m*-MeO-*p*-OH (**7o**), in similarly high yields, albeit lower than the product yield of benzaldehyde. In addition, *ortho* and *para* electron-withdrawing groups on the aldehyde aryl ring produced the desired products, *o*-F (**7b**), *p*-F (**7d**), *p*-NO<sub>2</sub> (**7k**), in excellent yields, and higher than the product yield of benzaldehyde. *m*-Substituted aldehydes, including *m*-Cl (**7f**), *m*-Br (**7i**), *m*-OH (**7n**) provided the desired products in lower yield than benzaldehyde. *m*-Fluorobenzaldehyde provided the desired product in high yield due to the electron-withdrawing nature of fluorine.

**Table 4.** Synthesis of DHPMs catalyzed by L-proline triflate under solvent-free conditions<sup>a</sup>



Entry	Product	R	Time (min)	Yield (%) <sup>b</sup>	Mp (°C)	
					Found	Ref.
1	<b>7a</b>	H	10	90	207-208	207-208 <sup>32</sup>
2	<b>7b</b>	2-F	10	96	235-236	235-237 <sup>29</sup>
3	<b>7c</b>	3-F	10	92	209-210	209-211 <sup>7</sup>
4	<b>7d</b>	4-F	10	94	182-184	182-184 <sup>33</sup>
5	<b>7e</b>	2-Cl	10	86	221-223	222-223 <sup>1</sup>
6	<b>7f</b>	3-Cl	10	90	193-195	192-193 <sup>33</sup>
7	<b>7g</b>	4-Cl	10	88	213-214	214-215 <sup>32</sup>
8	<b>7h</b>	2-Br	10	85	205-206	205-207 <sup>34</sup>
9	<b>7i</b>	3-Br	10	89	184-186	185-186 <sup>33</sup>
10	<b>7j</b>	4-Br	10	88	224-225	225-226 <sup>10</sup>
11	<b>7k</b>	4-NO <sub>2</sub>	10	97	209-211	210-211 <sup>32</sup>
12	<b>7l</b>	4-Me	10	89	213-215	213-215 <sup>9</sup>
13	<b>7m</b>	4-MeO	10	86	200-202	200-202 <sup>9</sup>
14	<b>7n</b>	3-OH	10	92	184-186	184-186 <sup>32</sup>
15	<b>7o</b>	3-MeO-4-OH	10	87	238-240	239-240 <sup>32</sup>

<sup>a</sup>Reaction conditions: aldehyde (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea (5.0 mmol) and L-ProTfO (0.6625 g) and microwave irradiation.

<sup>b</sup>Isolated yield.

The recovery and reuse of L-proline triflate in the Biginelli synthesis were investigated in the model reaction. The reusability of IL is presented in Table 5. A little loss of the catalytic activity was observed after

the fourth cycle. These results show that the L-proline triflate catalyst can be reused at least four times without significant loss of the activity.

**Table 5.** Recycling results of L-proline triflate in the Biginelli reaction<sup>a</sup>

Entry	Cycles	Yield (%)
1	1	90
2	2	90
3	3	90
4	4	89

<sup>a</sup>Reaction conditions: aldehyde (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea (5.0 mmol) and L-ProTfO (0.6625 g) under solvent-free microwave irradiation for 10 min.

<sup>b</sup>Isolated yield.

## Conclusions

In summary, we have developed the use of ultrasonic irradiation for the synthesis of L-proline triflate for the first time. The method offers several advantages, including mild reaction conditions, short reaction times, easy isolation, and excellent yields. L-proline triflate was shown to be an efficient, clean, and environmentally-friendly catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from aromatic aldehydes under solvent-free microwave irradiation. This is also the first time that L-proline triflate was used for the Biginelli reaction. The catalyst can be easily recovered and reused several times without a noticeable decrease in reactivity.

## Experimental Section

**General.** All solvents and chemicals used in the experiments were commercially available from Merck, Aldrich, and were used without further purification unless otherwise stated. Products were characterized by melting point (Buchi B-545), and <sup>1</sup>H and <sup>13</sup>C NMR (Bruker Advance, 500 MHz) spectroscopy. Ultrasonic bath (BRANSON 1510) and microwave oven Discover (CEM) were used for the syntheses.

### General procedure for the synthesis of L-proline triflate (3) under ultrasonic irradiation

L-Proline (1 mmol, 0.115 g) was dissolved in water (1 mL) and cooled in an ice-salt bath (0-5 °C). Then triflic acid (1mmol, 0.15 g) was added dropwise with stirring for 5 min. The reaction was carried out under ultrasound irradiation at room temperature. Upon completion, water was removed under vacuum at 70 °C. The product was extracted with diethyl ether (5 x 10 mL) to remove non-ionic residues. The combined organic layers were evaporated under vacuum to afford the pure L-proline triflate as a white solid (0.262 g, 99% yield). <sup>1</sup>H NMR (D<sub>2</sub>O) δ(ppm): 2.08-2.14 (m, 2H), 2.19-2.26 (m, 1H), 2.45-2.52 (m, 1H), 3.41-3.52 (m, 2H), 4.45-4.48 (m, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O) δ(ppm): 26.0, 30.9, 48.9, 62.3, 118.5, 126.1, 174.5.

**General procedure for recycling L-proline triflate**

After completion of the Biginelli reaction, the mixture was washed with cold water. The filtrate included L-proline and urea. Afterwards, water was removed from the mixture using a rotary evaporator at 70 °C. The crude product was extracted with acetone (3 x 20 mL) to remove urea. The combined organic layers were collected and concentrated to afford the recycled catalyst.

**General procedure for the synthesis of 5-ethoxycarbonyl-4-substituted-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7a-o).**

A mixture of the respective aldehyde (2.5 mmol), 1,3-dicarbonyl compound (2.5 mmol), urea (5.0 mmol), and L-ProTfO (0.6625 g, 10 mol%) was added into a round-bottom flask. The mixture was stirred and activated by conventional-heating or microwave-irradiation methods. Cold water (15 mL) was added and stirred for 10 min. The product was filtered and washed with water (3x15 mL) and recrystallized from ethanol to afford the pure product in almost quantitative yield. The filtrate was extracted with diethyl ether to remove organic residues and to recover the L-proline triflate.

**5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7a).** White solid (0.234 g, 90% yield), m.p. 207-208 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.08 (t, 3H, *J* 7.0 Hz), 2.23 (s, 3H), 3.97 (q, 2H, *J* 7.0 Hz), 5.13 (d, 1H, *J* 1.5 Hz), 7.21-7.29 (m, 3H), 7.29-7.32 (m, 2H), 7.69 (s, 1H), 9.14 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.0, 17.7, 54.0, 59.1, 99.3, 126.2, 127.2, 128.3, 144.8, 148.3, 152.1, 165.3.[1]

**5-Ethoxycarbonyl-4-(2-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7b).** White solid (0.267 g, 96% yield), m.p. 235-236 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.01 (t, 3H, *J* 7.0 Hz), 2.25 (s, 3H), 3.90 (q, 2H, *J* 7.0 Hz), 5.44 (s, 1H), 7.10-7.15 (m, 2H), 7.23-7.30 (m, 2H), 7.66 (s, 1H), 9.23 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.3, 18.2, 49.1, 59.6, 98.0, 115.8, 125.0, 129.4, 129.8, 132.1, 149.4, 152.0, 158.9-160.8, 165.5.[2]

**5-Ethoxycarbonyl-4-(3-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7c).** White solid (0.256 g, 92% yield), m.p. 209-210 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.08 (t, 3H, *J* 7.0 Hz), 2.24 (s, 3H), 3.98 (q, 2H, *J* 7.0 Hz), 5.15 (d, 1H, *J* = 3.5 Hz), 6.79-7.08 (m, 3H), 7.34-7.38 (m, 1H), 7.76 (s, 1H), 9.22 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 54.0, 59.8, 99.2, 113.5, 114.5, 122.7, 131.0, 148.1, 149.4, 152.5, 161.6-163.5, 165.7.[3]

**5-Ethoxycarbonyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7d).** White solid (0.261 g, 94% yield), m.p. 182-184 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.07 (t, 3H, *J* 7.0 Hz), 2.23 (s, 3H), 3.96 (q, 2H, *J* 7.0 Hz), 5.13 (s, 1H), 7.130 (t, 2H, *J* 9.0 Hz), 7.24 (t, 2H, *J* 9.0 Hz), 7.73 (s, 1H), 9.21 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 53.8, 59.7, 99.6, 115.5, 115.7, 128.7, 128.5, 141.6, 149.0, 152.4, 160.8-162.8, 165.7.[4]

**5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7e).** White solid (0.253 g, 86% yield), m.p. 221-223. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 0.97 (t, 3H, *J* 7.0 Hz), 2.28 (s, 3H), 3.88 (q, 2H, *J* 7.0 Hz), 5.62 (d, 1H, *J* 3.0 Hz), 7.23-7.27 (m, 1H), 7.30 (d, 2H, *J* 4.0 Hz), 7.38 (d, 1H, *J* 9.0 Hz), 7.66 (s, 1H), 9.24 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.4, 18.2, 52.0, 59.5, 98.4, 128.2, 129.3, 129.5, 129.9, 132.2, 142.2, 149.8, 151.8, 165.4.[5]

**5-Ethoxycarbonyl-4-(3-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7f).** White solid (0.265 g, 90% yield), m.p. 193-195 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.08 (t, 3H, *J* 7.0 Hz), 2.24 (s, 3H), 3.98 (q, 2H, *J* 7.0 Hz), 5.14 (d, 1H, *J* 3.5 Hz), 7.19 (d, 1H, *J* 7.5 Hz), 7.23 (s, 1H), 7.73 (d, 1H, *J* 9.0 Hz), 7.35 (t, 1H, *J* 9.0 Hz), 7.76 (s, 1H), 9.24 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 54.1, 59.8, 99.1, 125.4, 126.7, 127.7, 131.0, 133.4, 147.7, 149.4, 152.4, 165.6.[4]

**5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7g).** White solid (0.259 g, 88% yield), m.p. 213-214 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.07 (t, 3H, *J* 7.0 Hz), 2.23 (s, 3H), 3.96 (q, 2H, *J* 7.0 Hz), 5.12 (s, 1H), 7.23 (d, 2H, *J* 10.5 Hz), 7.37 (d, 2H, *J* 9.0 Hz), 7.76 (s, 1H), 9.23 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 53.9, 59.7, 99.2, 128.7, 128.9, 132.3, 144.3, 149.2, 152.4, 165.7.[1]

**5-Ethoxycarbonyl-4-(2-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7h).** White solid (0.287 g, 85% yield), m.p. 205-206 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 0.98 (t, 3H, *J* 7.0 Hz), 2.29 (s, 3H), 3.89 (q, 2H, *J* 7.0

Hz), 5.60 (s, 1H, *J* 1.5 Hz), 7.17 (t, 1H, *J* 7.0 Hz), 7.29-7.34 (m, 2H), 7.55 (d, 1H, *J* 7.5 Hz), 7.65 (s, 1H), 9.24 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.4, 18.1, 54.5, 59.5, 98.8, 122.8, 128.9, 129.2, 129.8, 133.1, 149.7, 151.7, 165.4.[6]

**5-Ethoxycarbonyl-4-(3-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7i).** White solid (0.301 g, 89% yield), m.p. 184-186 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.09 (t, 3H, *J* 7.0 Hz), 2.24 (s, 3H), 3.98 (q, 2H, *J* 7.0 Hz), 5.13 (d, 1H, *J* 3.0 Hz), 7.22 (d, 1H, *J* 8.0 Hz), 7.29 (t, 1H, *J* 8.0 Hz), 7.38 (s, 1H), 7.43 (d, 1H, *J* 9.0 Hz), 7.76 (s, 1H), 9.24 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 54.1, 55.8, 99.1, 122.0, 125.7, 129.6, 130.6, 131.3, 147.9, 149.4, 152.4, 165.6.[4]

**5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7j).** White solid (0.297 g, 88% yield), m.p. 224-225 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.08 (t, 3H, *J* 7.0 Hz), 2.23 (s, 3H), 3.97 (q, 2H, *J* 7.0 Hz), 5.11 (d, 1H, *J* 3.0 Hz), 7.17 (d, 2H, *J* 7.5 Hz), 7.51 (d, 2H, *J* 10.5 Hz), 7.73 (s, 1H), 9.21 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 54.0, 59.7, 99.3, 120.8, 129.0, 131.8, 144.7, 149.2, 152.4, 165.7.[7]

**5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7k).** Yellow solid (0.296 g, 97% yield), m.p. 209-211 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.08 (t, 3H, *J* 7.0 Hz), 2.25 (s, 3H), 3.98 (q, 2H, *J* 7.0 Hz), 5.27 (s, 1H), 7.49 (d, 2H, *J* 9.0 Hz), 7.86 (s, 1H), 8.20 (d, 2H, *J* 9.0 Hz), 9.32 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.5, 18.3, 54.2, 59.9, 98.7, 124.3, 128.1, 147.2, 147.9, 152.2, 152.5, 165.5.[1]

**5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7l).** White solid (0.244 g, 89% yield), m.p. 213-215 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.08 (t, 3H, *J* 7.0 Hz), 2.22 (s, 3H), 2.24 (s, 1H), 3.96 (q, 2H, *J* 7.0 Hz), 5.09 (s, 1H), 7.10 (s, 4H), 7.67 (s, 1H), 9.14 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.6, 18.2, 21.1, 54.1, 59.6, 99.9, 126.6, 129.4, 136.8, 142.4, 148.6, 152.7, 165.8.[8]

**5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7m).** White solid (0.249 g, 86% yield), m.p. 200-202 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.09 (t, 3H, *J* 7.0 Hz), 2.22 (s, 3H), 3.70 (s, 1H), 3.96 (q, 2H, *J* 7.0 Hz), 5.07 (d, 1H, *J* 3.0 Hz), 6.86 (d, 2H, *J* 10.5 Hz), 7.13 (d, 2H, *J* 10.5 Hz), 7.63 (s, 1H), 9.17 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.6, 18.2, 53.8, 55.8, 59.6, 100.1, 114.2, 127.9, 137.5, 148.5, 152.6, 158.9, 165.8.[8]

**5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7n).** Yellow solid (0.254 g, 92%), m.p. 184-186 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.12 (t, 3H, *J* 7.0 Hz), 2.25 (s, 3H), 4.01 (q, 2H, *J* 7.0 Hz), 5.09 (s, 1H), 6.64 (d, 1H, *J* 7.5 Hz), 6.68 (t, 2H, *J* 7.5 Hz), 7.10 (t, 1H, *J* 7.5 Hz), 7.66 (s, 1H), 9.12 (s, 1H), 9.37 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.0, 17.7, 53.8, 59.2, 99.5, 113.1, 114.2, 116.9, 129.2, 146.2, 147.9, 152.2, 157.3, 165.3.[1]

**5-Ethoxycarbonyl-4-(3-methoxy-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7o).** Yellow solid (0.266 g, 87%), m.p. 238-240 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 1.10 (t, 3H, *J* 7.0 Hz), 2.21 (s, 3H), 3.70 (s, 1H), 3.98 (q, 2H, *J* 7.0 Hz), 5.04 (s, 1H), 6.59 (d, 1H, *J* 9.0 Hz), 6.68 (d, 1H, *J* = 10.5 Hz), 6.78 (s, 1H), 7.61 (s, 1H), 8.88 (s, 1H), 9.10 (s, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 14.6, 18.2, 54.0, 56.1, 59.6, 100.1, 111.4, 115.8, 118.8, 136.4, 146.3, 147.7, 148.3, 152.7, 165.9.[1]

## Supplementary Material

Spectral data and copies of spectra of compounds are provided in the supplementary material file available on the Publisher's web site.



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