



## Biginelli Reaction-Carboxylic Acids as Catalysts

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Mono and dicarboxylic acids were found to be excellent catalysts for the synthesis of dihydropyrimidones/thiones. These are presented as alternate and cheap catalysts for the multicomponent reactions.

**Key Words:** Multicomponent reactions, Dihydropyrimidone, Dihydropyrimidothione, Acid catalysts.

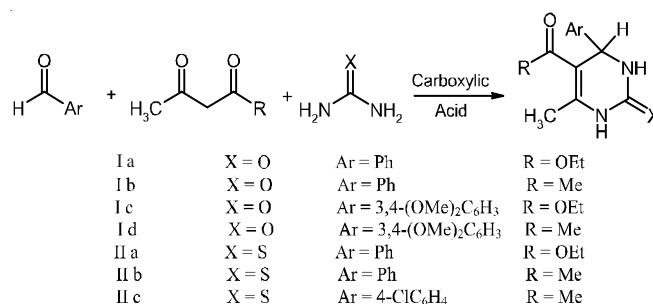
### INTRODUCTION

Pyrimidines are of vital importance in the life processes and the system has received the attention as it deserves both from the biological as well as from chemical field. It is evidenced from the literature regarding the diazines<sup>1</sup>. One of the pyrimidine derivatives *i.e.*, 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones\* (DHPM), also known as the Biginelli compounds<sup>2</sup>, are of particular biological importance due to their effectiveness as calcium channel blockers and other properties<sup>3-5</sup>.

These three component reactions, involving aldehydes, methylenic component (CH) and urea/thiourea in the presence of a catalyst/solvent have been extensively reviewed<sup>6</sup>. A number of effective catalysts have been reported for this reaction. Among these to cite a few are metal salts such as BiCl<sub>3</sub><sup>7</sup>, NiCl<sub>2</sub><sup>8</sup>, ZrCl<sub>4</sub><sup>9</sup>, Sr(NO<sub>3</sub>)<sub>2</sub><sup>10</sup>, Ln(OTf)<sub>3</sub><sup>11</sup>, solid support<sup>12</sup>, microwave assisted<sup>13</sup>, 1,3-dibromo-5,5-dimethylhydantoin<sup>14</sup>, iodine<sup>15</sup>, CuCl<sub>2</sub>·2H<sub>2</sub>O in aqueous surfactant system<sup>16</sup>, DDQ<sup>17</sup>, SnCl<sub>2</sub><sup>18</sup>, triphenylphosphine<sup>19</sup>, ammonium carbonate<sup>20</sup> and ionic liquids<sup>21</sup>. Several Brønsted and Lewis acids have been used in these reactions and in fact acetic acid was the original catalyst used by Biginelli<sup>22</sup>. Hydrochloric acid has often been employed<sup>23</sup>. Another organic acid catalyst, besides acetic acid reported is chloroacetic acid<sup>24</sup>. A recent paper has described this reaction carried out in low-melting tartaric acid-urea mixtures as a green method<sup>25</sup>.

To our best of knowledge other organic acids, although a large source of reagents/catalysts have not been explored for

promoting Biginelli reaction. Here we would like to report our findings for the use of organic acids (both mono and dicarboxylic acids) as catalysts in the Biginelli reaction. The raw materials employed were aromatic aldehydes, β-dicarbonyl compounds and urea or thiourea (**Scheme-I**). The list is by no means exhaustive so are the conditions. Yields are good to excellent. Better yields in many reactions can be obtained by varying time and other factors. Other substrates, solvents may also be gainfully employed.



**Scheme-I:** Synthesis of dihydropyrimidin-2-(1*H*)-one/thiones **Ia-d** and **IIa-c**

Although acetic acid has previously been used as combined catalyst and the solvent in the Biginelli condensation<sup>26</sup>, it was, however, interesting to see if this or other acids, in solvents such as ethanol can also function as catalysts.

TABLE-1  
SYNTHESIS OF DIHYDROPYRIMIDIN-2-(1*H*)-ONES/THIONES USING MONOCARBOXYLIC ACIDS

S. No.	Acid catalyst	Yield (%) / m.p. (°C) <sup>a,b</sup>			
		Ia	Ib	IIa	IIb
1	Formic acid	75 (203)	75 (220-222)	60 (205)	25 (220-225)
2	Acetic acid	60 (203)	– (220-222)	20 (205)	25 (220-225)
3	Propanoic acid	55 (203)	25 (220-222)	15 (205)	25 (220-225)
4	Butyric acid	75 (203)	55 (220-222)	71 (205)	69 (220-225)
5	Hexanoic acid	80 (188)	–	–	–
6	Palmitic acid	66 (187)	–	–	–
7	Oleic acid	68 (190)	–	–	–
8	Stearic acid	55 (203)	70 (220-222)	20 (205)	20 (220-225)

<sup>a</sup> **Ic** 72 %, m.p. 198 °C; **Id**, 71 %, m.p. 183 °C and **IIc**, 67 %, m.p. 181 °C. <sup>b</sup> 100 mg monocarboxylic acid (*n*-hexanoic acid for **Ic** and butyric acid for **IIc**).

## EXPERIMENTAL

All the chemicals and reagents used in the present study were commercial products. These were purified by usual methods of distillation (for liquids) and crystallization from appropriate solvents (for solids). Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer spectrum BX 1 and NMR on a Bruker 400 MHz spectrometer using tetramethylsilane as an internal reference.

**General procedure:** A mixture of 40 mmol of benzaldehyde, 40 mmol β-diketo compound, 45 mmol urea or thiourea and catalytic amount (a few drops of the liquid acid or a few crystals (ranging from 5-100 mg of the mono- or dicarboxylic acid as mentioned) in 10 mL of ethanol was heated under reflux for a few hours. The reaction was monitored by TLC. After cooling the reaction mixture was diluted with 100 mL of water, kept for a few hours, the precipitates were filtered off, washed with water and dried. A portion was recrystallized from ethanol to give the expected dihydropyrimidone (or thione). Some reactions were carried out by fusion on a hot plate (solvent less condition) and the contents were dissolved in ethanol and purified as usual. All the products of the reactions were compared with the authentic samples prepared by the literature methods and were found to be identical in all respects m.p., mixed m.p., FTIR or other spectra. Compound **Ia**: <sup>1</sup>H NMR (400 MHz, DMSO): δ = 1.06 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 5.12 (s, 1H), 7.21-7.32 (m, 5H), 7.60 (s, 1H), 9.14 (s, 1H). IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3239, 3110, 1725, 1702, 1646. MS (EI): *m/z* calcd. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: 260, 2884; found (%): 260, 2879.

## RESULTS AND DISCUSSION

A 10 mol % of the acid functioned well as a catalyst to give the desired **Ia** and then even a tenfold decrease *i.e.*, 1 mol % was effective (Tables 1 and 2). However, the yields, in some cases, where low, can be increased by using longer reaction periods. This successful attempt encouraged us to explore the use of other aliphatic carboxylic acids as catalysts in these reactions. Formic acid has previously been employed for the dihydropyrimidine synthesis but under microwave irradiation conditions<sup>9</sup> but with the present protocol comparable yield (75 %) of **Ia** was isolated. Reactions with other acids also gave reasonable yields of the products. Even the long chain fatty acids including the unsaturated oleic acid proved to be efficient catalysts. Table-1 lists the results of these reactions.

When different dioic acids were used in these reactions as catalysts (50 and 10 mg amounts), comparable yields of the products were obtained (Table-2). These results demonstrate the efficacy of dioic acids as catalysts of Biginelli reaction. With the decrease in amount of the catalyst the product yield in some cases were, however, lower as shown in Table-2.

TABLE-2  
SYNTHESIS OF DIHYDROPYRIMIDIN-2-(1*H*)-ONES USING DICARBOXYLIC ACIDS

S. No.	Acid catalyst	Yield (%) <sup>a</sup> <b>Ia</b>	Yield (%) <sup>b</sup> <b>Ia</b>
1	Oxalic acid	63	54
2	Malonic acid	76	43
3	Maleic acid	66	66
4	Adipic acid	68	48
5	Succinic acid	63	70
6	Fumaric acid	65	62

<sup>a</sup> 50 mg dioic acid. <sup>b</sup> 10 mg dioic acid.

Some of the reactions were also carried out by direct fusing the components in the presence of slight amount of different dioic acids (5 mg) and the results obtained are presented in Table-3. The product yields are found to be little lower in all these cases in general. Probably some of the components escaped or decomposed during this "direct" fusion.

TABLE-3  
SYNTHESIS OF DIHYDROPYRIMIDIN-2-(1*H*)-ONES/THIONES USING DIOIC ACIDS

S. No.	Acid catalyst <sup>a</sup>	Yield (%) <b>Ia</b>	Yield (%) <b>IIa</b>
1	Oxalic acid	59	32
2	Malonic acid	47	24
3	Maleic acid	67	40
4	Adipic acid	44	50
5	Succinic acid	62	27
6	Fumaric acid	54	36

<sup>a</sup> 5 mg dioic acid, without solvent.

## Conclusion

The present method provides yet another series of catalysts for the Biginelli reaction. The procedure is not only simple but also a cheaper alternative for this three component reaction.

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