

## Indion 190 수지: 편리한 친환경적인 재생 촉매를 이용한 효과적인 3, 4-Dihydropyrimidin-2(1H)-one의 one-pot합성

Atul Chaskar\*, Farhat Jaffer, Bhushan Langi, Sampat Yewale, and Akalpita Bodkhe  
C. K. Thakur research centre, Navi Mumbai, Maharashtra, India-410206  
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## Indion 190 Resin: A Green and Recyclable Catalyst for Facile and Efficient One-pot Synthesis of 3, 4-Dihydropyrimidin-2(1H)-one

Atul Chaskar\*, Farhat Jaffer, Bhushan Langi, Sampat Yewale, and Akalpita Bodkhe  
C. K. Thakur research centre, Navi Mumbai, Maharashtra, India-410206  
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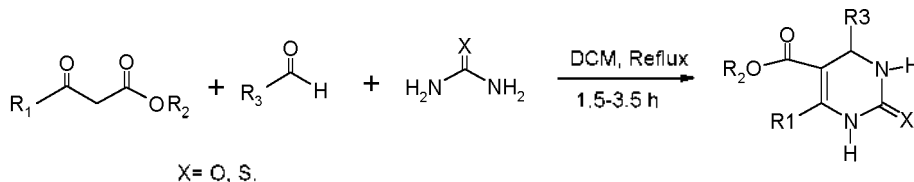
**주제어:** Biginelli 반응, Indion 190 수지, 아세토아세트산에틸, 요소, 3,4-dihydropyrimidin-2(1H)-ones, 다성분 반응

**Keywords:** Biginelli reaction, Indion 190 resin, ethyl acetoacetate, urea, 3,4-dihydropyrimidin-2(1H)-ones, multicomponent reaction

Recently Multi-component reactions (MCR's) are governing importance due to its wide variety of applications in organic and medicinal chemistry.<sup>1</sup> MCR's involves the reaction between three or more reactants in single reaction vessel to form new products, which essentially contain part of all starting materials.<sup>1</sup> MCR's are diversity oriented efficient and speedy reactions, due to which they have received tremendous attention in the drug discovery process.<sup>2</sup> One of the MCR's of current interest is the venerable Biginelli dihydropyrimidin-

imine synthesis.<sup>3</sup> Today 3,4-dihydropyrimidin-2(1H)-ones (DHPM) and its derivatives have received considerable amount of attention due to its wide spectra of biological activities. Hence several attempts have been made to synthesize the DHPM (Scheme 1).

In the attempt to prepare DHPM different types of acidic catalyst such as H<sub>2</sub>SO<sub>4</sub>,<sup>5</sup> BF<sub>3</sub>·EtOH/CuCl,<sup>6</sup> LaCl<sub>3</sub>·7H<sub>2</sub>O with catalytic concentrated HCl,<sup>7</sup> CeCl<sub>3</sub>·7H<sub>2</sub>O,<sup>8</sup> InCl<sub>3</sub>,<sup>9</sup> Heteropolyacids,<sup>10</sup> BiCl<sub>3</sub>,<sup>11</sup> Cu(OTf)<sub>2</sub>,<sup>12</sup> TMSCl,<sup>13</sup> LiClO<sub>4</sub>,<sup>14</sup> LiBr.<sup>15</sup>



Scheme 1

Physical Properties of Indion 190 resin: macroporous resin, styrene DVB matrix, SO<sub>3</sub><sup>-</sup> functional group, particle size range 0.42-1.2, Max. Operating temp. 150 °C, total exchange capacity 4.7 meq/g. Some of these properties are similar to the properties of Amberlyst 15.


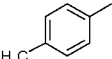
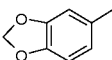
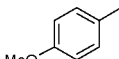
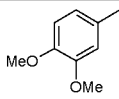
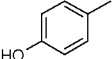
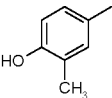
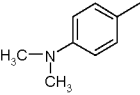
$\text{InBr}_3$ ,<sup>16</sup> Phenyl Pyruvic acid,<sup>17</sup>  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{HCl}$ ,<sup>18</sup> TMSI<sup>19</sup> and  $\text{CdCl}_2$ <sup>20</sup> have been used. Many of the above catalyst used are not ecofriendly and cause the problem during disposal. Further the methods used for synthesis of DHPM requires long reaction times, strong acidic condition, vigorous reaction conditions (high temperature) and they are difficult to handle on a large scale. The development of eco-friendly and recyclable catalytic system for Biginelli reaction is an active research area, in order to improve the reaction condition and yield. Hence we initiated the preparation of DHPM, by keeping in mind the development of green methodology and successfully attempted a single step efficient chemical method by using green catalyst, under mild condition.

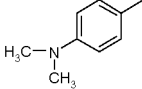
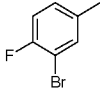
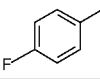
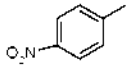
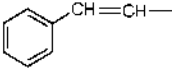






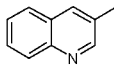


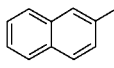
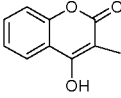
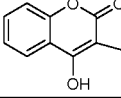
Here in, we report a simple efficient and effective protocol for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones by one pot three component cyclocondensation reaction of 1,3 dicarbonyl

compound (ethyl acetoacetate), aromatic aldehyde and urea using Indion 190 resin as a recyclable catalyst. An aldehydes, ethyl acetoacetate and urea in dichloromethane were stirred at reflux temperature in presence of Indion 190 resin. The reaction progress was monitored by TLC. After the completion of reaction, the reaction mixture and resin were separated by filtration. The solvent was removed under reduced pressure and the solid obtained was purified by recrystallisation from methanol. Isolated resin was washed with water, activated and reused for subsequent reaction. Physical and spectral data of known compounds are in agreement with those reported in the literature.<sup>20</sup>

A broad range of structurally diverse aromatic and heterocyclic aldehydes have been used in this condensation (Table 1).  $\alpha$ ,  $\beta$  unsaturated aldehyde react selectively with aldehyde functional group whereas acid sensitive heterocyclic aldehydes ex

Table 1. Indion 190 resin catalysed synthesis of Dihydropyrimidinones.

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	Time (h)	Yield	M.P. °C
1	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3	86	206-207
2	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3	92	214-216
3	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3	82	186-188
4	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.5	89	180-183
5	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.5	85	178-180
6	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.5	87	184-186
7	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.0	88	196-197
8	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.5	85	230-232

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	Time (h)	Yield	M.P. °C
9	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		S	3.0	90	248-250
10	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	2.0	85	199-200
11	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		S	2.0	89	156-158
12	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	1.5	84	207-208
13	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.0	81	227-230
14	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	2.0	85	202-203
15	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	2.0	87	210-212
16	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.0	82	181-183
17	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	2.0	89	193-194
18	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		S	2.0	86	167-169
19	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.0	79	213-215
20	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	2.5	89	246-248
21	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	2.0	90	256-257
22	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		S	2.5	88	242-243
23	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	1.5	92	182-185
24	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		O	3.0	76	278-279
25	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>		S	3.0	77	262-264
26	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	O	3.5	82	193

clusively gave dihydropyrimidones in high yield. We found that electron donating or withdrawing group on aromatic aldehydes gave almost good to excellent yield. Therefore the method can be use for wide range of reactants with different functional group. We have synthesized some novel compounds containing quinoline, pyrimidine, indole and coumarin units.

In conclusion, we have developed a simple, efficient and ecofriendly procedure for the synthesis of dihydropyrimidin-2(1H)-ones by condensation of ethyl acetoacetate, aldehydes and urea in presence of inexpensive and recyclable catalyst Indion 190 resin at mild reaction conditions.

### General Experimental Section

All commercial reagents are used as received without purification, and all solvents were reagent grade. The reaction mixture was stirred magnetically in a round bottom flask and was monitored by TLC using on 0.25 mm E-Merck silica gel 60 F<sub>254</sub> precoated glass plates, which were visualized with UV light, and then developed by using silica gel 60-120 mesh. Melting points were taken in open capillaries. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra in DMSO-*d*<sub>6</sub> were recorded on VXR-300 MHz using TMS as internal standard.

### General Procedure

A mixture of an aldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea or thiourea (15 mmol) and Indion 190 resin (2 gm) in dichloromethane (5 ml) was stirred at reflux temperature for the appropriate time (1.5-3.5 hr). After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure. The residue was washed with water and recrystallised from methanol.

Analytical and Spectral data for selected compounds.

#### 5-Ethoxycarbonyl-4-(3-1H-Indole)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (19)

IR (KBr): 3417, 3356, 3240, 2978, 1702, 1653,

1538, 1187, 1085, 870 cm<sup>-1</sup>

<sup>1</sup>H NMR DMSO-*d*<sub>6</sub> (δ-ppm): 9.17 (s, 1H, NH), 7.04 (s, 1H, NH), 8.48 (s, 1H, NH), 7.76 (s, 1H), 7.18-7.34 (m, 4H), 5.23 (d, 1H, *J* = 3.7 Hz), 3.97 (q, 2H, *J* = 7.2 Hz), 2.24 (s, 3H), 1.15 (t, 3H, *J* = 7.2 Hz)

<sup>13</sup>C NMR DMSO-*d*<sub>6</sub> (δ-ppm): 172.10, 155.25, 152.90, 136.90, 127.30, 123.20, 121.80, 119.10, 118.90, 111.15, 106.90, 104.35, 60.10, 34.15, 14.90, 13.90.

Elem. Anal. Calcd: C, 64.20; H, 5.72; N, 14.04; O, 16.04. Found: C, 63.89; H, 5.93; N, 14.37; O, 16.09.

#### 5-Ethoxycarbonyl-4-(3-quinoline)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (20)

IR (KBr): 3408, 3365, 3280, 1698, 1640, 1513, 1227, 779 cm<sup>-1</sup>

<sup>1</sup>H NMR DMSO-*d*<sub>6</sub> (δ-ppm): 9.25 (s, 1H, NH), 7.73 (s, 1H, NH), 8.32 (s, 1H), 7.63-7.79 (m, 4H), 7.80 (s, 1H), 5.12 (d, 1H, *J* = 2.8 Hz), 4.11 (q, 2H, *J* = 7.5 Hz), 2.28 (s, 3H), 1.09 (t, 3H, *J* = 7.5 Hz)

<sup>13</sup>C NMR DMSO-*d*<sub>6</sub> (δ-ppm): 172.50, 155.25, 153.35, 148.10, 147.15, 135.05, 135.05, 129.10, 127.30, 126.45, 126.10, 104.50, 60.10, 53.00, 14.90, 13.90.

Elem. Anal. Calcd: C, 65.58; H, 5.50; N, 13.50; O, 15.42. Found: C, 65.63; H, 5.61; N, 13.42; O, 15.37.

#### 5-Ethoxycarbonyl-4-(2-pyrimidine)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (21)

IR (KBr): 3413, 3385, 3245, 2965, 1709, 1658, 1540, 1235, 1090, 780 cm<sup>-1</sup>

<sup>1</sup>H NMR DMSO-*d*<sub>6</sub> (δ-ppm): 9.20 (s, 1H, NH), 7.65 (s, 1H, NH), 8.42 (d, 2H, *J* = 7.5 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 5.10 (d, 1H, *J* = 3.5 Hz), 4.02 (q, 2H, *J* = 7.0 Hz), 2.23 (s, 3H), 1.11 (t, 3H, *J* = 7.0 Hz).

<sup>13</sup>C NMR DMSO-*d*<sub>6</sub> (δ-ppm): 172.60, 168.70, 157.20, 155.85, 153.85, 119.90, 104.20, 60.10, 56.10, 15.15, 13.90

Elem. Anal. Calcd: C, 54.96; H, 5.38; N, 21.36; O, 18.30. Found: C, 54.84; H, 5.29; N, 22.04; O, 18.75.

**5-Ethoxycarbonyl-4-(4-hydroxyl-2H(1)-benzopyran-2-one-3-yl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (24)**

**IR (KBr):** 3389, 3240, 2943, 1721, 1705, 1619, 1562, 1235, 1123, 810  $\text{cm}^{-1}$

**<sup>1</sup>H NMR DMSO-*d*<sub>6</sub> ( $\delta$ -ppm):** 11.85 (s, 1H, OH), 9.80 (s, 1H, NH), 7.69 (s, 1H, NH), 7.30-7.80 (m, 4H), 4.85 (d, 1H,  $J = 3.5$  Hz), 4.23 (q, 2H,  $J = 6.8$  Hz), 2.35 (s, 3H), 1.21 (t, 3H,  $J = 6.8$  Hz)

**<sup>13</sup>C NMR DMSO-*d*<sub>6</sub> ( $\delta$ -ppm):** 172.50, 171.20, 164.15, 155.10, 153.60, 152.20, 131.15, 129.80, 122.30, 121.10, 117.80, 116.25, 94.50, 60.20, 43.25, 15.15, 14.15

**Elem. Anal. Calcd:** C, 59.30; H, 4.68; N, 8.14; O, 27.88. **Found:** C, 59.24; H, 4.76; N, 8.07; O, 28.01.

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