

V. Naveen Kumar, P. Someshwar, P. Narsimha Reddy, Y. Thirupathi Reddy, B. Rajitha\*

Department of Chemistry, National Institute of Technology, Warangal, India

Fax: 0091-9712-2459547; E-mail: [rajitabhargavi@yahoo.com](mailto:rajitabhargavi@yahoo.com)

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The condensation reaction of aldehydes,  $\beta$ -ketoesters and urea/thiourea in presence of a catalytic amount of  $\text{CuPy}_2\text{Cl}_2$  complex proceeded under very mild reaction conditions in high yield (80-90%).

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### Introduction.

There has been considerable interest in the development of preparative methods for the products of dihydropyrimidines-2(1*H*)-ones (DHPMS). This seems to be because of their pharmacologically importance as well as to understand the mechanism of reaction involved in what is commonly called the Bigenelli condensation [1]. The DHPMS compounds have shown promising activity as calcium channel blockers, antihypertensive agents,  $\alpha$ -1-a-antagonists, and neuropeptide Y(NPY) antagonists [2]. In addition, the dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products, including the batzelladine alkaloids, which have been found to be potent HIVgp-120-cd<sub>4</sub> inhibitors [3]. Many synthetic methods for the preparing DHPMS compounds under classical reflux [4a-h] (or) solvent free conditions [5-11] and microwave [12-15] (or) ultrasonic irradiation [16-17] have been reported.

Interest in the transition metal complex-catalyzed Bigenelli reaction has been growing during the last few years. Copper, palladium, nickel and cobalt derivatives have proved to display good catalytic activity toward this important type of condensation reaction [18-19]. With such catalysts, the reaction is completed in a shorter time and in excellent yield, as compared with previously reported methods [20]. Now, we found that an analogous condensation reaction can be conveniently performed under neutral and mild conditions in the presence of a catalytic amount of  $\text{CuPy}_2\text{Cl}_2$  [21-22]. Catalytic improvement is apparently due to the presence of two pyridine rings, which increases the electron deficiency on the nitrogen hence it is efficiently act as a Lewis acid.

### Results and Discussion.

The Bigenelli condensation reaction was carried out at 40-50 °C under a nitrogen atmosphere using an aldehyde, urea and ethyl acetoacetate to  $\text{CuPy}_2\text{Cl}_2$  molar ratio of 100:1. An aldehyde,  $\beta$ -ketoester and urea/thiourea (1:1:1.5mmol) were added into the mixture of  $\text{CuPy}_2\text{Cl}_2$  (0.01 mmol) dissolved in anhydrous acetonitrile (10 mL). The homogeneous reaction mixture was stirred at 40-50 °C for 1-3 hour. The solvent was evaporated under reduced pressure. The solid thus obtained was washed with ice-

cold water and recrystallized from ethanol to afford pure product in 80-90% yield.

Scheme I

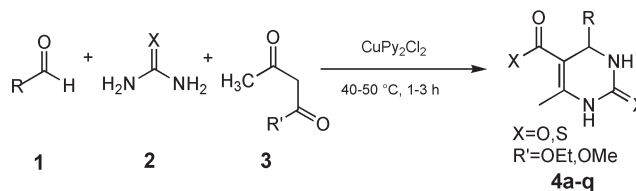


Table 1

$\text{CuPy}_2\text{Cl}_2$  Catalyzed Efficient Synthesis of Dihydropyrimidin-2(1*H*)-ones

Product	R	R <sup>1</sup>	X	Time (h)	Yield (%) [a]	m.p. (°C)
<b>4a</b> [4a]	C <sub>6</sub> H <sub>5</sub>	OEt	O	1.0	90	200-202
<b>4b</b> [4a]	4-(Cl)-C <sub>6</sub> H <sub>4</sub>	OEt	O	3.0	82	209-211
<b>4c</b> [4a]	4-(NO <sub>2</sub> )-C <sub>6</sub> H <sub>4</sub>	OEt	O	1.5	89	205-207
<b>4d</b> [4a]	3-(NO <sub>2</sub> )-C <sub>6</sub> H <sub>4</sub>	OEt	O	3.0	85	225-227
<b>4e</b> [4d]	3-(Cl)-C <sub>6</sub> H <sub>4</sub>	OEt	O	2.5	88	215-217
<b>4f</b> [4a]	4-(OCH <sub>3</sub> )-C <sub>6</sub> H <sub>4</sub>	OEt	O	2.5	82	198-200
<b>4g</b> [4a]	3-(NO <sub>2</sub> )-C <sub>6</sub> H <sub>4</sub>	OEt	S	2.0	85	203-205
<b>4h</b> [4a]	4-(OH)-C <sub>6</sub> H <sub>4</sub>	OEt	O	2.0	88	179-181
<b>4i</b> [4b]	4-(OH)-C <sub>6</sub> H <sub>4</sub>	OEt	S	3.0	90	195-198
<b>4j</b> [4b]	4-(OCH <sub>3</sub> )-C <sub>6</sub> H <sub>4</sub>	OEt	S	3.0	89	137-139
<b>4k</b> [4a]	4-(NO <sub>2</sub> )-C <sub>6</sub> H <sub>4</sub>	OMe	O	2.5	90	235-236
<b>4l</b> [4a]	4-(OCH <sub>3</sub> )-C <sub>6</sub> H <sub>4</sub>	OMe	O	3.0	84	191-193
<b>4m</b> [4c]	2-furyl	OEt	O	2.5	89	204-206
<b>4n</b> [4a]	C <sub>6</sub> H <sub>5</sub>	OMe	O	3.0	90	214-216
<b>4o</b> [4d]	3-(Cl)-C <sub>6</sub> H <sub>4</sub>	OMe	O	2.0	90	207-09
<b>4p</b> [4a]	4-(Cl)-C <sub>6</sub> H <sub>4</sub>	OMe	O	3.0	89	205-207
<b>4q</b> [4a]	4-(OH)-C <sub>6</sub> H <sub>4</sub>	OMe	O	3.0	88	175-177

[a] Yields refer to pure solid products, all products were characterized by comparison of their physical and spectral data with those of authentic samples.

### EXPERIMENTAL

#### General Procedure.

A solution of an appropriate  $\beta$ -ketoester (1 mmol), corresponding aldehyde (1 mmol), urea or thiourea (1.5 mmol), and  $\text{CuPy}_2\text{Cl}_2$  (0.01 mmol) in anhydrous acetonitrile (10 mL) was stirred at 40-50 °C for a certain period of time as required to com-

plete the reaction (TLC). The solvent was removed under reduced pressure to yield a solid, which was washed thoroughly with water, filtered and recrystallized from ethanol to afford pure product.  $^1\text{H}$  NMR and MS data for compounds **4a-q** are given below:

**4a:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.10 (t, 3H,  $J$  = 6.82 Hz,  $\text{CH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$ ), 3.92 (q, 2H,  $J$ =6.74,  $\text{OCH}_2$ ), 5.11 (d, 1H,  $J$ =3.05 Hz,  $\text{C}_4\text{-H}$ ), 7.71 (bs, 1H, NH), 7.20-7.35 (m, 5H, Ar-H), 9.16 (bs, 1H, NH); MS:  $m/z$ =261.1 ( $\text{M}^+$ ).

**4b:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.07 (t, 3H,  $J$  = 6.8 Hz,  $\text{CH}_3$ ), 2.20 (s, 3H,  $\text{CH}_3$ ), 3.94 (q, 2H,  $J$ =7.2 Hz,  $\text{OCH}_2$ ), 5.02 (s, 1H,  $\text{C}_4\text{-H}$ ), 6.64 (d, 2H,  $J$  = 8.2 Hz, Ar-H), 7.02 (d, 2H,  $J$ =8.2 Hz, Ar-H), 7.57 (bs, 1H, NH), 9.10 (bs, 1H, NH); MS:  $m/z$ =295 ( $\text{M}^+$ ), 265.

**4c:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.07 (t, 3H,  $J$  = 6.8 Hz,  $\text{CH}_3$ ), 2.24 (s, 3H,  $\text{CH}_3$ ), 3.96 (q, 2H,  $J$ =5.4 Hz,  $\text{OCH}_2$ ), 5.25 (s, 1H,  $\text{C}_4\text{-H}$ ), 7.50 (d, 2H,  $J$  = 7.3 Hz, Ar-H), 7.85 (bs, 1H, NH), 8.20 (d, 2H,  $J$ =7.2Hz, Ar-H), 9.31 (bs, 1H, NH); MS:  $m/z$ =306.29 ( $\text{M}^+$ ).

**4d:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.06 (t, 3H,  $J$  = 7.01 Hz,  $\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 3.98 (q, 2H,  $J$ =4.6 Hz,  $\text{OCH}_2$ ), 5.30 (d, 1H,  $J$ =2.64 Hz,  $\text{C}_4\text{-H}$ ), 7.60-7.70 (m, 2H, Ar-H), 7.95 (bs, 1H, NH), 8.11-8.17 (m, 2H, Ar-H), 9.38 (bs, 1H, NH); MS:  $m/z$ =306 ( $\text{M}^+$ ).

**4e:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.05 (t, 3H,  $J$  = 6.83 Hz,  $\text{CH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$ ), 3.96 (q, 2H,  $J$ =7.2 Hz,  $\text{OCH}_2$ ), 5.12 (s, 1H,  $\text{C}_4\text{-H}$ ), 6.65-6.92 (m, 3H, Ar-H), 7.05 (s, 1H, Ar-H), 7.61 (bs, 1H, NH), 9.13 (bs, 1H, NH); MS:  $m/z$ =295 ( $\text{M}^+$ ).

**4f:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.10 (t, 3H,  $J$  = 7.05 Hz,  $\text{CH}_3$ ), 2.16 (s, 3H,  $\text{CH}_3$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.96 (q, 2H,  $J$ =7.22 Hz,  $\text{OCH}_2$ ), 5.08 (d, 1H,  $\text{C}_4\text{-H}$ ), 6.86 (d, 2H,  $J$  = 8.52 Hz, Ar-H), 7.14 (d, 2H,  $J$ =8.54 Hz, Ar-H), 7.67 (bs, 1H, NH), 9.13 (bs, 1H, NH); MS:  $m/z$ =291.3 ( $\text{M}^+$ ).

**4g:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.06 (t, 3H,  $J$  = 7.01 Hz,  $\text{CH}_3$ ), 2.25 (s, 3H,  $\text{CH}_3$ ), 3.97 (q, 2H,  $J$ =4.6 Hz,  $\text{OCH}_2$ ), 5.29 (d, 1H,  $J$ =2.64 Hz,  $\text{C}_4\text{-H}$ ), 7.59-7.68 (m, 2H, Ar-H), 7.93 (bs, 1H, NH), 8.10-8.15 (m, 2H, Ar-H), 9.36 (bs, 1H, NH); MS:  $m/z$ =322 ( $\text{M}^+$ ), 292.

**4h:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.07 (t, 3H,  $J$  = 6.9 Hz,  $\text{CH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$ ), 3.95 (q, 2H,  $J$ =7.12 Hz,  $\text{OCH}_2$ ), 5.05 (d, 1H,  $J$ =2.78 Hz,  $\text{C}_4\text{-H}$ ), 6.68 (d, 2H,  $J$  = 8.42 Hz, Ar-H), 7.04 (d, 2H,  $J$ =8.49 Hz, Ar-H), 7.65 (bs, 1H, NH), 9.13 (bs, 1H, NH), 9.33 (bs, 1H, OH); MS:  $m/z$ =277 ( $\text{M}^+$ ), 247, 246.

**4i:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.07 (t, 3H,  $J$  = 6.95 Hz,  $\text{CH}_3$ ), 2.24 (s, 3H,  $\text{CH}_3$ ), 3.96 (q, 2H,  $J$ =7.16Hz,  $\text{OCH}_2$ ), 5.13 (d, 1H,  $J$ =2.75 Hz,  $\text{C}_4\text{-H}$ ), 6.67 (d, 2H,  $J$  = 8.46 Hz, Ar-H), 7.06 (d, 2H,  $J$ =8.47 Hz, Ar-H), 7.68 (bs, 1H, NH), 9.15 (bs, 1H, NH), 9.35 (bs, 1H, OH); MS:  $m/z$ =293 ( $\text{M}^+$ ), 263, 262.

**4j:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.05 (t, 3H,  $J$  = 7.25 Hz,  $\text{CH}_3$ ), 2.08 (s, 3H,  $\text{CH}_3$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.94 (q, 2H,  $J$ =7.25 Hz,  $\text{OCH}_2$ ), 5.02 (d, 1H,  $\text{C}_4\text{-H}$ ), 6.82 (d, 2H,  $J$  = 8.55 Hz, Ar-H), 7.11 (d, 2H,  $J$ =8.57 Hz, Ar-H), 7.65(bs, 1H, NH), 9.11 (bs, 1H, NH); MS:  $m/z$ =307.39 ( $\text{M}^+$ ).

**4k:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  2.28 (s, 3H,  $\text{CH}_3$ ), 3.53 (s, 3H,  $\text{OCH}_3$ ), 5.25 (d, 1H,  $J$  = 3.17 Hz,  $\text{C}_4\text{-H}$ ), 7.50 (d, 2H,  $J$  = 7.3 Hz, Ar-H), 7.85 (bs, 1H, NH), 8.20 (d, 2H,  $J$ =7.2Hz, Ar-H), 9.31 (bs, 1H, NH); MS:  $m/z$ =292.08 ( $\text{M}^+$ ), 274, 232, 186.

**4l:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  2.18 (s, 3H,  $\text{CH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 3.91 (s, 3H,  $\text{OCH}_3$ ), 5.13 (d, 1H,  $\text{C}_4\text{-H}$ ), 6.88 (d, 2H,  $J$  = 8.46 Hz, Ar-H), 7.17(d, 2H,  $J$ =8.49 Hz, Ar-H), 7.67 (bs, 1H, NH), 9.13 (bs, 1H, NH); MS:  $m/z$ =277.2 ( $\text{M}^+$ ).

**4m:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  1.07 (t, 3H,  $J$  = 6.8 Hz,  $\text{CH}_3$ ), 2.20 (s, 3H,  $\text{CH}_3$ ), 3.94 (q, 2H,  $J$ =7.2 Hz,  $\text{OCH}_2$ ), 5.02 (s, 1H,  $\text{C}_4\text{-H}$ ), 6.64 (m, 3H, Ar-H), 7.57 (bs, 1H, NH), 9.10 (bs, 1H, NH); MS:  $m/z$ =251.2 ( $\text{M}^+$ ).

**4n:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ): 2.26 (s, 3H,  $\text{CH}_3$ ), 3.54 (s, 3H,  $\text{OCH}_3$ ), 5.15 (d, 1H,  $J$ =3.13 Hz,  $\text{C}_4\text{-H}$ ), 7.24-7.36 (m, 5H, Ar-H), 7.78 (bs, 1H, NH), 9.16 (bs, 1H, NH); MS:  $m/z$ =247.09 ( $\text{M}^+$ ).

**4o:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  2.32 (s, 3H,  $\text{CH}_3$ ), 3.55 (s, 3H,  $\text{OCH}_3$ ), 5.38 (s, 1H, CH,  $\text{C}_4\text{-H}$ ), 7.66 (s, 1H, Ar-H), 7.91 (bs, 1H, NH), 8.01-8.12 (m, 3H, Ar-H), 9.41 (bs, 1H, NH); MS:  $m/z$ =281.7 ( $\text{M}^+$ ).

**4p:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  2.34 (s, 3H,  $\text{CH}_3$ ), 3.63 (s, 3H,  $\text{OCH}_3$ ), 5.40 (s, 1H, CH,  $\text{C}_4\text{-H}$ ), 7.63-7.72 (m, 2H, Ar-H), 7.95 (bs, 1H, NH), 8.11-8.18 (m, 2H, Ar-H), 9.41 (bs, 1H, NH); MS:  $m/z$ =281.7 ( $\text{M}^+$ ).

**4q:**  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ):  $\delta$  2.26 (s, 3H,  $\text{CH}_3$ ), 3.85 (s, 3H,  $\text{OCH}_2$ ), 5.26 (d, 1H,  $J$ =2.78 Hz,  $\text{C}_4\text{-H}$ ), 6.71 (d, 2H,  $J$  = 8.38 Hz, Ar-H), 7.24 (d, 2H,  $J$ =8.36 Hz, Ar-H), 7.63 (bs, 1H, NH), 9.11(bs, 1H, NH), 9.32 (bs, 1H, OH); MS:  $m/z$ =263.25 ( $\text{M}^+$ ).

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