CHAPTER-III

STANNOUS CHLORIDE CATALYZED SYNTHESIS
OF DIHYDROPYRIMIDINES UNDER SOLVENT FREE CONDITION

III. A. INTRODUCTION

A multicomponent reaction (MCR) is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses and they offer significant advantages over conventional linear-type syntheses. Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry. One prominent MCR that produces an interesting class of nitrogen heterocycles is the venerable Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli
reported the first synthesis of 3,4-dihydropyrimidin-2(1H)-ones of type 4 by a very simple one pot condensation reaction of an aromatic aldehyde, urea and ethylacetoacetate\textsuperscript{1}. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. A representative example of the Biginelli reaction is shown in the following scheme-\textbf{1}.

![Scheme 1: Biginelli dihydropyrimidine synthesis](image)

\textbf{R} = C_6H_5, \textbf{R}_1 = CH_3, \textbf{R}_2 = C_2H_5, \textbf{X} = O

**III. B. MECHANISM OF BIGINELLI REACTION**

Mechanism of the Biginelli reaction involves two steps: (1) formation of acyliminium ion and (2) addition of $\beta$-ketoester to an acyliminium ion followed by cyclization-dehydration steps leading to Biginelli dihydropyrimidines. Recently, the mechanism of the Biginelli reaction was reinvestigated in detail by Kappe.\textsuperscript{2} He proposed and established that the first step in this reaction, the acid catalysed formation of an acyl imine
intermediate 3A formed by reaction of the aldehyde with urea 3, is the key rate limiting step. Interception of the iminium 3 by ethylacetooacetate 2 produces an open chain ureide 4A which subsequently cyclises to the dihydropyrimidinones (Scheme-2).

1) Formation of acyliminium ion:
2) Addition, cyclization and dehydration steps:

Scheme-2: Proposed Mechanism of Biginelli reaction

III. C. BIOLOGICALLY ACTIVE DIHYDROPYRIMIDINES

Dihydropyrimidinones and their derivatives have attracted considerable interest because of their wide spectrum of therapeutic and pharmacological properties. As shown in scheme-3,dihydropyrimidinone 5 has excellent antiviral activity against the viruses of trachoma group and also exhibits antibacterial activity.
Pyrimidine-5-carboxamides of type 6 are reported to possess anticarcinogenic activity\(^5\), anti-inflammatory\(^6\) and analgesic activity.\(^7\) Recently, some of the dihydropyrimidines are also found to possess excellent antifungal activity\(^8\) against the radial growth of three fungal species viz.,
*Trichoderma hammatum*, *Trichoderma koningii* and *Aspergillus niger*. Appropriately functionalized DHPM analogs 7 and 8 have emerged as orally active antihypertensive agents.\(^9a\)\(^b\) Notably, Monastrol 9 is a novel cell-permeably molecule that blocks normal bipolar spindle assembly in mammalian cells causing cell cycle arrest and is considered a lead for the development of new anticancer drugs.\(^10\) The compound 10 has α1a adrenoceptor-selective antagonists.\(^11\) Moreover, several alkaloids containing the dihydropyrimidinone core unit have been isolated from marine source, which also shows interesting biological properties.\(^12\) Among these most notably are the batzelladine alkaloids 11, which have been found to be potent HIV gp-120-CD4 inhibitors.\(^13\) Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.

### III. D. SYNTHETIC STRATEGIES FOR DIHYDROPYRIMIDINES

The simple and direct methods for the synthesis of dihydropyrimidines, first reported by Biginelli in 1893, suffer from low yields (20–50%) of products in the cases of substituted aromatic and aliphatic aldehydes. This has led to the development of multistep synthetic strategies that produce somewhat better yields but lack the simplicity of one-pot, one-step synthesis.

The Lewis acid-catalyzed Biginelli reaction has also achieved considerable success. The use of a number of catalysts such as BF\(_3\)Et\(_2\)O,\(^{14a}\) FeCl\(_3\) ·6H\(_2\)O,\(^{14b}\) LiBr,\(^{14c}\) ZnCl\(_2\),\(^ {14d}\) BiCl\(_3\),\(^ {14e}\) LaCl\(_3\)·7H\(_2\)O,\(^ {14f}\) Mn(OAc)\(_3\)·2H\(_2\)O,\(^ {14g}\)
InCl$_3$, $^{14h}$ Cu(OTf)$_2$, $^{14i}$ lanthanide triflates, $^{14j}$ ZrCl$_4$, $^{14k}$ Yb$_{III}$ resin, $^{14l}$ CeCl$_3$·7H$_2$O, $^{14m}$ LiClO$_4$, $^{14n}$ RuCl$_3$, $^{14o}$ SmI$_2$, $^{14p}$ Sr(OTf)$_2$, $^{14q}$ La(OTf)$_3$, or Yb(OTf)$_3$ in the presence of a chiral Yb catalyst $^{14r}$ has been reported to be effective for this one-pot reaction.

With the emergence of high-throughput screening in the pharmaceutical industry over a decade ago, synthetic chemists were faced with the challenge of preparing large collections of molecules to satisfy the demand for new screening compounds. The unique exploratory power of multicomponent reactions such as the Biginelli three-component reaction was soon recognized to be extremely valuable to produce compound libraries in a time and cost-effective manner. D. Dallinger et al. $^{15}$ describes synthetic advances for the construction of Biginelli libraries via solution- and solid-phase strategies that are amenable to a high-throughput or combinatorial format (scheme-4).
Scheme 4 Solid-phase synthesis of DHPM-5-carboxylic acids

A zeolite catalyzed, single step and environmentally friendly process for the synthesis of dihydropyrimidinones 16, a pharmacologically important class of compounds, is also reported.\(^\text{16}\)

\[
\text{Scheme-5: Zeolite catalysed synthesis of dihydropyrimidine}
\]

Reusability of the catalyst and the ease of separation of pure product selectively and in high yields in comparison to the classical Biginelli reaction, are a few of the unique features of this process.
The use of PEG-400 as a promoter for the synthesis of 3,4-dihydropyrimidinones 20 under mild and neutral solvent-free conditions is also reported.\textsuperscript{17} This procedure offers several advantages, such as (i) PEG is a cost effective and environmentally benign reagent, (ii) green synthesis (avoiding hazardous and toxic organic solvents for work up) and (iii) applicability to a wide range of substituted aldehydes. Furthermore, better yields, simple reaction conditions, shorter reaction times and easy work up make this a green, facile and superior method for the synthesis of 3,4-dihydropyrimidinones (scheme-6).

\textbf{Scheme-6}: PEG-promoted synthesis of 3,4-dihydropyrimidinones under solvent-free conditions

Chiral phosphoric acids\textsuperscript{18} have been reported to effectively catalyze the asymmetric Biginelli reaction by forming chiral \textit{N}-acyliminium phosphate ion pairs 25, to which enantioselective addition of \(\beta\)-keto esters 23 should
occur to generate optically active 24 via the enantioenriched intermediate 26 (scheme-7).

**Scheme-7: Proposed Chiral Phosphoric Acid-Catalyzed Biginelli Reaction**

The optimal chiral phosphoric acid, derived from H8-binol, afforded the reaction in high yields with excellent enantioselectivities of up to 97% ee. A wide variety of substrates, including aldehydes and β-keto esters, could be tolerated. This reaction has an advantage of avoiding the contamination of transition metals in the manufacture of the medicinally relevant chiral 3,4-dihydropyrimidin-2-(1H)-ones.

Biginelli compounds 3,4-dihydropyrimidine-2-(1H)-ones 29 are synthesized in high yields via eco-friendly simple reaction procedure using Lactic acid: organocatalyst19(scheme-8). This new method is green and is free of
formation of any hazardous byproducts. The process has significant advantages over other reported method.

\[
\begin{align*}
\text{H} & \quad \text{O} & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{C} & \quad \text{O} & \quad \text{H}_2\text{N} & \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad \text{N} & \quad \text{H} & \quad \text{X}
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \quad \text{C} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{R}_2 & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Lactic acid} & \quad \text{EtOH, reflux}
\end{align*}
\]

**Scheme-8**: Lactic acid catalysed synthesis of 3,4-dihydropyrimidin-2-(1\(H\))-ones.

Chavan and his co-workers developed a simple, efficient and environmentally friendly process for synthesis of 3,4-dihydropyrimidinones 31 using a one pot three-component condensation of aromatic aldehydes, \(\beta\)-dicarbonyl compounds, and urea/thiourea in the presence of ionic liquid.\(^\text{20}\)

The cost-effective, new generation ionic liquid (IL), tri-(2-hydroxyethyl) ammonium acetate 30 was used as both solvent and catalyst (scheme-9). The reactions were carried out using both conventional heating and microwave energy. Application of IL technology with microwave energy represents an attractive and rapid alternative to the conventional acid base catalyzed thermal processes.

**Scheme-9**: Synthesis of ionic liquid tri-(2-hydroxyethyl) ammonium acetate.
Scheme 9: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones.

Al$_2$O$_3$/CH$_3$SO$_3$H (AMA) have been reported to be an efficient catalyst for the three-component condensation reaction of aldehyde, 1,3-dicarbonyl compound and urea/thiourea to afford the corresponding 3,4-dihydropyrimidin-2-(1H)-ones 32 in high isolated yield, which works very effectively regardless of the electronic nature of the substituent on the ring, although electron-donating groups precipitate the rate of reaction. The catalyst is recyclable and stable at room temperature, and the reaction protocol is simple, cost-effective and gives good isolated yield with high purity$^{21}$ (scheme-10).

Scheme 10: One-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and thiones using Al$_2$O$_3$/CH$_3$SO$_3$H (AMA).
Recently, a one-pot variant of Biginelli-type reaction\textsuperscript{22} using enaminone \textsuperscript{33} promoted by TMSCl was also reported (Scheme-11).

\begin{center}
\begin{tikzpicture}
  \node (1) at (0,0) {$\text{CHO}$};
  \node (2) at (1.5,0) {$+ \text{H}_2\text{N}-\text{NH}_2$};
  \node (3) at (3,0) {$+ \text{R}^2\text{R}^3\text{N}$};
  \node (4) at (4.5,0) {$\text{TMSCl}$};
  \node (5) at (6,0) {$\text{DMF, 85}^\circ\text{C}$};
  \node (6) at (7.5,0) {$\rightarrow \text{R}^2\text{R}^3\text{N}$};
  \node (7) at (9,0) {$\text{O}$};
  \node (8) at (9.5,0) {$\text{N}$};
  \node (9) at (10,0) {$\text{H}_2\text{N}$};
  \node (10) at (10.5,0) {$\text{NH}_2$};
  \node (11) at (12,0) {$\text{X}$};
  \node (12) at (13.5,0) {$\text{R}^1$};

  \node (13) at (15,0) {$\text{C}$};
  \node (14) at (15.5,0) {$\text{H}$};
  \node (15) at (16,0) {$\text{O}$};

  \node (16) at (18,0) {$\text{H}_2\text{N}$};
  \node (17) at (18.5,0) {$\text{NH}_2$};
  \node (18) at (19,0) {$\text{N}$};
  \node (19) at (19.5,0) {$\text{H}_2\text{N}$};
  \node (20) at (20,0) {$\text{NH}_2$};
  \node (21) at (20.5,0) {$\text{S}$};

  \node (22) at (22,0) {$\text{R}^1$};
  \node (23) at (22.5,0) {$\text{R}^2$};
  \node (24) at (23,0) {$\text{S}$};

  \node (25) at (25,0) {$\text{O}$};
  \node (26) at (25.5,0) {$\text{N}$};
  \node (27) at (26,0) {$\text{H}$};
  \node (28) at (26.5,0) {$\text{N}$};
  \node (29) at (27,0) {$\text{H}$};

  \node (30) at (27.5,0) {$\text{R}^3$};
  \node (31) at (28,0) {$\text{S}$};

  \node (32) at (29,0) {$\text{R}^2$};

  \draw (1) -- (2) -- (3) -- (4) -- (5) -- (6) -- (7) -- (8) -- (9) -- (10) -- (11) -- (12);
  \draw (13) -- (15) -- (18) -- (20) -- (24) -- (21) -- (23) -- (22) -- (25) -- (26) -- (27) -- (28) -- (29) -- (30) -- (31) -- (32);
\end{tikzpicture}
\end{center}

**Scheme-11**: TMSCl promoted synthesis of dihydropyrimidine

Most recently, Shen \textit{et al} developed an efficient one-pot synthesis of 4,5,6-triaryl-3,4-dihydropyrimidin-2(1H)-ones \textsuperscript{35, 36} via a three-component Biginelli-type condensation of aldehyde, 2-phenylacetophenone, and urea/thiourea in the presence of a catalytic amount of t-BuOK (20 mol %).\textsuperscript{23} The reactions proceeded efficiently at 70\textdegree C to afford the desired products in moderate to good yields (scheme-12).

\begin{center}
\begin{tikzpicture}
  \node (1) at (0,0) {$\text{R}^1\text{H}$};
  \node (2) at (1.5,0) {$+ \text{R}^2\text{H}$};
  \node (3) at (3,0) {$+ \text{R}^3\text{H}$};
  \node (4) at (4.5,0) {$\text{H}_2\text{N}-\text{NH}_2$};
  \node (5) at (6,0) {$\text{t-BuOK(20 mol\%) }$};
  \node (6) at (7.5,0) {$\text{EtOH, 70}^\circ\text{C}$};
  \node (7) at (9,0) {$\rightarrow \text{R}^1\text{R}^2\text{R}^3\text{N}$};
  \node (8) at (10,0) {$\text{O}$};
  \node (9) at (10.5,0) {$\text{N}$};
  \node (10) at (11,0) {$\text{H}_2\text{N}$};
  \node (11) at (11.5,0) {$\text{NH}_2$};
  \node (12) at (12,0) {$\text{S}$};

  \node (13) at (14,0) {$\text{R}^1$};
  \node (14) at (14.5,0) {$\text{R}^2$};
  \node (15) at (15,0) {$\text{S}$};

  \node (16) at (17,0) {$\text{R}^2$};

  \draw (1) -- (2) -- (3) -- (4) -- (5) -- (6) -- (7) -- (8) -- (9) -- (10) -- (11) -- (12) -- (13) -- (14) -- (15) -- (16);
\end{tikzpicture}
\end{center}

**Scheme-12**: Bronsted Base catalysed synthesis of Dihydropyrimidine
The use of other active methylene compounds in addition to β-ketoester in classic Biginelli reaction has emerged as one of the hot research areas in terms of the preparation of various novel dihydropyrimidinones. Just as the Biginelli reaction operates in the presence of Lewis acid or protic acid, these MCR reactions for the preparation of novel dihydropyrimidinones using various active methylene compounds, such as 5,5-dimethyl-1,3-cyclohexanedione,\textsuperscript{24} 1,3-cyclohexanedione,\textsuperscript{25} 1-tetralone,\textsuperscript{25-27} acetophenone,\textsuperscript{27} cyclopentanone,\textsuperscript{28} and aliphatic aldehydes,\textsuperscript{29} were also developed to be carried out using a Lewis or protic acid such as HCl, TMSCl/NaI, FeCl\textsubscript{3}, ZnI\textsubscript{2}, YbCl\textsubscript{3} and BF\textsubscript{3}.

**III. E. PRESENT WORK, RESULTS & DISCUSSION**

The new methodologies in all the reported methods of Biginelli reactions use only the β-ketoesters such as ethyl acetoacetate or methylacetoacetate and variations are designed only in the structures of the substituted aldehydes. As a result, the structures of known dihydropyrimidines either in improved yields or by the application of new techniques are always reported. From this viewpoint, we initiate a systematic investigation to look into the application of β-oxodithioesters in Biginelli reactions under solvent free conditions to synthesize the hitherto unreported dihydropyrimidinones in excellent yields.

β-oxodithioesters \textbf{39} are generally prepared by reacting any active methylene compound with CS\textsubscript{2} in the presence of a suitable base followed by alkylation with either dimethylsulfate or methyl iodide. This method gives poor yields
and also mixtures of dithioesters and ketene dithioacetals. Thus improved yields of $\beta$-oxodithioesters 39 are obtained by treating active methylene compounds 37 with (S,S)-dimethyl trithiocarbonate 38 in the presence of NaH\textsuperscript{30} (scheme-13).

$$\text{R}=\text{CH}_3, \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{Me}, \text{C}_6\text{H}_4\text{OMe}, \text{C}_6\text{H}_4\text{Cl}.$$  

**Scheme-13.** Synthesis of $\beta$-oxodithioester from active methylene compound and dimethyl trithiocarbonate

As a part of our programme towards green synthesis, we describe herein a simple and practical method for the synthesis of dihydropyrimidinones by Biginelli protocol using catalytic amount of SnCl\textsubscript{2}.2H\textsubscript{2}O under solvent-free conditions (scheme-14).

**Scheme-14.** Multicomponent synthesis of dihydropyrimidine

The reaction of benzaldehyde 40\textsubscript{a}, urea 41, and $\beta$-oxodithioester 39\textsubscript{a} was first tested with use of 20 mol\% stannous chloride as the catalyst at room
temperature. After 20 min the whole reaction mixture forms a paste that made it impossible to continue the stirring under room temperature. It was then warmed to 100°C, when the paste turned to a homogeneous liquid. Stirring was continued at this temperature for 1 h (monitored by TLC). The reaction went smoothly and the corresponding dihydropyrimidine 42a was obtained in 75% yield (Table 1). The yield was still as high as 75% even when the amount of SnCl₂ was reduced from 20 mol % to 10 mol %. The structure of 5-Methylmercaptocarbonyl-4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one (42a) was confirmed with the help of analytical and spectroscopic data as follows:

5-Methylmercaptocarbonyl-4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one (42a): Bright yellow powder. m.p.198–200°C. ¹H NMR (300 MHz, CDCl₃, δ ppm) 2.30 (s, 3H), 5.87 (d, J = 2.7 Hz, 1H), 6.32 (s, 1H, NH), 7.28–7.44 (m, 10H), 7.61 (s, 1H, NH); ¹³C NMR (75.5 MHz, CDCl₃, δ ppm) 20.5, 60.9, 119.4, 127.2, 128.1, 128.2, 128.7, 128.8, 129.9, 134.6, 136.5, 141.7, 152.6, 227.0; IR (KBr) (ν max, cm⁻¹) 1226, 1629, 1700, 3084, 3198 cm⁻¹; MS m/z 340 (M⁺). Anal. Calcd for C₁₈H₁₆N₂O₂S₂: C, 63.50; H, 4.74; N, 8.23; S, 18.84. Found: C, 63.58; H, 4.79; N, 8.30; S, 18.74.

The same process was successfully extended to a wide range of structurally varied aldehydes, urea and β-oxodithioesters to afford the corresponding hitherto unreported dihydropyrimidinones 42b–o in good yields (table-1). The use of 5 mol % of catalyst caused a slight decrease in the yield.
Table-1. SnCl\(_2\) Catalyzed Multicomponent Reaction: Preparation of Dihydropyrimidines under solvent free conditions

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 & \quad \text{Product} & \quad \text{Yield(\%)} \\
1 & \text{C}_6\text{H}_5 & \text{C}_6\text{H}_5 & 42a & 75 \\
2 & \text{C}_6\text{H}_5 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 42b & 75 \\
3 & \text{C}_6\text{H}_5 & 4\text{-ClC}_6\text{H}_5 & 42c & 73 \\
4 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & \text{C}_6\text{H}_5 & 42d & 71 \\
5 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 42e & 73 \\
6 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 4\text{-ClC}_6\text{H}_5 & 42f & 80 \\
7 & 4\text{-ClC}_6\text{H}_5 & \text{C}_6\text{H}_5 & 42g & 75 \\
8 & 4\text{-ClC}_6\text{H}_5 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 42h & 82 \\
9 & 4\text{-ClC}_6\text{H}_5 & 4\text{-ClC}_6\text{H}_5 & 42i & 76 \\
10 & 4\text{-CH}_3\text{C}_6\text{H}_5 & \text{C}_6\text{H}_5 & 42j & 70 \\
11 & 4\text{-CH}_3\text{C}_6\text{H}_5 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 42k & 73 \\
12 & 4\text{-CH}_3\text{C}_6\text{H}_5 & 4\text{-ClC}_6\text{H}_5 & 42l & 75 \\
13 & \text{CH}_3 & \text{C}_6\text{H}_5 & 42m & 70 \\
14 & \text{CH}_3 & 4\text{-OCH}_3\text{C}_6\text{H}_5 & 42n & 71 \\
15 & \text{CH}_3 & 4\text{-ClC}_6\text{H}_5 & 42o & 72
\end{align*}
\]
To evaluate the scope of this catalytic system, the range of metal salts was extended to various metal halides guided by the template reaction of benzaldehyde 40a, urea 41, and β-oxodithioester 39a. SnCl₂ was found to be the best catalyst, giving the highest yield of the product under a short duration of 1h. It was also observed that ZnCl₂ and FeCl₃ gave good yields of the product, while MgCl₂, BiCl₃, and LaCl₃ gave poor yields of the desired products (table 2).
Table-2. Evaluation of Different Catalytic Systems in Optimization of the
Dihydropyrimidine Synthesis$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time(h)</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl$_2$</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl$_2$</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>FeCl$_3$</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>AlCl$_3$</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>CuBr$_2$</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>CuI$_2$</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>MgCl$_2$</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>BiCl$_3$</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>LaC$_3$</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>CuCl$_2$</td>
<td>5</td>
<td>43</td>
</tr>
</tbody>
</table>

$^a$ Benzaldehyde 40a (5.0 mmol), urea (5.0 mmol), catalyst (10 mol %), β-oxodithioester 39a (5.0 mmol).

A control experiment in the absence of the catalyst provided no product. Moreover, it is noteworthy to mention that using different solvents such as DMSO, DMF, THF and acetonitrile did not improve the yields and thus we have optimized the reaction condition at 100°C for 1 h under solvent-free condition. Electronic variation on aryl aldehydes caused no appreciable changes in the efficiency of the condensations.
III. F. PLAUSIBLE MECHANISM FOR THE SYNTHESIS OF DIHYDROPYRIMIDINE

On the basis of all the results obtained, a plausible mechanism for the synthesis of 5-methylmercaptothiocarbonyl-4-aryl-3, 4-dihydropyrimidin-2(1H)-ones 42 is presented in scheme 15. The first step in this reaction, the acid-catalyzed formation of an acyl imine intermediate A formed by reaction of the aldehyde with urea, is the key rate-limiting step. Interception of the iminium ion by β-oxodithioester 39 produces an open-chain ureide B that subsequently cyclizes to the dihydropyrimidinones 42.

Scheme-15. Plausible mechanism for the synthesis of dihydropyrimidine 42 from β-oxodithioester 39.
III. G. CONCLUSION

In conclusion, we have successfully demonstrated the synthetic applications of $\beta$-oxodithioesters in multicomponent reactions to synthesize the hitherto unreported 5-methylmercaptothiocarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones. A particularly attractive feature of this approach avoiding the use of solvent and the ready availability of a wide range of substrates from cheap starting materials make this new strategy highly attractive in diversity oriented synthesis.

III. H. EXPERIMENTAL SECTION

General: Reagents were commercially purchased from Merck and used without further purification. Commercial solvents were used after distillation. Melting points were determined on a “Veego MP-I” capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin Elmer 983 and Shimadzu IR-408 spectrometers. Infrared spectra were recorded as thin films on KBr plates with $\nu$ max in cm$^{-1}$. $^1$H and $^{13}$C NMR spectra were recorded respectively on a Varian EM-390 (300 MHz and 75.5 MHz) spectrometer. The chemical shifts are reported in ppm ($\delta$ unit) downfield from tetramethylsilane as the internal standard. Mass measurements were carried out with Jeol JMSD-300 spectrometer. Elemental analyses were performed on a Heracus CHN-O-Rapid Analyzer.
Column chromatography was performed on Merck Silica Gel 60 (230-400 mesh) using analytical reagent grade hexane and ethyl acetate as eluents.

**General procedure for synthesis of dihydropyrimidine-2(1H)-ones 42a-o:** A mixture of aldehyde (5 mmol), urea (5 mmol), \(\beta\)-oxodithioester (5 mmol), and SnCl\(_2\) (0.4 mmol, 20 mol \%) was heated at 100 °C with stirring for 1−4h. Water (30 mL) was then added and the mixture extracted with chloroform (20 mL). The organic layer was dried with anhydrous Na\(_2\)SO\(_4\) and evaporated. The crude product was subjected to column chromatography on SiO\(_2\), using increasing amounts of ethyl acetate in petroleum ether as eluent. All new compounds were fully characterized by spectroscopy, mass spectrometry and elemental analysis.

**5-Methylmercaptothiocarbonyl-4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one (42a):** Bright yellow powder. m.p.198−200°C. \(^1\)H NMR (300 MHz, CDCl\(_3\), δ ppm) 2.30 (s, 3H), 5.87 (d, \(J = 2.7\) Hz, 1H), 6.32 (s, 1H, NH), 7.28−7.44 (m, 10H), 7.61 (s, 1H, NH); \(^13\)C NMR (75.5 MHz, CDCl\(_3\), δ ppm) 20.5, 60.9, 119.4, 127.2, 128.1, 128.2, 128.7, 128.8, 129.9, 134.6, 136.5, 141.7, 152.6, 227.0; IR (KBr) (ν max, cm\(^{-1}\)) 1226, 1629, 1700, 3084, 3198 cm\(^{-1}\); MS \(m/z\) 340 (M\(^+\)). Anal. Calcd for C\(_{18}\)H\(_{16}\)N\(_2\)O\(_2\): C, 63.50; H, 4.74; N, 8.23; S, 18.84. Found: C, 63.58; H, 4.79; N, 8.30; S, 18.74.
5-Methylmercaptothiocarbonyl-4-(4-methoxyphenyl)-6-phenyl-3,4-
dihydropyrimidin-2(1H)-one (42b):

Bright yellow powder. m.p. 182–183°C. $^{1}$H NMR (300 MHz, CDCl$_3$, δ ppm)
2.31 (s, 3H), 3.79 (s, 3H), 5.83 (d, $J = 2.1$ Hz, 1H), 6.17 (s, 1H, NH), 6.83 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.37–7.46 (m, 5H), 8.07 (s, 1H, NH); $^{13}$C NMR (75.5 MHz, CDCl$_3$, δ ppm) 20.4, 55.2, 60.4, 113.9, 119.6, 128.2, 128.4, 128.8, 129.8, 134.1, 134.6, 136.2, 152.7, 159.3, 227.2; IR (KBr) (ν max, cm$^{-1}$) 1244, 1610, 1691, 3095, 3213 cm$^{-1}$; MS m/z 370 (M$^+$$)$. Anal. Calcd for C$_{19}$H$_{18}$N$_2$O$_2$S$_2$: C, 61.60; H, 4.90; N, 7.56; S, 17.31. Found: C, 61.50; H, 4.84; N, 7.53; S, 17.44.

5-Methylmercaptothiocarbonyl-4-(4-chlorophenyl)-6-phenyl-3,4-
dihydropyrimidin2(1H)-one (42c). Yellow powder. m.p. 230-231°C. $^{1}$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.30 (s, 3H), 5.45 (s, 1H, NH), 5.93 (d, $J = 1.8$ Hz, 1H), 6.46 (s, 1H, NH), 7.28–7.41 (m, 9H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, δ ppm): 20.4, 60.8, 119.6, 127.1, 128.2, 128.7, 128.9, 129.7, 132.7, 135.3, 135.8, 141.5, 153.1, 226.8; IR (KBr) (ν max, cm$^{-1}$): 1256, 1614, 1695, 3086 cm$^{-1}$; MS: m/z = 374.5 (M$^+$). Anal. Calcd for C$_{18}$H$_{15}$N$_2$O$_2$S$_2$Cl: C, 57.67; H, 4.03; N, 7.47; S, 17.11. Found: C, 57.60; H, 4.14; N, 7.43; S, 17.34.

5-Methylmercaptothiocarbonyl-4-phenyl-6-(4-methoxyphenyl)-3,4-
dihydropyrimidin-2(1H)-ones (42d) yellow powder. m.p. 188-189°C. $^{1}$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.31 (s, 3H), 3.83 (s, 3H), 5.60 (s, 1H,
NH), 5.90 (d, $J = 2.1$ Hz, 1H), 6.72 (s, 1H, NH), 6.87 (d, $J = 6.6$ Hz, 2H), 7.26-7.39 (m, 7H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, $\delta$ ppm): 20.5, 55.4, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 140.1, 141.7, 152.6, 227.1; IR (KBr) ($\nu$ max, cm$^{-1}$): 1253, 1610, 1695, 3086, 3211 cm$^{-1}$; MS: $m/z$ = 370 (M$^+$). Anal. Calcd for C$_{19}$H$_{18}$N$_2$O$_2$S$_2$: C, 61.60; H, 4.90; N, 7.56; S, 17.31. Found: C, 61.59; H, 4.93; N, 7.53; S, 17.30.

5-Methylmercaptothiocarbonyl-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-ones (42e). Yellow powder. m.p. 207-208°C. $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 2.31 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H) 5.48 (s, 1H, NH), 5.85 (s, 1H), 6.61 (s, 1H, NH), 6.82 (d, $J = 6.3$ Hz, 2H), 6.85-6.89 (m, 2H), 7.26-7.30 (m, 2H), 7.36 (d, $J = 6.3$ Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, $\delta$ ppm): 20.5, 55.4, 60.9, 60.11, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 140.1, 141.7, 152.6, 227.1; MS: $m/z$ = 400 (M$^+$). Anal. Calcd for C$_{20}$H$_{20}$N$_2$O$_3$S$_2$: C, 59.98; H, 5.03; N, 6.99; S, 16.01. Found: C, 59.95; H, 5.07; N, 6.97; S, 16.05.

5-Methylmercaptothiocarbonyl-4-(4-chlorophenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-ones (42f). Yellow powder. m.p. 194-195°C. $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 2.31 (s, 3H), 3.78 (s, 3H), 5.43 (s, 1H, NH), 5.91 (s, 1H), 6.59 (s, 1H, NH), 6.89 (d, $J = 6.9$ Hz, 2H), 7.22-7.31 (m, 4H), 7.38 (d, $J = 6.6$ Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, $\delta$ ppm): 20.8, 55.8, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4,
131.6, 136.7, 140.1, 141.7, 153.6, 227.8; MS: m/z = 404 (M⁺). Anal. Calcd for C₁₉H₁₇N₂O₂S₂Cl: C, 56.36; H, 4.23; N, 6.92; S, 15.84. Found: C, 56.33; H, 4.25; N, 6.95; S, 15.81.

5-Methylmercaptothiocarbonyl-4-phenyl-6-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-ones (42g). Yellow powder. m.p. 224-225°C. ¹H NMR (300 MHz, CDCl₃, δ ppm): 2.30 (s, 3H), 5.52 (s, 1H, NH), 5.89(d, J = 1.8 Hz, 1H), 6.79(s, 1H, NH), 7.26-7.35 (m, 5H), 7.37-7.41 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃, δ ppm): 20.4, 60.8, 119.6, 127.1, 128.2, 128.7, 128.9, 129.7, 132.7, 135.3, 135.8, 141.5, 153.1, 226.8; MS: m/z = 374 (M⁺). Anal. Calcd for C₁₈H₁₅N₂O₂S₂Cl: C, 57.67; H, 4.03; N, 7.47; S, 17.11. Found: C, 57.65; H, 4.05; N, 7.49; S, 17.09.

5-Methylmercaptothiocarbonyl-4-(4-methoxyphenyl)-6-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-ones (42h). Yellow powder. m.p. 195-196°C. ¹H NMR (300 MHz, CDCl₃, δ ppm): 2.31 (s, 3H), 3.78 (s, 3H), 5.77 (d, J = 2.1 Hz, 1H), 6.32 (s, 1H, NH), 6.82 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.28-7.37 (m, 5H), 8.07 (s, 1H, NH); ¹³C NMR (75.5 MHz, CDCl₃, δ ppm): 20.5, 21.4, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 140.1, 141.7, 152.6, 227.1; IR (KBr) (ν max, cm⁻¹): 1253, 1610, 1695, 3086, 3211 cm⁻¹; MS: m/z = 404 (M⁺). Anal. Calcd for C₁₀H₁₇N₂O₂S₂Cl: C, 56.36; H, 4.23; N, 6.92; S, 15.84. Found: C, 56.39; H, 4.21; N, 6.95; S, 15.81.
5-Methylmercaptothiocarbonyl-4-(4-chlorophenyl)-6-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-ones (42i). Yellow powder. m.p. 226-227°C. 

$^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 2.31 (s, 3H), 5.5 (s, 1H, NH), 5.96 (d, $J$ = 2.1 Hz, 1H), 6.64 (s, 1H, NH), 7.25-7.34 (m, 4H), 7.37-7.39 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, $\delta$ ppm): 20.5, 21.4, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 141.4, 141.7, 152.6, 227.1; IR (KBr) ($\nu$ max, cm$^{-1}$): 1256, 1617, 1695, 3086, 3210 cm$^{-1}$; MS: m/z = 407 (M$^+$). Anal. Calcd for C$_{18}$H$_{14}$N$_2$OS$_2$Cl$_2$: C, 52.81; H, 3.45; N, 6.84; S, 15.67. Found: C, 52.85; H, 3.41; N, 6.85; S, 15.65.

5-Methylmercaptothiocarbonyl-4-phenyl-6-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-ones (42j). Yellow powder. m.p. 203-205°C. $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 2.30 (s, 3H), 2.37 (s, 3H), 5.43 (s, 1H, NH), 5.92 (d, $J$ = 2.1 Hz, 1H), 6.44 (s, 1H, NH), 7.18 (d, $J$ = 5.8 Hz, 2H), 7.26-7.35 (m,5H), 7.37 (d, $J$ = 5.8 Hz, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, $\delta$ ppm): 20.5, 21.4, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 141.4, 152.6, 227.1; IR (KBr) ($\nu$ max, cm$^{-1}$): 1259, 1619, 1697, 3083, 3210 cm$^{-1}$; MS: m/z = 354 (M$^+$). Anal. Calcd for C$_{19}$H$_{18}$N$_2$OS$_2$: C, 64.38; H, 5.12 N, 7.90 S, 18.09. Found: C, 64.35; H, 5.15; N, 7.95; S, 18.06.

5-Methylmercaptothiocarbonyl-4-(4-methoxyphenyl)-6-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-ones (42k). Yellow powder.
m.p. 228-229°C. $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.17 (s, 3H), 2.32 (s, 3H), 3.82 (s, 3H), 5.58 (s, 1H, NH), 5.90 (d, $J = 1.8$ Hz, 1H), 6.62 (s, 1H, NH), 6.88 (d, $J = 6.6$ Hz, 2H), 7.25-7.31 (m, 2H), 7.32-7.38 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, δ ppm): 20.6, 21.5, 56.1, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 140.1, 141.7, 152.6, 227.1; MS: m/z = 384 (M$^+$). Anal. Calcd for C$_{20}$H$_{20}$N$_2$O$_2$S$_2$: C, 62.47; H, 5.24; N, 7.29; S, 16.68. Found: C, 62.45; H, 5.27; N, 7.26; S, 16.69.

5-Methylmercaptothiocarbonyl-4-(4-chlorophenyl)-6-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-ones (42l). Yellow powder. m.p. 197-198°C. $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.17 (s, 3H), 2.30 (s, 3H), 5.43 (s, 1H, NH), 5.90 (d, $J = 1.8$ Hz, 1H), 6.59 (s, 1H, NH), 7.26-7.35 (m, 4H), 7.36-4.41 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, δ ppm): 20.5, 21.4, 60.9, 119.1, 127.1, 128.0, 128.1, 128.6, 129.4, 131.6, 136.7, 140.1, 141.7, 152.6, 227.2; MS: m/z = 388 (M$^+$). Anal. Calcd for C$_{19}$H$_{17}$N$_2$O$_2$S$_2$: C, 58.67; H, 4.41; N, 7.20; S, 16.49. Found: C, 58.65; H, 4.43; N, 7.24; S, 16.47.

5-Methylmercaptothiocarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (42m). Yellow powder. m.p. 150-151°C. $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.31 (s, 3H), 2.40 (s, 3H), 5.67 (s, 1H, NH), 5.77 (d, $J = 2.1$ Hz, 1H), 6.32 (s, 1H, NH), 7.29-7.32 (m, 3H), 7.37-7.40 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$, δ ppm): 20.4, 24.4, 60.9, 119.6, 126.2, 127.6, 128.5, 143.2, 145.2, 153.1, 226.5; MS: m/z = 278 (M$^+$). Anal.
Calcd for C_{13}H_{14}N_{2}S_{2}: C, 56.09; H, 5.07; N, 10.06; S, 23.04. Found: C, 56.07; H, 5.09; N, 10.09; S, 23.02.

5-Methylmercaptothiocarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (42n).

Yellow powder. m.p. 153-155°C. ^1H NMR (300 MHz, CDCl₃, δ ppm): 2.32 (s, 3H), 2.41 (s, 3H), 3.76 (s, 3H), 5.68 (s, 1H, NH), 5.79 (d, J = 2.1 Hz, 1H), 6.33 (s, 1H, NH), 7.29-7.31 (m, 2H), 7.38-7.40 (m, 2H); ^13C NMR (75.5 MHz, CDCl₃, δ ppm): 20.4, 24.4, 55.1, 60.9, 119.6, 126.2, 127.6, 128.5, 143.2, 145.2, 153.1, 226.5; MS: m/z = 308 (M⁺). Anal. Calcd for C_{14}H_{16}N_{2}O_{2}S_{2}: C, 54.42; H, 5.99; N, 7.68; S, 16.34. Found: C, 54.43; H, 5.97; N, 7.70; S, 16.35.

5-Methylmercaptothiocarbonyl-4-(4-Chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (42o).

Yellow powder. m.p. 147-149°C. ^1H NMR (300 MHz, CDCl₃, δ ppm): 2.31 (s, 3H), 2.43 (s, 3H), 5.69 (s, 1H, NH), 5.78 (d, J = 2.1 Hz, 1H), 6.32 (s, 1H, NH), 7.29-7.31 (m, 2H), 7.37-7.40 (m, 2H); ^13C NMR (75.5 MHz, CDCl₃, δ ppm): 20.7, 24.5, 60.7, 119.5, 126.1, 127.7, 128.5, 143.1, 145.2, 153.3, 226.7; MS: m/z = 342 (M⁺). Anal. Calcd for C_{13}H_{13}ClN_{2}O_{2}S_{2}: C, 49.91; H, 4.19; N, 8.95; S, 20.50. Found: C, 49.90; H, 4.17; N, 8.97; S, 20.51.
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