INTRODUCTION

Since the beginning of 1980s, the chemists have developed significant interest in dihydropyrimidinones [1]. This is primarily because of the noticeable resemblance between structures of dihydropyrimidinones and Hantzsch type [2] dihydropyridines (Fig. 1). Later on, dihydropyrimidinones (DHPMs) were also reported to possess a similar pharmacological activity as that of DHP calcium antagonists of the nifedipine type and a lot of research effort was directed in this field [3,4]. In recent time, the research focus on dihydropyrimidinones has deviated from calcium antagonists to other potential drug molecules, e.g. adrenoreceptor antagonists, which are effective against benign prostatic hyperplasia [5].

In 1940s, pharmacological action of DHPMs was first reported by McKinstry & Reading [6], leading to the synthesis of nitrofuryl substituted analog nitractin, which showed promising results in combating trachoma viruses [7]. It was also found to possess moderate antibacterial property [8]. Benign prostatic hyperplasia (BPH) is a progressive enlargement of the prostate, causing a number of obstructive and irritative symptoms [9]. Nonselective $\alpha_1$-adrenoceptor antagonists like terazosin are currently being used in the treatment of BPH [10]. However, it was found that the functional potency of several $\alpha_1$ antagonists matches suitably with the binding affinity for $\alpha_{1a}$ subtype. Therefore, efforts are being made to develop $\alpha_1$-selective antagonists as alluring drug molecules for the treatment of BPH with minor side effects. The DHP calcium antagonist, nignudipine (Fig. 2) was shown to be a potent antagonist of the $\alpha_1$ receptor subtype.

Dihydropyrimidinones synthesized by various methods using a variety of catalysts such as boric acid in acetic acid [11], heteropolyacid [12], polystyrenesufonic acid [13], zinc perchlorate [14], cupric chloride [15], palladium oxide [16], TMSCl [17], zinc oxide [18], polyphosphate ester [19], ionic liquid was also employed to synthesize dihydropyrimidinones [20]. There are also reports of synthesis of dihydropyrimidinones using microwave irradiation [21-23].

The catalytic potential of water extract of pericarp of soap nut fruit was satisfactorily proved in synthesis of aldimines and 1,8-dioxooctahydroxanthenes [24]. Therefore, we extended the application of this biocatalyst for synthesis of dihydropyrimidinones, which are a vital group of biologically active organic compounds [25]. Most of the catalysts reported so far for the condensation of aromatic aldehydes with $\alpha$-dicarbonyl compounds...
compounds and carbamide suffer from certain disadvantages like toxic nature, economically expensive, work in a particular organic solvent, difficulty in their separation from the product, consumption of large amount of energy to provide high temperature required by the reaction, hazards in their use, etc. It is always desirable to replace such conventional catalysts with the green alternatives present in nature. Thus, it is desirable to develop chemical processes which can be carried out without solvent, however there are reactions which occur only in a suitable solvent. Application of water-soluble homogeneous catalysts gets promoted in presence of water as solvent [26]. It helps to recover catalysts and increases the reusability of the catalyst. Water as a solvent also offers great advantage in isolation of highly pure products. Moreover, water at high temperatures acts like a pseudo-organic solvent, because there is substantial decrease in its dielectric constant. Solvating ability of water is also enhanced and approaches that of ethanol or acetone [27].

Classical one-pot Biginelli protocol requires long reaction time (about 20 h) and does not give satisfactory product output [28]. Yields are improved in multi-step synthesis [29] but the process is more complicated than one-pot Biginelli reaction.

In continuation of our efforts for the environmental friendly alternatives as compare to conventional organic synthetic routes [30,31], in this work an aqueous extract of pericarp of soap nut fruit was employed as catalyst to synthesize of 3,4-dihydropyrimidinones by one-pot reaction of ethyl ester of acetoacetic acid, benzaldehyde and carbamide.

**EXPERIMENTAL**

Melting points were determined, as a standard laboratory practice, in open capillaries and reported as uncorrected. Reagent grade chemicals were purchased from Spectrochem Co., S.D. Fine Chem. and others and were used as received. IR spectra were recorded on a Perkin-Elmer 1310 FT-IR spectrometer using KBr pellets. $^1$H NMR and $^{13}$C NMR spectra were recorded on Varian (75 MHz) instrument using CDCl$_3$ as solvent and TMS as internal reference. Thin layer chromatography technique, run on silica gel G (Merk), was used to observe advance of the reaction. Mass spectroscopic analysis was done using Shimadzu QP 2010 GCMS with an ion source temperature of 200 °C.

**General procedure for the synthesis of 4-aryl substituted 3,4-dihydropyrimidinones:** A mixture of ethyl ester of acetoacetic acid (1 equiv.), substituted aldehyde (1 equiv.) and carbamide (or thiocarbamide) (1.2 equiv.) was stirred with aqueous extract of pericarp of soap nut fru (10 mL) at room temperature for an appropriate time as indicated in Table-1. On completion of the reaction (ascertained on the basis of TLC, hexane/ethyl acetate 8:2), the reaction mixture was washed with cold water to remove unreacted carbamide/thiocarbamide and then filtered on suction pump (Scheme-I). Residual solid product was washed thoroughly with cold water and recrystallized by ethanol to yield pure product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of aqueous extract of pericarp of <em>Sapindus trifoliatus</em> fruit (mL)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>300</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>240</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>150</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>150</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>150</td>
<td>95</td>
</tr>
</tbody>
</table>

**Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate** (Table-2, entry 1): IR (KBr, $\nu_{max}$, cm$^{-1}$): 3440, 3220 (-NH), 1725 (-COO-) and 1650 (C=O, NH-CO-NH). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ ppm: 1.10 (t, 3H, -CH$_3$, ...
of ethoxy group), 2.34 (s, 3H, vinylic -CH3), 4.06 (q, 2H, -OCH2-), 5.40 (d, 1H, -CH-), 5.81 (s, 1H, -NH-), 7.26-7.32 (m, 5H, Ar-H), 8.22 (s, 1H, -NH-); 13C NMR (DMSO-δD, 75 MHz) 7.21 (d, 2H, Ar-H), 7.69 (s, 1H, -NH-), 7.94 (d, 2H, Ar-H), 8.76 (d, 2H, Ar-H), 165.61 (-COO-).

**Scheme-I**

**TABLE-2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde -R group</th>
<th>Urea/thiourea</th>
<th>Reaction time (min)</th>
<th>Yield (%)a</th>
<th>Melting point (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>Urea</td>
<td>150</td>
<td>95</td>
<td>204-206</td>
<td>[20]</td>
</tr>
<tr>
<td>2</td>
<td>4-CH3</td>
<td>Urea</td>
<td>200</td>
<td>90</td>
<td>171-173</td>
<td>[20]</td>
</tr>
<tr>
<td>3</td>
<td>4-OH</td>
<td>Urea</td>
<td>200</td>
<td>92</td>
<td>227-229</td>
<td>[20]</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl</td>
<td>Urea</td>
<td>150</td>
<td>90</td>
<td>209-211</td>
<td>[20]</td>
</tr>
<tr>
<td>5</td>
<td>4-O-CH3</td>
<td>Urea</td>
<td>240</td>
<td>90</td>
<td>200-202</td>
<td>[20]</td>
</tr>
<tr>
<td>6</td>
<td>4-NO2</td>
<td>Urea</td>
<td>150</td>
<td>95</td>
<td>207-209</td>
<td>[33]</td>
</tr>
<tr>
<td>7</td>
<td>3,4-(OCH3)2</td>
<td>Urea</td>
<td>200</td>
<td>90</td>
<td>242-243</td>
<td>–</td>
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<tr>
<td>8</td>
<td>4-OH-3-OCH3</td>
<td>Urea</td>
<td>200</td>
<td>93</td>
<td>230-232</td>
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<tr>
<td>9</td>
<td>3-NO2</td>
<td>Urea</td>
<td>150</td>
<td>95</td>
<td>227-229</td>
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<tr>
<td>10</td>
<td>2-Cl</td>
<td>Urea</td>
<td>150</td>
<td>85</td>
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</tr>
<tr>
<td>11</td>
<td>2-OH</td>
<td>Urea</td>
<td>200</td>
<td>85</td>
<td>202-203</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>3,4-(OCH3)2</td>
<td>Thiourea</td>
<td>240</td>
<td>85</td>
<td>176-178</td>
<td>[33]</td>
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<tr>
<td>13</td>
<td>4-CH3</td>
<td>Thiourea</td>
<td>180</td>
<td>90</td>
<td>193-195</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>4-NO2</td>
<td>Thiourea</td>
<td>180</td>
<td>95</td>
<td>206-207</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>4-OH-3-OCH3</td>
<td>Thiourea</td>
<td>200</td>
<td>90</td>
<td>226-229</td>
<td>–</td>
</tr>
</tbody>
</table>

aReaction conditions: Equimolar reactants, room temperature, 10 mL biocatalyst; bIsolated yield after purification.

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidinone-2(1H)-one (Table-2, entry 3): IR (KBr, vs, cm⁻¹): 3242 (N-H), 1705 (C=O of -COO-) and 1615 (C=S, NH-CO-NH); 1H NMR (CDCl3, 300 MHz) δ ppm: 1.07 (t, 3H, -CH3), 2.27 (s, 3H, vinylic -CH3), 3.95 (q, 2H, -OCH2-), 4.28 (s, 3H, -OCH3), 5.21 (s, 1H), 6.58 (dd, 1H, Ar-H), 6.86 (d, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 8.36 (s, 1H, -NH), 9.08 (s, 1H, -NH), 9.22 (s, 1H, -OH); 13C NMR (CDCl3, 75 MHz) δ ppm: 14.86, 18.73, 54.76, 61.24, 102.31, 118.15.

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidinone-2(1H)-one (Table-2, entry 4): IR (KBr, vs, cm⁻¹): 3225 (N-H), 1720 (COO-) and 1615 (C=S, NH-CO-NH); 1H NMR (CDCl3, 300 MHz) δ ppm: 1.12 (t, 3H, -CH3), 2.30 (s, 3H, vinylic -CH3), 3.91 (q, 2H, -OCH2-), 5.70 (d, 1H, -CH-), 7.21 (d, 2H, Ar-H), 7.69 (s, 1H, -NH-), 7.94 (d, 2H, Ar-H), 8.76 (s, 1H, -NH-); 13C NMR (CDCl3, 75 MHz) δ ppm: 14.18, 18.62, 55.72, 60.21, 101.55, 118.17, 130.32, 142.29, 152.31, 153.39, 159.17, 165.83.

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidinone-2(1H)-one (Table-2, entry 5): IR (KBr, vs, cm⁻¹): 3242 (N-H), 1705 (C=O of -COO-) and 1615 (C=S, NH-CO-NH); 1H NMR (CDCl3, 300 MHz) δ ppm: 1.07 (t, 3H, -CH3), 2.23 (s, 3H, vinylic -CH3), 3.95 (q, 2H, -OCH2-), 4.08 (s, 3H, -OCH3), 5.21 (s, 1H), 6.58 (dd, 1H, Ar-H), 6.86 (d, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 8.56 (s, 1H, -NH), 9.08 (s, 1H, -NH), 9.22 (s, 1H, -OH); 13C NMR (CDCl3, 75 MHz) δ ppm: 14.18, 18.73, 54.76, 61.24, 102.31, 118.15, 134.56, 145.36, 153.31, 165.97.

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidinone-2(1H)-one (Table-2, entry 9): IR (KBr, vs, cm⁻¹): 3326, 3089 (N-H), 1705 (-COO-), 1625 (C=S, NH-CO-NH); 1H NMR (CDCl3, 300 MHz) δ ppm: 1.10 (t, 3H, -CH3) and 3.94-4.03 (q, 2H, -OCH2-), 2.27 (s, 3H, vinylic -CH3), 5.30 (d, 1H, -CH2-), 7.49-7.86 (m, 3H, Ar-H), 8.22 (bs, 2H, -NH-).
9.32 (s, 1H, Ar-H); 13C NMR (CDCl₃, 75 MHz) δ ppm: 13.97 (-CH₃ of ester), 17.80 (vinylic -CH₃), 55.74 (-CH₂), 59.33 (-OCH₃), 121.50, 123.75, 127-132, 147, 149.34, 151.80 (Ar-C and =C), 165.01 (-COO-).

5-Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidine-2(1H)-one (Table-2, entry 10): IR (KBr, νmax, cm⁻¹): 3235, 3168 (N-H), 1720 (C=O of -COO-) and 1639 (C=O, NH-CO-NH); ¹H NMR (CDCl₃, 300 MHz) δ ppm: 1.13 (t, 3H, -CH₃), 2.34 (s, 3H, vinylic -CH₃), 4.12 (q, 2H, -OCH₂-), 5.39 (d, 1H, -CH-), 6.8 (m, 2H, Ar-H), 7.3 (s, 1H, Ar-H), 8.2 (s, 1H, -NH).

5-Ethoxycarbonyl-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidine-2(1H)-one (Table-2, entry 12): IR (KBr, νmax, cm⁻¹): 3283, 3179 (N-H), 1715 (C=O), 1635 (C=O, NH-CO-NH) and 1463 (Ar-C=C); ¹H NMR (CDCl₃, 300 MHz) δ ppm: 1.18 (t, 3H, -CH₃), 2.34 (s, 3H, vinylic -CH₃), 3.87 (s, 6H, -OCH₃), 4.12 (q, 2H, -OCH₂-), 5.39 (d, 1H, -CH-), 6.8 (m, 2H, Ar-H), 7.3 (s, 1H, Ar-H), 8.2 (s, 1H, NH). 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidine-5-carboxylate (Table-2, entry 9): IR (KBr, νmax, cm⁻¹): 3326, 3089 (-NH), 1705 (COO-), 1625 (C=O, NH-CO-NH); ¹H NMR (DMSO-d₆, 300 MHz) δ ppm: 1.10 (t, 3H, -CH₃) and 3.94-4.03 (q, 2H, -OCH₂-) of ethoxy group, 2.27 (s, 3H, vinylic -CH₃), 5.30 (d, 1H, -CH-), 7.49-7.86 (m, 3H, Ar-H), 8.22 (bs, 2H, -NH), 9.32 (s, 1H, Ar-H); ¹³C NMR (DMSO-d₆, 75 MHz) δ ppm: 13.97 (-CH₃ of ester), 17.80 (vinylic -CH₃), 55.74 (-CH₂), 59.33 (-OCH₃), 121.50, 123.75, 127-132, 147, 149.34, 151.80 (Ar-C and =C), 165.01 (-COO-).

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydroxypyrimidine-5-carboxylate (Table-2, entry 14): IR (KBr, νmax, cm⁻¹): 3289 (N-H), 1718 (-COO-) of ethoxy group, 2.27 (s, 3H, vinylic -CH₃), 5.30 (d, 1H, -CH-), 7.49-7.86 (m, 3H, Ar-H), 8.22 (bs, 2H, -NH), 9.32 (s, 1H, Ar-H); ¹H NMR (CDCl₃, 300 MHz) δ ppm: 1.13 (t, 3H, -CH₃), 2.34 (s, 3H, vinylic -CH₃), 3.87 (s, 6H, -OCH₃), 4.12 (q, 2H, -OCH₂-), 5.39 (d, 1H, -CH-), 6.8 (m, 2H, Ar-H), 7.3 (s, 1H, Ar-H), 8.2 (s, 1H, NH), 9.16 (s, 1H, NH).

Ethyl 6-methyl-4-(3,4-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydroxypyrimidine-5-carboxylate (Table-2, entry 2): IR (KBr, νmax, cm⁻¹): 3325, 3168 (N-H), 1715 (C=O), 1635 (C=O, NH-CO-NH); ¹H NMR (CDCl₃, 300 MHz) δ ppm: 1.18 (t, 3H, -CH₃), 2.34 (s, 3H, vinylic -CH₃), 3.87 (s, 6H, -OCH₃), 4.12 (q, 2H, -OCH₂-), 5.39 (d, 1H, -CH-), 6.8 (m, 2H, Ar-H), 7.3 (s, 1H, Ar-H), 8.2 (s, 1H, NH). 5-Ethoxycarbonyl-6-methyl-4-(4-hydroxy-3-methoxyphenyl)-3,4-dihydropyrimidine-2(1H)-one (Table-2, entry 15): IR (KBr, νmax, cm⁻¹): 3514 (O-H), 3278 and 3123 (Ar-H), 1528 (N-O); ¹H NMR (CDCl₃, 300 MHz) δ ppm: 1.14 (s, 3H, -CH₃), 2.12 (s, 3H, vinylic -CH₃), 3.84 (s, 3H, -OCH₃), 4.03 (q, 2H, -OCH₂-), 5.22 (s, 1H), 6.78 (d, 1H, Ar-H), 6.85 (d, 1H, Ar-H), 7.13 (s, 1H, Ar-H), 8.72 (s, 1H, -NH), 9.34 (s, 1H, -NH), 10.28 (s, 1H, -OH).

RESULTS AND DISCUSSION

It was reported that an aqueous extract of the pericarp of soap nut fruit had the ability to catalyze the transformation of aldimines [24]. It was one-step reaction of aldehyde with amine, thus, a similarity is drawn between aldimine synthesis and Biginelli reaction as both involved aldehyde and -NH₂ functional groups, although -NH₂ in Biginelli was from urea (or thiourea) and not amine. Even then, it was decided to extend catalytic application of water extract of pericarp of soap nut fruit in the synthesis of 3,4-dihydropyrimidinones by condensation of ethylacetocetate, benzaldehyde and urea (Scheme-1).

The driving force behind the use of aqueous extract of pericarp of Sapindus trifoliatus (soap nut) fruits as a catalyst was its ability to solubilize organic compounds by the formation of micelles in water. This property of aqueous extract of soap nut was promising as insolubility of most organic compounds in water was an obstacle in the application of water as preferred reaction medium to carry out organic reactions. Aqueous extract of soap nut pericarp forms micelles when agitated. These micelles, because of their characteristic structure, were expected to bring organic reactants together and make reaction possible.

Plausible mechanism of aldimine synthesis catalyzed by soap nut extract: The reaction as proposed might be proceeded via Kappe mechanism. This assumption is derived from the effective completion of the aldimine synthesis reaction [24]. In aldimine synthesis, the reaction between aromatic aldehydes and aromatic primary amines take place in much shorter time. Although, in the present context, it is urea and not aromatic amine but still aldehyde and urea are expected to be the first to react to form the intermediate (a) as proposed by Kappe [32]. The micelles, due to their peculiar structure, facilitate collisions among reactant molecules and also drive out the water molecules formed.

Effect of amount of aqueous extract on reaction time and yield: It was necessary to find out optimum conditions for this conversion of aldehyde, urea and ethyl acetoacetate into dihydropyrimidinone (DHPM). A set of experiments with differing process parameters e.g. time and amount of catalyst (2.5-30 mL) was carried out. Table-1 indicates that the most appropriate way of synthesizing dihydropyrimidinone was by using 10 mL of aqueous extract of soap nut pericarp, in the role of a catalyst, yielding more than 90% expected compound (entry 3, Table-1). The same reaction parameters were then applied to condense differently substituted aromatic aldehydes with carbamide or thiourea and ethylacetoacetate as β-carbonyl compound, affording the desired products (Table-2). The reactions involving thiourea (Table-2, entries 13-15) also produced expected compounds in good amount. It was apparent that for the reaction conditions employed, the nature of the substituents did not make any significant impact on reaction yields.

A number of differently substituted aromatic aldehydes with groups/atoms having electron-donating or electron-withdrawing inductive effect in the ortho, meta and para-positions were subjected to react with urea/thiourea and ethyl acetoacetate as β-carbonyl compound in presence of aqueous extract of pericarp of Sapindus trifoliatus fruit. All the aldehydes underwent efficient conversion into respective 3,4-dihydropyrimidinones in excellent yields (Table-2). Significant characteristic of this protocol is relative stability of other chemically reactive groups present in reactants.

Conclusion

An easy, fast and efficient synthetic methodology to obtain 3, 4-dihydropyrimidinones is devised using a catalytic amount of water extract of pericarp of soap nut fruits. The protocol offers several notable advantages like high substrate conversions, easy handling, clear reaction form, metal-free catalyst and less reaction time, thus making it a convenient and interesting alternative for the metamorphosis of 3,4-dihydropyrimidinones. In all cases, product separation could be simply
accomplished in a pure form without the need for any additional purification steps to be taken.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

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