One-Pot Multicomponent Synthesis of Novel 2-Thioxo-Benzo[6,7]Chromeno[2,3d]Pyrimidin-4-one Derivatives using Cetylpyridinium Chloride

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ABSTRACT

The novel 2-thioxo-benzo[5,6]chromeno[2,3-d]pyrimidin-4-one derivatives were prepared by one pot multicomponent condensation reaction involving thiobarbituric acids, aromatic aldehydes and β-napthol in acetonitrile-water as solvent using surfactant, cetylpyridinium chloride (CPC) at water bath temperature in good yields. The structures of the compounds were confirmed by elemental analyses and spectral data.

Indexing terms/Keywords

Multi-component; Chromeno-pyrimidinone; Thiobarbituric acids; CPC
1. INTRODUCTION

Multi-component, one-pot syntheses have received considerable attention because of their wide range of applications in pharmaceutical chemistry for generation of structural diversity and combinatorial libraries for drug discovery.[1] The use of multicomponent reaction (MCRs) increases due to its flexible, atom economic in nature, operational simplicity and proceed through a sequence of reaction equilibria, yielding the target product.[2] MCRs have also been found to be useful in synthesizing structurally diverse bioactive heterocyclic compounds.[3] The use of water reduces the harmful organic solvents and is regarded as the greener method in Chemistry.[4] Nitrogen-containing heterocycles are of broad pharmaceutical interest which justifies the continuing efforts in the development of new synthetic strategies.[5]

Chromene derivatives represent an important class of compounds in many natural products[6] and have been reported to possess various pharmacological activities such as antimicrobial,[7] antitumor,[8] antiaggregating,[9] antidepressant[10] and antiproliferative activities.[11] Among the nitrogen containing heterocycles, the chromeno-pyrimidine derivatives are known to possess antiallergic,[12] antimicrobial,[13] antioxidant,[14] anti-inflammatory,[15] and anticancer activities.[16] In the field of medicinal chemistry, functionally substituted chromene have been found to play an increasing role in approaching synthetic promising compounds.[17]

As surfactant, at an ambient condition in an aqueous medium, aggregates to form micelles with hydrophobic tail and hydrophilic head, micellar surfactants as catalysts are widespread[18] and found to be used in different reactions as a route for synthesis in aqueous solutions.[19] The studies of surfactant-promoted reactions have been increasing, such as, reaction of 1,4-quinone with oxygen nucleophiles in aqueous micelles.[20] surfactant assisted organic reactions in water,[21] Pictet-Spengler reactions.[22]

In view of the above biological activities, various synthetic methods have been reported for the preparation of chromeno-pyrimidinones derivatives. In continuation of our work on the synthesis of fused heterocyclic compounds derived from thiobarbituric acids,[23] in our study, we report the synthesis of the novel chromeno[3,2-d]pyrimidinones derivatives (2) in one-pot, multicomponent reaction using the surfactant cetylpyridinium chloride (CPC) (Scheme 1). The reactions occur via a three component, one pot reaction between thiobarbituric acid, aldehydes (1) and β-naphthol using CPC in acetonitrile:water (1:1) as solvent, heating at water bath temperature. Addition of the surface active agents in aqueous organic solvent has been known and the use of the surfactant as catalyst has been studied for various organic reactions.

2. General procedure for synthesis of compound (2a). In a typical experiment, p-nitrobenzaldehyde (1.0 mmol), β-naphthol (1.0 mmol), thiobarbituric acid (1.0 mmol) and CPC (0.015 mmol %) were taken in a round bottom flask using water and acetonitrile as solvent in 1:1 ratio. The reaction mixture was refluxed for 8 hours in water bath temperature. The reaction was monitored by TLC. After the completion of reaction, the solid was separated and washed with water several times to remove the surfactant and washed again with acetonitrile to remove all the starting substrate to give the pure product, 2a (85%).

5-(4-nitrophenyl)-2-thioxo-2,3-dihydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(5H)-one (2a). Yellow solid: m.p. 207-210°C; IR (KBr): νmax 3541, 1651, 1537, 1445, 1350, 1198, 1132, 1015, 849 cm⁻¹; 1H NMR (DMSO-d₆, 300 MHz): δ 5.70 (s, 1H), 6.72 (m, 1H, ArH), 6.85 (m, 1H, ArH), 7.01 (d, 2H, J=7.6 Hz, ArH), 7.24 (m, 4H, ArH), 7.67 (d, 2H, J=7.6 Hz, ArH), 10.90 (br s, 1H, NH), 11.20 (br s, 1H, NH); 13C NMR (DMSO-d₆, 75 MHz): δ 173.57, 152.88, 145.70, 128.26, 123.52, 121.89, 117.44, 111.20 (br s, 1H, NH); HRMS (EI) calcd for C₂₃H₁₇N₃O₃S: 461.53; found 461.104.

5-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(5H)-one (2b). White solid: m.p. 198-203°C; IR (KBr): νmax 3524, 1660, 1537, 1443, 1359, 1201, 1134, 1013, 866 cm⁻¹; 1H NMR (DMSO-d₆, 300 MHz): δ 5.80 (s, 1H), 6.97-7.22 (m, 10H, ArH), 11.32 (br s, 1H, NH), 11.69 (br s, 1H, NH); 13C NMR (DMSO-d₆, 75 MHz): δ 173.37, 164.01, 163.03, 142.73, 129.78, 128.93, 128.01, 95.98, 30.60; HRMS (EI) calcd for C₂₃H₁₇CIN₂O₂S: 439.0464; found 439.0478.

5-(1H-indol-3-yl)-2-thioxo-2,3-dihydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(5H)-one (2c). Orange solid: m.p. 188-192°C; IR (KBr): νmax 3538, 1655, 1528, 1377, 1277, 1213, 1157 cm⁻¹; 1H NMR (DMSO-d₆, 300 MHz): δ 6.80 (s, 1H), 6.97-7.22 (m, 10H, ArH), 12.28 (br s, 1H, NH), 12.32 (br s, 1H, NH), 13.01 (br s, 1H, NH); 13C NMR (DMSO-d₆, 75 MHz): δ 178.19, 163.26, 161.46, 145.05, 141.54, 137.1129, 54.124, 53.123, 118.35, 113.86, 112.88, 109.23, 29.50; HRMS (EI) calcd for C₂₃H₁₇CIN₂O₂S: 304.3127; found 304.3238.
5-(3-hydroxynaphthalen-1-yl)-2-thioxo-2,3,4a,5-tetrahydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(12H)-one(2d): Reddish Orange solid; m.p. 195-198°C; IR (KBr): v = 3452, 3032, 1678, 1564, 1458, 1211, 1138, 814 cm\(^{-1}\); 1H NMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 5.56 (s, 1H), 7.15 (m, 2H, ArH), 7.22 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.60 (m, 2H, ArH), 7.88 (m, 2H, ArH). 8.22 (m, 2H, ArH), 11.55 (br s, 1H, NH). 12.20 (br s, 1H, NH). 13C NMR (DMSO-d\(_6\), 75 MHz): \(\delta\) 174.88, 173.46, 171.60, 157.07, 145.37, 135.88, 132.70, 128.62, 120.92, 112.01, 109.78, 99.35, 75.71; HRMS (EI) calcd for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_2\)S: 386.1198; found 386.0725.

5-(4-dimethylaminophenyl)-2-thioxo-2,3-dihydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(5H)-one(2e): Reddish orange solid; m.p. 201-203°C; IR (KBr): v = 3457, 3119, 1634, 1537, 1495, 1373, 1194, 1142, 1011 cm\(^{-1}\); 1H NMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 3.00 (s, 3H, NCH\(_3\)), 3.02 (s, 3H, NCH\(_3\)). 5.90 (s, 1H), 6.75 (m, 2H, ArH), 7.22 (m, 2H, ArH), 7.40 (m, 2H, ArH). 8.22 (m, 2H, ArH), 8.48 (m, 2H, ArH). 11.98 (br s, 1H, NH). 12.05 (br s, 1H, NH). 13C NMR (DMSO-d\(_6\), 75 MHz): \(\delta\) 178.02, 173.46, 160.25, 156.78, 150.11, 148.25, 131.42, 129.80, 126.61, 126.49, 123.14, 119.11, 109.14, 43.16, 30.86; HRMS (EI) calcd for C\(_{25}\)H\(_{23}\)N\(_3\)O\(_2\)S: 401.1198; found 401.4809.

5-(4-carbdehydeophenyl)-2-thioxo-2,3-dihydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(5H)-one(2f): Orange solid; m.p. 201-203°C; IR (KBr): v = 3522, 3148, 1670, 1574, 1518, 1433, 1298, 1207, 1148 cm\(^{-1}\); 1H NMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 4.50 (s, 1H), 5.90 (s, 1H). 7.12-8.25 (m, 10H, ArH). 11.62 (br s, 1H, CHO). 12.25 (br s, 1H, NH). 12.42 (br s, 1H, NH). 13C NMR (DMSO-d\(_6\), 75 MHz): \(\delta\) 178.22, 157.26, 145.48, 135.25129.79, 128.60, 128.04, 120.60, 124.88, 123.13, 119.10, 109.13, 31.81, 29.56, 22.43, 14.48; HRMS (EI) calcd for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_2\)S: 386.423; found 386.0725.

5-Propyl-2-thioxo-2,3-dihydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(5H)-one(2g): Black solid; m.p. 188-192°C; IR (KBr): v = 3178, 1686, 1582, 1522, 1316, 1165 cm\(^{-1}\); 1H NMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 0.82 (m, 3H, CH\(_3\)), 1.18 (m, 2H, CH\(_2\)), 2.28 (m, 2H, CH\(_2\)), 5.78 (m, 1H). 7.12 (m, 2H, ArH). 7.32-7.46 (m, 2H, ArH). 7.65-7.72 (m, 2H, ArH). 11.98 (br s, 1H, NH). 12.05 (br s, 1H, NH). 13C NMR (DMSO-d\(_6\), 75 MHz): \(\delta\) 178.22, 157.26, 145.48, 135.25129.79, 128.60, 128.04, 120.60, 124.88, 123.13, 119.10, 109.13, 31.81, 29.56, 22.43, 14.48; HRMS (EI) calcd for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_2\)S: 324.092; found 324.3968.

5-(2,4-dimethoxyphenyl)-2-thioxo-2,3,4a,5-tetrahydro-1H-benzo[6,7]chromeno[2,3-d]pyrimidin-4(12H)-one(2h): White solid; m.p. 185-187°C; IR (KBr): v = 3181, 1688, 1576, 1543, 1495, 1379, 1260, 1175, 1034, 949 cm\(^{-1}\); 1H NMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 3.73 (s, 3H, OCH\(_3\)). 3.85 (s, 3H, OCH\(_3\)). 4.65 (s, 1H). 7.08-7.23 (m, 5H, ArH). 7.40-8.13 (m, 4H, ArH). 12.34 (br s, 1H, NH). 12.48 (br s, 1H, NH). 13C NMR (DMSO-d\(_6\), 75 MHz): \(\delta\) 178.49, 161.73, 159.44, 155.17, 154.09, 150.11, 145.35, 132.24, 127.99, 126.06, 125.90, 122.59, 121.59, 121.17, 118.39, 116.98, 56.25, 55.46, 28.84; HRMS (EI) calcd for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_2\)S: 420.4809; found 420.38.
Table 1: Optimization of reaction condition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (hr)</th>
<th>2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SDS (1mmol)</td>
<td>H₂O</td>
<td>R.T</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>SDS (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>R.T</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>SDS (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>80°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>SDS (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>Reflux</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>TTAB (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>Reflux</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>CTAB (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>Reflux</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>CPC (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>Reflux</td>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>TEAB (1mmol)</td>
<td>CH₃CN: H₂O</td>
<td>Reflux</td>
<td>14</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>CPC (1.5mmol)</td>
<td>CH₃CN: H₂O</td>
<td>Reflux</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>CPC (1mmol)</td>
<td>H₂O</td>
<td>Reflux</td>
<td>24</td>
<td>53</td>
</tr>
</tbody>
</table>

From the observation of the optimization studies, the multi-component reaction (MCR) of this greener system was further studied to a variety of thiobarbituric acid and aldehydes (1) with β-napthol using CPC as catalyst in water:acetonitrile (1:1) on refluxing at water bath temperature to yield 2 (table 2). The formation of 2 is assumed to proceed through the in situ intramolecular cyclization of the intermediate [A] which is formed by nucleophilic addition of β-napthol to the condensation product of thiobarbituric acid and aldehyde (scheme 2). We have observed that the reaction was more favourable with the electron withdrawing group and less facile with the electron releasing group.
Table 2: Reaction of thiobarbituric acid with aldehydes (1) to give the products, 2.

\[
\begin{align*}
\text{Entry} & \quad \text{Aldehyde (1)} & \quad \text{Product (2)} & \quad \text{Time (hr)} & \quad \text{Yield (%)} & \quad \text{m.p (°C)} \\
1 & \quad \text{CHO} & \quad \text{CHO} & \quad 8 & \quad 85 & \quad 207-210 \\
2 & \quad \text{CHO} & \quad \text{CHO} & \quad 10 & \quad 80 & \quad 198-203 \\
3 & \quad \text{CHO} & \quad \text{CHO} & \quad 4 & \quad 93 & \quad 188-192 \\
4 & \quad \text{CHO} & \quad \text{CHO} & \quad 3 & \quad 85 & \quad 195 \\
5 & \quad \text{CHO} & \quad \text{CHO} & \quad 4 & \quad 85 & \quad 205-208 \\
6 & \quad \text{CHO} & \quad \text{CHO} & \quad 4 & \quad 92 & \quad 201-203 
\end{align*}
\]
Conclusion

In conclusion, an efficient way of synthesising substituted chromeno pyrimidine derivatives in good yields was developed. A series of chromeno pyrimidine derivatives which were able to synthesise from this greener one pot multi component reaction of thiobarbituric acid, aromatic aldehydes, β-napthol using surfactant and acetonitrile:water as solvent has been described. The reaction products were characterised by IR, $^1$H NMR, $^{13}$C NMR & Mass spectral data.

REFERENCES


