Microwave assisted synthesis of thiaodiazolo-pyrimidin-2-thiones

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A series of 1-(1,3,4-thiaodiazolo)-2-thioxo-pyrimidines 4a-g are synthesized by the condensation of monosubstituted thioureas 1a-g, ethyl acetoacetate 2 and aryl aldehyde 3 in dry media using microwave irradiation. The reaction time is brought down from hours to minutes along with yield enhancement.

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Thiaodiazolo-pyrimidin-2-thiones have been found pharmacologically important as antitumour, anti-allergic, antiviral, antifungal, anti-inflammatory and antihypertensive agents. The wider therapeutic application of thiaodiazolo-pyrimidin-2-thione derivatives prompted us to synthesize these class of novel compounds. Several conventional and non-conventional methods have been reported for the synthesis of thiaodiazolo-pyrimidin-2-thiones. However, these methods are associated with many drawbacks like, multistep synthetic route, longer reaction time with drastic conditions, difficult workup, low yield and use of expensive and hazardous chemicals. These drawbacks have been overcome by synthesizing the title compounds under microwave irradiation using solid supports. Microwave assisted organic synthesis proceeds with facile reactions to furnish good yield within very short time period. Further, this technique avoids the usage of excess organic solvents and harmful acids and bases during the catalysis of the reaction. Solution phase microwave reaction have some limitations for example, super heating of the solvent may result in explosion. So the solid supported dry media synthesis has been adopted as an efficient and ecofriendly technique. Chemical reactions can be carried out easily at atmospheric pressure in open vessels under solid support by using domestic microwave oven. These solid supports, viz. alumina, silica gel, montmorillonite, provide acidic, basic and neutral environment and they reduce the amount of toxic wastes and byproducts in chemical transformations.

Wider therapeutic applications of thiaodiazolo-pyrimidin-2-thiones prompted us to synthesize some novel derivatives in dry media using microwave irradiation, by condensing ethyl acetoacetate, aldehyde and thiourea.

Results and Discussion

Thioureas 1a-g were reacted with ethyl acetoacetate 2 and aldehyde 3 using acidic alumina as solid support under microwave irradiations to obtain substituted-2-thioxopyrimidines 4a-g (Scheme I). The reaction was completed in 7-8 min. The same reaction took 3-4 hr for completion with low yield in conventional method (Table I). Use of montmorillonite K10 clay instead of acidic alumina, reduced reaction time with high yield. These observations clearly show the efficiency of solid supported microwave reaction, over conventional reaction, in terms of reaction time and yield.

The structures of synthesized substituted-2-thioxopyrimidines 4a-g were confirmed from spectral and analytical data (Table I). IR band at 1220-1232 cm⁻¹ due to thioxogrup and the band at 1420-1427 cm⁻¹ due to C=N linkage indicated the formation of 2-thioxopyrimidines 4a-g. The IR absorption bands at 3450-3455 cm⁻¹ and 1715-1730 cm⁻¹ showed the presence of secondary amino group and keto group, respectively in the synthesized compound.

All the aromatic protons appear at δ 6.3-8.5 in ¹H NMR analysis. A doublet at δ 5.2-5.4 is observed due to a tertiary hydrogen atom in the pyrimidine ring. Similarly, a broad singlet is observed at δ 10.6-10.8 due to secondary amino hydrogen in synthesized 2-thioxopyrimidines 4a-g.

Experimental Section

Microwave irradiations were carried out in Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W). IR spectra (υ, cm⁻¹) were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr-pellets; and ¹H NMR spectra on a FTNMR Hitachi-R-600 (60 MHz) instrument using TMS as internal reference (chemical shifts in δ, ppm).
\[
\text{R}^1=3\text{-Nitrophenyl} \\
\text{R}=(a)\text{ Phenyl} \quad (b)\text{ 3-Nicotinyl} \quad (c)\text{ 4-Nicotinyl} \quad (d)\text{ 2-Furyl} \\
(e)\text{ 2-Thionyl} \quad (f)\text{ Heptyl} \quad (g)\text{ Nonyl}
\]

\textbf{Scheme I}

\textbf{Table 1} — Comparison of reaction time period and yields of products \textit{4a-g} and their \textsuperscript{1}H NMR spectra

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p  (^\circ\text{C})</th>
<th>(\text{Method A Time (hr)})</th>
<th>(\text{Method B Time (min)})</th>
<th>% Yield</th>
<th>(\text{Method A}^{\text{1}})</th>
<th>(\text{Method B}^{\text{1}})</th>
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<tr>
<td>\textit{4a}</td>
<td>Phenyl</td>
<td>157</td>
<td>4.0</td>
<td>8.0</td>
<td>55</td>
<td>75</td>
<td></td>
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<tr>
<td>\textit{4b}</td>
<td>3-Nicotinyl</td>
<td>162</td>
<td>3.5</td>
<td>7.0</td>
<td>59</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>\textit{4c}</td>
<td>4-Nicotinyl</td>
<td>174</td>
<td>3.5</td>
<td>7.5</td>
<td>57</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>\textit{4d}</td>
<td>2-Furyl</td>
<td>148</td>
<td>3.0</td>
<td>7.5</td>
<td>63</td>
<td>85</td>
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</tr>
<tr>
<td>\textit{4e}</td>
<td>2-Thionyl</td>
<td>142</td>
<td>3.0</td>
<td>7.0</td>
<td>65</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>\textit{4f}</td>
<td>Heptyl</td>
<td>125</td>
<td>4.0</td>
<td>8.0</td>
<td>52</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>\textit{4g}</td>
<td>Nonyl</td>
<td>132</td>
<td>4.0</td>
<td>8.0</td>
<td>50</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1} All the synthesized compounds \textit{4a-g} showed satisfactory C, H, and N analysis with variations ± 0.40%.
Elemental analyses were performed by means of Heraeus CHN-Rapid Analyzer. Temperatures of reaction mixture were measured on AZ, Mini Gun type non-contact IR thermometer, model no. 8868. All the melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The purity of the compounds were checked on aluminium plates coated with silica gel (Merk).

**General procedure for the synthesis of N-(5-substituted-1,3,4-thiadiazolo)thioureas 1a-g.** These were prepared according to literature method. 18

**General procedure for the synthesis of 1-(5-substituted-1,3,4-thiadiazolo)-6-methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ethyl carboxylate 4a-g**

Conventional method (Method A). Equimolar amount (0.01 mole) of thioureas 1a-g, ethyl acetocacetate 2 and aldehyde 3 were dissolved in 20 ml of EtOH. To this 1 ml of conc. HCl was added. The resulting solution was refluxed for 3-4 hr. After the completion of reaction as checked by TLC, the refluxing mixture was cooled and poured into the crushed ice to obtain solid product 4a-g. The product was filtered, washed with cold water and recrystallized from MeOH.

**Microwave method (Method B).** 0.01 mole of thioureas 1a-g, ethyl acetocacetate 2 and aldehyde 3 were dissolved in 10 mL of EtOH and the resulting solution was adsorbed over 20 g of acidic alumina or montmorillonite K<sub>10</sub> clay in a 100 mL beaker. The reaction mixture was dried in air and subjected to microwave irradiation for 7-8 min. Reaction was monitored at an interval of 30 seconds using TLC. The product 4a-g was extracted with EtOH (4×10 mL) and obtained in solid state after removing EtOH by distillation, under reduced pressure. The product was recrystallized from MeOH.

**Conclusion**

Solid supported condensation of monosubstituted thioureas 1a-g with ethyl acetocacetate 2 and aryl aldehyde 3 under microwave irradiation gave 1-(1,3,4-thiadiazolo)-2-thioxo-pyrimidines 4a-g with 87% yield. The reaction completed in 7-8 min compared to 3-4 hr in conventional heating with low yield. Further, the usage of organic solvents has been minimised by adopting solid supported microwave reactions.

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**References**