Microwave assisted one-pot synthesis of nitrogen and oxygen containing heterocycles from acyl Meldrum’s acid# †

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One-pot syntheses of biologically active nitrogen and oxygen containing heterocyclic compounds such as uracils and thiouacils and 1,4-benzothiazines, 4-methylcoumarins and 4H-1,4-dihydropyridines, using acyl Meldrum’s acids are reported.

Keywords: Meldrum’s acid, microwave assisted synthesis, uracils, benzothiazines, coumarins, dihydropyridines

1, 4-Dihydropyridines are important because of their biological activity and some such as amoldipine¹ are important drugs for the treatment of angina and hypertension because of their vasodilator properties. They have been used in the treatment of benign prostatic hyperplasia and cancer therapy.¹²⁴⁻¹²⁶ Uracils and thiouracils are widely utilized due to their pharmacological properties and inhibitory effect such as anti-inflammatory and anti-viral activities; uracil is a constituent of RNA.¹³ Coumarins are another significant group of highly useful and important natural products and are used as additives in food and cosmetics, as optical brightening agents and dispersed fluorescent and laser dyes.¹⁴ Derivatives of coumarins usually occur naturally as secondary metabolites present in seeds, roots and leaves of many plant species. Uracils,¹⁵⁻¹⁸, coumarins,¹⁹⁻²¹ dihydropyridines,¹⁴⁻¹⁸ and 1,4-benzothiazines¹⁹,²⁰ have been prepared under conventional conditions. Meldrum’s acid behaves as versatile C₅O₂ synthon and contains active methylene group (pKa 5.1) and thus, appears to be an attractive alternative to the synthetically well established acyclic malonic esters²¹⁻²³. The present work includes synthesis of biologically active nitrogen and oxygen containing heterocyclic compounds such as uracils and thiouracils 3, and 1,4-benzothiazines 4, 4-methylcoumarins 5 and 4H-1,4-dihydropyridines 6, using acyl Meldrum’s acids in one-pot fashion. After alcoholysis of the acyl Meldrum’s acid under microwave irradiation, addition of urea (or thiourea), 2-aminothiophenol, phenols and aromatic aldehydes and ammonium acetate, followed by MW irradiation of reaction mixture affords compounds 3, 4, 5, and 6, respectively (Scheme I). In conclusion, a convenient and efficient environment friendly methodology has been developed for the synthesis of these heterocycles using acyl Meldrum’s acids.

Experimental Section

All chemicals were synthetic grade (S.D. Fine Chem. Ltd, Mumbai, India). The acyl Meldrum’s acids were prepared in the laboratory.²⁵,²⁶ The products were characterized by comparison of their physical constants with those of authentic samples and by NMR and IR spectroscopic methods. The melting points were determined by open capillary method and are uncorrected. A Kenstar (OM9918C, 2350 W) monomode microwave oven was used to carry out the reactions.

General procedure for the preparation of compounds 3-6. A mixture of the acyl Meldrum’s acid 1 (0.02 mol, 3.16 g) and excess methanol or ethanol (10 mL) in an Erlenmeyer flask was irradiated for 5-6 min at power level 30. The progress of reaction was monitored by TLC (hexane-ethyl acetate 2:1). After completion of the generation of ketoesters 2 in situ, 0.01 mole of the appropriate reagent(s) [aromatic aldehyde and ammonium acetate, 2-aminothiophenol (or phenol) and sulfuric acid, urea (or thiourea)] was added and mixed thoroughly and the resultant mixture was again irradiated under microwave to afford the desired compounds. The physical characterization data are given in Table I.

The characteristic IR absorptions for the compounds synthesized are given below.

1,4-Dihydropyridines: 3404, 3325 (NH), 1675, 1635 (C=O), 1590, 1529 cm⁻¹ (C=C).

4(H)-1,4-Benzothiazines: 3310 (NH), 1650-1620 (C=O), 1596-1585 (C=C), 1290-1020 (C-O), 730-650 cm⁻¹ (C=S-O).

Note

‡ This work was presented at the C. V. Raman Memorial Seminar on Feb 28, 2004 at North Maharashtra University, Jalgaon 425 001, India
# This paper is dedicated to late Prof. R. B. Mane, Department of Chemistry, Shivaji University, Kolhapur 416 004, India
Scheme I

Table I — Yields and melting points of the compounds 3-6

<table>
<thead>
<tr>
<th>Compd</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Lit.19,27,28 m.p. (°C)</th>
<th>Compd</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Lit.19,27,28 m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>3</td>
<td>75(^a)</td>
<td>310(dec.)</td>
<td>311-12</td>
<td>5a</td>
<td>2-10</td>
<td>90(^d)</td>
<td>127-28</td>
<td>128</td>
</tr>
<tr>
<td>3b</td>
<td>3</td>
<td>65(^a)</td>
<td>281-83</td>
<td>282-84</td>
<td>5b</td>
<td>2-10</td>
<td>89(^d)</td>
<td>170-72</td>
<td>172</td>
</tr>
<tr>
<td>3c</td>
<td>3</td>
<td>70(^a)</td>
<td>327-29</td>
<td>326-31</td>
<td>5c</td>
<td>2-10</td>
<td>95(^d)</td>
<td>207-208</td>
<td>208</td>
</tr>
<tr>
<td>3d</td>
<td>3</td>
<td>70(^a)</td>
<td>262-64</td>
<td>263-65</td>
<td>5d</td>
<td>2-10</td>
<td>89(^d)</td>
<td>131-32</td>
<td>132</td>
</tr>
<tr>
<td>4a(^b)</td>
<td>6-8</td>
<td>90(^e)</td>
<td>115-16(^e)</td>
<td>–</td>
<td>6a</td>
<td>3.5-6</td>
<td>90(^d)</td>
<td>193-94</td>
<td>195</td>
</tr>
<tr>
<td>4b(^b)</td>
<td>6-8</td>
<td>90(^e)</td>
<td>142-44</td>
<td>144</td>
<td>6b</td>
<td>3.5-6</td>
<td>82(^d)</td>
<td>192-93</td>
<td>193</td>
</tr>
<tr>
<td>4c(^b)</td>
<td>6-8</td>
<td>92(^c)</td>
<td>170-71</td>
<td>171</td>
<td>6c</td>
<td>3.5-6</td>
<td>85(^d)</td>
<td>204-205</td>
<td>205</td>
</tr>
<tr>
<td>6d</td>
<td>3.5-6</td>
<td>92(^d)</td>
<td>187-89</td>
<td>189</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

(a) Recrystallized from aq. ethanol (b) DMSO (5 mL) used to dissolve the aminophenol (c) Recrystallized from methanol (d) Recrystallized from ethanol (e) Anal. Caled for C\(_{11}\)H\(_{11}\)NO\(_2\): C, 59.71; H, 5.01; N, 6.33; O, 14.46; S, 14.49. Found: C, 59.62; H, 4.95; N, 6.11; O, 14.32; S, 14.34%. \(^1\)H NMR (DMSO-\(d_6\)+CDCl\(_3\)): \(\delta\) 7.00-6.46 (m, 4H, Ar-H), 3.72 (s, 3H, CH\(_3\)), 2.29 (s, 3H, C=CH\(_3\)).
4-Methylcoumarins: 1670-1712 (C=O), 1620-1600 (C=C bond), and 3500 cm\(^{-1}\) (OH) in case of 7-hydroxy-4-methyl coumarins.

Uracils and thiouracils: 3400-3250 (NH), 1730 (C=O), 1660-1640 cm\(^{-1}\) (C=S).

References