A General Synthesis of Substituted 2,3-Dihydro-4H-1,3-benzoxazin-4-ones

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The condensation of salicylamide (1) with aldehydes and ketones (2) to give substituted 2,3-dihydro-4H-1,3-benzoxazin-4-ones (3) has usually been accomplished with acid catalysis along with some mechanism for removing water formed during the reaction. Generally, hydrochloric acid has been used as the catalyst, along with a dehydrating agent or azeotropic removal of water. The conditions used have been numerous\(^1,2,3\) and have varied with the carbonyl compound. We should like to report a new, general procedure which gives consistently high yields of pure product. The procedure utilizes polyphosphate ester\(^4\) (PPE) as both the catalyst and the dehydrating agent.

\[
\begin{array}{cccc}
\text{O} & \text{NH}_2 & + & \text{O} = \text{C} \text{R}^1 \text{R}^2 \\
\text{OH} & & & \rightarrow \\
\text{1} & & & \text{2} \\
\end{array}
\]

In Table 1, the melting points are of the crude products as isolated from the reaction. As can be seen, the yields are high and the products are quite pure.

Preparation of Substituted 2,3-Dihydro-4H-1,3-benzoxazin-3-ones;
General Procedure:
To polyphosphate ethyl ester (PPE): 2.2 g. 0.02 mol; M.W. = 432.14\(^5\) in a 50 ml round-bottom flask was added a slurry of salicylamide (1.37 g. 0.01 mol) and aldehyde or ketone (0.011 mol) in chloroform (15 ml). (Paraaldehyde was used as the source of acetaldelyde.) The reaction mixture was refluxed for the time shown in the table. The solvent was removed under aspirator vacuum and the residue hydrolyzed by adding 10% aqueous sodium hydroxide or sodium hydrogen carbonate (50 ml). The mixture was stirred in the base for a few minutes; white or yellow solid was formed. Occasionally it was necessary to break lumps with a glass rod to obtain complete hydrolysis. The product was collected by filtration and washed thoroughly with water and dried. In the reactions using heptanal and acetonaphone, the product was washed with petroleum ether (30–60°; 5 x 1 ml) before drying to remove remaining starting material.
Table 1. 2,3-Dihydro-4H-1,3-benzoxazin-4-ones (3) obtained from Aldehydes or Ketones (2) and Salicylamide (1)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Reflux hr</th>
<th>Yield %</th>
<th>Ref.¹</th>
<th>Yield %</th>
<th>m.p. (crude product)</th>
<th>Ref.¹</th>
<th>m.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₃</td>
<td>1.75</td>
<td>83</td>
<td>33</td>
<td>143–147</td>
<td>144–146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>n-C₅H₁₁</td>
<td>3</td>
<td>57</td>
<td>14</td>
<td>77–80</td>
<td>82–83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>C₆H₅</td>
<td>2.5</td>
<td>89</td>
<td>82</td>
<td>165–168</td>
<td>168–169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>2.5</td>
<td>89</td>
<td>47</td>
<td>131–134</td>
<td>135–137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>C₆H₅</td>
<td>4.5</td>
<td>38</td>
<td>20</td>
<td>225–227</td>
<td>226–227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-=-(CH₂)₄-</td>
<td>5</td>
<td>72</td>
<td>47</td>
<td>134–137</td>
<td>135–137</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-=-(CH₂)₃-</td>
<td>5</td>
<td>92</td>
<td>82</td>
<td>186–188</td>
<td>188–190</td>
<td></td>
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</table>

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