A Facile Synthesis of 2-Alkyl(aryl)-6- and -7-nitro-3-oxo-3,4-dihydro-2H-1,4-benzoxazines 1

D. R. SHRIDHAR, S. S. GANDHI, K. SRINIVASA RAO

Chemistry Division, IDPL Research Centre, Indian Drugs & Pharmaceuticals Limited, Hyderabad-500037 (A.P.), India

2-Substituted 3-oxo-3,4-dihydro-2H-1,4-benzoxazine derivatives, a class of compounds which possess interesting pharmacological and antimicrobial properties2,3,4 are usually obtained in two-steps by condensation of α-aminophenols with the corresponding α-haloacyl halides or alkyl α-haloacetates followed by cyclisation of the resulting intermediates. However, the above methods suffer from one or more drawbacks such as low overall yields, longer reaction times, and contamination of the end products with by-products. More recently, we have reported5 a convenient one-step synthesis of some 3-oxo-3,4-dihydro-2H-1,4-benzoxazines by reaction of the respective α-aminophenol with chloroacetyl chloride in refluxing isobutyl methyl ketone in presence of aqueous sodium hydrogen carbonate.

Miller et al.6,7,8 have recently reported the synthetic utility of potassium fluoride for C-, O-, and S-alkylation in many systems, as well as for intermolecular self-condensation of enolizable ketones5, and these reactions have been explained on the basis of the strong hydrogen bonding nature of potassium fluoride. Furthermore, the strong basic character of potassium fluoride even in the non-polar solvent medium has been very well documented9,10. These observations led us to investigate the utilisation of potassium fluoride for a simple synthesis of the title nitro-substituted benzoxazinones. Thus, we report herein a facile and more convenient one-step synthesis for large scale preparation of 2-substituted 6- and -7-nitro-3-oxo-3,4-dihydro-2H-1,4-benzoxazines 3 by potassium fluoride-assisted O-alkylation of 4- and 5-nitro-2-aminophenols 1 with
### Table. 2-Substituted 6-(or 7-)-Nitro-3-oxo-1,4-dihydro-2H-1,4-benzoxazines 3a-j

<table>
<thead>
<tr>
<th>Product</th>
<th>Position of NO₂ group</th>
<th>R¹</th>
<th>R²</th>
<th>Yield* [%]</th>
<th>m.p. [°C]</th>
<th>Molecular formula or Lit. m.p. [°C]</th>
<th>I.R. (nujol)* ν_{c=ν}, [cm⁻¹]</th>
<th>¹H-N.M.R. (DMSO-d₆)* δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>7-NO₂</td>
<td>H</td>
<td>H</td>
<td>82</td>
<td>234*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1680</td>
<td>4.75 (s, 2H); 7.10 (d, J=7-7.5 Hz, 1H); 7.75-9.95 (m, 2H); 11.25 (br, s, 1H)</td>
</tr>
<tr>
<td>3b</td>
<td>6-NO₂</td>
<td>H</td>
<td>H</td>
<td>59</td>
<td>235*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1685</td>
<td>4.75 (s, 2H); 7.15 (d, J=7-7.5 Hz, 1H); 7.7-7.85 (m, 2H); 11.0 (br, s, 1H)</td>
</tr>
<tr>
<td>3c</td>
<td>7-NO₂</td>
<td>CH₃</td>
<td>H</td>
<td>87</td>
<td>208*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1685</td>
<td>1.60 (d, J=6 Hz, 3H); 4.80 (q, J=6 Hz, 1H); 7.10 (d, J=7-7.5 Hz, 1H); 7.75-7.95 (m, 2H); 11.3 (br, s, 1H)</td>
</tr>
<tr>
<td>3d</td>
<td>6-NO₂</td>
<td>CH₃</td>
<td>H</td>
<td>63</td>
<td>190*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1680</td>
<td>1.60 (d, J=6 Hz, 3H); 4.70 (q, J=6 Hz, 1H); 7.00 (d, J=7-7.5 Hz, 1H); 7.8 (m, 2H); 10.7 (br, s, 1H)</td>
</tr>
<tr>
<td>3e</td>
<td>7-NO₂</td>
<td>CH₃</td>
<td>CH₃</td>
<td>63</td>
<td>209*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1680</td>
<td>1.70 (s, 6H); 7.00 (d, J=7-7.5 Hz, 1H); 7.9-8.1 (m, 2H); 9.35 (br, s, 1H)</td>
</tr>
<tr>
<td>3f</td>
<td>6-NO₂</td>
<td>CH₃</td>
<td>CH₃</td>
<td>61</td>
<td>205*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1680</td>
<td>1.50 (t, J=6 Hz, 3H); 1.25-2.15 (m, 2H); 1.45 (t, J=6 Hz, 1H); 2.6 (d, J=7-7.5 Hz, 1H); 7.8-8.0 (m, 2H)</td>
</tr>
<tr>
<td>3g</td>
<td>7-NO₂</td>
<td>C₆H₅</td>
<td>H</td>
<td>72</td>
<td>196*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1690</td>
<td>1.15 (t, J=6 Hz, 3H); 1.75-2.15 (m, 2H); 1.45 (t, J=6 Hz, 1H); 2.6 (d, J=7-7.5 Hz, 1H); 7.8-8.0 (m, 2H)</td>
</tr>
<tr>
<td>3h</td>
<td>6-NO₂</td>
<td>C₆H₅</td>
<td>H</td>
<td>54</td>
<td>164*</td>
<td>C₂₃H₂₀N₂O₄ (208.1)</td>
<td>1690</td>
<td>1.20 (t, J=6 Hz, 3H); 1.85-2.15 (m, 2H); 1.45 (t, J=6 Hz, 1H); 2.5 (d, J=7-7.5 Hz, 1H); 7.85-8.05 (m, 2H); 9.7 (br, s, 1H)</td>
</tr>
<tr>
<td>3i</td>
<td>7-NO₂</td>
<td>C₆H₅</td>
<td>H</td>
<td>67</td>
<td>195*</td>
<td>C₂₃H₂₀N₂O₄ (270.2)</td>
<td>1685</td>
<td>5.85 (s, 1H); 6.90 (d, J=6 Hz, 1H); 7.45 (s, 5H); 7.85-8.0 (m, 2H); 9.45 (br, s, 1H)</td>
</tr>
<tr>
<td>3j</td>
<td>6-NO₂</td>
<td>C₆H₅</td>
<td>H</td>
<td>45</td>
<td>187*</td>
<td>C₂₃H₂₀N₂O₄ (270.2)</td>
<td>1680</td>
<td>5.80 (s, 1H); 7.05 (d, J=7-7.5 Hz, 1H); 7.45 (s, 5H); 7.75-7.9 (m, 2H)</td>
</tr>
</tbody>
</table>

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*The reported overall yields of 3 are of pure crystallized products.

*The microanalyses of the new compounds showed the following deviations from the calculated values: C ± 0.35, H ± 0.45, N ± 0.47.

*Recorded on a Perkin-Elmer model 298 spectrometer.

*¹H-N.M.R. spectra measured at 90 MHz on a Varian A-90 (EM-390) spectrometer using TMS as an internal standard.

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The more easily accessible α-bromoalkanoic acid ethyl esters 2 in dimethylformamide or dimethyl sulfoxide, followed by in situ intramolecular cyclisation of the resulting O-alkylated aminophenol in presence of excess of fluoride ion.

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{Br} \quad \text{C} \quad \text{COOC}_2\text{H}_5 \\
\text{OH} \quad \text{NH}_2 & \quad \text{R}^1 \quad \text{R}^2
\end{align*}
\]

Speciﬁcally, the reaction was carried out in a dry process.

Six hitherto unreported 2-substituted-6- and -7-nitrobenzoxazinones (3c, 3e, 3f, 3g, 3i, and 3j) were also prepared by this method in good yields and the results are summarised in the Table. The structures of products 3 were conﬁrmed by microanalyses, and I.R. and ¹H-N.M.R. spectrometry.

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2-Substituted 6-(or 7-)-Nitro-3-oxo-1,4-dihydro-2H-1,4-benzoxazines 3a-j: General Procedure:

To a stirred suspension of potassium ﬂuoride (10 g) in dry dimethylformamide (50 ml) is added the α-bromoalkanoic acid ethyl ester 2 (0.066 mol) and the stirring is continued for 15 min at room temperature. To this mixture is added the nitro-o-aminophenol 1 (0.066 mol) and the mixture is stirred for 6 h at 50-50 °C and left overnight at room temperature. It is then poured into ice/water (300 ml), the resulting light yellow solid is filtered, washed with water, and dried. Recrystallisation from ethanol gives pure 3 as yellow shining needles.

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