A CONVENIENT ONE-POT SYNTHESIS OF 3-NITRO-2H-CHROMENES BY ULTRASONIC AGITATION ON BASIC ALUMINA

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Abstract - The condensation of \( \alpha \)-hydroxybenzaldehydes with \( \beta \)-nitrostyrene derivatives was carried out on basic alumina. Sonic acceleration of this condensation provides a convenient synthesis of 2-phenyl-3-nitro-2H-1-benzopyrans in good yields.

3-Nitrochromenes are an important class of biologically active oxygen heterocycles.1–4 In view of the reported radioprotecting effects of \( \Delta^3 \)-chromenes containing electron attracting substituents5 and our continuous interest in the chemistry of conjugated nitroalkenes6, we became interested in the synthesis of 2-phenyl-3-nitro-2H-chromenes. Conventional synthesis3,7,8 of these compounds involve the condensation of \( \beta \)-nitrostyrene derivatives with the corresponding \( \alpha \)-hydroxybenzaldehydes in pyridine3, and triethylamine7,8. Unfortunately, the yields are modest, reaction times are long, and isolation of the desired product is tedious.

Aluminum oxide is known to be an effective catalyst for a number of condensation reactions9, including the Knoevenagel reaction10,11 and the synthesis of 4H-chromenes12. Consequently, we explored the application of basic alumina13 in the syntheses of \( \Delta^3 \)-chromenes. Preliminary studies involved the reactions of salicylaldehyde with \( \beta \)-nitrostyrene adsorbed on basic alumina in the absence of solvent. The highest yields (82%) of 3-nitro-2-phenylchromene were obtained when the molar ratio of aldehyde to nitrostyrene was 2:1. Nearly pure 2-phenyl-3-nitrochromene was obtained by simply extracting the reaction mixture with acetone. Unfortunately, we found that the reaction yields decreased in the presence of solvents, thus jeopardizing the use of solid reactants. However, we soon discovered that solid reagents could be dissolved in an appropriate solvent, mixed with alumina, the solvent removed, and the reaction allowed to proceed. The reaction time was relatively long but was decreased through the use of sonification;14 such sonic acceleration is rapidly gaining recognition in heterogeneous reaction systems.15,16

—139—
We wish to report that ultrasonic agitation of a variety of 2-hydroxybenzaldehydes and p-nitrostyrene derivatives on basic alumina provides a rapid and simple procedure for the syntheses of 2-phenyl-3-nitro-2H-1-benzopyrans, \( \mathbf{3} \). The results are summarized in Table I.

![Chemical Structures]

\[
\text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
\text{a} \quad \text{H} \quad \text{H} \\
\text{b} \quad \text{H} \quad \text{OCH}_3 \\
\text{c} \quad \text{OEt} \quad \text{H} \\
\text{d} \quad \text{OEt} \quad \text{OCH}_3 \\
\text{e} \quad \text{H} \quad \text{H} \quad \text{Cl}
\]

\( \mathbf{4} \) a \( R = H \) \\
\( b \) \( R = \text{COCH}_3 \)

<table>
<thead>
<tr>
<th>Compound No</th>
<th>Time (h)</th>
<th>Yielda</th>
<th>Mp(^b) ( ^\circ\text{C} )</th>
<th>Lit. Mp</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>2.0</td>
<td>85</td>
<td>92-93</td>
<td>92.5-93.5</td>
<td>7</td>
</tr>
<tr>
<td>3b</td>
<td>2.5</td>
<td>76</td>
<td>121-122</td>
<td>120</td>
<td>3</td>
</tr>
<tr>
<td>3c</td>
<td>2.5</td>
<td>68</td>
<td>89-90</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>3d</td>
<td>3.5</td>
<td>42</td>
<td>129-130</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>3e</td>
<td>4.0</td>
<td>47</td>
<td>117-118</td>
<td>116</td>
<td>3</td>
</tr>
<tr>
<td>4a</td>
<td>4.0</td>
<td>36</td>
<td>210-211</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>-</td>
<td>-</td>
<td>169-170</td>
<td>-</td>
<td>19</td>
</tr>
</tbody>
</table>

\( a \) - isolated and unoptimized yields based on p-nitrostyrene \\
\( b \) - uncorrected

In a typical experiment, basic alumina\(^ {13} \) (13-15 g) was added to a mixture of 2-hydroxybenzaldehyde (10 mmol) and p-nitrostyrene (5 mmol) at room temperature and stirred for 1 min. [When the reactants were solid, a minimum amount (4-5 ml) of diethyl ether or dichloromethane was used to dissolve them prior to the addition of the alumina and then the solvent was removed under reduced pressure]. The reaction mixture was then subjected to sonic agitation\(^ {14} \) at 30-35°C for the time indicated in Table I. The product was extracted into acetone or dichloromethane (5x15 ml). Removal of the solvent under reduced pressure afforded the 2H-chromenes. Further purification (removal of traces of aldehyde) was carried out by passing a solution (CH\(_2\)Cl\(_2\)) of the chromene through a small column of basic alumina. The products exhibited physical and spectral characteristics in accord with the assigned structures.
ACKNOWLEDGEMENT  We wish to thank the Department of Energy for support of this research.

REFERENCES AND NOTES

13. Basic alumina (Aldrich Chemical Co., no. 19,944-3) ~150 mesh was heated at 250-300°C overnight prior to use.
14. Branson Ultrasonic cleaner, Model B-22-4, 117V 60Hz.
17. 1H-NMR (CDCl3) δ: 8.01(s,1H,C4-H), 7.4-6.8(m,7H,Ar-H), 6.48(s,1H,C2-H), 4.01(q,4H,2x-OCH2), 1.38(t,3H,CH3) and 1.36(t,3H,CH3); 13C-NMR (CDCl3) δ: 74.15(C2), 64.6(OCH2), 64.4(OCH2), 14.75 and 14.69(CH3); Anal. Calcd. for C19H19N05: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.99; H, 5.85; N, 4.10.
18. 1H-NMR (CDCl3) δ: 8.02(s,1H,C4-H), 7.26-6.75(m,6H,Ar-H), 6.58(s,1H,C2-H), 4.03(q,4H,2x-OCH2), 3.8(s,3H,-OCH3), 1.39(t,6H,2xCH3); 13C-NMR(CDCl3) δ: 74.12(C2), 64.6(OCH2), 64.5(-OCH3), 56.4(-OCH3) and 14.8(CH3); Anal. Calcd. for C20H21N06: C, 64.69; H, 5.66; N, 3.77. Found: C, 64.51; H, 5.37; N, 3.66.
19. 1H-NMR(CDCl3) δ: 7.42-7.18(m,8H,Ar-H), 6.9(d,1H,C4-H), 5.4(d,J2,3 = 10Hz,1H,C2-H), 5.18(d,J3,4 = 8.6Hz,1H,C3-H), 4.5(d,J2,3 = 10Hz,1H,C2-H), 2.15(J2,3 = 10Hz,1H,C2-H); Anal. Calcd. for C19H34ClNO5: C, 58.70; H, 4.03; N, 4.03. Found: C, 58.52; H, 4.05; N, 3.98. Received, 21st September, 1984