A Convenient Synthesis of 2-(2-Arylethyl)-3-ethoxycarbonyl-5-methoxyindoles via the Wittig-Horner Reaction

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Recently, 2-substituted indoles have been used as intermediates for the synthesis of many alkaloids and their analogs1, 2, 3. The thermolysis of azirines4 is reported to give 2-(2-arylviny1)-indoles. Similarly, the Wittig reaction5 of arylaldehydes with 2-indoly1methyltriphenylphosphonium bromide also furnishes 2-(2-arylviny1)-indoles. The latter compounds have been prepared in many steps from indole-2-carboxylic acid6, 7.

Here we report a facile side-chain bromination of N-benzensulfonyl or N-benzoyl derivatives of ethyl 5-methoxy-2-methylindole-3-carboxylate (1 or 2) by N-bromosuccinimide in boiling carbon tetrachloride to give 3 or 4. Bromination of 2-methylindole derivatives usually gives only ring brominated products8, 9. Compounds 3 or 4 then react smoothly with triethyl phosphate to give the phosphonate esters 5 or 6, respectively, which upon reaction with aryl aldehydes 7 in the presence of sodium hydride in dry tetrahydrofuran at 5–10°C afford the 2-(2-arylviny1)-indoles 8a–c in 45–50% yield with concomitant loss of the N-protective group during work-up. Based on previous observations5, we have assigned trans-geometry to the olefinic double bond in compounds 8a–c. Indoles 8a–c are smoothly hydrogenated in ethanol in the presence of 10% palladium on charcoal to give the title compounds 9a–c in excellent yields.

\[ \text{H}_2\text{CO} \text{COOC}_2\text{H}_5 \xrightarrow{\text{NBS}} \text{H}_2\text{CO} \text{COOC}_2\text{H}_5 \]

\[ 1 \quad x = \text{C}_6\text{H}_5 \quad \text{SO}_3^- \]

\[ 2 \quad x = \text{C}_6\text{H}_5 \quad \text{CO}^- \]

\[ \text{P(OCC}_2\text{H}_5) \quad \xrightarrow{\text{NBS}} \quad \text{H}_2\text{CO} \text{COOC}_2\text{H}_5 \]

\[ \text{Ar} - \text{CH} = \text{O} (7) / \text{NaH} / \text{THF} \]

\[ 5 \quad 6 \]

\[ \text{H}_2\text{CO} \text{COOC}_2\text{H}_5 \xrightarrow{\text{H}_2/\text{Pd}} \text{H}_2\text{CO} \text{COOC}_2\text{H}_5 \]

\[ 8a \quad \text{Ar} = \text{C}_6\text{H}_5 \]

\[ 8b \quad \text{Ar} = \text{H}_{3}\text{CO} \]

\[ 8c \quad \text{Ar} = \text{C}_6\text{H}_5 \]

\[ 9a-c \]

We have noted that deprotonation of the phosphonate ester by sodium hydride occurs only in the presence of aryl aldehydes, while in their absence the phosphonate ester is unaffected by sodium hydride even in refluxing tetrahydrofuran, in accordance with previous reports10.
**Table. Indoles 3, 4, 5, 6, 8a-c, and 9a-c prepared**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield [%]</th>
<th>m.p. [°C] (solvent)</th>
<th>Molecular formula</th>
<th>I.R. (KBr)</th>
<th>'H-N.M.R. (CDCl₃/CDCl₃)</th>
<th>α [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>95</td>
<td>151-152° (CCl₄)</td>
<td>C₈H₇BrNO₂S</td>
<td>1685 (C=O); 1530, 1180 (SO₂); 1.50 (t, 3H); 3.73 (s, 3H); 4.40 (q, 2H); 5.40 (s, 2H); 6.7-8.0 (m, 8H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>106° (CCl₄)</td>
<td>C₈H₇BrNO₂</td>
<td>1680-1655 (C=O); 1.47 (t, 3H); 3.80 (s, 3H); 4.47 (q, 2H); 5.36 (s, 2H); 6.4-8.0 (m, 5H)</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>98</td>
<td>130° (n-C₆H₁₄)</td>
<td>C₈H₁₇NO₂S_Ps</td>
<td>1690 (C=O); 1360, 1160 (SO₂); 1.30 (t, 6H); 1.46 (t, 3H); 1.50 (s, 3H); 4.10 (q, 4H); 4.30 (q, 2H); 4.36 (d, 2H, J₉=16 Hz); 6.7-8.1 (m, 8H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>98</td>
<td>Oil</td>
<td>C₈H₁₇NO₂P</td>
<td>1710-1700 (C=O); 1.30 (t, 6H); 1.60 (t, 3H); 4.00 (s, 3H); 4.10 (q, 4H); 4.50 (d, 2H, J₉=16 Hz); 4.60 (q, 2H); 6.4-8.1 (m, 8H)</td>
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<td></td>
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<tr>
<td>8a</td>
<td>45</td>
<td>215° (C₆H₆/MeO₆)</td>
<td>C₈H₇N₂O₂</td>
<td>3350 (NH₂); 1685 (C=O); 1.48 (t, 3H); 3.90 (s, 3H); 4.20 (q, 2H); 7.0-9.0 (m, 9H); 9.40 (s, 1H)</td>
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<tr>
<td>8b</td>
<td>48</td>
<td>188° (C₆H₆/MeO₆)</td>
<td>C₈H₇N₂O₂</td>
<td>3300 (NH₂); 1680 (C=O); 1.50 (t, 3H); 3.80 (s, 3H); 3.83 (s, 3H); 3.85 (s, 3H); 4.50 (q, 2H); 6.6-8.2 (m, 8H); 9.40 (s, 1H)</td>
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<td></td>
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<tr>
<td>8c</td>
<td>50</td>
<td>178° (C₆H₆/MeO₆)</td>
<td>C₈H₇N₂O₂</td>
<td>3340 (NH₂); 1680 (C=O); 1.45 (t, 3H); 3.90 (s, 3H); 4.40 (q, 2H); 5.93 (s, 2H); 6.6-8.1 (m, 8H); 9.30 (s, 1H)</td>
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<tr>
<td>9a</td>
<td>95</td>
<td>177-178° (C₆H₆/MeO₆)</td>
<td>C₈H₇N₂O₂</td>
<td>3340 (NH₂); 1690 (C=O); 1.40 (t, 3H); 2.90-3.20 (t, 2H); 3.30-3.50 (t, 2H); 3.93 (s, 3H); 4.50 (q, 2H); 6.8-7.7 (m, 7H); 10.13 (s, 1H)</td>
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<tr>
<td>9b</td>
<td>95</td>
<td>137° (C₆H₆/MeO₆)</td>
<td>C₈H₇N₂O₂</td>
<td>3340 (NH₂); 1690 (C=O); 1.40 (t, 3H); 2.70-3.10 (t, 2H); 3.10-3.43 (t, 2H); 3.53 (s, 3H); 3.66 (s, 3H); 3.80 (s, 3H); 4.30 (q, 2H); 6.6-7.7 (m, 6H); 10.13 (s, 1H)</td>
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<tr>
<td>9c</td>
<td>95</td>
<td>116° (C₆H₆/MeO₆)</td>
<td>C₈H₇N₂O₂</td>
<td>3300 (NH₂); 1695 (C=O); 1.40 (t, 3H); 2.70-3.00 (t, 2H); 3.10-3.40 (t, 2H); 3.73 (s, 3H); 4.30 (q, 2H); 5.80 (s, 2H); 6.4-7.6 (m, 6H); 9.60 (s, 1H)</td>
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</table>

a Yield of pure, isolated product.

b Satisfactory microana[lyses obtained: C ± 0.40, H ± 0.09, N ± 0.22.

b CHCl₃ solution.

Ethyl 1-Benzoyl-5-methoxy-2-methylindole-3-carboxylate (2): The experimental procedure is the same as that reported earlier for 1. The crude product is purified by passing through a column of silica gel using petroleum ether (b.p. 60-80 °C)/benzene (1:1) as eluent. Recrystallisation from carbon tetrachloride/petroleum ether (b.p. 60-80 °C) gives 2 as white needles; yield: 85%; m.p. 74 °C.

Bromination of Indoles 1 and 2: A finely powdered mixture of 1 or 2 (0.003 mol) and N-bromosuccinimide (0.003 mol) in dry carbon tetrachloride (200 ml) containing benzyl peroxide (10 mg) is refluxed for 4 h. Succinimide is filtered off and concentration of the filtrate affords the crystalline bromo compounds 3 or 4; yield: 90-95%.

Phosphonate Esters 5 or 6: A mixture of the bromomethylindole 3 or 4 (0.003 mol) and triethyl phosphate (0.0033 mol) is heated at 155-160 °C for 3 h under nitrogen and the excess triethyl phosphate is removed under vacuum to leave the phosphonate ester 5 or 6 as a single product; yield: 98%.

2-(2-ArylvinyI)-3-ethoxy carbonyl-5-methylindoles 8a-c; General Procedure: To a well-stirred solution of the phosphonate ester 5 or 6 (2.55 mmol) and aryl aldehyde (7 % mmol) in dry tetrahydrofuran (25 ml) under nitrogen at 5 °C sodium hydride (0.12 g, 5 mmol) is added slowly, so that the evolution of hydrogen is not too vigorous. The resulting bright yellow solution is stirred for 24 h at room temperature. Then the solvent is distilled off, the residue is decomposed with ice/water (15 ml), and extracted with ethyl acetate (3 x 20 ml). The dried (sodium sulphate) extract affords 8a-c upon concentration and cooling; yield: 45-50%.

Catalytic Reunion of 8a-c; General Procedure: A solution of 8a-c (0.20 g) in ethanol (10 ml) is hydrogenated over 10% palladium on charcoal (25 mg) at 50 psi for 20 h. Filtration of the catalyst and concentration of the filtrate gives the 2-(2-arylvinyI)-3-ethoxy carbonyl-5-methylindoles 9a-c as white crystals; yield: 95%.

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