Note

Synthesis of some 3-phenyl-4-methyl-6-(6-arylpypyridin-2-yl)- and 3-phenyl-4-methyl-6-(4,6-diarylpypyridin-2-yl) coumarins

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Various 3-phenyl-4-methyl-6-(6-arylpypyridin-2-yl) coumarins 5a-f and 3-phenyl-4-methyl-6-(4,6-diarylpypyridin-2-yl) coumarins 7a-f have been synthesized by reacting 3-phenyl-4-methyl-6-coumarinoylmethylpyridinium bromide 3 with Mannich bases 4a-f and α,β-unsaturated ketones 6a-f respectively under Krohnke’s reaction condition.

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Various 3- and 4-pyridyl substituted coumarins possess variety of physiological activities1-4. These important physiological properties had prompted us to explore the synthetic routes for such coumarin derivatives and in our earlier work we had reported the syntheses of various 3-(2-pyridyl) and 8-(2-pyridyl) coumarins5 utilizing Krohnke’s reaction. Now in continuation of our work on synthesis of pyridyl substituted coumarins, in the present work we report the synthesis of some new 3-phenyl-4-methyl-6-(6-arylpypyridin-2-yl) coumarins 5a-f and 3-phenyl-4-methyl-6-(4,6-diarylpypyridin-2-yl)coumarins 7a-f (Scheme I).

The compounds 5a-f and 7a-f have been synthesized in good yield by reacting 3-phenyl-4-methyl-6-coumarinoylmethyl pyridinium bromide 3 with Mannich bases 4a-f and α,β-unsaturated ketones 6a-f respectively under Krohnke’s reaction condition. The required 3-phenyl-4-methyl-6-coumarinoylmethyl pyridinium bromide 3 was prepared from 3-phenyl-4-methyl-6-acetyl coumarin6 1 by bromination followed by reaction with dry pyridine.

The formation of pyridine nucleus in compounds 5a-f and 7a-f involves the Krohnke’s mechanism7-8. The key step is the Michael addition of coumarinoylmethyl pyridinium bromide 3 to aryl vinyl ketone (generated in situ from 4 during the course of the reaction) or α,β-unsaturated ketone 6, resulting in a 1,5-dionylpyridinium derivative which subsequently undergoes cyclization in the presence of NH4OAc / AcOH to afford pyridine ring.

Experimental Section

IR spectra were recorded in KBr on a Nicolet 400D spectrophotometer and 1H NMR in CDCl3 on a Hitachi R-1500, 60 MHz spectrometer using TMS as an internal standard. 13C NMR were recorded on Brucker Avance 300 spectrometer using CDCl3 as solvent and TMS as an internal standard.

Preparation of 3-phenyl-4-methyl-6-(o-bromoacetyl) coumarin 2. To a solution of 3-phenyl-4-methyl-6-acetyl coumarin 1 (0.01 mole) in glacial acetic acid (20 mL) was added bromine (0.01 mole) in glacial acetic acid (10 mL) with stirring during half hour at room temperature. The reaction mixture was stirred at room temperature for three hours. It was then poured into ice-cold water and the solid separated out was filtered out. It was then washed with water and dried. The product was recrystallized from chloroform to white needles, yield 78%, m.p. 142°C (Found: C, 60.3; H, 3.5. C18H13BrO3 requires C, 60.5; H, 3.6%); IR: 1727 (δ-lactone carbonyl of coumarin), 1682 (C=O stretching of -COCH2Br), 3000 cm⁻¹ (aromatic C-H stretching); 1H NMR (CDCl3): δ 2.36 (3H, s, -CH3), 4.47 (2H, s, -COCH2Br), 7.39-8.36 (8H, m, Ar-H).

Preparation of 3-phenyl-4-methyl-6-coumarinoylmethyl pyridinium bromide 3. A solution of 3-phenyl-4-methyl-6-(o-bromoacetyl) coumarin 2 (0.03 mole) in dry toluene (100 mL) was taken and pyridine (0.03 mole) was added. The reaction mixture was then refluxed in oil bath for two hours. The reaction mixture was then allowed to cool to room temperature and was kept at such for four to five hours. The pyridinium salt was separated out as fine white flakes. It was filtered out and washed with hot toluene and dried. It was recrystallized form acetic acid, yield 80%, m.p. 212°C (dec) (Found: C, 63.2; H, 4.0; N, 3.3. C23H18BrNO3 requires C, 63.3; H, 4.1; N, 3.2%).

Preparation of 3-phenyl-4-methyl-6-(6-arylpypyridin-2-yl) coumarins 5a-f and 3-phenyl-4-methyl-6-(4,6-diarylpypyridin-2-yl) coumarins 7a-f: General procedure. To a well stirred solution of 3-phenyl-4-methyl-6-coumarinoylmethylpyridinium bromide 3
(0.004 mole) in glacial acetic acid (15 mL) was added ammonium acetate (0.06 mole) and an appropriate Mannich base\textsuperscript{5} 4a-f (0.006 mole) or an appropriate α,β-unsaturated ketone\textsuperscript{10,11} 6a-f (0.004 mole) in glacial acetic acid (10 mL). The reaction mixture was stirred at room temperature for 15 minutes and then refluxed in an oil-bath at 140-150°C for 6 hr and left overnight. The reaction mixture was poured in water (75 mL) and the crude product obtained was extracted with chloroform (3 × 30 mL). The organic layer was washed with 10% NaHCO\textsubscript{3} (20 mL), water (20 mL) and dried over anhydrous sodium sulphate. Excess chloroform was distilled out and the crude material obtained was adsorbed on silica gel and column
chromatographed using benzene as an eluent to give 5a-f in 56–61% yield and 7a-f in 59–68% yield.

All the compounds were characterized by elemental analysis, IR and 1H NMR data. The structure of one compound in each series (5a and 7d) was also supported by 13C NMR spectral data (Table I).

Acknowledgement

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References

1 Moffett R B, J Med Chem, 7, 1964, 446.

Table 1 — Characterization data of compounds 5a-f and 7a-f

<table>
<thead>
<tr>
<th>Compd*</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (%) (Calc.)</th>
<th>1H NMR (δ ppm)</th>
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<tr>
<td>5a**</td>
<td>178-80</td>
<td>59</td>
<td>C12H19NO2</td>
<td>83.3 (83.4)</td>
<td>2.4 (3H, s, -CH3) 7.2-8.6 (16H, m, Ar-H)</td>
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<td>5b</td>
<td>184-86</td>
<td>61</td>
<td>C12H17NO2</td>
<td>83.1 (83.2)</td>
<td>2.42 (6H, s, two -CH3)</td>
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<tr>
<td>5c</td>
<td>218-20</td>
<td>58</td>
<td>C12H15NO2</td>
<td>83.6 (83.3)</td>
<td>2.35 (9H, s, three -CH3)</td>
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<tr>
<td>5d</td>
<td>190-91</td>
<td>60</td>
<td>C12H13NO2</td>
<td>80.0 (80.1)</td>
<td>2.4 (3H, s, -CH3), 3.8 (3H, s, OCH3)</td>
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<td>5e</td>
<td>181-82</td>
<td>60</td>
<td>C12H15BrNO2</td>
<td>69.0 (69.2)</td>
<td>2.4 (3H, s, -CH3), 7.0-8.6 (15H, m, Ar-H)</td>
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<tr>
<td>5f</td>
<td>224-26</td>
<td>56</td>
<td>C12H16ClNO2</td>
<td>76.6 (76.5)</td>
<td>2.36 (3H, s, -CH3), 7.1-8.5 (15H, m, Ar-H)</td>
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<tr>
<td>7a</td>
<td>198-00</td>
<td>65</td>
<td>C13H17NO2</td>
<td>85.2 (85.1)</td>
<td>2.4 (3H, s, -CH3), 7.2-8.6 (20H, m, Ar-H)</td>
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<tr>
<td>7b</td>
<td>228-30</td>
<td>68</td>
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<td>2.4 (3H, s, -CH3), 3.9 (6H, s, two -CH3)</td>
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<td>7c</td>
<td>214-16</td>
<td>61</td>
<td>C13H15NO3</td>
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<td>2.3 and 2.4 (6H, two singlet merged, two -CH3), 3.8 (3H, s, OCH3)</td>
</tr>
<tr>
<td>7d**</td>
<td>224-26</td>
<td>60</td>
<td>C13H17NO3</td>
<td>82.5 (82.4)</td>
<td>2.3 (3H, s, -CH3), 3.85 (3H, s, OCH3)</td>
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<td>2.38 (3H, s, -CH3), 6.0 (2H, s, Ar-H)</td>
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<tr>
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<td>2.4 (3H, s, -CH3), 7.2-8.6 (19H, m, Ar-H)</td>
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</table>

* All compounds exhibited the characteristic IR bands at 3000–2900 (aromatic C-H stretching), 2900–2800 (methyl C-H stretching), 1600-1400 (C=C aromatic and C=N of pyridine stretching), 1770–1700 cm⁻¹ (β-lactone carbonyl of coumarin).

** 13C NMR: Compound 5a: δ 17.0, 55.7, 114.5, 117.4, 118.0, 118.5, 121.0, 124.0, 128.6, 130.4, 132.2, 134.8, 136.1, 138.0, 148.0, 153.2, 155.3, 157.0, 161.0 and 13C NMR: Compound 7d: δ 17.4, 56.2, 115.3, 116.8, 116.9, 117.5, 121.0, 124.8, 127.3, 127.8, 128.8, 129.0, 130.0, 130.6, 131.0, 131.2, 135.5, 135.9, 139.7, 148.9, 150.0, 153.5, 155.9, 157.3, 160.6, 161.2.

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7 Kroehnke F, Synthesis, 1, 1976, 1.