Note

A simple synthesis of hydroxyisoflavanones

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Received 30 March 1999; accepted (revised) 25 August 2000

The isoflavonoids 7-hydroxyisoflavanone 4a, 7-hydroxy-3', 4'-dimethoxyisoflavanone 4b, 5, 7-dihydroxy-3', 4'-dimethoxyisoflavanone 4c, 5, 7-dihydroxy-2-methoxyisoflavanone 4d, 5, 7-dihydroxy-3', 4'-dimethoxyisoflavanone 4e and 5, 7-dihydroxy-4'-methoxyisoflavanone 4f have been conveniently prepared by using paraformaldehyde and diethylamine as a base.

Isoflavonones exhibit variable antifungal activity depending on the nature of substituents present in the isoflavone moiety besides functioning as biosynthetic intermediates to other phytoalexines such as pterocarpans and isoflavans. Recent studies on isoflavonone group of natural products have roused interest owing to their diversified interaction with topoisomerase II DNA cleaving agent and also as inhibitor of tyrosine-specific protein kinase immunosuppressants. The isoflavonones have a very limited distribution in the plant kingdom and are restricted to the sub family papilionoidae of the leguminaceae family.

Among the methods available for the preparation of isoflavonones, reduction of the double bond of isoflavones using different reducing agents, synthesis via 3-hydroxyisoflavonone, and also from 2-hydroxyphenyl benzyl ketones and arylation of chroman-4-one esters have already been reported by previous workers. The other reported method involves the insertion of a methylene group on to the desoxybenzoin skeleton. The method involving the protection of the hydroxyl group by benzyl group was not satisfactory due to poor yield. Recently a convenient method for the protection of phenolic hydroxy groups using chlorodimethyl ether has been reported from our laboratory. As an

### Table 1—Physical data of Isoflavanones 3a-f

<table>
<thead>
<tr>
<th>Compd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Reaction period (hr)</th>
<th>m.p. (°C)</th>
<th>Lit m.p. (°C)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>3a²</td>
<td>OCH₂OCH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1.5</td>
<td>51</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>3b²</td>
<td>OCH₂OCH₃</td>
<td>H</td>
<td>H</td>
<td>OCH₃</td>
<td>1.5</td>
<td>oily</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>3c²</td>
<td>OCH₂OCH₃</td>
<td>OCH₂OCH₃</td>
<td>H</td>
<td>H</td>
<td>1.5</td>
<td>oily</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>3d³</td>
<td>OCH₂OCH₃</td>
<td>OCH₂OCH₃</td>
<td>OCH₃</td>
<td>H</td>
<td>1.5</td>
<td>oily</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>3e³</td>
<td>OCH₂OCH₃</td>
<td>OCH₂OCH₃</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>1.5</td>
<td>oily</td>
<td>-</td>
<td>80</td>
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†¹H NMR (CDCl₃) : 3.60 (s, 3H, OCH₂OCH₃), 4.05 (t, 1H, J=7Hz, H-3), 4.82 (d, 2H, J=7Hz, CH₂ at position 2), 5.38 (s, 2H, OCH₂OCH₃), 6.62 (m, 2H, H-6 & H-8), 7.22 (s, 5H, C₅H₅) and 7.80 (d, 1H, J=9Hz, H-5)

†²¹H NMR (CDCl₃) : 3.55 (s, 3H, OCH₂OCH₃), 3.98 (s, 6H, 2x OCH₃ at 3', 4'-position), 4.28 (t, 1H, J=8Hz, H-3), 4.56 (d, 2H, J=8Hz, CH₂ at position 2), 5.25 (s, 2H, OCH₂OCH₃) and 6.83-7.22 (m,6H, Ar-H)

§¹¹H NMR (CDCl₃) : 3.56 (s, 6H, 2x OCH₂OCH₃), 4.00 (t, 1H, J=8Hz, H-3) 4.67 (d, 2H, J=8Hz, CH₂ at 2-position), 5.20 (s, 2H, OCH₂OCH₃), 5.28 (s, 2H, OCH₂OCH₃), 6.31 (d, 1H, J=2Hz, H-6), 6.42 (d, 1H, J=2Hz, H-8) and 7.30 (s, 5H, C₅H₅)

†³¹H NMR (CDCl₃) : 3.50 & 3.56 (each s of 3H, 2x OCH₂OCH₃), 3.75 (s,3H,OCH₃ at C₅), 4.30 (s, 1H, J=8Hz, H-3), 4.56 (d,2H, J=8Hz, CH₂ at position 2), 5.15 & 5.30 (each s of 3H, 2x OCH₂OCH₃), 6.42 & 6.52 (each d of 1H, J=3Hz, H-6 & H-8) and 6.87-7.30 (m, 4H, aromatic protons)

†⁴¹H NMR(CDCl₃) : 3.48 & 3.52 (each s of 3H, 2x OCH₂OCH₃), 3.80 (s, 6H, 2x OCH₃ at 3', 4'-positions), 4.40 (t, 1H, J=7Hz, H-3), 4.56 (d,2H,J=7Hz, CH₂ at position 2), 5.25 & 5.35 (each s of 2H, 2x OCH₂OCH₃), 6.30-7.00 (m,5H, Ar-H)

†⁵¹H NMR (CDCl₃) : 3.52 & 3.57 (each s of 3H, 2x OCH₂OCH₃), 3.83 (s, 3H, OCH₃ at 4'-position), 3.90 (t, 1H, J=8Hz, H-3), 4.70 (d, 2H, J=8Hz, CH₂ at position 2) 5.25 & 5.30 (each s of 2H, 2x OCH₂OCH₃), 6.42 & 6.53, (each d of 1H, J=3Hz, H-6 & H-8) and 6.88-7.35 (m, 4H, Ar-H)
extension of this work we report herein a simple synthesis of hydroxyisoflavanones by employing paraformaldehyde in the presence of diethylamine as a base. Use of ethoxy methyl chloride in alkaline medium was also tried but isolation of the final product had been found to be difficult.

Although various methods are available for the synthesis of isoflavanones the use of paraformaldehyde and diethylamine as a base has not been reported. Therefore in the present study, we have achieved a simple synthesis of hydroxy isoflavanoids in about 70-80% yield.

Accordingly, the hydroxyphenyl benzyl ketones were reacted with chlorodimethyl ether in dry acetone in presence of anhydrous potassium carbonate to afford the corresponding methoxymethyl ethers of 2-hydroxyphenyl benzyl ketones. The methoxymethyl ethers containing a free hydroxy group was dissolved in methanol and refluxed with paraformaldehyde (2 mmole) and diethylamine (2 mmole) for 1 to 1.5 hr. The progress and completion of the reaction was monitored by TLC. Methanol was removed and the reaction mixture was diluted with 10% hydrochloric acid and warmed for 10 min. On cooling white needles separated out which were filtered, dried, recrystallised and characterised.

In summary, the present work provides an improved method for the preparation of hydroxy isoflavanones.

![Diagram](https://example.com/diagram.png)

**Table II—Physical data of hydroxyisoflavanones 4a-f**

<table>
<thead>
<tr>
<th>Compd</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Reaction period (min)</th>
<th>m.p. °C</th>
<th>Lit m.p. °C</th>
<th>Co-IR</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>10</td>
<td>174</td>
<td>174</td>
<td>Co-OR</td>
<td>70</td>
</tr>
<tr>
<td>4b²</td>
<td>OH</td>
<td>H</td>
<td>OCH₃</td>
<td>H</td>
<td>10</td>
<td>185</td>
<td>-</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>4c³</td>
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<td>OH</td>
<td>H</td>
<td>H</td>
<td>10</td>
<td>162</td>
<td>163.5</td>
<td>Co-IR</td>
<td>70</td>
</tr>
<tr>
<td>4d⁴</td>
<td>OH</td>
<td>OH</td>
<td>OCH₃</td>
<td>H</td>
<td>10</td>
<td>170</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>4e⁵</td>
<td>OH</td>
<td>OH</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>10</td>
<td>190</td>
<td>-</td>
<td>Co-IR</td>
<td>70</td>
</tr>
<tr>
<td>4f⁶</td>
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<td>OH</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>10</td>
<td>170</td>
<td>169</td>
<td>Co-IR</td>
<td>75</td>
</tr>
</tbody>
</table>

¹¹H NMR (CD₃OD): 4.05 (t, 1H, J=7Hz, H-3), 4.82 (d, 2H, J=7Hz, H-2), 7.05 (s, 1H, H-8), 7.16 (d, 1H, J=9Hz, H-6), 7.22-7.57 (bm, 5H, C₆H₅ of ring B), 8.00 (d, 1H, J=9Hz, H-5) and 12.10 (s, phenolic OH group); IR (nujol): 3590 (phenolic OH), 1690 (>C=O group), 1300, 1100cm⁻¹ (aromatic ring). Found: C, 75.1; H, 4.8. Calcd for C₅H₁₀O₃: C, 75.0; H, 5.0.

¹²H NMR (CD₃OD): 3.80 (s, 6H, 2x OCH₃), 4.05 (t, 1H, J=7Hz, H-3), 4.82 (d, 2H, J=7Hz, H-2), 6.60 (s, 1H, H-8), 6.57 (d, 1H, J=9Hz, H-6), 7.00 (d, 1H, J=9Hz, H-5), 7.22-7.50 (bm, 3H, Ar-H at ring B), 12.2 (s, phenolic OH group); IR (nujol): 03580 (phenolic OH), 1670 (>C=O group), 1400, 1350, 1190cm⁻¹ (aromatic ring). Found: C, 68.1; H, 5.0. Calcd for C₁₆H₁₄O₄: C, 68.0; H, 5.3%

¹³H NMR (CD₃ OD): 4.00 (t, 1H, J=7Hz, H-3), 4.81 (d, 2H, J=7Hz, H-2) 6.91 (d, 1H, J=2Hz, H-8) 7.02 (d, 1H, J=2Hz, H-6), 7.35-7.72 (bm, 5H, C₆H₅ of ring B), 12.00 (s, 2H, phenolic OH groups); IR (nujol): 3410 (phenolic OH group), 1650 (>C=O group). 1365, 1200, 1150cm⁻¹ (aromatic ring). Found: C, 70.0; H, 4.5. Calcd for C₁₆H₁₄O₄: C, 70.3; H, 4.6%.

¹⁴H NMR (CD₃OD): 3.81 (s, 3H, OCH₃), 4.80 (d, 2H, J=7Hz, H-2), 6.65 (s, 1H, H-8), 6.80 (s, 1H, H-6), 6.70-7.22 (m, 4H, Ar-H at ring B), 12.60 (s, 2H, phenolic OH groups); IR (nujol): 3480 (phenolic OH group), 1675 (>C=O group) 1400, 1250, 1120cm⁻¹ (aromatic ring). Found: C, 67.25; H, 4.8. Calcd for C₁₆H₁₄O₄: C, 67.0; H, 4.9%

¹⁵H NMR (CD₃OD): 3.80 (s, 6H, 2x OCH₃), 4.05 (t, 1H, J=7Hz, H-3), 4.81 (d, 2H, J=7Hz, H-2), 6.62 (s, 1H, H-8), 6.78 (s, 1H, H-6), 6.98-7.25 (m, 3H, Ar-H at ring B), 12.65 (s, 2H, phenolic OH groups); IR (nujol): 3390 (phenolic OH group), 1630 (>C=O group). 1410, 1350, 1150cm⁻¹ (aromatic ring). Found: C, 64.5; H, 5.3. Calcd for C₁₆H₁₄O₄: C, 64.6; H, 5.0%

¹⁶H NMR (CD₃OD): 3.83(s,3H,OCH₃), 4.05 (t, 1H, J=7Hz, H-3), 4.82 (d, 2H, J=7Hz, H-2) 6.48 (s, 1H, J=2Hz, H-8), 7.02 (d, 2H, J=9Hz, H-3' & H-5' of ring B), 7.60 (d, 2H, J=9Hz, H-2' & H-6' of ring B) 12.12 (s, 2H, phenolic OH groups); IR (nujol): 3410 (phenolic OH group), 1650 (>C=O group). 1365, 1200, 1150cm⁻¹ (aromatic ring). Found: C, 67.0; H, 4.8. Calcd for C₁₆H₁₄O₄: C, 67.1; H, 4.9%
Experimental Section

Ethers of 2-hydroxyphenyl benzyl ketones: General procedure. 2, 4-dihydroxyphenyl benzyl ketone and 2, 4, 6-trihydroxyphenyl benzyl ketone were prepared as per the literature procedures. One millimole of a hydroxy phenyl benzyl ketone was taken in dry acetone (200 mL) and to it chloromethyl methyl ether (1.1 mmole) and freshly dried K$_2$CO$_3$ (30 g) were added. The reaction mixture was refluxed for 20 min on a water bath. $K_2$CO$_3$ was filtered off and acetone removed. The crude product was chromatographed over a column of silica gel using ether-benzene (1:1) mixture to get pure methoxymethoxy ether of 2-hydroxyphenyl benzyl ketones.

Methoxymethoxyisoflavanones: General procedure. Methoxymethoxy ether of 2-hydroxyphenyl benzyl ketone (1 mmole) was refluxed in methanol along with paraformaldehyde (2 mmole) and diethyletheramine (2 mmole) for 1.5 hr or till the TLC showed complete conversion to the product. Methanol was distilled off and the product was deposited on cooling followed by recrystallisation from aqueous methanol to afford colourless crystals. The physical data of isoflavones 3a-b are given in Table II.

Hydroxyisoflavanones: General procedure. Methoxymethoxyisoflavanone was heated in methanolic hydrochloric acid (10 mL, 10%) on a water bath for 10 min. The solution was concentrated to half of its volume and equal amount of water was added to it. On cooling solid separated out which was filtered, dried and recrystallized from dilute methanol to afford hydroxyisoflavanones (Table II).

References