SYNTHESIS OF 2,2-DIMETHYL-2H-CHROMENES

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Abstract — The antijuvenile hormones precocenes I and II (1,2), and related 2,2-dimethyl-2H-chromenes (12,13) were synthesized by oxidative cyclization of o-isoprenylphenols with m-chloroperbenzoic acid, followed by dehydration of the corresponding 3-chromanols with methyltriphenoxypophosphonium iodide.

Precocene I (7-methoxy-2,2-dimethyl-2H-chromene, 1) and precocene II (6,7-dimethoxy-2,2-dimethyl-2H-chromene, 2) isolated from the plant Ageratum houstonianum are potentially useful insect antijuvenile hormone. Owing to this attractive biological property, several synthetic methods have been reported.

In continuation of our studies on the synthesis of biologically active natural products, we wish to report an alternative method for the synthesis of precocenes and related chromenes by oxidative cyclization of o-isoprenylphenols and subsequent dehydration.

The o-isoprenylphenols 3,4,5 and 6 were prepared according to Yamada's method. Compound 5 was more conveniently obtained by isoprenylation of methoxyhydroquinone with 2-methylbut-3-en-2-ol in aqueous formic acid.
The oxidative cyclization of substrates 3-6 were performed with m-chloroperbenzoic acid in methylene chloride solution at 0°C. Catalytic amounts of concentrated hydrochloric acid were added in order to avoid the formation of 2,3-dihydrobenzofurans and maximize the production of 2,2-dimethyl-3-chromanols 7-10 (Scheme 1).

Yields and spectral properties of chromanols 7-10 prepared under these conditions are described in Table 1.

Table 1. Chromanols obtained by oxidative cyclization of o-prenylphenols 3 + 6.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Yield(%)</th>
<th>I.r. spectra(ν cm⁻¹)</th>
<th>H-nmr spectra(δ ppm)</th>
<th>M.spectra;m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>40</td>
<td>3310, 1490, 1370, 1360</td>
<td>1.32(s,3H), 1.36(s,3H), 2.09(br s,1H), 2.72(dd, 1H,J=17;3Hz), 3.06(dd, 1H,J=17;3Hz), 3.66-3.92 (m,1H), 3.78(s,3H), 6.5-6.9(m,3H).</td>
<td>H²08(100), 175 (49), 137(96)</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>3450, 1620, 1580, 1500, 1445, 1380, 1365</td>
<td>1.34(s,3H), 1.38(s,3H), 1.83(br s,1H), 2.69(dd, 1H,J=16;5Hz), 3.03(dd,1H, J=17;5Hz), 3.7-3.9(m,1H), 3.79(s,3H), 6.44(s,1H,J=13Hz), 6.53(dd,1H,J=8;3Hz), 6.98(d,1H,J=8Hz).</td>
<td>H²08(29), 175 (5), 137(100)</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>3450, 1510, 1375br</td>
<td>1.32(s,3H), 1.38(s,3H), 1.74(br s,1H), 2.66(dd, 1H,J=17;5Hz), 3.01(dd,1H, J=17;5Hz), 3.6-6.0(m,1H), 3.88(s,3H), 5.26(br s,1H), 6.44(s,1H), 6.64(s,1H)</td>
<td>H²24(34), 191 (7), 154(14), 153(100)</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>3515, 1630, 1480, 1390, 1380</td>
<td>1.31(s,3H), 1.37(s,3H), 1.82(br s,1H), 2.66(dd,1H, J=17;5Hz), 3.01(dd,1H,J=17;5Hz), 3.76(s,1H,J=5Hz), 5.91 (s,2H), 6.43(s,1H), 6.54(s,1H)</td>
<td>H²22(29), 189 (6), 152(12), 151(100)</td>
</tr>
</tbody>
</table>

a. Obtained in KBr (7,9,10) and neat (8); b. Performed in CDCl₃ solution using TMS as internal standard.

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Attempted dehydration of chromanol 7 by means of a variety of reagents (POCl₃/Py; TsCl/Py and DMF; MsCl/Py and DMF) gave only low conversions (10-45%). Better results were obtained by reaction of 7 with methyltriphenylophosphonium iodide in dry HMPA solution, to afford the chromene 12 in 80% yield. In view of this, dehydration of chromanol 8,10 and 11 were carried out using this procedure. The results obtained are summarized in Table 2.

Table 2. 2,2-Dimethyl-2H-chromenes prepared by dehydration of chromanols.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Chromene</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>12</td>
<td>H</td>
<td>OMe</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>OMe</td>
<td>H</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>O-CH₂O</td>
<td></td>
<td>45ᵇ</td>
</tr>
<tr>
<td>11ᵃ</td>
<td>2</td>
<td>OMe</td>
<td>OMe</td>
<td>55ᵇ</td>
</tr>
</tbody>
</table>

a. Compound 11 was obtained by methylation of 9 with Me₂SO₄-KOH; b. No attempts were made to improve yields.

Experimental details of this chromene synthesis will be reported in a forthcoming paper.

ACKNOWLEDGMENT

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REFERENCES AND NOTES


10. These synthetic compounds were characterized by comparison of their physical and spectral properties with those of authentic samples.

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