A Novel Route to Phloroglucinols – Synthesis, Structure, and Reactions of [n](2,4)Phloroglucinophanes**

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Dedicated to Professor Hermann Stetter on the occasion of his 65th birthday

Aldehyde enol ethers can be acylated to b-dicarbonyl- and 1,3,5-tricarbonyl-compounds in very good yields with reactive acid chlorides such as di- and trichloroacetyl chloride, phosgene or malonic acid dichloride 11. The ketone enol ethers 2 react – except with malonic acid dichloride – analogously; with 1, the 4-hydroxy-2H-pyran-2-ones 6 and/or phloroglucinols 7 are obtained (Table 1). Since the pyranones 6 can be converted into the phloroglucinols 7[2] the reaction of 2 with 1 enables a generally applicable synthesis of phloroglucinol and its derivatives in very good yields.

The extension of this reaction to enol ethers of cyclic ketones 8 leads to the bicycles 9 and/or 10 and/or the [n](2,4)phloroglucinophanes 11, which allow interesting conclusions to be drawn about the structure and reaction behavior of metacyclophanes owing to the possibility of tautomerism in the arene moiety (Table 1). Aqueous work-up of 8a–c and 1 affords the bicycles 9a–c (yields 84, 88, and 91%, respectively), while work-up of 8a, b and 1 in methanol furnishes the 9,9- and 10,10-dimethylketals of 9a, b, respectively. In the reaction of 8c–g with 1 the hydrochlorides of the methyl ethers of 10c, d and 11e–g can be isolated (yields 70, 31, 18, 55, 28%).

The expected competition between the tautomers 9–11 can be deduced from the side views of the X-ray crystallographically determined structures of 9a (n = 3), 9c (n = 5), and 11f (n = 9), where in each case R = H. In 9a there is a strain-free coupling of 4-cyclohexene-1,3-dione and cyclohexanone in the chair form and in 9c a combination of 4-cyclohexene-1,3-dione with cyclooctanone in the energetically less favorable chair-chair conformation. In 11f the twelve-membered ring is almost strain-free and orthogonally coupled with the arene.

Table 1. 4-Hydroxy-2H-pyran-2-ones 6 and phloroglucinols 7 (selection).

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R'</th>
<th>R²</th>
<th>6 (%)</th>
<th>7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>5a (43)</td>
<td>7a (52)</td>
</tr>
<tr>
<td>2b</td>
<td>C₂H₅</td>
<td>H</td>
<td>H</td>
<td>6a (24)</td>
<td>7d (79)</td>
</tr>
<tr>
<td>2c</td>
<td>CH(CH₃)₂</td>
<td>H</td>
<td>H</td>
<td>6b (11)</td>
<td>7e (80)</td>
</tr>
<tr>
<td>2d</td>
<td>C(CH₃)₂</td>
<td>H</td>
<td>H</td>
<td>6c (30)</td>
<td>7f (53)</td>
</tr>
<tr>
<td>2e</td>
<td>CH₃</td>
<td>CH₂</td>
<td>CH₃</td>
<td>6d (15)</td>
<td>7g (16)</td>
</tr>
</tbody>
</table>

The compounds 9—11 show different chemical behavior, depending on ring size and ring strain. The hydrochlorides of 10c (R=CH₃) and 11f, g (R=CH₃) with n = 5, 8, 9 can be cleaved to the corresponding hydroxy compounds 9c and 11f, g (R=H) even with water, whereas in the case of 10d (R=CH₃) and 11e (R=CH₃), with n = 6, 7, no cleavage of ether takes place even under drastic conditions (conc. HBr). Comparable with the conversion of deoxyhumulone into humulone and its rearrangement to isohumulone[14] is the reaction of 11f (R=H), whose autoxidation and rearrangement to the obviously more stable bicycle 12f, however, takes place much more rapidly; this can be explained in terms of a decrease in strain on going from an 11- to a 12-membered ring.

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1, 1663-77-8; 2a, 116-11-0; 2b, 926-66-9; 2c, 4188-63-0; 2d, 4188-70-9; 2e, 53110-70-3; 2f, 41623-41-0; 2g, 61142-47-0; 6a, 675-10-5; 6b, 83436-27-5; 6c, 31246-34-1; 6d, 18742-94-4; 7a, 2174-64-3; 7b, 28334-98-7; 7c, 64507-45-5; 7d, 83436-28-6; 7e, 83436-39-7; 7f, 23848-22-8; 8a, 931-51-1; 8b, 50438-50-1; 8c, 50438-51-2; 8d, 70578-46-0; 8e, 13659-75-1; 8f, 57620-91-4; 8g, 32400-32-1; 9a, 83436-30-0; 9b, 83436-31-1; 9c, 83436-32-2; 9d, 10,10-dimethylketal, 83436-34-4; 9e, 83436-33-3; 10d (R=CH₃), 83436-36-6; 10d (R=CH₃). HCl, 83436-35-5; 11e (R=CH₃), 83436-38-8; 11e (R=CH₃). HCl, 83436-37-7; 11f (R=H), 83436-40-2; 11f (R=CH₃). HCl, 83436-39-9; 11a (R=H), 83436-42-4; 11a (R=CH₃). HCl, 83436-41-3; 12f, 83436-43-5;