Cycloadducts Synthesis and Relative Stereochemistry Determined by NMR and DFT-GIAO calculations

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INTRODUCTION

The isobenzofuran-1(3H)-ones (or phthalides) and dihydro, tetrahydro, and hexahydro derivatives are a group of secondary metabolites mostly produced by several genera of the family Apiaceae. These bicyclic \( \gamma \)-lactones have been studied because of their wide range of bioactivities. In our work, the Diels-Alder reaction was chosen as the key step to obtain tetrahydroisobenzofuran-1(3H)-ones derivatives from C-5 substituted butenolides, since \( \alpha,\beta \)-unsaturated \( \gamma \)-lactones act as excellent dienophiles in cycloaddition reactions with dienes.

RESULTS AND DISCUSSION

For the reaction between generic lactone 1 and cyclopentadiene (Cp) only the adducts anti-end \( \textit{o} \) and anti-exo \( \textit{a} \) should be formed (Scheme 1)\(^a\). However, the adduct syn-end \( \textit{n} \) was also isolated for lactone 1c (Table 1).

Scheme 1. Possible adducts (enantiomers are not represented) for the DA reaction between C-5 substituted butenolides and cyclopentadiene.

Table 1. Reactions of lactones 1a-c with cyclopentadiene

<table>
<thead>
<tr>
<th>Lactone:</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
<th>Adduct ratio</th>
<th>Syn-end</th>
<th>Anti-exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OR group</td>
<td>A</td>
<td>98</td>
<td>95</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>1a: OAc</td>
<td>B</td>
<td>96</td>
<td>97</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>1b: OH</td>
<td>C</td>
<td>91</td>
<td>83</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>1c: OiPr</td>
<td></td>
<td></td>
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</tbody>
</table>

\(^a\) A: 3.4 eq.of Cp, 20h; B: 2.4 eq., DCM, 20h; C: 4.3 eq., 96h. 
\(^b\) Combined yield of pure products after chromatography. 
\(^c\) (%) Determined by CG/MS.

The relative stereochemistry of the products was established by NMR experiments (Fig.1) and DFT calculations. In adducts from lactone 1c, for example, the COSY presented a cross correlation signal of H-13’ with H-3 and H-4 for the endo adducts. Moreover, a NOE enhancement of 5% was observed on H4 from H13’ on syn-end and anti-end isomers, while this effect has not been observed in anti-exo. A NOE enhancement of 4.0% was observed on H-9 by irradiating H-4 on anti-exo.

Figure 1. Representation of positive NOE interactions, COSY correlations and coupling constants for butenolide 1c cycloadducts.

On the \(^1\)H NMR spectra were observed coupling constants between H-4 and H-5 of 1.62 Hz for anti-exo adduct and 1.50 Hz for anti-end adduct whereas for the syn isomer, this constant is 6.63 Hz. The unequivocal assignment of all \(^1\)H and \(^13\)C signals were possible with the assistance of HETCOR experiments and DFT-GIAO calculations.

CONCLUSION

The DA reactions with C-5 substituted \( \alpha,\beta \)-unsaturated \( \gamma \)-lactones and cyclopentadiene was successfully employed to synthesize seven analogues of tetrahydroisobenzofuran-1(3H)-ones which were structurally elucidated by NMR techniques and DFT calculations.

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REFERENCES