Synthetic Approaches to 4-(Hydroxymethyl)benzoates and Cyclophanes

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Introduction:

The Diels-Alder reaction is known as a 4+2 cycloaddition because a conjugated diene having 4 pi electrons combines with a dienophile having 2 pi electrons to produce a cyclohexene ring.

In a typical Diels-Alder reaction, the diene is the electron-rich species, so electrons are donated from its highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the electron-poor dienophile.

If the dienophile is an alkene, the initial bicyclic adduct is an 1,4-diene, and the bicyclic compounds.

Coumalic acid derivatives can be electron-poor dienes. Since these dienes contain the diene is electron poor and the dienophile is electron rich.

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In an inverse electron demand Diels-Alder reaction, the donation is reversed because molecular orbital (LUMO) of the electron-poor dienophile.

Donated from its highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the electron-poor dienophile.

These catalysts act as electron-withdrawing groups for the diene, making it more electron poor and therefore more likely to accept donation of electrons from the dienophile. The Diels-Alder reaction applied in this way can be used in a novel synthesis of paracyclopaphenes. Paracyclopaphenes contain an aromatic core in which the para positions are tethered by an aliphatic chain. Paracyclophanes are useful in the study of strain and pi stacking and are also present in some natural products. A paracyclopaphene could be produced by an inverse electron demand Diels-Alder reaction in which a coumalate is tethered to an alkene, which serves as the dienophile. The initial reaction will form a bicyclic compound that will spontaneously extrude carbon dioxide, producing an aromatic ring tethered at the para positions.

Experimental:

Previous investigations by Vosburg, Scherer, and Leonard suggested that hydroxy acids could be effective catalysts of the cycloaddition of methyl isodehydroacetate and propargyl acetate. Several additional catalysts were screened in order to probe the specific requirements for catalysts. The effect of 2,3-dimethylsuccinic acid, succinic acid, citric acid, and lactic acid on the reaction between methyl isodehydroacetate and propargyl acetate in a pressure tube heated at 180 °C was investigated. Data points were taken at 4, 7, and 10 hours using GC/MS to analyze percent completion.

Catalyst Percent product after 4 hours Percent product after 7 hours Percent product after 10 hours

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Percent product after 4 hours</th>
<th>Percent product after 7 hours</th>
<th>Percent product after 10 hours</th>
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</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>60</td>
<td>74</td>
<td>85</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>60</td>
<td>74</td>
<td>85</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>35</td>
<td>36</td>
<td>66</td>
</tr>
<tr>
<td>2,3-Dimethylsuccinic acid</td>
<td>25</td>
<td>42</td>
<td>58</td>
</tr>
</tbody>
</table>

Citic acid was the most effective catalyst for this reaction. Its structure could allow it to coordinate to the carbonyl of methyl isodehydroacetate by way of two hydrogen bonds resulting in a 7-membered ring.

The experimental data was confirmed by further NMR studies and GC/MS analysis.

An ester with a smaller tether was produced from coumalyl chloride and 5-hexyn-1-ol. The substrate with the larger tether would yield a cyclophane which is rather unstrained. The substrate bearing a smaller tether will enable a study of the effect of strain on the reaction. It is possible that dimerization or metacyclophane formation will be competitive pathways in this instance.

Conclusions:

Key contributions to this project include:

- Identification of citric acid as an effective catalyst for the inverse electron demand Diels-Alder reaction of coumalates and alkenes
- Preparation of two bifunctional substrates for study of the tandem intramolecular cycloaddition-fragmentation
- A manuscript of complete research methods and results is in preparation.

Literature Cited:


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