The Effect of Lewis Acids on the Intramolecular Diels-Alder Reaction of the Furan Diene

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Abstract: Lewis acids have been found to accelerate the intramolecular Diels-Alder reaction of the furan diene and dienophile are connected by four-carbon atoms [2-(4-alkyl-5-alkyny1)furans]. The methodology has been extended to include acetylenic dienophiles [2-(1,1-dimethyl-4-oxo-5-alkynyl)-furans], which cyclize to give the oxatricyclic ring system (5,6,7,8-tetrahydro-5,5-dimethyl-8-oxo-2H-2,4a-epoxynaphthalene).

The antibiotic Podosporin A I was isolated from the fungus Podospora decipiens and possesses the unique benzo[d]xanthene ring system. Our interest in the intramolecular Diels-Alder reaction of the furan diene (IMDAF) prompted us to investigate the possibility of using the IMDAF to prepare the C-D rings of Podosporin A. Our synthetic analysis provided oxatricyclo adduct 2, which was later simplified to compound 3 as a model for our study. Since the IMDAF reaction of precursors containing gem-dialkylated four carbon atoms has not been investigated, we chose to explore first the IMDAF reaction involving compounds such as 4.

The IMDAF reaction of a furan diene connected to the diene by a four carbon chain are known to have an equilibrium which is unfavourable starting material. Methods employed to overcome this unfavourable equilibrium to date include heat, β-cyclodextrin, aqueous solutions, alkylated side chains, and high pressure. The success of the first four methods has been limited to precursors having substituted dienophiles. Although high pressure shifted the equilibrium of a variety of systems containing substituted dienophiles to tricyclo adducts exclusively, they were formed in modest yields ranging from 40-60%. Since the above methods required long reaction times (2-14 days) and/or access to specialized equipment we sought a more generally accessible method to improve the yields of adducts and reduce the reaction times.

Lewis acids have been used successfully to catalyze the intramolecular Diels-Alder reaction employing furan as the diene component. In addition Lewis acids have also been used in the intramolecular Diels-Alder reaction; however, their use in the IMDAF reaction has been limited to one unsuccessful report involving a five atom side arm and one example involving a three atom side arm (one nitrogen and two carbon atoms) with an internally substituted magnesium salt. We herein report the effect of Lewis acids on the IMDAF reaction of compounds 4-18 (Schemes 1 and 2).

Scheme 2

Compound 6 was treated with a variety of Lewis acids under various conditions. The most effective catalyst in terms of a starting material:adduct ratio (SM:A, 35:65), yield (97%), and ease of handling was methylaluminum dichloride; the SM:A ratio was attained after only 2.5 hours at -50°C. These results are greatly improved over previous observations employing either florisil or 2.0M calcium chloride, stirring compound 6 for 4 days in florisil provided no adduct while calcium chloride gave a 50:50 SM:A ratio. Interestingly, zinc iodide was the least effective catalyst (r.t., 39h; SM:A, 65:35) in spite of its proven utility in the intermolecular Diels-Alder reaction with furans.

The SM:A ratios observed for the Lewis acid MeAlCl₂ were shown to be thermodynamic and not kinetic ratios. Treating pure tricyclo adduct 20 with one equivalent of MeAlCl₂ in methylene chloride at -50°C for 2.5 hours provided a SM:A ratio of 35:65, which is identical to that obtained when treating precursor 6 under the same conditions.

Table 1 illustrates the effect of MeAlCl₂ on the IMDA reaction of compounds 5-16 (entries 1-12) along with the results from stirring the precursors in florisil/methylene chloride. A few points are noteworthy. The Lewis acid mediated IMDAF reactions provides, in all cases, higher SM:A ratios and yields when compared to the results from florisil/methylene chloride. The starting material and adducts are easily separated by flash chromatography and recycling the starting material provides large quantities of adducts. The gem-dimethyl precursors 11 and 14 (unsubstituted dienophile) provided their corresponding adducts in 88% and 96% yield respectively when stirred in florisil/CH₂Cl₂ for 12 hours. This increase in SM:A ratio when compared to the results from compounds 5 and 8 can be attributed to the 'gem-dialkyl effect'.

1H NMR analysis of the adducts obtained from both the florisil- and Lewis acid mediated IMDA reaction of compounds 5-16...
Table 1: Results of Various IMDAF Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Lewis Acid</th>
<th>Temp. °C</th>
<th>Time h</th>
<th>SM: Adduct Ratio</th>
<th>Adduct Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>5</td>
<td>florisil</td>
<td>-78</td>
<td>1</td>
<td>0.100</td>
<td>19 99 (99)</td>
</tr>
<tr>
<td>2.</td>
<td>6</td>
<td>florisil</td>
<td>-73</td>
<td>2.5</td>
<td>0.100</td>
<td>51 25 (51)</td>
</tr>
<tr>
<td>3.</td>
<td>7</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>78.22</td>
<td>11 (65)</td>
</tr>
<tr>
<td>4.</td>
<td>8</td>
<td>florisil</td>
<td>-78</td>
<td>1</td>
<td>0.100</td>
<td>22 99 (99)</td>
</tr>
<tr>
<td>5.</td>
<td>9</td>
<td>florisil</td>
<td>-78</td>
<td>12</td>
<td>0.100</td>
<td>23 97 (97)</td>
</tr>
<tr>
<td>6.</td>
<td>10</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>82.18</td>
<td>18 97 (97)</td>
</tr>
<tr>
<td>7.</td>
<td>11</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>0.100</td>
<td>25 88 (88)</td>
</tr>
<tr>
<td>8.</td>
<td>12</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>68.32</td>
<td>31 99 (97)</td>
</tr>
<tr>
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<td>8</td>
<td>73.27</td>
<td>27 12 (67)</td>
</tr>
<tr>
<td>10.</td>
<td>14</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>0.100</td>
<td>28 96 (96)</td>
</tr>
<tr>
<td>11.</td>
<td>15</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>78.23</td>
<td>29 98 (98)</td>
</tr>
<tr>
<td>12.</td>
<td>16</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>85.15</td>
<td>30 13 (62)</td>
</tr>
<tr>
<td>13.</td>
<td>17</td>
<td>florisil</td>
<td>-78</td>
<td>8</td>
<td>78.22</td>
<td>18 93 (93)</td>
</tr>
<tr>
<td>14.</td>
<td>18</td>
<td>Me_{2}AlCl</td>
<td>-78</td>
<td>8</td>
<td>85.15</td>
<td>30 13 (62)</td>
</tr>
</tbody>
</table>

a) number in parentheses is the yield of adduct based on recovered starting material

indicated the side arm was orientated exo with respect to the oxygen bridge (Scheme 3); adducts resulting from an endo side arm transition state were neither detected nor isolated.

Scheme 3

Precursor 4 did not provide any tricyclo adduct 3 (Scheme 1) when treated with MeAlCl_{2} in methylene chloride at -78°C (by $^1$H NMR). This result led us to explore the possibility of employing acetylenic dienophiles in the IMDAF reaction; cuprate addition on the tricyclic α,β-unsaturated ketone 32 would presumably lead to 33 (Scheme 4) which would be equivalent to compound 3 (Scheme 1).

Lewis acids were found to accelerate the IMDAF reaction with precursors containing an acetylenic dienophile (entries 13 and 14, Table 1). The milder Lewis acid dimethylaluminum chloride was used at -50°C. These conditions provided the highly strained adducts 31 and 32 in 80% and 97% yield respectively with the bulkier trimethylsilylated acetylenic diene in precursor 17 providing a lower SM:A ratio (12:88) than the methyl substituted acetylene (0:100). The short reaction times and high yields of adducts 31 and 32 are in contrast with previous reports of thermal IMDA reactions involving internally activated acetylenic dienophiles.

Lithium dimethylcuprate added smoothly to adduct 32 in the presence of HMPA and trimethylsilyl chloride (Scheme 4) to afford...
We have shown that Lewis acids can be employed to accelerate the rate at which equilibrium is achieved in the IMDAF reaction where the dienophile is attached to the diene via a four carbon atom side arm. Reaction times were reduced to a few hours (instead of days) and in most cases, increased starting material: adduct ratios were observed when compared to the results involving florasil. Application of tricycloadducts arising from acetylenic precursors towards the preparation of Podosporin A are currently in progress.

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References and Notes

11. Compounds 5-10 were prepared as previously described. A compounds 4 and 11-18 were prepared by standard methods and will be presented in detail in a full paper.
12. The Lewis acids employed in CH2Cl2 (conditions; starting material: adduct ratios) were: SnCl4 (-78°C, 1h; 24:76); BF3Et2O (-50°C, 3h; 28:72); TiCl4 Ti(O)Pr2 (-50°C, 2h; 20:68); Me2AlCl, EtAlCl2 and Et2AlCl (-50°C, 2h; 35:65).
13. A typical procedure for the Lewis acid mediated IMDAF is as follows: To a solution, at -78°C of a precursor (0.34 mmol) in methylene chloride (10 ml, dry, distilled) under an atmosphere of argon was added 1.1 equivalents of a Me2AlCl. The solution was warmed to the appropriate temperature and after 2-3 hours quenched with cold sodium bicarbonate (10%) and extracted with methylene chloride. The solvent was removed in vacuo (no external heating). The ratio of starting material: adduct was determined by integrating the 1H NMR spectrum.
16. The stereochemistry of the adducts was determined by using a combination of coupling constants and n.o.e. experiments.
17. All new compounds provided analytical and/or spectroscopic data consistent with their structures.
18. The major product was identified as a dimer of compound 4 arising from an intermolecular Friedel-Crafts reaction of the alkene on the furan ring of a second molecule.
19. For a recent example of a Lewis acid (Et2AlCl) mediated intramolecular Diels-Alder reaction with a side arm activated acetylenic dienophile, see: Tascner, M.J.; Cyr, P.T. Tetrahedron Lett. 1990, 37, 5297.
20. Optimization of the experimental conditions may result in complete adduct formation for the trimethylsilyl substituted precursor 17.