π-FACIAL SELECTIVITY IN DIELS-ALDER REACTIONS OF CROSSED-CONJUGATED KETONES Bearing AN OXA-SPIRO-RING WITH STERICALLY UNDEMANDING DIENES

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Abstract – The Diels-Alder reactions of cross-conjugated ketones bearing an oxa-spiro-ring with some simple sterically undemanding dienes (cyclopentadiene, 2,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene) afforded the adduct with high π-facial selectivity under mild conditions. The π-facial selectivity can be explained in terms of Cieplak model.

INTRODUCTION
The Diels-Alder reaction has been widely studied, and the mechanistic aspects of this reaction have been much discussed. Winterfeldt et al. have investigated the stereoselectivity in the Diels-Alder reaction of the oxa-spiro-compounds (I) and (2) with sterically hindered bicyclic chiral cyclopentadiene derivatives. Under high pressure conditions, the Diels-Alder reaction gave exclusively the endo-adduct resulting from attack of the diene to the face bearing the oxygen atom of the oxa-spiro-ring in spite of the fact that electronic repulsion between the π-electrons of the diene and the lone pair of the oxygen atom is expected. Houk et al. carried out theoretical calculations on model compounds of this reaction and suggested that the high facial selectivity was a consequence of the lower steric demand of the oxygen atom relative to the CH2 group. In the course of our synthetic study of scyphostatin, we observed high π-facial selectivity in the reaction of 1 with cyclopentadiene even thought it is not sterically demanding. This prompted us to examine this reaction in more detail. Although the π-facial selectivity in the Diels-Alder reaction of unsymmetric 1,3-diienes with dienophiles has been widely investigated, that of unsymmetric dienophiles has not received as much attention. Our investigation herein presents one of a limited number of examples of such reaction.
RESULTS AND DISCUSSION

Treatment of spiro-compounds (1-3) with dienes (cyclopentadiene, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene) afforded only one or a mixture of two adducts (Scheme 1). The relative configuration of all of the adducts was assigned by $^1$H NMR NOE experiments and/or X-Ray structural analysis. In the case of 4c, X-Ray analysis was carried out on the epoxidation product from 4c, prepared by mCPBA oxidation.

Table 1 summarizes the results of the Diels-Alder reaction of oxa-spiro lactone (1) with dienes. The Diels-Alder reaction of oxa-spiro lactone (1) with cyclopentadiene in CH$_2$Cl$_2$ and CF$_3$CH$_2$OH preferentially afforded the adduct (4a), which results from reaction to the face of the dienophile bearing the spiro ring oxygen atom (4a : 5a = 96 : 4, Table 1, Entries 1, 3). The Diels-Alder reaction of spiro lactone (1) with cyclopentadiene was accelerated in CF$_3$CH$_2$OH (Table 1, Entry 3). When CH$_3$CN was used as the solvent, the $\pi$-facial selectivity in the Diels-Alder reaction of spiro lactone (1) with cyclopentadiene slightly decreased (4a : 5a = 91 : 9, Table 1, Entry 2). The Diels-Alder reaction of spiro...
lactone (1) with 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene required the use of ZnCl2. The reaction of 1 with two dienes (1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene) gave adducts (4b) and (4c) as the only observable isomer, respectively (Table 1, Entries 4, 5). It turned out that the Diels-Alder reaction of spiro lactone (1) with sterically undemanding dienes proceeds with high π-facial selectivity under mild conditions and the high π-facial selectivity is an essential feature of the spiro lactone (1).

Table 2. Diels-Alder Reaction of Spiro Ether (2) with Cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conditions</th>
<th>6 : 7</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2Cl2</td>
<td>25 °C, 7 days</td>
<td>97 : 3</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>CH3CN</td>
<td>25 °C, 7 days</td>
<td>94 : 6</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>TFEa</td>
<td>25 °C, 1 days</td>
<td>94 : 6</td>
<td>86</td>
</tr>
</tbody>
</table>

aTFE: CF3CH2OH. bThe ratio was determined by the 1H NMR integral value of the crude product. cIsolated yield after purification.

Table 3. Diels-Alder Reaction of Spiro Ketone (3) with Cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conditions</th>
<th>8 : 9</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2Cl2</td>
<td>25 °C, 7 days</td>
<td>66 : 34</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>CH3CN</td>
<td>25 °C, 7 days</td>
<td>61 : 39</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>TFEa</td>
<td>25 °C, 7 days</td>
<td>60 : 40</td>
<td>82</td>
</tr>
</tbody>
</table>

aTFE: CF3CH2OH. bThe ratio was determined by the 1H NMR integral value of the crude product. cIsolated yield after purification.

Tables 2 and 3 show the results of the Diels-Alder reaction of spiro ether (2) and spiro ketone (3) with cyclopentadiene, respectively. Here again the predominant product was the one arising from facial attack from the side bearing the oxygen atom in the Diels-Alder reaction of spiro ether (2). Thus, the reaction in CH2Cl2 gave product in a ratio of 6 : 7 = 97 : 3 (Table 2, Entry 1). When CH3CN was used as the solvent, the π-facial selectivity slightly decreased (6 : 7 = 94 : 6, Table 2, Entry 2). The Diels-Alder reaction was again accelerated in CF3CH2OH (6 : 7 = 94 : 6, Table 2, Entry 3).

The Diels-Alder reaction of spiro ketone (3) with cyclopentadiene in CH2Cl2 and CH3CN at 25 °C for 7 days afforded the adducts (8) and (9) as a mixture (Table 3, Entries 1, 2). The reaction of spiro ketone (3) with cyclopentadiene in CF3CH2OH at 25 °C took 7 days to furnish a mixture of the adducts (8) and (9) in a ratio of 8 : 9 = 60 : 40 (82 %, Table 3, Entry 3). Reactions in the other solvents were even slower. Thus, the π-facial selectivity in the Diels-Alder reaction of spiro ketone (3) was very low relative to those of the reactions of spiro compounds (1) and (2).

The electron density of spiro compounds (1-3) was calculated at the 6-31G* level (Figure 1).9 Compared with the electron cloud over O1, that over C4 of oxa-spiro compounds (1) and (2) more greatly expanded in the direction of the reaction. Thus, the steric repulsion between oxa-spiro compounds (1) and (2), and the diene may contribute to the π-facial selectivity in the Diels-Alder reaction just as described by Houk.
et al.4 However, the degree of extension of the electron cloud over C4 and C1 of spiro ketone (3) to the reaction site was comparable and thus the facial selectivity can not be explained by steric repulsion.

The observed facial selectivity in the Diels-Alder reaction of spiro compound (3) can be rationalized in terms of the Cieplak model (Figure 2).10 Although the electron donor ability of bond C5-C4 and C5-C1 are comparable, the carbonyl group should slightly decrease the donating ability of C5-C1 thus favoring...
attack from this side.\textsuperscript{11}

The transition state in the Diels-Alder reaction of spiro lactone (1) with cyclopentadiene was calculated at PM3 level (Figure 3). The result shows that the transition state for 4\textit{a} is slightly more stable than that for 5\textit{a}. The structure shows that it is suitable for hyperconjugative interaction between the $\sigma^*$ bond of the newly forming C-C bond at C10 and the C5-C4 bond (4\textit{a}) or the C5-O1 bond (5\textit{a}) in accordance with the Cieplak model.\textsuperscript{12}

In summary, we have found that the Diels-Alder reaction of cross-conjugated ketones (1) and (2) bearing a spiro ring gives adducts with high $\pi$-facial selectivity under mild conditions even with simple sterically undemanding dienes. The observed selectivities can be rationalized with the Cieplak model. Further examinations to support our reasoning are currently underway.

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**REFERENCES AND NOTES**


8. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center; 4a: CCDC-193077; 4b: CCDC-193078; epoxy-4c: CCDC-193079. A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2, 1EZ, U. K. (fax: (+44)1223-336-033; e-mail: deposit@ccdc.ac.uk).

9. The calculations were preformed using *PC Spartan Pro*, Wavefunction, Inc. Irvine, CA 92715.

