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

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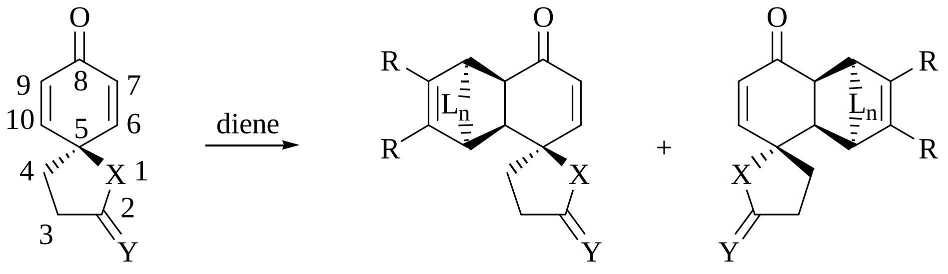
Abstract – The Diels-Alder reactions of cross-conjugated ketones bearing an oxa-spiro-ring with some simple sterically undemanding dienes (cyclopentadiene, 2,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene) afforded the adduct with high π-facial selectivity under mild conditions. The π-facial selectivity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

INTRODUCTION

The Diels-Alder reaction has been widely studied,[1] and the mechanistic aspects of this reaction have been much discussed.[2] Winterfeldt *et al.* have investigated the stereoselectivity in the Diels-Alder reaction of the oxa-spiro-compounds (**1**) and (**2**) with sterically hindered bicyclic chiral cyclopentadiene derivatives.[3] 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 CH_2 group.[4] 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.[5] This prompted us to examine this reaction in more detail. Although the π-facial selectivity in the Diels-Alder reaction of unsymmetric 1,3-dienes with dienophiles has been widely investigated,[6] that of unsymmetric dienophiles has not received as much attention.[7] Our investigation herein presents one of a limited number of examples of such reaction.



1-3
1: X = O, Y = O
2: X =O, Y = H, H
3: X = CH_2, Y = O

4a-c, **6**, **8** **5a**, **7**, **9**
4a, **5a**: X = O, Y = O, R = H, L_n = CH_2
4b, **5b**: X = O, Y = O, R = H, L_n = $(CH_2)_2$
4c, **5c**: X = O, Y = O, R = Me, L_n = H, H
6, **7**: X = O, Y = H, H, R = H, L_n = CH_2
8, **9**: X = CH_2, Y = O, R = H, Ln = CH_2

Scheme 1

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.[8] In the case of **4c**, X-Ray analysis was carried out on the epoxidation product from **4c**, prepared by *m*CPBA oxidation.

Table 1. Diels-Alder Reaction of Spiro Lactone (**1**) with Dienes

Entry	Diene	Solvent	Conditions	Product	**4**	:	**5**[c]	Yield/%[d]
1	CP[a]	CH_2Cl_2	35 °C, 3 days	**4a**, **5a**	96	:	4	99
2	CP[a]	CH_3CN	35 °C, 3 days	**4a**, **5a**	91	:	9	72
3	CP[a]	TFE[a]	37 °C, 4 h	**4a**, **5a**	96	:	4	87
4	CH[a]	CH_2Cl_2	$ZnCl_2$ (0.6)[b] 25 °C, 5 days	**4b**, **5b**	>99	:	<1	72
5	DB[a]	CH_2Cl_2	$ZnCl_2$ (0.7)[b] 25 °C, 5 days	**4c**, **5c**	>99	:	<1	69

[a] CP: Cyclopentadiene, CH: 1,3-Cyclohexadiene, DB: 2,3-Dimethyl-1,3-butadiene, TFE: CF_3CH_2OH. [b] Equivalents in parentheses. [c] The ratio was determined by the ^{1}H NMR integral value of the crude product. [d] Isolated yield after purification.

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_2Cl_2 and CF_3CH_2OH 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_3CH_2OH (Table 1, Entry 3). When CH_3CN was used as the solvent, the π-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 $ZnCl_2$. 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

Entry	Solvent	Conditions	**6**	:	**7**[b]	Yield/%[c]
1	CH_2Cl_2	25 °C, 7 days	97	:	3	61
2	CH_3CN	25 °C, 7 days	94	:	6	46
3	TFE[a]	25 °C, 1 days	94	:	6	86

[a] TFE: CF_3CH_2OH. [b] The ratio was determined by the ^1H NMR integral value of the crude product. [c] Isolated yield after purification.

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

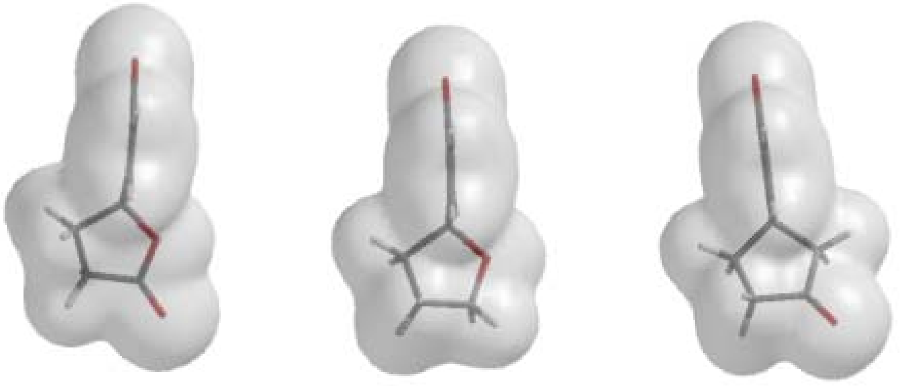
Entry	Solvent	Conditions	**8**	:	**9**[b]	Yield/%[c]
1	CH_2Cl_2	25 °C, 7days	66	:	34	7
2	CH_3CN	25 °C, 7 days	61	:	39	7
3	TFE[a]	25 °C, 7 days	60	:	40	82

[a] TFE: CF_3CH_2OH. [b] The ratio was determined by the ^1H NMR integral value of the crude product. [c] Isolated 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 CH_2Cl_2 gave product in a ratio of **6** : **7** = 97 : 3 (Table 2, Entry 1). When CH_3CN 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 CF_3CH_2OH (**6** : **7** = 94 : 6, Table 2, Entry 3).

The Diels-Alder reaction of spiro ketone (**3**) with cyclopentadiene in CH_2Cl_2 and CH_3CN 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 CF_3CH_2OH 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**).

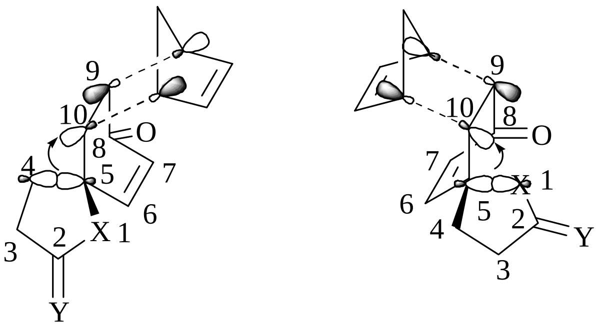
The electron density of spiro compounds (**1**-**3**) was calculated at the 6-31G* level (Figure 1).[9] Compared with the electron cloud over O1, that over C4 of oxa-spiro compounds (**1**) and (**2**) more greatly expanded in the direction of the reaction. Thus, the steric repulsion between oxa-spiro compounds (**1**) and (**2**), and the diene may contribute to the π-facial selectivity in the Diels-Alder reaction just as described by Houk



1 **2** **3**

Figure 1. The electron density of spiro compounds (**1-3**) calculated at 6-31G* level.

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.



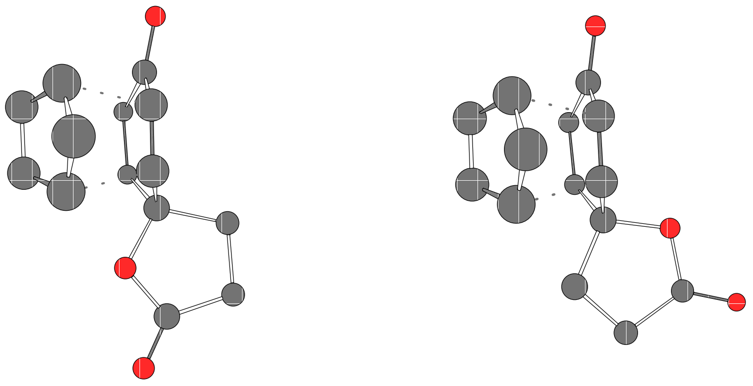
1: X = O, Y = O
2: X = O, Y = H, H
3: X = CH_2, Y = O

σ-donor ability: $\sigma_{CC} >> \sigma_{CO}$

TS for **4a**, **6**, **8** TS for **5a**, **7**, **9**

Figure 2. Cieplak model in the Diels-Alder reaction of spiro compounds (**1-3**).

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



TS for **4a**: -13.31 kcal/mol TS for **5a**: -12.67 kcal/mol

Figure 3. PM3 calculated transition state in the Diels-Alder reaction of spiro lactone (**1**) with cyclopentadiene.

attack from this side.[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 **4a** is slightly more stable than that for **5a**. The structure shows that it is suitable for hyperconjugative interaction between the σ* bond of the newly forming C-C bond at C10 and the C5-C4 bond (**4a**) or the C5-O1 bond (**5a**) in accordance with the Cieplak model.[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 π-facial selectivity under mild conditions even with simple sterically undemanding dienes. The observed selectivities can be ratinalized with the Cieplak model. Further examinations to support our reasoning are currently underway.

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