

Communication

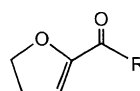
Exo-Selectivity in the Diels-Alder Reaction of Cyclopentadiene with Activated Cyclic Dienophiles in Flexible Conformation

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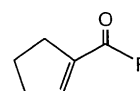
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Diels-Alder reaction is one of the most widely used reactions in organic synthesis due to its versatility and its high regio- and stereoselectivity. Although the *cis* rule is quite generally followed, the *endo* addition rule appears to be obeyed only in the addition of cyclic dienes to cyclic dienophiles.¹ It is well known that activated cyclic dienophiles in the rigid *s-trans* conformation such as maleic anhydride predominantly give *endo* cycloadducts in the reactions with cyclopentadiene. On the other hand, recent studies revealed that the Diels-Alder reaction of the cyclic dienophiles containing the exocyclic double bond in the rigid *s-cis* conformation such as itaconic anhydride, α -methylene- γ -butyrolactone, and 5-methylene-1,3-dioxolan-4-ones afforded predominantly *exo* cycloadducts.² Conformationally unconstrained cyclic dienophiles such as **1** have not been fully explored. There have been only some scattered reports on Diels-Alder reactions of activated cyclic dienophiles in flexible conformation and their results are not consistent.³ We have previously observed complete *exo* selectivity in the Diels-Alder reaction of cyclopentadiene with activated cyclic sugar dienophiles in the flexible conformation.⁴ Therefore, we investigated the stereoselectivity of the Diels-Alder reaction between cyclopentadiene and cyclic dienophiles having flexible conformation in order to know whether the *exo* selectivity in this type of reaction is general and in the hope to get some insight on the *exo* selectivity of the reaction. Although our theoretical study based on a part of the present results was published,⁵ it could not provide us clear picture for the origin of the *exo* selectivity. Moreover, the calculation failed to explain the *exo* selectivity in the reaction of cyclopentadiene with **1** and with **3**. Herein we report the *exo* selective Diels-Alder reaction of cyclopentadiene with model cyclic dienophiles **1**~**4** and the temperature effect and Lewis acid effect on the *exo* selectivity.

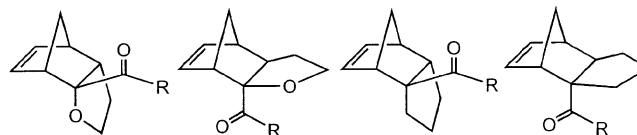


1 R = H
2 R = CH₃



3 R = H
4 R = CH₃

Reaction of 5-formyl-2,3-dihydrofuran (**1**)⁶ with cyclopentadiene provided a mixture of *exo* cycloadduct **5a** and *endo* cycloadduct **5b** in 5 : 1 ratio in 71% yield at 160 °C in a sealed tube and 12 : 1 ratio in 33% yield at room temperature. On the other hand, complete *exo* selectivity was observed in the cycloaddition of **1** and cyclopentadiene in the presence of BF₃·OEt₂ at -78 °C in methylene chloride. Cycloaddition of **1** with cyclopentadiene catalyzed by Et₂AlCl also afforded predominantly the *exo* adduct, whereas the reaction in the presence of SnCl₄ provided more



5a R = H **5b** R = H **7a** R = H **7b** R = H
6a R = CH₃ **6b** R = CH₃ **8a** R = CH₃ **8b** R = CH₃

endo adduct than in the absence of the Lewis acid although the *exo* adduct were still predominant. The lower temperature appears to be favorable for the formation of *exo* adducts. The results of the cycloaddition of **1** with cyclopentadiene are summarized in entries 1~6 of Table 1. Because of the slight or substantial decomposition of reactants and products in certain cases, the *exo/endo* ratio and yield were determined at the point just before the appearance of any decomposition products. The prolonged reaction time, therefore,

Table 1. Diels-Alder Reaction of Cyclopentadiene with Cyclic Dienophiles **1** and **2**

Entry	Dieno- phile	Lewis Acid	Tempera- ture(°C)	Reaction Time ^a	Product	Ratio <i>exo/endo</i>	Yield (%) ^b
1	1		160	7 hr	5a/5b	5 : 1	71
2	1		RT	7 days	5a/5b	12 : 1	33
3	1	SnCl ₄	-30	30 min	5a/5b	1.3 : 1	5
4	1	SnCl ₄	-78	30 min	5a/5b	4 : 1	10
5	1	Et ₂ AlCl	-78	30 min	5a/5b	40 : 1	5
6	1	BF ₃ ·OEt ₂	-78	30 min	5a/5b	100 : 0	6
7	2		160	7hr	6a/6b	9 : 1	30
8	2		RT	4 days	6a/6b	12 : 1	23
9	2	SnCl ₄	-30	30 min	6a/6b	2.7 : 1	20
10	2	SnCl ₄	-78	50 min	6a/6b	3 : 1	16
11	2	Et ₂ AlCl	-78	30 min	6a/6b	15 : 1	10
12	2	BF ₃ ·OEt ₂	-78	1.5 hr	6a/6b	20 : 1	20

^a The reaction was stopped just before appearance of any decomposition products. ^b Isolated yield. The yield could be enhanced when the reaction time was prolonged.

could enhance the yields in several reactions listed in Table 1 and Table 2. The Diels-Alder reaction of 5-acetyl-2,3-dihydrofuran (**2**), prepared from dihydrofuran and *N,N*-di-methylacetamide, with cyclopentadiene afforded a mixture of *exo* cycloadduct **6a** and *endo* cycloadduct **6b** in 9 : 1 ratio in 30% yield at 160 °C in a sealed tube and in 12 : 1 ratio in 23% yield at room temperature. The diastereomeric ratio in the reaction of **2** with cyclopentadiene showed the similar trend with that in the reaction of **1** and cyclopentadiene although the *exo* selectivity was less pronounced (entries 7~12 of Table 1). Thus, more *exo* cycloadducts were produced at higher temperature than at lower one and in the presence of BF₃OEt₂ or Et₂AlCl than in the absence of Lewis acids.

Cycloaddition of carbocyclic enal **3**⁷ with cyclopentadiene also afforded *exo* isomer **7a**, the major and *endo* isomer **7b**, the minor as shown in entries 1~4 in Table 2. The cycloaddition of carbocyclic enone **4**⁷ gave an equal amount of *exo* adduct **8a** and *endo* adduct **8b**, independent to the reaction temperature and presence of Lewis acids (entries 5~8 of Table 2). The reactions of **3** and **4** with cyclopentadiene at

Table 2. Diels-Alder Reaction of Cyclopentadiene with Cyclic Dienophiles **3** and **4**

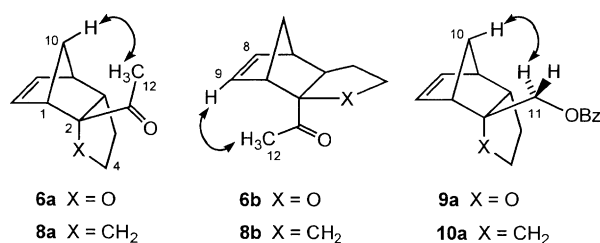
Entry	Dieno- phile	Lewis Acid	Tempera- ture(°C)	Reaction Time ^a	Product	Ratio <i>exo/endo</i>	Yield (%) ^b
1	3		160	4 days	7a/7b	2 : 1	12
2	3		90	7 days	7a/7b	5 : 1	24
3	3	SnCl ₄	-30	60 min	7a/7b	2 : 1	30
4	3	Et ₂ AlCl	-78	60 min	7a/7b	7 : 1	62
5	4		160	4 days	8a/8b	1 : 1	12
6	4		90	7 days	8a/8b	2 : 1	20
7	4	SnCl ₄	-78	30 min	8a/8b	1 : 1	44
8	4	Et ₂ AlCl	-78	30 min	8a/8b	1 : 1	66

^a The reaction was stopped just before appearance of any decomposition products. ^b Isolated yield. The yield could be enhanced when the reaction time was prolonged.

room temperature were too sluggish to follow, while the reaction in the presence of BF₃·OEt₂ resulted in extensive decomposition even at -78 °C.

The stereochemistry of the cycloadducts was assigned by NOE experiments. The NOE interaction existed between the acetyl proton H-12 (2.23 ppm in **6a** and 2.24 ppm in **8a**) and H-10 (1.79 ppm in **6a** and 1.85 ppm in **8a**) in *exo*-isomers **6a** and **8a**, while the NOE interaction existed between H-12 (2.17 ppm in **6b** and 2.14 ppm in **8b**) and the H-9 (6.05 ppm in **6b** and 6.01 ppm in **8b**) in *endo* cycloadducts **6b** and **8b** as shown in Figure 1. The chemical shifts of acetyl protons further confirmed the assignment made by NOE experiments. Thus, it is known that the ¹H NMR chemical shift of *exo* acetyl protons usually appears at lower field than that of *endo* acetyl protons in norbornene systems.⁸ Aldehydes **5a** and **7a**, were converted into the corresponding benzoates **9a** and **10a**, respectively for the determination of stereochemistry. Irradiation of the H-11 signal of **9a** at 4.54 ppm enhanced the H-10 signal at 1.70 ppm. The NOE measured for the H-10 signal of **10a** at 1.82 ppm upon irradiation of the H-11 signal at 4.35 ppm was also in agreement with the structure of the *exo* cycloadduct depicted in Figure 1.

Furano-dienophiles **1** and **2** rendered the higher *exo* selectivity than carbocyclic dienophiles **3** and **4**. The origin of this difference is not clear yet; it might be the steric effect of the methylene group of the carbocycle, the electronic or stereo-electronic effect of the oxygen of the furanoid ring, or the combined effects of them. Temperature effect on the *exo/endo* ratio shown in Table 1 and Table 2 might be explained by assuming that, unlike in most other Diels-Alder reactions, the *exo* adducts are the kinetic products and the *endo* isomers are thermodynamic products. Yet, we were not able to observe the isomerization between *exo* and *endo* cycloadducts. Addition of Lewis acids affected dramatically the stereochemical course of the reactions of **1** and of **2** while the effect was much less pronounced in the reactions of **3** and of **4**. It is well known that Lewis acids usually enhance the *endo* selectivity in most of Diels-Alder reactions.⁹ In the present study, the *exo* cycloadducts increased by addition of nonchelating BF₃OEt₂ and Et₂AlCl while the *endo* isomers increased with SnCl₄ in the reactions of **1** and of **2**. In the presence of SnCl₄, the *s-trans* conformation of compounds **1** and **2** would be more favorable than the *s-cis* conformation owing to chelation by SnCl₄ (Figure 2). In fact, SnCl₄ has been regarded as a chelating Lewis acid and the direct evidence for the chelation of SnCl₄ with β-alkoxy aldehydes has also been obtained by NMR study.¹⁰ On the other hand,

**Figure 1.** NOE interactions determined for cycloadducts **6a**, **6b**, **8a**, and **8b** and derivatives **9a** and **10a**.

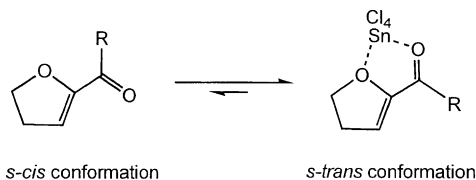


Figure 2. Preferred *s-trans* conformation of compounds **1** and **2** by chelation with SnCl_4 .

$\text{BF}_3 \cdot \text{OEt}_2$ and Et_2AlCl have been known as nonchelating Lewis acids although there has been recent reports that certain trivalent boron and aluminum species are capable of forming pentacoordinate complexes.¹¹ It is, therefore, reasonable to assume that the population of *s-trans* conformation of **1** and **2** in the presence of SnCl_4 would increase by chelation of SnCl_4 with the ring oxygen and the carbonyl oxygen and consequently the decreased *exo* selectivity might be related to the decreased population of *s-cis* conformation. It is, however, not yet clear whether the overwhelming *exo* selectivity in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ or Et_2AlCl is owing to the preferred *s-cis* conformation of **1** and **2**. Decreased *exo* selectivity of **2** and **4** compared with **1** and **3**, respectively, might be attributable to the nonbonding interaction between the methylene group of cyclopentadiene and the methyl group of the compounds **2** and **4** in the *exo* transition state.

In conclusion, we found that the *exo* cycloadduct is the major product in the cycloaddition of cyclopentadiene with cyclic dienophiles having the flexible conformation **1**–**3**. We also found that $\text{BF}_3 \cdot \text{OEt}_2$ is the Lewis acid of choice for predominant generation of *exo* cycloadducts and the lower temperature is desirable for the *exo* selectivity. We are currently involved in the synthesis of natural products employing this useful *exo* selective Diels–Alder reaction.

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