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A novel attractive interaction in the Diels–Alder reaction of *N*-protected pyrroles with allene-1,3-dicarboxylates

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Abstract—The *endo*/*exo* selectivities of Diels–Alder reactions of *N*-protected pyrroles with allene-1,3-dicarboxylates were studied under Lewis acid assisted and thermal reaction conditions. A novel attractive effect between the *N*-protective carbonyl group of pyrrole and the ester group of allene-1,3-dicarboxylates operates to control the selectivity in the above Diels–Alder reaction. This new attractive effect to give the *exo* adduct is more effective than the Alder orbital effect. © 2001 Published by Elsevier Science Ltd.

The Diels–Alder reactivity of *N*-acylpyrrole toward a typical dienophile such as maleic anhydride is known to be lower than that of cyclopentadiene and furan. Consequently, high pressure is required for the reaction of *N*-benzoylpyrrole with maleic anhydride[1] and for *N*-acetylpyrrole with an acetylenic dienophile.[2] However, allene-1,3-dicarboxylates react well with *N*-alkoxycarbonylpyrrole and with cyclopentadiene and furan.[3] We had developed a one-pot synthesis of allene-1,3-dicarboxylates from 1,3-acetonedicarboxylates with DMC,[4] and a novel crystallization-induced asymmetric transformation from a diastereomeric mixture of di-(−)-L-menthyl allene-1,3-dicarboxylates, which was applied to an asymmetric synthesis of (−)-epibatidine.[5] The normal *endo* stereoselectivity of cyclopentadiene[3a,b] and furan[3c] in the Diels–Alder reaction with allene-1,3-dicarboxylates has been extensively studied. In the synthesis of (−)-epibatidine, we found that the Diels–Alder reaction of di-(−)-L-menthyl allene-1,3-dicarboxylate with *N*-Boc-pyrrole proceeded to give the *endo* adduct exclusively,[5] while the *endo*/*exo* selectivity in the reactions of dimethyl allene-1,3-dicarboxylates differed markedly.[6] This observation prompted us to examine the origins of the *endo* and *exo* selectivity. We report herein a new aspect on the *endo*/*exo* selectivity of the Diels–Alder reaction of *N*-protected pyrroles with allene-1,3-dicarboxylates.

Reactions of *N*-protected pyrroles with allene-1,3-dicarboxylates were carried out under Lewis acid assisted and thermal reaction conditions (Methods I and II). The results are summarized in Table 1. The reaction of dimethyl allene-1,3-dicarboxylate with *N*-methoxycarbonyl- or *N*-benzyloxycarbonylpyrrole promoted by aluminum chloride in dichloromethane at −78°C gave the Diels–Alder products **A**, which were a mixture (ca. 1: 2) of the *endo* and *exo* adducts (entries 1 and 3). The same Diels–Alder adducts were also obtained in the reactions heated at 90°C in toluene (entries 2[6] and 4). In the reaction of *N*-Boc-pyrrole promoted by aluminum chloride the *exo* selectivity varied to *endo* selectivity, whereas the thermal reaction without Lewis acid gave a slightly *exo* selective adducts (entries 5 and 6). Changing the alkoxy group of the allene-1,3-dicarboxylate to ethyl and cyclohexyl significantly increased the *endo* selectivity in aluminum chloride assisted reactions, although the selectivity was not observed under thermal conditions (entries 7–10). This alteration of the selectivity depending on the reaction conditions was also observed for the reactions of di-(−)-L-menthyl (*R*)-allene-1,3-dicarboxylate[5] with *N*-Boc-pyrrole (entries 11 and 12). Changing the nitrogen substituent of the pyrrole to a bulky pivaloyl group also increased the *endo* selectivity (entries 13 and 14). This was especially true in the reaction of *p*-toluenesulfonylpyrrole with dimethyl allene-1,3-dicarboxylate, which gave the *endo* adduct exclusively, even though the reaction was conducted under thermal conditions (entries 15 and 16).

In the above reactions, the electron deficient *N*-protected pyrroles reacted as a diene in Diels–Alder reactions to give the cycloadducts **A** as a major product. However, a small amount (less than 10%) of the Friedel–Crafts product **B** was also obtained in some

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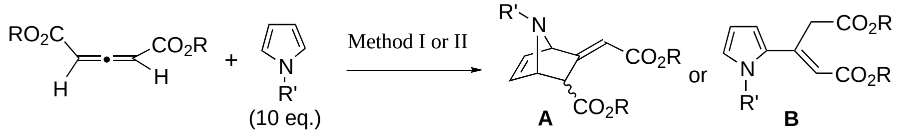
reactions (entries 2–4, 6–9, 11, 13 and 14). It was observed that the Friedel–Crafts reaction and the Diels–Alder reaction were competitive under thermal and Lewis acid catalyzed reaction conditions. On the other hand, the reactions of the electron rich pyrroles with dimethyl allene-1,3-dicarboxylate gave exclusively 2-alkenylated pyrroles **B**[7] (entries 17–20). The regio- and stereoselectivities relating to the position of the pyrrole moiety and the *E*/*Z* isomer of the α,β-unsaturated ester moiety were completely regulated in the reaction.[8] The predominance of the Friedel–Crafts alkylation of the electron rich pyrroles can be attributed to the high stability of the ionic intermediate **C**, as shown in Scheme 1.

According to semi-empirical PM3 calculations, the *exo* adduct (R = Me, R′ = Boc) is more stable (by 0.7 kcal/mol) than the *endo* adduct. We tried to confirm whether or not the Diels–Alder reaction was in equilibrium under the reaction conditions I and II. In the reactions using the *endo* adducts (R = Me, R′ = Boc) and (R = *c*-Hex, R′ = Boc), both *endo* adducts were recovered in 85–92% yield under conditions I (−78°C, 1 day, 9 equiv. of *N*-Boc-pyrrole) and conditions II (90°C, 2 day, 9 equiv. of *N*-Boc-pyrrole), and no *exo* adducts were detected in the reaction mixture. Therefore, these results confirmed that the Diels–Alder reaction in Table 1 was kinetically controlled.

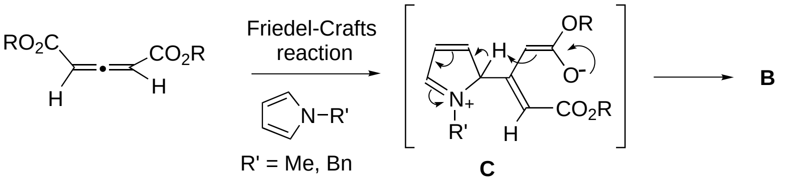
Compared with the highly *endo* selective Diels–Alder reaction of cyclopentadiene[3a,b] or furan[3c] with allene-1,3-dicarboxylate, the *endo*/*exo* selectivity in the above Diels–Alder reaction of pyrroles could not be rationalized based solely on Alder's rule and steric effects.

Table 1. The reaction of allene-1,3-dicarboxylate with *N*-protected pyrroles

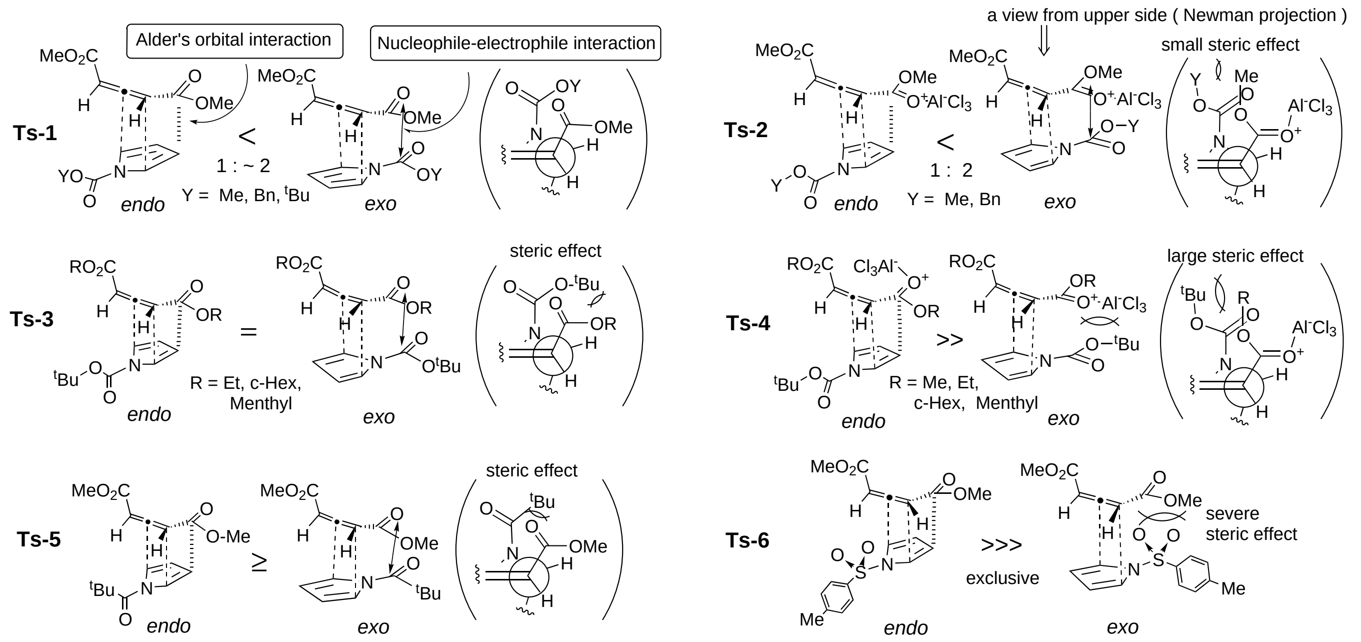


Entry	R	R′	Method[a]	Time (days)	Product	Yield (%)	*Endo*:*exo*
1	Me	CO_2Me	I	1	**A**	65	35:65
2			II	2	**A**[b]	64	37:63
3	Me	CO_2Bn	I	1	**A**[b]	78	33:67
4			II	1	**A**[b]	63[c]	37:63
5	Me	$CO_2{}^tBu$	I	0.5	**A**	53	67:33
6			II	2	**A**[b]	91[d]	45:55
7	Et	$CO_2{}^tBu$	I	1	**A**[b]	73	100:0
8			II	2	**A**[b]	66[e]	50:50
9	*c*-Hex	$CO_2{}^tBu$	I	2	**A**[b]	60	100:0
10			II	2	**A**	69[f]	49:51
11	(−)-Menthyl	$CO_2{}^tBu$	I	2.5	**A**[b]	85	100:0
12			II	3.5	**A**	84	50:50
13	Me	Pivaloyl	I	1	**A**[b]	77	67:33
14			II	2	**A**[b]	96[g]	54:46
15	Me	*p*-Tos	I	1	**A**	62	100:0
16			II	3	**A**	70	100:0
17	Me	Me	I	1	**B**	93	–
18			II	1	**B**	93	–
19	Me	Bn	I	1	**B**	87	–
20			II	0.5	**B**	70	–

[a] Method I: $AlCl_3$ (1.2 equiv.) was added in dichloromethane at −78°C.
Method II: The reaction mixture was heated at 90°C in toluene.
[b] The Friedel–Crafts type product B was observed in less than 10% yield.
[c] The *Z*-isomers of A (*exo*, 8%) was observed.
[d] The *Z*-isomers of A (*endo*, 7%; *exo*, 10%) was observed.
[e] The *Z*-isomers of A (*exo*, 9%) was observed.
[f] The *Z*-isomers of A (*exo*, 13%) was observed.
[g] The *Z*-isomers of A (*endo*, 5%; *exo*, 14%) was observed.



Scheme 1.



Scheme 2. Comparison of transition states in Diels–Alder reaction.

Namely, the *exo* selectivity in entries 1–4 was very curious since these molecules lack significant steric hindrance in the *endo* transition state so that the usual *endo* selectivity would be expected by secondary orbital control (the Alder rule). Therefore, it was suggested that another new attractive interaction might exist in the *exo* transition state in this Diels–Alder reaction of the dimethyl allene-1,3-dicarboxylate with *N*-alkoxycarbonylpyrrole. Transition state energy calculations (R = Me, R′ = CO_2Me) using semi-empirical PM3 revealed that the energy of the *exo* transition state was 0.77 kcal/mol more stable than that of the *endo* transition state.[9] This energy difference corresponded well with the *exo* selectivity of these reactions. We thought the attractive nucleophile–electrophile interaction[10] as a candidate of the new attractive interaction, which would operate between one of the two oxygens of an ester group in the dienophile and the carbonyl carbon of *N*-alkoxycarbonyl- or *N*-acylpyrrole. The proposed transition states in the Diels–Alder reaction are illustrated in Scheme 2. The *endo* and *exo* transition states in the reactions of *N*-alkoxycarbonylpyrroles with dimethyl allene-1,3-dicarboxylate (entries 1–6) are depicted as **Ts-1** (thermal) and **Ts-2** ($AlCl_3$ assisted). If the energy of the new interaction is larger than that of the Alder orbital interaction, the *exo* selectivity can be explained reasonably well except for the Lewis acid assisted reaction of *N*-Boc-pyrrole (entry 5), in which considerable steric interactions between the Me group of the ester and the *t*-Bu group of the carbamate would have to be added (**Ts-4**). Next, the transition states in the reaction of *N*-Boc-pyrrole with allene-1,3-dicarboxylates bearing the bulky R group (entries 7–12) are depicted as **Ts-3** (thermal) and **Ts-4** ($AlCl_3$ assisted). The *exo* predominance is diminished in **Ts-3** by the small steric repulsion between the *t*-butoxyl group and the bulky R (Et, *c*-Hex, menthyl) groups of the esters (entries 8, 10 and 12). On the other hand, the high *endo* selectivity in the Lewis acid assisted reactions (entries 7, 9 and 11) can be rationalized by the large steric repulsion between the ester moiety coordinated with the Lewis acid and the *tert*-butoxycarbonyl group in **Ts-4**. The difference of the *endo* selectivity in the reaction of the pyrroles having *N*-pivaloyl and *N*-sulfonyl substituents (entries 13–16) can also be attributed to the presence or the absence of the new attractive interaction based on the bulkiness of the *N*-protective groups in the transition states, **Ts-5** and **Ts-6**.

It should be noted that this new attractive interaction is more effective than the Alder secondary orbital control in the above reactions. Such a fundamental effect in the Diels–Alder reaction of pyrrole derivatives had not been known until now because of the low reactivity of pyrroles. However, we were able to observe this novel effect by using less hindered and highly reactive allene derivatives as dienophiles. Further studies are under way in our laboratory.

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