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The High Pressure Diels-Alder Reactions of 5-Methoxy-2-methyl-4-(*p*-nitrophenyl)oxazole with Ethylenic Dienophiles

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The high pressure Diels-Alder reactions of 5-methoxy-2-methyl-4-(*p*-nitrophenyl)oxazole with ethylenic dienophiles such as *N*-methylmaleimide, *N*-phenylmaleimide, dimethyl maleate and dimethyl fumarate gave the corresponding adducts in good to excellent yields. The effects of pressure, temperature, solvents on the yields were investigated. The high pressure also increased the formation of 3-hydroxypyridine derivatives via the elimination of methanol from the adducts. The stereospecificity of the reaction was confirmed for the reactions with maleate and fumarate.

The Diels-Alder reactions of oxazoles have been studied extensively in connection with the synthesis of vitamin B_6.[1)] The reasonable Diels-Alder reactivity of oxazoles opened their widespread use in organic synthesis.[2)] The authors have reported the reactions with reactive dienophiles such as alkyl-substituted maleimides, diethyl azodicarboxylate, 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione, and dimethyl acetylenedicarboxylate.[3)] However, some dienophiles were found to give adducts in very low yields or sometimes to give no adduct in the reactions under atmospheric pressure. As the acceleration of the cycloaddition reaction under high pressure is well documented,[4)] the high pressure Diels-Alder reactions of 5-methoxy-2-methyl-4-(*p*-nitrophenyl)oxazole (**1**) with some typical ethylenic dienophiles were studied.

Results and Discussion

The Diels-Alder Reaction of 1 with *N*-Substituted Maleimides. *N*-Phenylmaleimide (**2a**) was reported to give Diels-Alder adducts with **1** in low yields under atmospheric pressure owing to the ready retro-Diels-Alder reaction.[3)] In the reaction of **1** and **2a** at 40 °C, the equilibrium lay to the side of the adducts but the rate was so slow that long time is required to reach the equilibrium. On the other hand, at 80 °C the rate was fast enough but the equilibrium was on the side of the starting materials and the yields of the adducts became low. Therefore, the reaction was investigated under high pressure of 10 kbar. The reaction in benzene at 25 °C and 10 kbar (Table 1, Run 4) gave the *endo* **3a** and the *exo*-adduct **4a** in 64.5 and 35.4% yields, without accompanying 3-hydroxypyridine derivative **5a**. Product ratios depend upon the reaction temperature and time (Table 1, Run 4—5), and the yield of the *exo*-adduct increased with the increase in reaction time.

This is ascribed to the fast retro-Diels-Alder reaction of the *endo*-adduct **3a** in comparison to that of the *exo*-adduct **4a**. That is to say, the **3a** produced preferentially at the initial stage of the reaction is decomposed by the retro-Diels-Alder reaction to give the starting **1** and **2a**, which affords **3a** and **4a** in the forward Diels-Alder reaction. In this manner, the yield of **4a** increased with the increase in the reaction time at the expense of the yield of **3a**. The retro-Diels-Alder reaction was not observed when the reaction was carried out for 2 h or less, showing constant product ratios within the experimental error (Table 2 (B)). When the reaction was continued more than 5 h, the retro-Diels-Alder reaction of **3a** apparently increased the composition of **4a** (Table 2(B)). The accelerating effect of the pressure was not enough under 1 kbar. However,

Table 1. Product Composition of the Diels-Alder Reaction of **1** and Maleimides

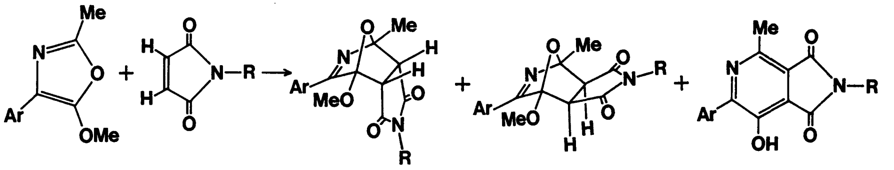
Run	R	Pressure/kbar	Solvent	Temp	Time	Product yield/%[a)]			Total yield
				°C	h	**3**	**4**	**5**	%
1	C_6H_5	a.p.[b)]	C_6H_6	40	240	43	17	—	60
2	C_6H_5	a.p.[b)]	C_6H_6	60	25	41	18	—	59
3	C_6H_5	a.p.[b)]	C_6H_6	80	50	13	21	—	34
4	C_6H_5	10	C_6H_6	60	25	64.5	35.4	—	99.9
5	C_6H_5	10	C_6H_6	60	100	45.1	54.0	—	89.1
6	C_6H_5	10	CH_2Cl_2	60	50	24.2	55.5	18.5	98.2
7	C_6H_5	10	CH_2Cl_2	60	100	0.2	0.5	97.8	98.5
8	C_6H_5	10	CH_3CN	60	100	4.7	—	85.8	90.5
9	CH_3	a.p.[b)]	C_6H_6	60	25	52	14	—	66
10	CH_3	10	C_6H_6	60	50	55.2	30.8	12.2	98.2
11	CH_3	10	C_6H_6	60	100	47.0	9.9	43.0	99.9
12	CH_3	10	CH_2Cl_2	60	100	—	—	99.8	99.8

a) Isolated yields (%) using silica-gel column chromatography. b) Atomospheric pressure.

Table 2. Effect of Pressure, Time, and Solvent on the Product Composition[a] of the Diels–Alder Reaction of **1** and **2a**[b]

Solvent	Pressure	Time	Products/%			Recovered oxazole/%
	kbar	h	**3a**	**4a**	**5a**	
(A) Effect of Pressure						
C_6H_6	1	25	30	18	—	52
C_6H_6	3	25	68	32	—	—
C_6H_6	5	25	63	37	—	—
C_6H_6	10	25	65	35	—	—
(B) Effect of Reaction Time						
C_6H_6	10	1/6	80	20	—	—
C_6H_6	10	1/2	78	22	—	—
C_6H_6	10	1	80	20	—	—
C_6H_6	10	2	78	22	—	—
C_6H_6	10	5	74	26	—	—
C_6H_6	10	25	65	35	—	—
(C) Effect of Solvent						
C_6H_6	10	25	65	35	—	—
$CH_3COOC_2H_5$	10	25	65	35	—	—
$C_2H_5OC_2H_5$	10	25	63	19	18	—
CH_3CN	10	25	17	—	73	—
CH_3OH	10	25	—	—	100	—

a) Compositions of the products were calculated on the basis of the NMR intensities of OCH_3 and CH_3 groups of the products and unreacted **1**. b) The reactions were carried out at 60 °C using an equimolar amount (0.2 mmol) of **1** and **2a**.



1 **2** **3** (endo) **4** (exo) **5**

Ar = p-$NO_2C_6H_4$ a R=Ph
b R=Me

3 kbar was found enough for acceleration of this reaction (Table 2(A)).

When the reaction of **1** and **2a** was carried out in dichloromethane or acetonitrile, the elimination of methanol from **3a** and **4a** occured, and *N*-phenyl-5-hydroxy-2-methyl-6-(*p*-nitrophenyl)-3,4-pyridinedicarboxyimide (**5a**) was obtained along with the adducts **3a** and **4a**. This may be brought out by the catalytic action of protic species such as water contained in the solvents. The fact that the reaction in methanol gave **5a** as the sole product (Table 2) also supported the above explanation. Similar result was obtained in the reaction of **1** with *N*-methylmaleimide (**2b**). In this system, the reaction in benzene at 10 kbar also gave **5b** in a high yield which was different from the reaction in atmospheric pressure. The difference in the yields of **5a** and **5b** (Table 1, Run 5 and 11) indicates that the high pressure acceleration of methanol elimination from adducts is faster for the adducts of **2b** than for those of **2a**.

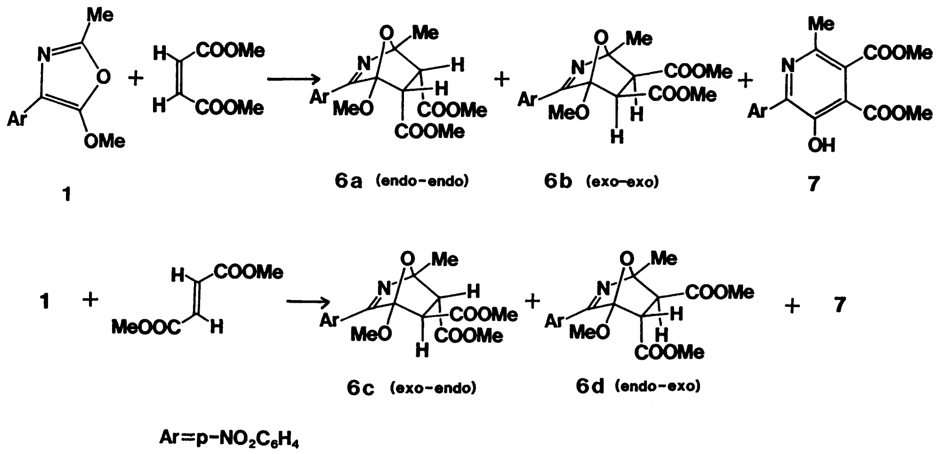
In order to compare the ability of methanol elimination, the equimolar amount (100 mg) of **3a** and **4a** dissolved in wet benzene[5] was treated at 60 °C under 10 kbar for 50 h. The NMR measurement of the reaction mixture revealed that the *endo*-adduct **3a** was present unchanged completely. On the other hand, survived **4a** was 82% and the corresponding amount (18%) of **5a** was present. This means that the elimination of methanol occurs to the *exo*-adduct more easily.

The Diels–Alder Reaction of 1 with Dimethyl Maleate and Dimethyl Fumarate. The reaction of **1** with dimethyl maleate at 60 °C under 10 kbar gave two adducts **6a** (mp 129.0 °C) and **6b** (mp 159.0 °C) together with a methanol elimination product **7**. The large coupling constants (J=10.3 and 9.1 Hz) of methine protons of both adducts indicate that the methine protons of each adducts locate in *cis* configuration. The stereochemistry of the dienophile is retained in the adducts. The possible structures of the adducts are **5**-*endo*-**6**-*endo* (**6a**) or **5**-*exo*-**6**-*exo* (**6b**). The assignment of the structures of **6a** and **6b** was based on the chemical shift of the methine protons. The adduct having signals of the methine protons at lower fields (δ 3.56 and 3.68) was assigned to **6a**, and the adduct with the methine proton signals at higher fields (δ 3.01 and 3.18) to **6b**, on the analogy of the adducts of *N*-substituted maleimide with **1**.[3] A larger coupling

Table 3. The Yields and NMR Chemical Shifts of the High-Pressure Diels-Alder Reaction Products of 1 with Dimethyl Maleate and Dimethyl Fumarate

Dienophile	Solvent	Temp	Time	Product yield/%				
		°C	h	**6a**	**6b**	**6c**	**6d**	**7**
(A) Yields								
Dimethyl maleate	C_6H_6	50	50	11.9	1.6	—	—	—[a]
	C_6H_6	60	100	7.4	0.6	—	—	70.5
	CH_2Cl_2	50	50	41.1	2.4	—	—	21.9
Dimethyl fumarate	C_6H_6	50	50	—	—	0.6	0.5	—[b]
	CH_2Cl_2	50	150	—	—	2.6	2.5	6.7[c]
	CH_2Cl_2	60	115	—	—	11.2	8.8	6.1[c]
(B) ^1H NMR Chemicals Shifts (/ppm) and Coupling Constants								
C-CH_3				2.00	2.15	1.83	2.12	2.55
O-CH_3				3.50	3.50	3.45	3.48	—[e]
O-CH_3				3.59	3.69	3.72	3.66	3.98
O-CH_3				3.65	3.77	3.84	3.84	4.02
Methine-H[d]				3.56	3.01	3.19	3.24	—
Methine-H[d]				3.67	3.18	3.82	3.47	—
J/Hz				10.3	9.1	5.7	5.4	—

a) 76% of **1** was recovered. b) 89% of **1** was recovered. c) A considerable amount of oxazole was recovered. d) Doublet signals were observed. e) A broad singlet signal of hydroxyl group was observed at δ 11.02.



constant (J=10.3 Hz) of the *endo-endo*-adduct **6a** than the *exo-exo*-adduct **6b** (J=9.1 Hz)[6] supports the above assignment. In this case, the 5-*endo*-6-*endo*-adduct **6a** showed a C-CH_3 signal at a higher field (δ 2.00) than that of the 5-*exo*-6-*exo*-adduct **6b** (δ 2.15). This is probably caused by an anisotropic effect of closely located C=O of the ester group on C_6. The NMR spectrum of the third product shows two OCH_3 signals of ester groups (δ 3.98 and 4.02), a C-CH_3 (δ 2.55), an AB quartet of aromatic protons, and broad OH signal (δ 11.02). The absence of signals of third OCH_3 group and methine protons characterized the structure **7**, which was also supported by its IR spectrum and analytical data.

The reaction of dimethyl fumarate and **1** also gave two adducts and **7**. Although the adducts were difficult to isolate each other by silica gel column chromatography, NMR spectrum indicates that they are a mixture of two adducts which are different from **6a** and **6b**. Their smaller coupling constants (J=5.7 and 5.4 Hz) of methine protons indicate that the methine protons locate in *trans* configuration. The possible structures of the adducts having *trans* configuration are 5-*exo*-6-*endo* **6c** or 5-*endo*-6-*exo* **6d**, and the assignment was achieved by comparing of the chemical shift of the C-CH_3 group. The adduct having a C-CH_3 singlet at a higher field (δ 1.83) was assigned to 5-*exo*-6-*endo*-adduct **6c** by taking account of NMR feature of dimethyl maleate adducts described above. The reaction of dimethyl maleate was found to be faster than that of dimethyl fumarate in contrast to the usual Diels-Alder reaction.[7]

Experimental

The IR spectra were recorded on Perkin-Elmer model 983 and the ^1H NMR spectra were recorded in $CDCl_3$ solutions at 90 MHz on a Varian Spectrometer model EM390 using TMS as an internal standard.

Materials. 5-Methoxy-2-methyl-4-(*p*-nitrophenyl)oxazole (**1**) was prepared as described in the previous paper.[3] Solvents were dried in appropriate methods and stored over molecular sieves type 4A after distillation.

General Procedure of the High Pressure Diels-Alder Reaction of 1 with Maleimides. A solution of **1** (1.0 mmol) and maleimide (2.0 mmol) dissolved in 5 ml of a solvent was treated under the reaction conditions listed in the Table 1, using a Hikari Kouatsu high pressure reaction apparatus.[8] The reaction mixture was separated by silica gel column chromatography, and the isolated products were identified by comparison of its IR and NMR spectra with those of the samples obtained before.[3]

The Reaction of 1 with Dimethyl Maleate. A benzene solution of **1** (2.0 mmol) and dimethyl maleate (4.0 mmol) was treated under 10 kbar at 50 °C for 25 h. After removal of solvent, the reaction mixture was separated by silica gel column chromatography to give three products.

First Product 6a: Pale yellow crystals; mp 128.0—129.0 °C. Found: C, 54.17; H, 4.79; N, 7.38%. Calcd for $C_{17}H_{18}N_2O_8$: C, 53.97; H, 4.80; N, 7.41%.

Second Product 6b: Colorless crystals; mp 158.0—159.0 °C. Found: C, 54.04; H, 4.75; N, 7.42%. Calcd for $C_{17}H_{18}N_2O_8$: C, 53.97; H, 4.80; N, 7.41%.

Third Product 7: Pale yellow needles; mp 198.0—200.0 °C. Found: C, 55.38; H, 4.06; N, 8.04%. Calcd for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.08; N, 8.09%.

The Reaction of 1 with Dimethyl Fumarate. The reaction was carried out in the same procedure as the reaction of dimethyl maleate. Column chromatography (silica gel/benzene–hexane) isolated **7** and a mixture of two adducts. However, the separation of the two adducts (**6c** and **6d**) was unsuccessful.

References

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5) Distilled benzene was shaken with water in a separatory funnel and separated benzene layer was used without further treatment.

6) For example the *endo*- and *exo*-adducts of *N*-methylmaleimide with **1** show methine coupling constants, *J*=7.5 and *J*=6.5 Hz, respectively.

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