

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

Toshikazu IBATA,* Hiroyuki NAKAWA, Yasushi ISOGAMI, and Kiyoshi MATSUMOTO†
Institute of Chemistry, College of General Education, Osaka University, Toyonaka, Osaka 560

†College of Liberal Arts and Sciences, Kyoto University, Kyoto 606

(Received May 6, 1986)

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 B₆.¹⁾ 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 ₆ H ₅	a.p. ^{b)}	C ₆ H ₆	40	240	43	17	—	60
2	C ₆ H ₅	a.p. ^{b)}	C ₆ H ₆	60	25	41	18	—	59
3	C ₆ H ₅	a.p. ^{b)}	C ₆ H ₆	80	50	13	21	—	34
4	C ₆ H ₅	10	C ₆ H ₆	60	25	64.5	35.4	—	99.9
5	C ₆ H ₅	10	C ₆ H ₆	60	100	45.1	54.0	—	99.1
6	C ₆ H ₅	10	CH ₂ Cl ₂	60	50	24.2	55.5	18.5	98.2
7	C ₆ H ₅	10	CH ₂ Cl ₂	60	100	0.2	0.5	97.8	98.5
8	C ₆ H ₅	10	CH ₃ CN	60	100	4.7	—	85.8	90.5
9	CH ₃	a.p. ^{b)}	C ₆ H ₆	60	25	52	14	—	66
10	CH ₃	10	C ₆ H ₆	60	50	55.2	30.8	12.2	98.2
11	CH ₃	10	C ₆ H ₆	60	100	47.0	9.9	43.0	99.9
12	CH ₃	10	CH ₂ Cl ₂	60	100	—	—	99.8	99.8

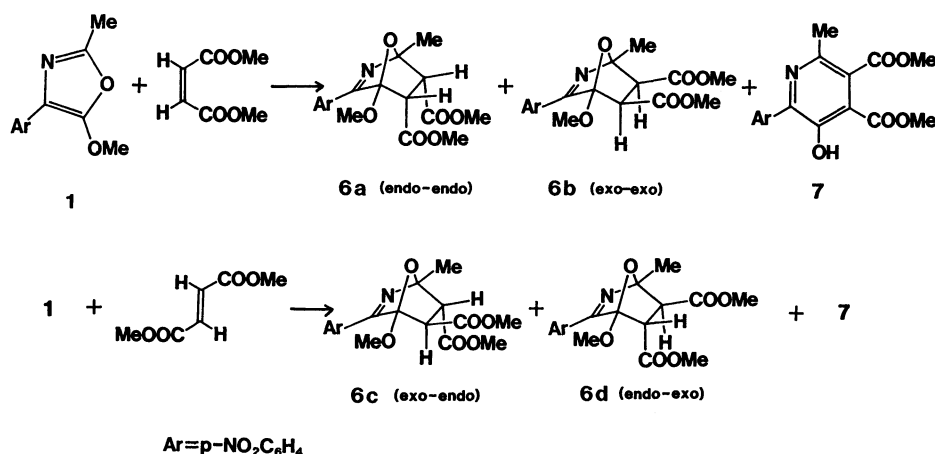
a) Isolated yields (%) using silica-gel column chromatography. b) Atmospheric pressure.

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 ₆ H ₆	50	50	11.9	1.6	—	—	— ^{a)}
	C ₆ H ₆	60	100	7.4	0.6	—	—	70.5
	CH ₂ Cl ₂	50	50	41.1	2.4	—	—	21.9
Dimethyl fumarate	C ₆ H ₆	50	50	—	—	0.6	0.5	— ^{b)}
	CH ₂ Cl ₂	50	150	—	—	2.6	2.5	6.7 ^{c)}
	CH ₂ Cl ₂	60	115	—	—	11.2	8.8	6.1 ^{c)}
(B) ¹ H 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-CH₃ 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 C₆. The NMR spectrum of the third product shows two OCH₃ signals of ester groups (δ 3.98 and 4.02), a C-CH₃ (δ 2.55), an AB quartet of aromatic protons, and broad OH signal (δ 11.02). The absence of signals of third OCH₃ 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 meth-

ine 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-CH₃ group. The adduct having a C-CH₃ 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 CDCl₃ 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.⁹ 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 C₁₇H₁₈N₂O₈: 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 C₁₇H₁₈N₂O₈: 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 C₁₆H₁₄N₂O₇: 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

- 1) E. E. Harris, R. A. Firestone, K. Pfister III, R. R. Boetter, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, and W. Reuter, *J. Org. Chem.*, **27**, 2705 (1962).
- 2) A. R. Katritzky and A. Roulton, *J. Adv. Heterocycl. Chem.*, **17**, 99 (1974); and references cited therein.
- 3) T. Ibata, S. Nakano, H. Nakawa, J. Toyoda, and Y. Isogami, *Bull. Chem. Soc. Jpn.*, **59**, 433 (1986).
- 4) J. R. McCabe and C. A. Eckert, *Acc. Chem. Res.*, **7**, 251 (1974).
- 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.
- 7) R. Huisgen, R. Grashey, and J. Sauer, "The Chemistry of Alkene," Vol 1, p. 920; Interscience Publishers: New York (1964).
- 8) K. Matsumoto, A. Sera, and T. Uchida, *Synthesis*, **1985**, 1.