HIGH-PRESSURE REACTIONS OF PYRROLES WITH DIMETHYL ACETYLENEDICARBOXYLATE[1]

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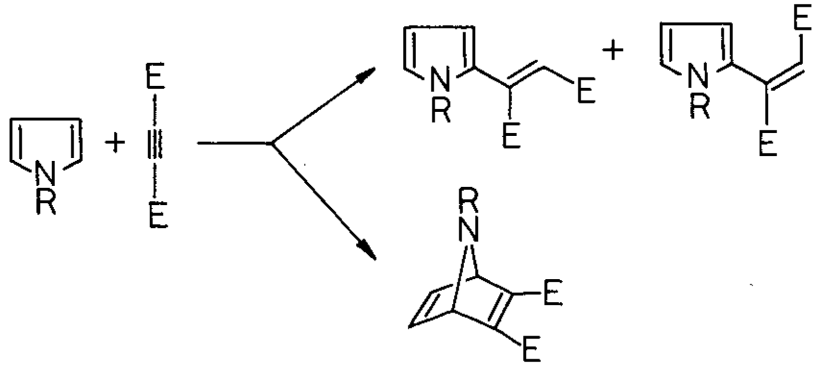
Abstract — The cycloaddition reactions of pyrroles with dimethyl acetylenedicarboxylate were performed under the conditions of 15 kbar and 40 °C in dichloromethane.

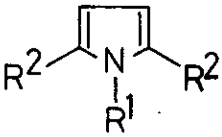
Pyrrole possesses aromatic character, *i.e.*, resonance energy is *ca.* 21-24 kcal/mol,[2] but there has been current interest in the cycloaddition reactions of pyrroles[3] in connection with the synthetic interest of 7-azabicyclo[2.2.1]hepta-2,5-dienes.[4] Generally, the reaction of pyrroles with common dienophiles proceeds by two alternative pathways, that is, [4 + 2] cycloaddition or a Michael-type addition (Scheme I).[5]

Scheme I



In analogy with the previous investigations of thiophene[6] and furan,[7] it would be expected these cycloaddition reactions have also the negative activation volumes,[8] and hence the reactions may be accelerated under high pressure conditions.[9] An additional interest is to determine whether or not the selectivity of the reaction course could vary at high pressure.

Consequently, the reactions of pyrroles (1) with dimethyl acetylenedicarboxylate (DMAD) have been studied and the results are summarized in Table 1 (Chart I).



1a : $R^1 = R^2 = H$
b : $R^1 = Me$, $R^2 = H$
c : $R^1 = COCH_3$, $R^2 = H$
d : $R^1 = H$, $R^2 = Me$

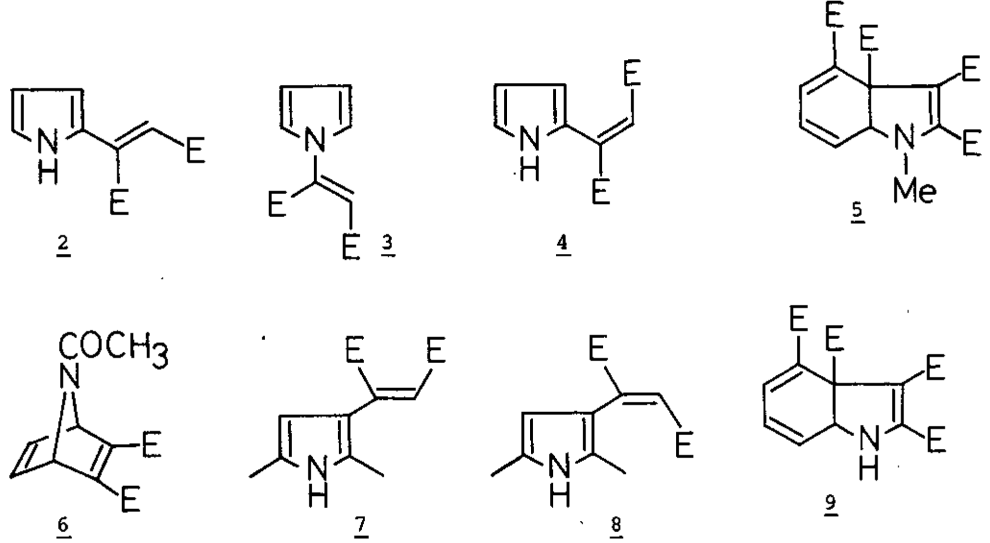
Table 1. Cycloaddition reactions of pyrroles with dimethyl acetylenedicarboxylate

Run	1	Pressure	Solvent	Temp, °C	Time, h	Product yields (%)
1a)	a	1 atm	—	RT	90	2(42) + 3(6) + 4(25)
2	a	15 kbar	CH_2Cl_2	40	15	2(16) + 3(3) + 4(2)
3b)	b*	1 atm	—	RT	48	5(70)
4b)	b*	1 atm	Et_2O	reflux	96	5(>80)
5	b	15 kbar	CH_2Cl_2	40	17	5(50)
6	b*	15 kbar	CH_2Cl_2	40	6	5(100)
7c)	c**	1 atm	—	125	7	6(45)
8	c	15 kbar	CH_2Cl_2	40	4	6(57)
9	c	15 kbar	CH_2Cl_2	40	24	6(83)
10	d	1 atm	CH_2Cl_2	reflux	30	no reaction
11	d	15 kbar	CH_2Cl_2	40	20	7 + 8 (20%, ~3 : 1)

a) Ref. 10. b) Ref. 11. c) Ref. 12.
*1b : DMAD = 1 : 2. **1c : DMAD = 1 : 10.

In the reaction with pyrrole (1a), it gave a mixture of complex products, from which 2, 3 and 4 were isolated. Although it has been reported that the reaction in refluxing ether gave a 1 : 2 adduct 9,[10] such an adduct could not be identified. The result indicates that the Michael-type addition is also a main pathway at high pressure. As compared with the reactions at atmospheric pressure,[10]

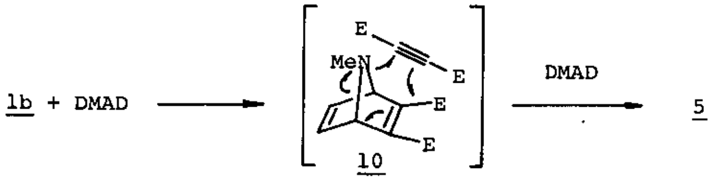
Chart I (E = COOMe)



the yield of 4 reduces considerably. This may be ascribed to the relatively hindered structure of 4.

N-Methylpyrrole (1b) gave only a single product 5. A reasonable pathway for the formation of 5 has been proposed by Acheson *et al.* as outlined in Scheme II.[11]

Scheme II

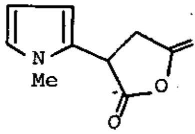


As expected, when the molar ratio of DMAD to 1b was increased the reaction proceeded quantitatively (Run 6). All attempts to isolate the initially formed adduct 10 were fruitless. This is probably due to the very fast reaction of second step associated with the relative instability of 10. N-Acetylpyrrole (1c) afforded only the Diels-Alder adduct 6 in an improved yield.

In the case of the reaction with 1d the adducts were formed firstly at high pressure. For example, no adducts were obtained in the reaction between 1d and DMAD at reflux in dichloromethane for 30 h. When the reaction was conducted at 15 kbar, two Michael-type adducts 7 and 8 were obtained in an approximate ratio of 3 : 1.

In conclusion, pyrroles having no substituent on nitrogen gave only Michael-type adducts. On the other hand, those having an electron withdrawing substituent on nitrogen gave cleanly the [4 + 2] cycloadducts.

The reaction of pyrroles with maleic anhydride (MA) was also briefly examined. Thus, 1b gave only a Michael-type adduct 11 in quantitative yield (15 kbar, 16 h, 25 °C) in accordance with the reported result at ordinary pressure[13] and no adducts derived from the [4 + 2] cycloaddition were obtained. In the case of the reaction with 1a a dicarboxylic acid derivative was also obtained by the concomitant hydrolysis.[13] No adducts were obtained in the reaction of 1c with MA.



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All attempts to observe reactions of pyrroles with dimethyl maleate and methyl acrylate at 15 kbar and 40 °C were fruitless and no signs of adduct formation were observed.

EXPERIMENTAL

General Methods —— All boiling and melting points are uncorrected. For details of instrumentation and measurements, see ref. 6b and 7c. All high pressure reactions were performed at a concentration of 2-3 M of the reactants in dry CH_2Cl_2. For a description of our high-pressure equipment and of the general procedure for high pressure reactions, see ref. 6b.

Commercially available pyrrole (1a), N-methylpyrrole (1b), and 2,5-dimethylpyrrole (1d) were used. N-Acetylpyrrole (1c) was prepared from pyrrole and N-acetylimidazole according to the literature.[14]

Unless otherwise stated, structures were confirmed by comparison of their IR and NMR spectra with authentic samples.

Reaction of Pyrrole (1a) with DMAD. A solution of pyrrole (3 mmol) and DMAD (3 mmol) in 1 ml of CH_2Cl_2 was subjected to 15 kbar hydrostatic pressure for 15 h at 40 °C. The crude product (800 mg) was separated by silica gel column (eluted with C_6H_6-Et_2O) to afford 2 (130 mg; 16%), 3 (20 mg; 3%), and 4 (16 mg; 2%).

Reaction of N-Methylpyrrole (1b) with DMAD. Similar treatment of a 1 : 1 mixture of 1b and DMAD for 17 h gave 5 in 50% yield estimated by ^1H NMR. Use of a 1 : 2 mixture of 1b and DMAD under the similar conditions for 6 h gave 5 in quantitative yield.

5: mp 152-156 °C (lit.[11] 145-147 °C).

IR($CHCl_3$), 1740, 1720, 1685, 1580 cm^{-1}.

^1H NMR($CDCl_3$), δ 2.77, 3.60, 3.74, 3.78, 3.89(each 3H, s), 4.83(1H, dd, J = 4, 1 Hz), 5.97(1H, dd, J = 10, 4 Hz), 6.28(1H, ddd, J = 10, 6, 1 Hz), 7.12(1H, d, J = 6 Hz).

Reaction of N-Acetylpyrrole (1c) with DMAD. A 1 : 1 mixture of 1c and DMAD was subjected to 15 kbar for 24 h at 40 °C. The reaction proceeded cleanly and the yield of 6 was 83% as estimated by ^1H NMR.

Reaction of 2,5-Dimethylpyrrole (1d) with DMAD. A 1 : 1 mixture of 1d and DMAD was refluxed in CH_2Cl_2 for 30 h under N_2 atmosphere. However, no signs of adduct formation were observed by NMR measurement. Instead, the treatment of the same mixture at 15 kbar and 40 °C for 20 h gave 7 and 8 in 20% yield as estimated by ^1H NMR. After purification of the crude product (960 mg) by column chromatography on silica gel, 7 (109 mg; 11%) and 8 (40 mg; 5%) were isolated.

7: bp 135 °C/0.12-0.15 mmHg.

IR(Neat), 3380, 1720, 1610 cm^{-1}.

^1H NMR($CDCl_3$), δ 2.03, 2.18, 3.69, 3.79(each 3H, s), 5.85(1H, d, J = 3 Hz), 6.78(1H, s), 7.93(1H, br).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%.

Found: C, 60.46; H, 6.32; N, 5.74%.

8: mp 89.5-91.5 °C (recryst from Et_2O).

IR($CHCl_3$), 3475, 3350, 1730, 1700, 1590 cm^{-1}.

^1H NMR($CDCl_3$), δ 2.15, 2.22, 3.70, 3.89(each 3H, s), 5.89(1H, br s), 7.43 (1H, s), 8.11(1H, br).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%.

Found: C, 60.88; H, 6.38; N, 5.91%.

ACKNOWLEDGEMENT The authors wish to thank Professor Takashi Tokoroyama, Osaka City University, for valuable discussions and continuous encouragement.

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Received, 24th May, 1982