

SYNTHETIC CONTROL BY INTERNAL HYDROGEN BONDING.
THE INTRAMOLECULAR DIELS-ALDER REACTION OF
NITROFURAN AND α,β -UNSATURATED CARBOXAMIDES

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The intramolecular Diels-Alder reaction of N-(5-nitrofurfuryl)-N-(2-hydroxyphenyl) α,β -unsaturated carboxamides gives good yields of cycloadducts when internal hydrogen bonding is present.

It is well known that the electron rich diene reacts easily with the electron deficient dienophile to form the Diels-Alder adduct. On the other hand, the cycloaddition reaction of the electron deficient diene is generally promoted by the dienophile with electron donating substituents, that is, the Diels-Alder reaction with "inverse electron demand."¹⁾

Among various electron deficient dienes, there are only a few reports related to the dienes substituted with the strongly electron withdrawing nitro group.²⁾ Especially, there is only one report on the Diels-Alder reaction of nitrofuran with maleic anhydride reported by Van Campen et al.³⁾

In the present communication, we wish to report an efficient method for the Diels-Alder reaction of the electron deficient diene like nitrofuran with suitable dienophiles based on the following results; the intramolecular Diels-Alder reaction of furan and sterically hindered dienophiles is successfully achieved by employment of the internal metal chelate.⁴⁾

When the magnesium salt of N-(5-nitrofurfuryl)-N-(2-hydroxyphenyl)-methacrylamide (1a) was prepared and refluxed in benzene for 7h, the adduct 2a was obtained in 57% yield and several other minor spots were detected on the thin layer chromatogram.

The result indicates that the cycloaddition reaction might be accelerated by the internal chelate, but some difficulties arose because of side reactions caused from the presence of nitro group. Then the cycloaddition reaction of the amide 1a, without converting to the metal salt, was tried with the expectation that the internal hydrogen bonding should promote the cycloaddition. When a benzene solution of the amide 1a was refluxed for 7h, the adduct 2a was obtained in 75% yield.

Among possible conformers of the amide 1a, only the s-cis conformer, in which the diene and the dienophile approach closely, leads to the cycloaddition reaction^{5),6)}, and it is assumed that the s-cis conformer 3 in the amide 1 is favoured by the internal hydrogen bonding. (Eq. 2)

In order to determine the existence and the role of the intramolecular hydrogen bonding of the amide 1a, analogous amides in which internal hydrogen bonding is not possible, (i.e. the amide 1b with unsubstituted phenyl group and the amide 1c with 2-methoxyphenyl group), were prepared and their reactions were examined under the same condition. Amides 1b and 1c gave the adducts 2b and 2c in only 30% and 11% yields, respectively, as expected. (Table I)

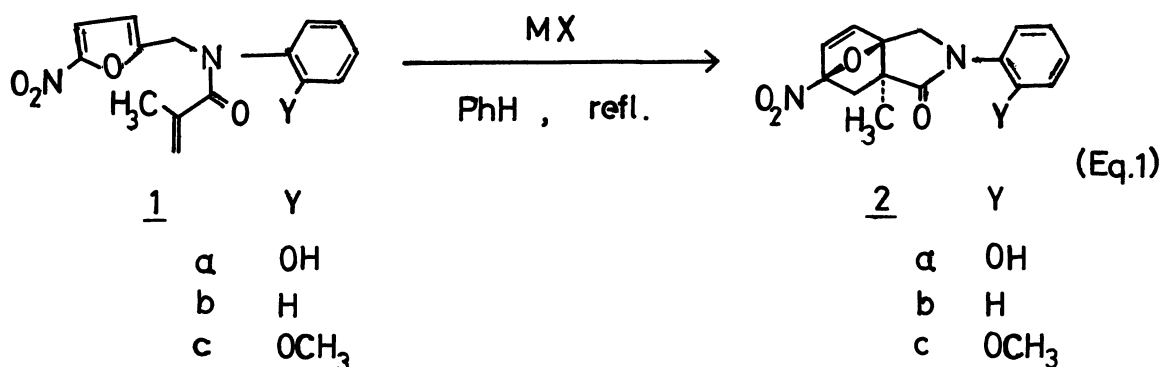
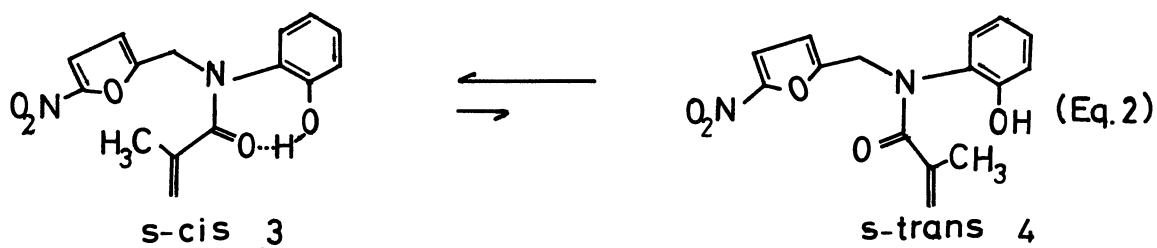


Table I The Diels-Alder reaction of 1

	Y	MX	reaction time(h)	yield of <u>2</u> (%)
1a	OH	MgBr	7	57
1a	OH	none	7	75
1b	H	none	7	30
1c	OCH ₃	none	7	11



Further, the existence of the intramolecular hydrogen bonding of the amide 1a was supported by IR spectra, that is, the absorptions of the carbonyl group of 1a, 1b and 1c are at 1600 cm⁻¹, 1650 cm⁻¹, and 1650 cm⁻¹, respectively. Thus, it is confirmed experimentally that the s-cis conformer 3 is preferable to s-trans conformer 4 in the amide 1a by the internal hydrogen bonding to accelerate the cycloaddition reaction.

The yield of the adduct 2a was increased to 94% by employing toluene as solvent instead of benzene. Similar reactions with other sterically hindered α,β -unsaturated carboxamides 5 were tried and the adducts 6 were obtained in good

yields as shown in Table II. The adducts 6c and 6e gave lower yields in comparison with the others probably because of the steric hindrance of the dienophile.

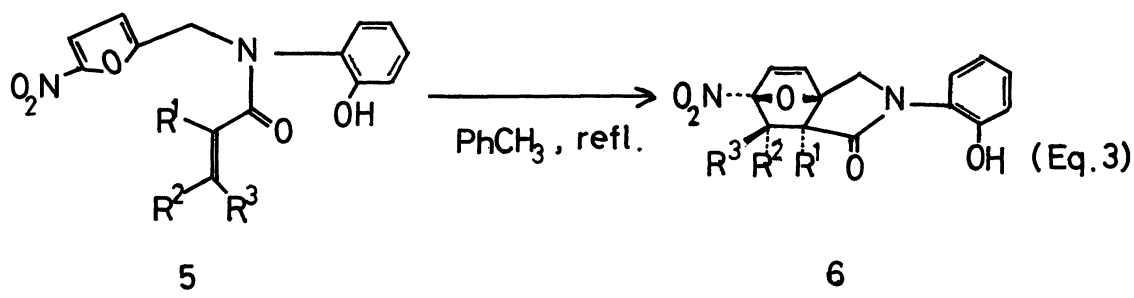


Table II The Diels-Alder reaction of 5^{7),8)}

	$\begin{array}{c} \text{R}^2 \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}^3 \end{array}$	reaction time(h)	yield of <u>6</u> (%)
5a		7	94
5b		9	93
5c		9	73
5d		7	96
5e		9	30

Typical experimental procedure is as follows: after the toluene solution (20 ml) of the amide 5a (100 mg, 0.33 mmol) was refluxed for 7h, the solvent was evaporated. The residue was purified by silica gel column chromatography to afford the amide 6a (94 mg) : mp 221.0-222.0°C (dichloromethane); IR (KBr) 3400, 1650 cm^{-1} ; NMR (DMSO- d_6) δ =1.20 (3H, s), 1.88 (1H, d, $J=12\text{Hz}$), 2.70 (1H, d, $J=12\text{ Hz}$), 3.95 (1H, d, $J=12\text{ Hz}$), 4.52 (1H, d, $J=12\text{ Hz}$), 6.28-7.28 (6H, m), 9.20 (1H, s); Found: m/e 302.0872. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5$: M, 302.0903.

It is noted that the internal hydrogen bonding promotes the intramolecular Diels-Alder reaction of the electron deficient diene such as nitrofurane and sterically hindered α,β -unsaturated carboxylic acid derivatives.

Acknowledgement

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Reference and Note

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- 7) Physical properties and spectral data of cycloadducts shown in Table II are as follows; 6b: mp 207.0-208.0°C (dichloromethane); IR(KBr) 3060, 1650 cm^{-1} ; NMR (DMSO- d^6) δ =1.18 (3H, d, J=7Hz), 1.72 (1H, d, J=7Hz), 2.18-2.42 (1H, m), 3.57 (1H, d, J=12Hz), 4.47 (1H, d, J=12Hz), 6.28-7.28 (6H, m), 9.27 (1H, s); Found: m/e 302.0899. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5$: M, 302.0903. 6c: mp 189.0-190.0°C (dichloromethane); IR(KBr) 3300, 1645 cm^{-1} ; NMR (DMSO- d^6) δ =1.22 (3H, s), 1.25 (3H, s), 2.95-3.55 (1H, m), 3.85 (1H, d, J=12Hz), 4.48 (1H, d, J=12Hz), 6.28-7.28 (6H, m), 9.32 (1H, s); Found: m/e 316.1107. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$: M, 316.1061. 6d: mp 224.5-225.5°C (dichloromethane); IR(KBr) 3200, 1665 cm^{-1} ; NMR (DMSO- d^6) δ =1.08-1.98 (6H, m), 3.08-3.42 (1H, m), 3.90 (1H, d, J=12Hz), 4.52 (1H, d, J=12Hz), 6.32-7.32 (6H, m), 9.33 (1H, s); Found: m/e 328.1055. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_5$: M, 328.1059. 6e: mp 200.0-200.5°C (dichloromethane); IR(KBr) 3300, 1650 cm^{-1} ; NMR (DMSO- d^6) δ =0.65-2.12 (8H, m), 2.98-3.48 (1H, m), 3.92 (1H, d, J=12Hz), 4.50 (1H, d, J=12Hz), 6.35-7.32 (6H, m), 9.45 (1H, s); Found: m/e 342.1208. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$: M, 342.1217.
- 8) Only one of two stereoisomers was obtained. In this case the exo mode of cyclization (trans ring junction) is preferred. See reference 5 and 9.
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