  Bull. Chem. Soc. Jpn., 56, 1107—1112 (1983)

Synthetic Control by Internal Interaction. The Intramolecular Diels-Alder Reactions of Furan Derivatives and α, β-Unsaturated Amides

Toyonori TAKEBAYASHI, Nobuharu IWASAWA, and Teruaki MUKAIYAMA*

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

(Received July 23, 1982)

An efficient method for the acceleration of the intramolecular Diels-Alder reaction was established utilizing the internal interaction——the internal hydrogen bonding and the internal coordination of a magnesium salt. The intramolecular Diels-Alder reaction between nitrofuran derivatives and various acrylic acid derivatives give good yields of the cycloadducts when internal hydrogen bonding is present. When cyclic α,β-unsaturated amides are employed as dienophile, the corresponding cycloadducts are obtained in high yield utilizing internal coordination of a magnesium salt.

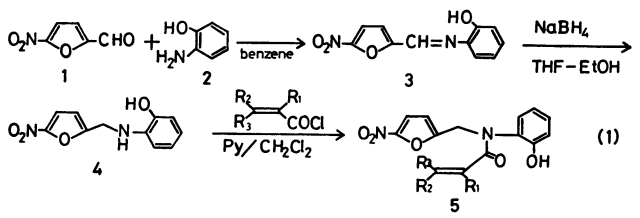
The intramolecular Diels-Alder reaction is one of the most expedient methods for the stereoselective construction of polycyclic systems and is often employed as a key step for the total synthesis of various complex natural products.[1] In general, the intramolecular Diels-Alder reaction profits from entropical factors due to the spatial proximity of the reaction parameters, and many examples are known that verify this feature. However, it is sometimes difficult to obtain the cycloadducts even in the intramolecular Diels-Alder reaction. For example, furan is known as a relatively unreactive diene because of its aromaticity, and only a few examples on the intramolecular Diels-Alder reactions of furan derivatives with reactive dienophiles such as fumaric acid or acrylic acid derivatives have been reported.[2] Then we assumed that even in the unfavorable combination of dienes and dienophiles such as furan moiety and sterically hindered acrylic acid derivatives, it would be possible to obtain the corresponding cycloadducts by manipulating some artificial control on the reaction. Based on these assumptions, we have explored an efficient method for the acceleration of the intramolecular Diels-Alder reaction utilizing the intramolecular interactions —that is, the internal coordination of a magnesium salt and the internal hydrogen bonding.[3,4]

In the present paper, we wish to report this new concept for the acceleration of the intramolecular Diels-Alder reaction between furan derivatives and various sterically hindered α,β-unsaturated amides in detail.

Results and Discussion

It is well known that electron-rich dienes and electron-deficient dienophiles react easily to afford the cycloadducts in good yields. On the other hand, electron-deficient dienes preferentially react with dienophiles substituted with electron-donating groups, that is, the Diels-Alder reaction with "inverse electron demand."[5] Of these reactants, electron-deficient dienes, only a few papers related to dienes substituted with the strongly electron-withdrawing groups such as nitro group have been noted.[6] Notably, there has been only one example of the Diels-Alder reaction of nitrofuran with maleic anhydride reported by Van Campen *et al.*,[7] though they were unable to isolate the corresponding cycloadduct. It seems that, in this case, the cycloaddition reaction is impossible, as both nitrofuran and maleic anhydride are strongly electron-deficient. So the promotion of the reaction of this unfavorable combination of diene and dienophile was undertaken based on the intramolecular interaction taking the intramolecular Diels-Alder reaction between nitrofuran (*i.e.* the electron-deficient diene) and α,β-unsaturated amides (*i.e.* the electron-deficient dienophile), as a model.

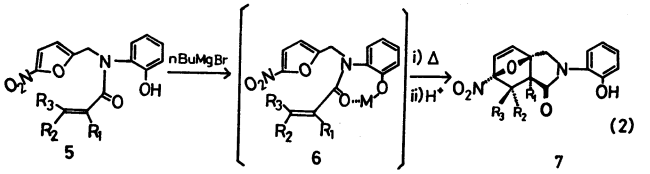
In the first place, *N*-(5-nitrofurfuryl)-*N*-(2-hydroxyphenyl)acrylamides (**5**), the Diels-Alder reagents, were prepared from 5-nitrofurfural (**1**) and 2-hydroxyaniline (**2**) as shown in Eq. 1.



With the expectation that the formation of internal chelate complex **6** would bring both diene and dienophile groups to come closely to promote the cycloaddition reaction effectively, the reaction of the magnesium salt of amide **5** was examined, and the results are summarized in Table 1.

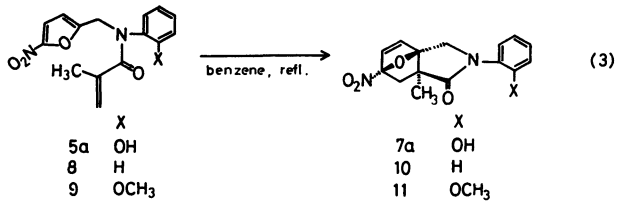
As shown in Table 1, cycloadducts **7a—c** were obtained only in 44—58% yield,[8] though starting material **5** was consumed completely and several minor products were detected on the thin-layer chromatography. This result indicates that the cycloaddition reaction might be accelerated by the formation of

Table 1. The Diels-Alder reaction of **5** with magnesium salt



Amide	R_1	R_2	R_3	Solvent	Reaction time/h	Yield of **7** %
5a	CH_3	H	H	Benzene	3	46
				Benzene	7	57
5b	H	CH_3	H	Toluene	7	47
				Toluene–THF	9	42
5c	H	CH_3	CH_3	Toluene	7	48
				Toluene–THF	9	44

internal chelate, but some difficulties arose because of side reactions caused by the presence of a nitro group. Then the cycloaddition reaction of amide **5**, without converting to its magnesium salt, was tried on the assumption that the internal hydrogen bonding would be sufficient for the effective promotion of the cycloaddition reaction. Amides **5a**, **8**, and **9** were prepared to compare the reactivity, and to determine the existence and the role of the internal hydrogen bonding, and their reactions were examined under the same conditions (Eq. 3).



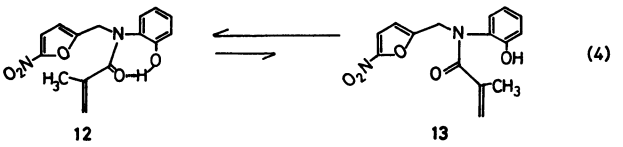
(3)

When a benzene solution of amide **5a** was refluxed for 7 h, adduct **7a** was obtained in 75% yield, but amides **8** and **9**, in which there is no internal hydrogen bonding, gave adducts **10** and **11** in only 30 and 11% yields, respectively, under the same conditions. Further, the existence of the internal hydrogen bonding in amide **5a** was supported by its IR spectra, that is, the absorptions of the carbonyl group of **5a**, **8**, and **9** are at 1600, 1650, and 1650 cm^{-1}, respectively.

These results indicate that the internal hydrogen bonding performs an important part on the acceleration of this cycloaddition reaction as expected.

Among possible conformers of amide **5a**, only conformer **12**, in which the diene and the dienophile approach closely, leads to the cycloaddition reaction.[2)]

In this case, it is apparent that the internal hydrogen bonding of the phenolic hydrogen to the carbonyl oxygen is sufficient to fix the conformation of this molecule to favorable conformer **12** (Eq. 4).

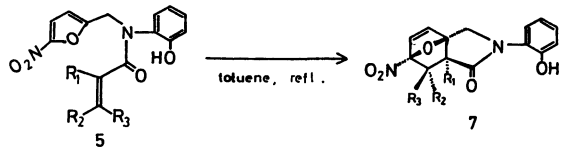


(4)

The yield of adduct **7a** increased to 94% when the reaction was performed in refluxing toluene. Similar reactions with other sterically hindered α,β-unsaturated amide **5** were tried, and adducts **7** were obtained in good yields as shown in Table 2.

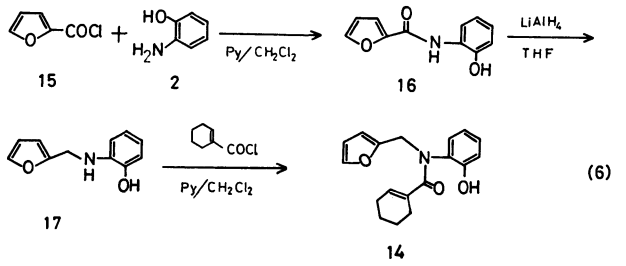
The intramolecular cycloaddition reaction between furan moiety and cyclic α,β-unsaturated amide gives the tetracyclic compounds in one step, which are useful for the construction of polycyclic system. Moreover, there is no report on the intramolecular Diels-Alder reaction using the cyclic α,β-unsaturated amide as dienophile, probably because of its high steric hindrance. Then we next tried the cycloaddition reaction between furan derivatives and 1-cyclohexenecarboxamide utilizing the internal interaction—that is, the internal hydrogen bonding or the internal coordination of the metal salt. *N*-Furfuryl-*N*-(2-hydroxyphenyl)-1-cyclohexenecarboxamide (**14**) was prepared from 2-furoyl chloride (**15**) and 2-hydroxyaniline (**2**) as shown in Eq. 6.

TABLE 2. THE DIELS–ALDER REACTION OF **5**



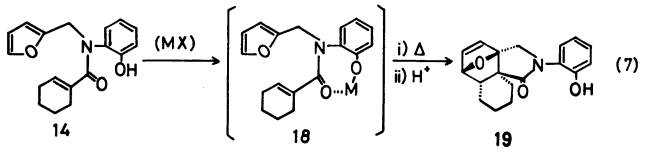
(5)

Amide	R_2, R_1, R_3	Reaction time/h	Yield of **7**/%
5a		7	94
b		9	93
c		9	73
d		7	96
e		9	30



(6)

With starting material **14** in hand, we then examined the reaction of amide **14** and its magnesium salts based on the same assumption described above (Eq. 7).



(7)

When amide **14** was heated in the refluxing benzene or toluene, only a trace of the cycloadduct was detected. Then, amide **14** was converted to its magnesium salt by the treatment with the Grignard reagent, and the reaction was performed in refluxing toluene. And, in this case, the reaction was effectively accelerated to afford cycloadduct **19** in 38% yield. To increase the yield of **19**, the effect of the solvent was examined. The results are summarized in Table 3. As shown in this Table, remarkable increase in the yield of cycloadduct **19** was not observed. Moreover, the effect of the reaction time was also investigated. When the reaction was continued for 14 h, the yield of cycloadduct **19** increased to 41%. However, longer reaction time decreased the yield of cycloadduct **19**, and only 14% yield of **19** was obtained, when the reaction was run

Table 3. The effect of reaction temperature[a)]

Solvent	Reaction temp/°C	Reaction time/h	Yield of **19** %
Benzene	Reflux	7	Trace
Toluene	Reflux	7	38
Xylene	Reflux	7	18
Cumene	115—120	7	17
DMF	Reflux	5	—
DMF–Benzene (4 : 1)	115—120	7	9
DMF–Toluene (1 : 1)	120—125	7	11
Toluene–THF (25 : 2)	107	7	16

a) Magnesium chloride was used as the metal salt.

Table 4. The reaction with various metal salts[a)]

Metal salt	Reaction time/h	Yield of **19**/%
–OMgCl	7	39
–OMgBr	7	30
–OZnCl	11.5	32
$-OAlCl_2$	9	Trace
$-OB(C_2H_5)_2$	10	25
$-OBBr_2$	7	—

a) The reaction was carried out in refluxing toluene.

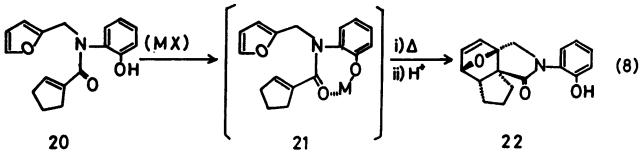
for 33.5 h. We also found that starting material **14** was recovered in 30% yield, when the magnesium salt of cycloadduct **19** was refluxed in toluene for 7 h. This result indicates that the reaction is an equilibrating one and both cycloaddition reaction and the retro Diels-Alder reaction proceed concurrently at high temperature. And this could partly explain the rather moderate yield of cycloadduct **19** in this reaction.

Finally, we examined other metal salts such as Zn, Al, and B, which are thought to be stronger Lewis acids than Mg. However, as shown in Table 4, the use of these metal salts rather decreased the yield of adduct **19**.

It is well known that the Diels-Alder reaction is accelerated by the Lewis acid,[9)] but, at the same time, side reactions such as polymerization often occur, because both dienes and dienophiles are rather unstable under the acidic conditions.[10)] And in this case magnesium which is regarded as a week Lewis acid, is most favorable, that is, strong enough to accelerate the reaction effectively but not too strong to cause the side reactions. Further, the cycloaddition reaction of other cyclic α,β-unsaturated amides were examined. Molecular models show that in the case of 1-cyclohexenecarboxamide **14**, the axial protons in the cyclohexene ring seem to disturb the approach of the furan ring, and it is assumed that more planar cyclic α,β-unsaturated amides would show higher reactivity in the cycloaddition reaction. Based on this assumption, 1-cyclopentenecarboxamide derivative **20** and 1,5-cyclohexadienecarboxamide derivative **23** were prepared, and their reactivities were examined under the various reaction conditions. The results are summarized in Tables 5 and 6.

As clearly shown in these Tables, these two compounds show higher reactivity than the 1-cyclohexenyl derivative, and the corresponding cycloadducts were obtained in high yields by forming the internal chelate complexes

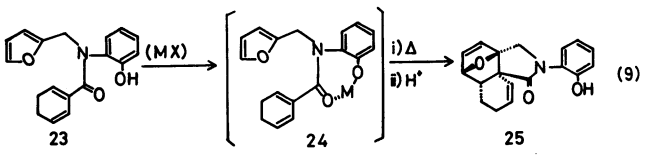
Table 5. The Diels-Alder reaction of **20**[a)]



Metal salt	Solvent	Reaction time/h	Yield of **22**/%
None	Benzene	7	18
–OMgBr	Benzene	7	65
None	Toluene	7	51
–OMgBr	Toluene	1	85
–OMgCl	Toluene	1	84
–OMgI	Toluene	1	84
–OZnCl	Toluene	1	21
–OMgBr	DME	1	31

a) The reaction was carried out under reflux temperature.

Table 6. The Diels-Alder reaction of **23**[a)]



Metal salt	Solvent	Reaction time/h	Yield of **25** %
None	Toluene	10	Trace
–OMgBr	Toluene	7	52
	Toluene–THF[b)]	5	75
–OMgCl	Toluene–THF[b)]	5	77

a) The reaction was carried out under reflux. b) THF was added to dissolve the magnesium salt of **23** and the reaction solution was heated to reflux at 107.5 °C.

of magnesium. These results indicate that steric hindrance of the dienophile remarkably affects the reactivity of the intramolecular Diels-Alder reaction, and that by employing coordinating property of magnesium ingeniously, dramatic acceleration of the reaction could be achieved.

In conclusion, it is noted that an efficient and general method is established for the acceleration of the intramolecular Diels-Alder reaction by employing internal hydrogen bonding or the internal coordination of a magnesium salt. By employing this method, various cycloadducts, which cannot be obtained in the previous intramolecular Diels-Alder reaction, have become available in high yields.

Experimental

Measurements. All the melting points were uncorrected. NMR spectra were recorded with a Hitachi R-24B spectrometer. IR spectra were measured with a Hitachi EPI-G2 spectrometer. Mass spectra were measured with a JEOL JMS 01-SG spectrometer.

Materials. All organic solvents used were distilled according to the general methods and stored over sodium metal or molecular sieves as a drying agent.

2-Hydroxy-N-(5-nitrofurfurylidene)aniline (3). 2-Hydro-

xyaniline (2.02 g, 18.5 mmol) was added to the benzene solution (20 ml) of 5-nitrofurfural (2.59 g, 18.4 mmol) at room temperature. A yellow precipitate was formed immediately. After 30 min the precipitate was filtered and recrystallized from benzene to afford **3** as yellow needles (3.73 g, 88%). Mp 158 °C (decomp) (benzene); IR (KBr) 3360, 3160, 1625, 1525, and 1332 cm^{-1}; NMR (DMSO-d_6) δ=6.25—7.53 (6H, m), 8.48 (1H, s), 8.70 (1H, broad); Found: C, 56.91; H, 3.30; N, 11.96%; Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07%.

N-(2-Hydroxyphenyl)-5-nitrofurfurylamine (4). 2-Hydroxy-*N*-(5-nitrofurfurylidene)aniline (**3**) (3.22 g, 13.9 mmol) was dissolved in 165 ml of THF and 66 ml of 95% ethanol. The mixture was cooled to −35——40 °C. The solution of sodium borohydride (0.79 g, 20.8 mmol) dissolved in 0.8—1.3 ml water and 9 M (1 M=1 mol dm^{-3}) hydrochloric acid were alternately added dropwise to the stirred solution so that pH 6—8 was maintained. During the addition, care was taken to maintain the temperature between −35 and −45 °C. After the addition of the sodium borohydride was complete, the solution was stirred at −35 °C for 1.5 h and hydrolyzed with water. After being acidified with acetic acid–ethanol solution to pH 3—4, the mixture was neutralized with 6 M sodium hydroxide. To the solution dichloromethane was added and the organic layer was washed with water, dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by silica-gel column chromatography using benzene–ethyl acetate (5 : 1) and amine **4** was obtained (2.72 g, 70%; unstable to light). Mp 85 °C; IR (KBr) 3320, 3130, 1490, and 1350 cm^{-1}; NMR ($CDCl_3$) δ=4.33 (2H, s), 4.63 (2H, broad), 6.30 (1H, d, J=4 Hz), 6.37—6.70 (4H, m), 7.07 (1H, d, J=4 Hz).

N-(5-Nitrofurfuryl)-N-(2-hydroxyphenyl)methacrylamide (5a). To a solution of amine **4** (0.82 g, 3.76 mmol) in 10 ml of dichloromethane and dry pyridine (0.43 g, 5.46 mmol) was added dropwise methacryloyl chloride (0.48 g, 4.55 mmol) in 5 ml of dichloromethane at −20 °C under an argon atmosphere. After the addition was complete, the reaction mixture was stirred at room temperature for 3 h. Then the organic layer was washed with 2 M hydrochloric acid and water. After being dried over Na_2SO_4, the solvent was evaporated *in vacuo* and the residue was purified by silica-gel column chromatography using benzene–ethyl acetate (5 : 1) and amide **5a** was obtained as yellow needles (0.77 g, 71%). Mp 146—147 °C (dichloromethane); IR (KBr) 3250, 1605, 1590, and 1350 cm^{-1}; NMR (DMSO-d_6) δ=1.75 (3H, s), 4.67 (1H, m), 4.90 (3H, m), 6.48 (1H, d, J=4 Hz), 11.10 (1H, broad); Found: *m/e*302.0943. Calcd for $C_{15}H_{14}N_2O_5$: M, 302.0903. By similar procedure amides **5b—e**, **8**, and **9** were also prepared. **5b**: Mp 170—171 °C (dichloromethane); IR (KBr) 3200, 1605, 1580, and 1360 cm^{-1}; NMR (DMSO-d_6) δ=1.73 (3H, dd, J=7 and 2 Hz), 4.47 (1H, d, J=14 Hz), 5.15 (1H, d, J=14 Hz), 5.62 (1H, d, J=14 Hz), 6.29—7.25 (7H, m), 9.33 (1H, s); Found: *m/e* 302.0917. Calcd for $C_{15}H_{14}N_2O_5$: M, 302.0902, **5c**: Mp 163—164 °C (dichloromethane); IR (KBr) 3230, 1605, 1580, and 1360 cm^{-1}; NMR (DMSO-d_6) δ=1.35 (3H, s), 2.07 (3H, s), 4.42 (1H, d, J=16 Hz), 5.13 (1H, d, J=16 Hz), 5.35 (1H, m), 6.28—7.20 (6H, m), 9.22 (1H, s); Found: *m/e* 316.1054. Calcd for $C_{16}H_{16}N_2O_5$: M, 316.1059. **5c**: Mp 154—155 °C (dichloromethane); IR (KBr) 3200, 1605, 1560, and 1350 cm^{-1}; NMR (DMSO-d_6) δ=1.35—2.35 (6H, m), 4.40 (1H, d, J=14 Hz), 5.03 (1H, d, J=14 Hz), 5.62 (1H, m), 6.18—7.52 (6H, m), 9.35 (1H, s); Found: *m/e* 328.1048. Calcd for $C_{17}H_{16}N_2O_5$: M, 328.1059. **5e**: Oil; IR ($CHCl_3$) 3340, 1620, 1500, and 1360 cm^{-1}; NMR ($CDCl_3$) δ=0.90—2.70 (8H, m), 4.82 (2H, s), 5.82 (1H, s), 6.35 (1H, d, J=4 Hz), 6.50—7.40 (6H, m). **8**: Oil; IR (liquid) 1650, 1490, and 1350 cm^{-1}; NMR ($CDCl_3$) δ=1.73 (3H, s), 4.73 (2H, s), 5.30 (2H. s), 6.40 (1H, d, J=4 Hz), 6.82—7.47 (6H, m). **9**: Mp 97—98 °C (dichloromethane); IR 1650, 1500, and 1350 cm^{-1}; NMR ($CDCl_3$) δ=1.42 (3H, s), 3.72 (3H, s), 4.88 (4H, m), 6.35 (1H, d, J=4 Hz), 6.57—6.90 (5H, m).

Intramolecular Diels-Alder Reaction.[8] *2,3,3a,6,7,7a-Hexahydro-2-(2-hydroxyphenyl)-7a-methyl-6-nitro-3a,6-epoxy-1H-isoindol-1-one (7a).* After the toluene solution (20 ml) of amide **5a** (100 mg, 0.33 mmol) was refluxed for 7 h, the solvent was evaporated. The residue was purified by silica-gel column chromatography to afford cycloadduct **7a** (94 mg, 94%). Mp 221—222 °C (dichloromethane); IR (KBr) 3400, 1650, 1540, and 1360 cm^{-1}; NMR (DMSO-d_6) δ=1.20 (3H, s), 1.88 (1H, d, J=12 Hz), 6.28—7.28 (6H, m), 9.20 (1H, s); Found: *m/e* 302.0872. Calcd for $C_{15}H_{14}N_2O_5$: M, 302.0903. By similar procedure the intramolecular Diels-Alder reaction of amides **5b—e**, **8**, and **9** were performed to afford cycloadducts **7b—e**, **10**, and **11**. **7b**: Mp 207—208 °C (dichloromethane); IR (KBr) 3060, 1650, 1550, and 1380 cm^{-1}; NMR (DMSO-d_6) δ=1.18 (3H, d, J=7 Hz), 2.67—3.20 (2H, m), 3.57 (1H, d, J=12 Hz), 4.47 (1H, d, J=12 Hz), 6.28—7.28 (6H, m), 9.27 (1H, s); Found: *m/e* 302.0899. Calcd for $C_{15}H_{14}N_2O_5$: M, 302.0903. **7c**: Mp 189—190 °C (dichloromethane); IR (KBr) 3300, 1645, 1545, and 1370 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=12 Hz), 4.48 (1H, d, J=12 Hz), 6.28—7.28 (6H, m), 9.32 (1H, s); Found: *m/e* 316.1107. Calcd for $C_{16}H_{16}N_2O_5$: M, 316.1061. **7c**: Mp 225—226 °C (dichloromethane); IR (KBr) 3200, 1665, 1550, and 1370 cm^{-1}; NMR (DMSO-d_6) δ=1.08—1.98 (6H, m), 3.08—3.42 (1H, m), 3.90 (1H, d, J=12 Hz), 4.52 (1H, d, J=12 Hz), 6.32—7.32 (6H, m), 9.33 (1H, s); Found: *m/e* 328.1055. Calcd for $C_{17}H_{16}N_2O_5$: M 328.1059, **7e**: Mp 200—201 °C (dichloromethane); IR (KBr) 3300. 1650, 1540, and 1370 cm^{-1}; NMR (DMSO-d_6) δ=0.65—2.12 (8H, m), 2.98—3.48 (1H, m), 3.92 (1H, d, J=12 Hz), 4.50 (1H, d, J=12 Hz), 6.35—7.32 (6H, m), 9.45 (1H, s); Found: *m/e* 342.1208. Calcd for $C_{18}H_{18}N_2O_5$: M, 342.1217. **10**: Mp 132—133 °C. (benzene–cyclohexane); IR (KBr) 1696, 1550, and 1360 cm^{-1}; NMR ($CDCl_3$) δ=1.18 (3H, s), 2.27 (1H, d, J=12 Hz), 3.23 (1H, d, J=12 Hz), 4.27 (2H, d, J=4 Hz), 6.67 (2H, d, J=2 Hz), 6.90—7.68 (5H, m); Found: C, 62.94; H, 4.83; N, 9.59%; Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79%. **11**: Mp 162—163 °C (dichloromethane); IR (KBr) 1695, 1530, and 1340 cm^{-1}; NMR ($CDCl_3$) δ=1.25 (3H, d, J=2 Hz), 1.90 (1H, d, J=10 Hz), 2.87 (1H, d, J=10 Hz), 3.78 (3H, s), 3.93 (1H, d, J=12 Hz), 4.43 (1H, d, J=12 Hz), 6.47—6.80 (6H, m); Found: C, 60.53; H, 5.00; N, 8.80%; Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86%.

N-(2-Hydroxyphenyl)-2-furancarboxamide (16). Under an argon atmosphere 2-furoyl chloride (22.9 g, 0.18 mol) was added to the suspension of 2-hydroxyaniline (19.1 g, 0.18 mol) and dry triethylamine 35 ml in 400 ml dichloromethane at 0—5 °C and the mixture was stirred at room temperature for 2 h. After 2 M hydrochloric acid was added to the mixture to afford amide **16** (20.2 g, 57%), a white precipitate formed was filtered. The filtrate was extracted with dichloromethane and the extract was washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to afford amide **16** (8.76 g, 25%). Mp 165—166 °C (benzene); IR (KBr) 3390, 3100, and 1635 cm^{-1}; NMR ($CDCl_3$) δ=6.37—7.47 (7H, m), 8.00 (1H, m), 8.83 (1H, broad); Found: C, 65.05; H, 4.37; N, 7.01%; Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89%.

N-(2-Hydroxyphenyl)-2-furfurylamine (17). Under an argon atmosphere, amide **16** (25.0 g, 0.12 mol) in 220 ml THF solution was added dropwise to the suspension of $LiAlH_4$ (6.1 g, 0.16 mol) in 30 ml of THF at −5—0 °C. After the mixture was refluxed for 1 h, saturated sodium sulfate solution was

added cautiously in an ice-cold bath. The precipitate was filtered and washed with ethyl acetate. The filtrate was washed with 2 M hydrochloric acid and neutralized with sodium hydrogencarbonate, and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was distilled and amine **17** was obtained as a colorless oil (2.80 g, 80%). Bp 110 °C/0.2 mmHg (1 mmHg≈133.322 Pa); mp 62 °C; IR (liquid) 3340 and 1610 cm^{-1}; NMR ($CDCl_3$) δ=4.12 (2H, s), 5.25 (2H, s), 6.03 (2H, m), 6.33—6.70 (4H, m), 7.10 (1H, s).

N-Furfuryl-N-(2-hydroxyphenyl)-1-cyclohexenecarboxamide (14). To a solution of amine **17** (1.42 g, 7.50 mmol) in 20 ml of dichloromethane and dry pyridine (0.89 g, 11.26 mmol) 1-cyclohexenecarbonyl chloride (1.40 g, 7.54 mmol) in 14 ml of dichloromethane was added dropwise at −20 °C under an argon atmosphere. After the addition was complete, the mixture was stirred at room temperature for 3 h. Then the organic layer was washed with 2 M hydrochloric acid and water. After being dried over Na_2SO_4, the solvent was evaporated and the residue was recrystallized from benzene and amide **14** was obtained as white needles (1.85 g, 83%). Mp 171—172 °C (benzene); IR (KBr) 3400 and 1610 cm^{-1}; NMR ($CDCl_3$) δ=1.02—1.67 (4H, m), 1.67—2.33 (4H, m), 4.82 (2H, s), 5.67—6.00 (1H, m), 6.10 (2H, m), 6.60—7.33 (6H, m); Found: C, 72.68; H, 6.41; N, 4.45%; Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71%. By similar procedure amide **20** was prepared. **20**: Mp 114—115 °C (benzene); IR (KBr) 3130 and 1610 cm^{-1}; NMR ($CDCl_3$) δ= 1.28—2.50 (6H, m), 4.78 (2H, s), 5.85 (1H, m), 6.07 (2H, m), 6.52—7.40 (6H, m); Found: C, 72.26; H, 6.07; N, 4.84%; Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94%.

N-Furfuryl-N-(2-hydroxyphenyl)-1,5-cyclohexadienecarboxamide (23). To 1-methyl-2-chloropyridinium tosylate (1.95 g, 6.5 mmol) in 15 ml of dichloromethane was added a mixture of amine **17** (1.00 g, 5.30 mmol), 1,5-cyclohexadienecarboxylic acid[11] (0.67 g, 5.42 mmol) and triethylamine (0.87 g, 13.11 mmol) in 40 ml of dichloromethane. After being stirred overnight at room temperature under an argon atmosphere, 2 M hydrochloric acid (10 ml) was added to the reaction mixture and the resulting mixture was washed with water (20 ml) three times. The organic layer was dried over Na_2SO_4 and concentrated under the reduced pressure. Amide **23** was isolated after separation by silica-gel column chromatography using benzene–ethyl acetate (5 : 1) (0.48 g, 30%). Mp 139—140 °C (cyclohexane–benzene); IR (KBr) 3150 and 1610 cm^{-1}; NMR ($CDCl_3$) δ=1.92 (4H, m), 4.86 (2H, m), 5.27—6.33 (5H, m), 6.43—7.33 (6H, m); Found: C, 72.97; H, 5.63; N, 4.64%; Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%.

Intramolecular Diels-Alder Reaction Using Halophenoxy Magnesium Salt.[8] *1,2,3,3a,6,6a,7,8,9,10-Decahydro-(2-hydroxyphenyl)-3a,6-epoxybenz[d]isoindol-1-one (19).* To a solution of amide **14** (100.3 mg, 0.337 mmol) in 3 ml of THF was added dropwise butylmagnesium chloride (0.39 ml, 0.86 mol dm^{-3} ether solution) at −78 °C under an argon atmosphere. After the solution being concentrated under the reduced pressure at room temperature, toluene (30 ml) was added and the reaction mixture was refluxed for 14 h under an argon atmosphere. To the solution was added 2 M hydrochloric acid (10 ml), and the organic layer was extracted with dichloromethane. The extract was washed with water and dried over Na_2SO_4. The solution was concentrated under the reduced pressure. Cycloadduct **21** was isolated after separation by the thin-layer chromatography using benzene–ethyl acetate (5 : 1) (44.0 mg, 44%). Mp 138—139 °C (cyclohexane); IR (KBr) 3180 and 1660 cm^{-1}; NMR ($CDCl_3$) δ=0.50—2.10 (8H, m), 2.83 (1H, d, J=5 Hz), 3.58 (1H, d, J=12 Hz), 4.10 (1H, d, J=12 Hz), 4.85 (1H, d, J=5 Hz), 6.37 (2H, s), 6.53—6.97 (4H, m), 7.88 (1H, broad); Found: C, 72.71; H, 6.46; N, 4.77%; Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71%. By similar procedures the intramolecular Diels-Alder reaction of amides **20** and **23** were performed to afford cycloadducts **22** and **25**. **22**: Mp 182—183 °C (benzene); IR (KBr) 3500 and 1670 cm^{-1}; NMR ($CDCl_3$) δ=1.33—2.32 (6H, m), 2.93—3.43 (1H, m), 3.97 (1H, d, J=12 Hz), 4.43 (1H, d, J=12 Hz), 4.87 (1H, d, J=5 Hz), 6.42 (2H, s), 6.63—7.30 (4H, m), 8.18 (1H, s); Found: C, 72.17; H, 6.15; N, 4.90%; Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94%. **25**: Mp 151—152 °C (benzene); IR (KBr) 3450 and 1650 cm^{-1}; NMR ($CDCl_3$) δ=0.90—2.22 (4H, m), 2.67—3.22 (1H, m), 3.87 (1H, d, J=11 Hz), 4.38 (1H, d, J=11 Hz), 4.82 (1H, d, J=4 Hz), 5.43 (1H, d, J=10 Hz), 5.85 (1H, m), 6.20 (2H, s), 6.43—7.20 (4H, m), 7.87 (1H, s); Found: C, 73.18; H, 5.77; N, 4.90%; Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%.

References

1) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).

2) a) H. W. Gschwend, M. J. Hillman, B. Kisis, and R. K. Rodebaugh, *J. Org. Chem.*, **41**, 104 (1976); b) K. A. Parker and M. R. Adamechuk, *Tetrahedron Lett.*, **1978**, 1689.

3) T. Mukaiyama, T. Tsuji, and N. Iwasawa, *Chem. Lett.*, **1979**, 697.

4) T. Mukaiyama and T. Takebayashi, *Chem. Lett.*, **1980**, 1013.

5) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966); **6**, 16 (1967).

6) N. N. Podogornova, E. S. Lipina, and U. V. Perekalin, *Nauchn. Dokl., Gertsenovskie Cheteniva*, **27**, 22 (1974); *Chem. Abstr.*, **85**, 192214x (1976); D. Alkeksiev, I. Mladenov, E. Lipina, and V. Perekalin, *Izv, Khim.*, **9**, 439 (1976); *Chem. Abstr.*, **87**, 84587d (1977); c) T. Severin and I. Ipack, *Chem. Ber.*, **109**, 3541 (1976).

7) M. G. Van Campen and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

8) Only one of two stereoisomers was obtained. In this case, based on models and spectral analogy, the exo mode cyclization (trans ring junction) was preferred. The coupling constant between proton Ha and Hb in adducts **19**, **22**, and **25** are 5, 5, and 4 Hz, respectively, suggesting a dihedral angle of 40° or 45° (according to models, the corresponding angle for the alternative structure would be about 90° resulting in no spin-spin coupling) (Fig. 1). These results agree with

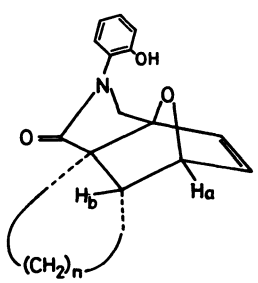


Fig. 1. Stereochemistry of cycloadducts.

spectral data presented by K. A. Parker[2b] for a related set of compounds. In the case of nitrofuran derivatives, we cannot tell the stereochemistry of the formed cycloadduct from the coupling constant becase a nitro group is present in the place of Ha proton. But in the intramolecular Diels-Alder reaction of furan derivatives, it is well known[2,12] that only the exo mode

of cycloadducts are formed, and, in this case also, we assume that only the exo mode of cycloaddition was preferred.

9) P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960).
10) G. I. Fray and R. Robinson, *J. Am. Chem. Soc.*, **83**, 249 (1961).
11) H. Plieninger and G. Ege, *Chem. Ber*, **94**, 2088 (1961).
12) D. Bilovic, *Croat. Chem. Acta*, **40**, 15 (1968); D. D. Sternbach and D. M. Rossana, *Tetrahedron Lett.* **23**, 303 (1982).