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SYNTHETIC CONTROL BY INTERNAL COORDINATION OF METAL SALTS
THE INTRAMOLECULAR DIELS-ALDER REACTIONS OF N-FURFURYL-N-(2-HYDROXYPHENYL)ACRYLAMIDES

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An efficient method for acceleration of the intramolecular Diels-Alder reactions was established. The magnesium salts of N-furfuryl-N-(2-hydroxyphenyl)acrylamides, including a sterically hindered β,β-dimethylacrylamide derivative, afforded the corresponding cycloadducts in good yields.

The 7-oxabicyclo[2.2.1]heptyl system has been widely employed as important intermediates in organic synthesis.[1)] The most straightforward approach to the construction of the 7-oxabicyclo[2.2.1]heptyl system takes advantage of the Diels-Alder reaction between furan and a suitable dienophile. Unfortunately, due to the aromatic character of furan and the strain of the bicyclo[2.2.1]heptane system, the cycloadducts can be obtained in respectable yields only when very reactive dienophiles are employed. The Diels-Alder reactions of furan with olefins activated by only one electron-withdrawing substituent take place slowly and mixtures of several isomers are formed in low yields.[2)] Parker et al.[3)] recently reported that the cycloadducts of furan and acrylic dienophiles were obtained in good yields by the intramolecular Diels-Alder reactions. But the cycloadducts were obtained in relatively low yields when sterically hindered dienophiles such as crotonamides were used.

We now wish to report an efficient method for acceleration of the intramolecular Diels-Alder reactions of furan and sterically hindered dienophiles.

Among various conformers of amide 1, the rate of cycloaddition reaction widely depends upon the population of the s-cis conformer in which the diene and the dienophile groups come nearby.[3,4)] It is supposed that when the metal salt of the N-furfuryl-N-(2-hydroxyphenyl)acrylamide 1 is introduced for the intramolecular Diels-

Alder reaction, s-cis conformer would be increased by the coordination of the carbonyl oxygen to the metal as depicted in 2. At the same time, it is also expected that the metal would behave as a weak Lewis acid to activate the dienophiles.[5)] Based on the above assumption, the Diels-Alder reactions of 1a and its metal salts were examined. When a benzene solution of the amide 1a was refluxed for 2.25 h, the cyclized product 3a was obtained in 23% yield. The alkali metal salts of 1a generated in situ from 1a gave 3a in slightly better yields, and further, its magnesium salts generated in situ from 1a by the treatment with organomagnesium reagents afforded 3a in high yields under the same conditions. (Table I)

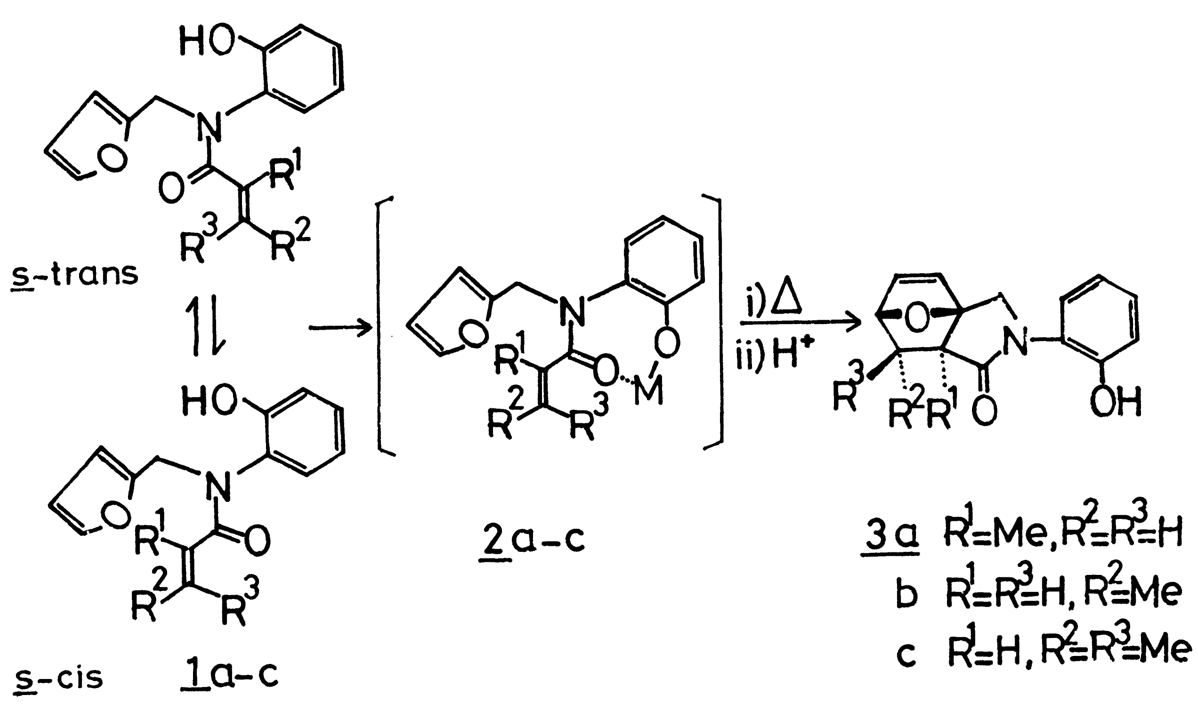

Table I. The Diels-Alder reaction of 1a and its metal salts.[a)]

salt	yield of 3a	salt	yield of 3a
-OH	23%	-OMgBr	90
-OLi	45	-OMgI	95
-ONa	29	$-O)_2Mg$	80
-OK	40	$-O)_2Zn$	55
-OMgCl	79		

a) Benzene solutions of 1a and its salts were refluxed for 2.25 h.

Crotonamide 1b and β,β-dimethylacrylamide 1c were less reactive than 1a owing to both the steric hindrance and the electron donating property of the substituents. Especially, the cycloadducts between furan derivatives and β,β-dimethylacrylic acid derivatives have never been reported.[6)] In fact, 1b gave the adducts 3b in only 5% yield in refluxing toluene for 4.5 h, and 1c gave no adduct in refluxing toluene for several hours. On the other hand, when 1b and 1c were converted to their magnesium salts and then toluene solutions of the salts were heated to reflux, the cycloadducts 3b and 3c were obtained in good yields (See Table II).

Table II. The Diels-Alder reaction of 1b and 1c.

compound	salt	reaction time	yield of 3b or 3c
1b	-OH	4.5 h	5%
1b	-OMgCl	4.5	63
1b	-OMgBr	4.5	53
1b	-OMgI	4.5	46
1b	$-O)_2Mg$	4.5	43
1c	-OH	7.0	0
1c	-OMgBr	7.0	76

A general procedure is described for the preparation of 2,3,6,7-tetrahydro-2-(2-hydroxyphenyl)-7a-methyl-3a,6-epoxyisoindol-1-one 3a from 1a via bromomagnesium salt of 1a: To an ether (3 ml) solution of 1a (0.42 mmol) was added an ether solution of butylmagnesium bromide (0.42 mmol) at -78°C. The solvent was evaporated at room temperature in vacuo and benzene (4.2 ml) was added to the residue. The mixture was refluxed for 2.25 h, cooled to room temperature and 2N HCl (10 ml) was added. The organic layer was extracted with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate and then evaporated in vacuo. The residue was purified by silica gel column chromatography.

Various cycloadducts[7)] shown in Table I, II were prepared by this procedure; 3a: mp 144.0-144.5°C (recrystallized from hexane-benzene); IR (KBr) 3300, 1640 cm^{-1}; NMR ($CDCl_3$) δ =1.17 (3H,s), 1.20 (1H, d,J=12 Hz), 2.55 (1H, dd, J=12 Hz, 5 Hz), 4.04 (1H, d, J=12 Hz), 4.43 (1H, d, J=12 Hz), 4.95(1H, dd, J=5 Hz, 1 Hz), 6.3-6.5 (2H, m) 6.8-7.2 (4H, m), 8.03 (1H, s); Found: C, 69.86; H, 5.86; N, 5.59%; Calcd. for $C_{15}H_{15}NO_3$: C, 70.12; H, 5.88; N, 5.44%. 3b: mp 191.0-191.5°C (recrystallized from ethyl acetate); IR (KBr) 3070, 1650 cm^{-1}; NMR ($CDCl_3$) δ =1.00 (3H, d, J=7 Hz), 2.20

(1H, d, J=3 Hz), 2.5-2.8 (1H, m), 4.00(1H, d, J=11 Hz), 4.45 (1H, d, J=11 Hz), 4.85 (1H, dd, J=5 Hz, 1 Hz), 6.2-6.5 (2H, m), 6.75-7.2 (4H, m), 7.9-8.15 (1H, s); Found: C, 70.15; H, 5.82; N, 5.45%; Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44%. 3c: mp 164.5-165.0°C (recrystallized from benzene); IR (KBr) 3300, 1635 cm^{-1}; NMR ($CDCl_3$) δ =1.05 (3H, s), 1.44 (3H, s), 2.29 (1H, s), 3.97(1H, d, J=11 Hz), 4.45 (1H, d, J=14 Hz), 4.40 (1H, s), 6.43 (2H, s), 6.75-7.15 (4H, m), 7.95 (1H, s); Found: C, 70.78; H, 6.26; N, 5.23%; Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6,32; N, 5.16%.

Thus an efficient method for acceleration of the intramolecular Diels-Alder reactions by the internal coordination of the metal salts was established. Various cycloadducts of furan and acrylic acid derivatives were obtained in good yields even when sterically hindered dienophiles were used. The cycloadduct 3c is a useful precursor of some monoterpenes and synthetic approach to these terpenes is now in progress.

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