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AN EFFICIENT METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF TRICYCLIC COMPOUNDS

—— THE INTRAMOLECULAR DIELS-ALDER REACTION OF CYCLIC α,β-UNSATURATED CARBOXAMIDES ——

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An efficient method for the stereoselective synthesis of tricyclic compounds was studied by the intramolecular Diels-Alder reaction utilizing the internal coordination of the magnesium salt. The magnesium salts of N-(2,4-alkadienyl)-N-(2-hydroxyphenyl) cyclopent-1-enecarboxamides afford predominantly trans-fused cycloadducts via exo-mode of cyclization.

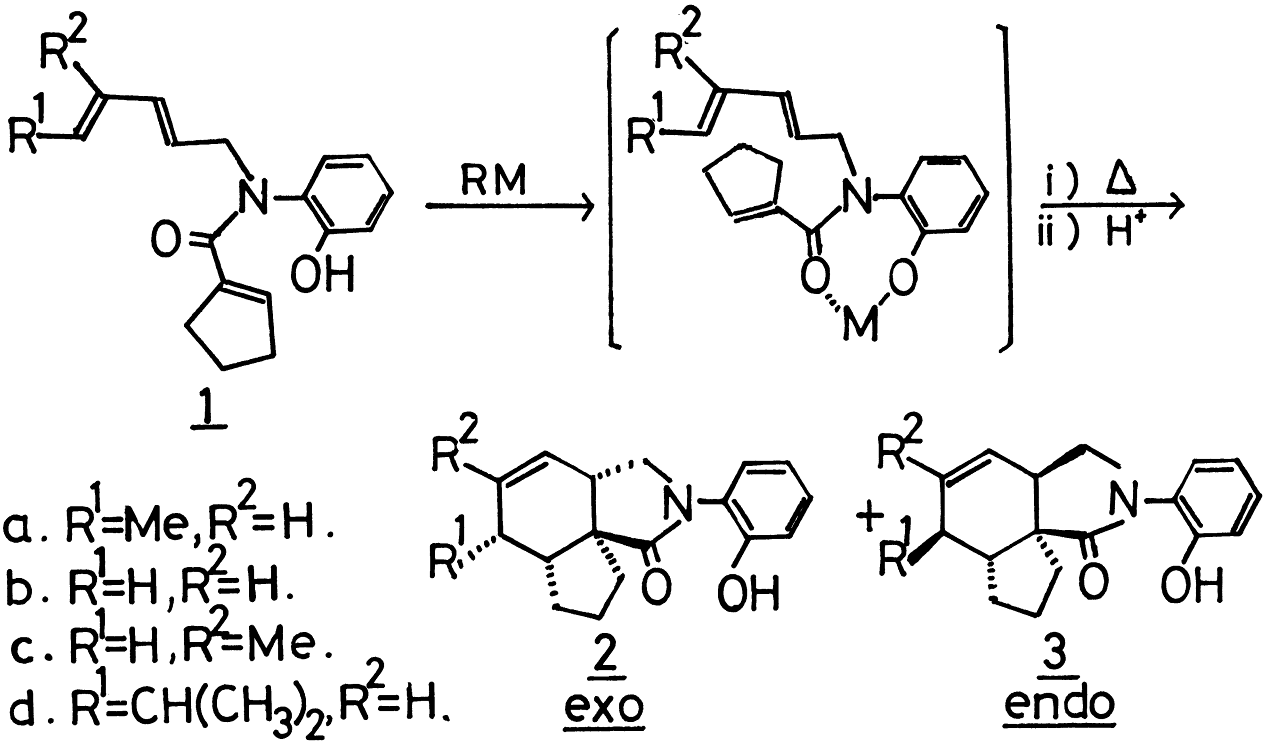
The recent development of the intramolecular Diels-Alder reaction as a basic synthetic strategy makes it possible to synthesize various complex natural products.[1a)]

The intramolecular Diels-Alder reaction of the cyclic α,β-unsaturated carboxylic acid derivatives with various dienes furnishes a facile method for the stereoselective construction of a variety of substituted tricyclic systems. However, the employment of sterically hindered cyclic dienophiles, such as cyclopent-1-enecarboxylic acid derivatives has scarcely been studied[1b)] partly owing to the diminished reactivity in the cycloaddition reactions.

Recently we have reported an efficient method for the acceleration of the intramolecular Diels-Alder reaction between furan and various sterically hindered dienophiles such as β,β-dimethylacrylamide,[2)] utilizing the internal coordination of the magnesium salt.

In the present communication, we wish to disclose our results on the efficient and stereoselective synthesis of tricyclic compounds by the intramolecular Diels-Alder reaction of cyclopent-1-enecarboxylic acid derivatives bearing acyclic diene components by forming the internal chelate; namely, when the amide 1 is converted to its metal salt, the coordination of the metal center to the carbonyl oxygen could make the diene and dienophile groups come close together to accelerate the cycloaddition reaction,[2)] and, furthermore it could be expected that formation of the rigid internal chelate complex should have a significant effect on controlling the endo-exo stereoselection.

When the toluene solution of the amide 1a was refluxed for 17 h, equal amounts of two stereoisomeric adducts 2a and 3a were obtained in 46% yield. On the other



a. R^1=Me, R^2=H.
b. R^1=H, R^2=H.
c. R^1=H, R^2=Me.
d. R^1=CH(CH$_3$)$_2$, R^2=H.

Table The Diels-Alder Reaction of 1a, 1b, 1c, and 1d a) 3)

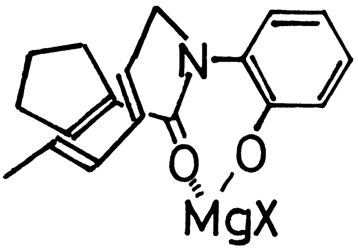
compound	metal salt	reaction time (h)	yield (%)	isomeric ratio 2:3
1a	-OH	17	46	50 : 50 b)
	-OMgCl	10	80	85 : 15 b)
	-OMgBr	10	78	80 : 20 b)
	-OMgI	10	78	83 : 17 b)
1b	-OH	6	29	40 : 60 a)
	-OMgCl	4	91	62 : 38 c)
	-OMgBr	4	86	62 : 38 c)
	-OMgI	4	81	60 : 40 c)
1c	-OH	20	30	42 : 58 c)
	-OMgCl	10	71	60 : 40 c)
	-OMgBr	10	75	65 : 35 c)
	-OMgI	10	75	61 : 39 c)
1d	-OH	11	25	60 : 40 b)
	-OMgCl	10	74	76 : 24 b)
	-OMgBr	10	70	80 : 20 b)
	-OMgI	10	70	88 : 12 b)

a) The reactions were carried out in refluxing toluene.
b) GC analysis performed on 2 m, 2% OV-17 chromosorb W column at 200°C.
c) Inseparable by TLC or GC. Product ratio determined by ^{1}H-NMR.

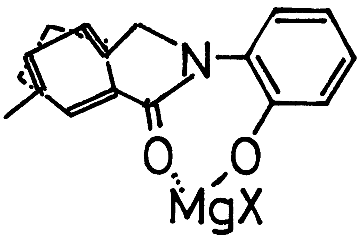
hand, when the toluene solution of the magnesium chloride salt of the amide 1a, prepared in situ by the treatment of 1a with n-butylmagnesium chloride, was refluxed for 10 h, the adducts 2a and 3a were obtained in 80% yield and the isomeric ratio of the products came up to 85:15. The ratio of these two stereoisomers was determined by gas chromatography and the configuration of the predominantly formed adduct was determined to be exo by X-ray analysis for 2a.[4] Similarly, the reactions of the magnesium salts of the amide 1 bearing various acyclic dienes were carried out, and in each case, dramatic acceleration of reaction rate and remarkable change in diastereoselection were observed.

These results indicate that the Diels-Alder reaction of the amide 1 is surely accelerated by the internal coordination of the magnesium salt as described above. Moreover, in this magnesium salt mediated intramolecular Diels-Alder reaction, the exo-cycloadducts are preferentially produced.

In these intramolecular Diels-Alder reactions of acyclic diene systems, it is generally known that both endo and exo cycloadducts are formed,[5],[6] and recently W. R. Roush[5b] has reported that in the Lewis acid catalyzed intramolecular Diels-Alder reactions of terminally activated triene esters, the endo cycloadducts were preferentially formed presumably owing to the secondary orbital control increased by the Lewis acid activation. Contrary to this observation, our results clearly show that exo-mode of cyclization is preferred when the amide 1 is converted to its magnesium salt. This selectivity could be explained by taking into account the planarity of the amide group employed in the present experiment. In this case, there is little energy difference in the transition state between endo-mode and exo-mode when the reaction is carried out without metal salts. On the other hand, when the amide 1 is converted to its magnesium salt, the coordination of the metal to the carbonyl oxygen should make the conformation of the molecule more rigid and the endo-mode of cyclization (A) would become more strained compared with the exo-mode of cyclization (B). Thus, in these systems, it is concluded that steric factor is more influential than the secondary orbital control in the stereoselection of the formed cycloadducts.



endo(A)
(more strained)



exo(B)

It is noted that a novel method for the stereoselective synthesis of tricycli compounds is established utilizing the intramolecular Diels-Alder reaction of cyclopent-1-ene carboxylic acid derivative bearing various acyclic diene components. It is made clear that the internal coordination of magnesium salt not only accelerates the reaction effectively, but also has an influential effect on the stereoselection in this reaction. Application of this reaction to the natural product synthesis is now in progress.

Acknowledgement.

We wish to express our thanks to Mr. Tadashi Hata for the X-ray analysis of the cycloadduct.

References

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

3) Physical properties and spectral data of the predominantly formed cycloadducts shown in Table are as follows;
2a: mp 100∿101°C (cyclohexane); IR (KBr) 2945, 1654 cm^{-1}; NMR ($CDCl_3$) δ=1.11 (3 H, d, J=7 Hz) δ=1.23∿1.90 (6 H, m), δ=2.07∿3.07 (3 H, m), δ=3.50∿4.20 (2 H, m), δ=5.50∿6.13 (2 H, m), δ=6.67∿7.23 (4 H, m), δ=8.77 (1 H, s); Found: C, 76.10; H, 7.48; N, 5.00%, Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94%.
2b: mp 113∿114°C (cyclohexane); IR (KBr) 2960, 1651 cm^{-1}; NMR ($CDCl_3$) δ=1.05∿2.38 (8 H, m), δ=2.38∿3.28 (2 H, m), δ=3.43∿4.10 (2 H, m), δ=5.91 (1 H, broad), δ=6.63∿7.17 (4 H, m), δ=8.72 (1 H, s); Found: C, 75.76; H, 7.13; N, 5.25%, Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%.
2c: mp 129∿130°C (cyclohexane); IR (KBr) 2970, 1642 cm^{-1}; NMR ($CDCl_3$) δ=1.42 (3 H, s), δ=1.10∿1.90 (6 H, m), δ=1.96∿3.08 (4 H, m), δ=3.48∿3.98 (2 H, m), δ=5.44∿5.60 (1 H, m), δ=6.68∿7.28 (4 H, m), δ=8.86 (1 H, s); Found: C, 76.27; H, 7.53; N, 4.95%, Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94%.
2d: mp 142∿143°C (cyclohexane); IR (KBr) 2960, 1648 cm^{-1}; NMR ($CDCl_3$) δ=1.02 (6 H, d, J=5 Hz), δ=1.08∿2.08 (8 H, m), δ=2.58∿2.96 (2 H, m), δ=3.58∿4.18 (2 H, m), δ=5.98 (2 H, s), δ=6.72∿7.24 (4 H, m), δ=8.84 (1 H, s); Found: C, 76.92; H, 8.01; N, 4.57%, Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50%.

4) Cycloadduct 2a was converted to its p-bromophenacyl ether to get a good single crystal for the X-ray analysis.

5) a) W. R. Roush, A. I. Ko and H. R. Gillis, J. Org. Chem., 45, 4264 (1980). b) W. R. Roush and H. R. Gillis, ibid., 45, 4267 (1980). c) W. R. Roush and S. M. Peseckis, J. Am. Chem. Soc., 103, 6696 (1981).

6) As for the stereoselection of the intramolecular Diels-Alder reaction of the acyclic triene systems in which diene and dienophile groups are linked by ester linkage, see the following examples; a) J. D. White, B. G. Sheldon, B. A. Solheim and J. Clardy, Tetrahedron Lett., 1978, 5189. b) J. D. White and B. G. Sheldon, J. Org. Chem., 46, 2273 (1981).

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