CHEMISTRY LETTERS, pp. 513-516, 1982.

SYNTHETIC CONTROL BY INTERNAL COORDINATION OF METAL SALTS
THE INTRAMOLECULAR ENE REACTIONS OF N-(3-METHYL-2-BUTENYL)-N-(2-HYDROXYPHENYL)ACRYLAMIDES

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An efficient method for acceleration of the intramolecular ene reactions is established. The magnesium salts of N-(3-methyl-2-butenyl)-N-(2-hydroxyphenyl)acrylamides afford the corresponding cyclized products in high yields with the predominant formation of δ-lactams.

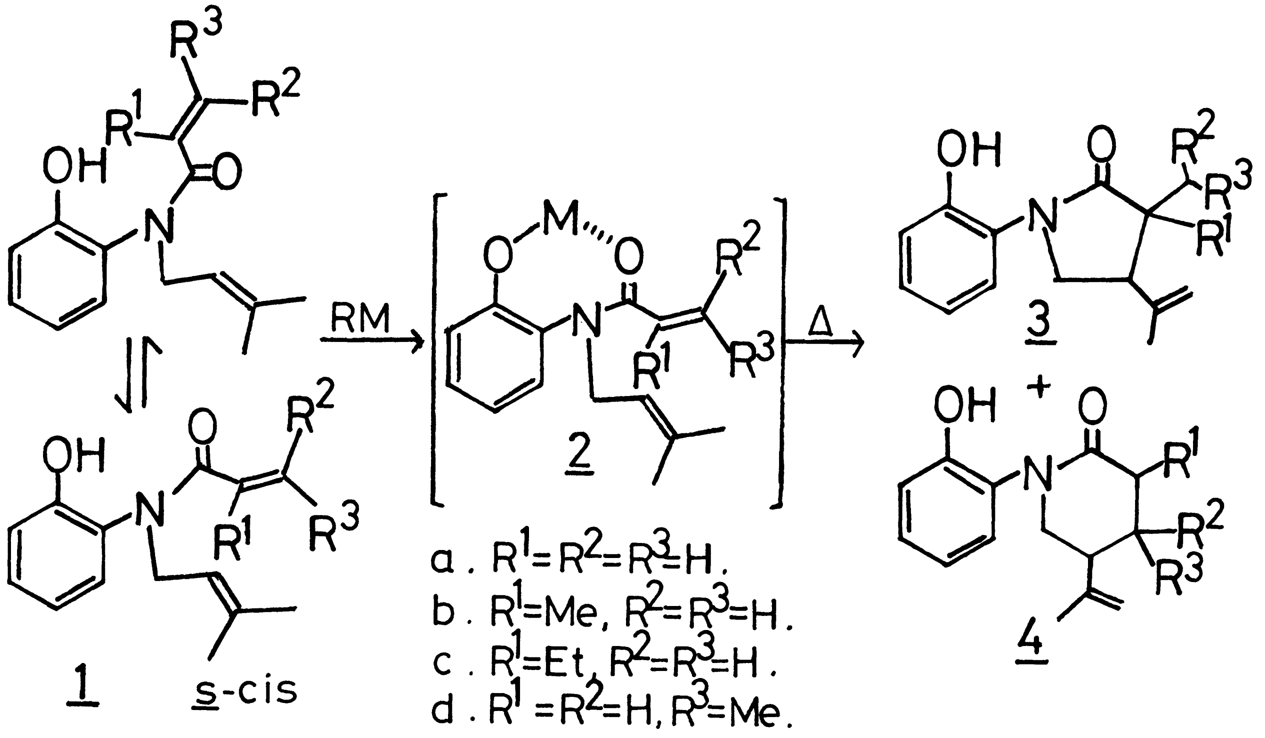
The intramolecular ene reaction is one of the most fascinating methods to construct cyclic compounds owing to its high regio- and stereoselectivities.[1) Unfortunately, the activation energy for an ene reaction is, in general, much higher than that for a mechanistically analogous Diels-Alder reaction, and therefore it is often necessary to conduct the reaction under pyrolytic conditions, which has limited its use in organic synthesis. Since the enophile, like the dienophile in the Diels-Alder reaction, should be electron deficient, complexation of Lewis acids to enophile should accelerate the ene reaction, and recently several examples were reported using $AlCl_3$, $SnCl_4$ or $TiCl_4$ as catalyst.2) However, longer exposure to these strong Lewis acids at higher temperature is often necessary because of the greater activation energy of the ene reaction, and complex mixture of products is formed by the acid-initiated side reactions.

Based on these observations and our previous study on the magnesium salts mediated intramolecular Diels-Alder reaction,3) we wish to disclose our results on the intramolecular ene reaction accelerated by the formation of internal chelate complex.

In order for the reaction to proceed smoothly, it is required that the amide 1 should take the s-cis conformation in which ene and enophile groups come nearby. And it is assumed that when the amide 1 is converted to its metal salt, the coordination of the metal to the carbonyl oxygen should increase the population of the desired conformer as depicted in 2, and it makes the two reaction sites come close to perform the reaction under the entropically advantageous condition.

Further, internal coordination of the metal salt to the carbonyl oxygen should activate the enophile effectively and it would be expected that even weak Lewis acids could make the ene reaction proceed under rather mild conditions.

Based on these assumptions, the reactions of amide 1a and its various metal salts were examined. When a p-xylene solution of the amide 1a was refluxed for



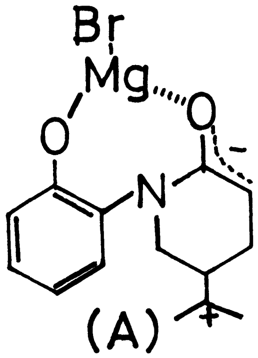
6 h, no cyclized product was obtained and only 60% of starting material was recovered presumably owing to the easiness of polymerization of acrylic group. The lithium salt of 1a also gave no cyclized product and aluminum or titanium salt of 1a resulted in complex mixture of products as expected. However, its magnesium salts, generated in situ from 1a on treatment with organomagnesium reagents, afforded the cyclized products 3a and 4a in good yields even within shorter reaction time. (Table I)

Table I. The ene reaction of 1a and its magnesium salts[a)]

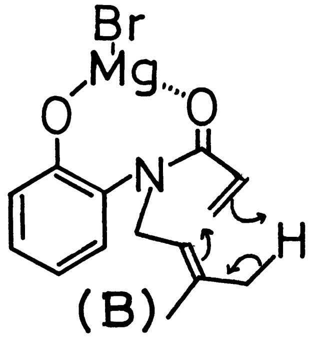
salt	reaction time (h)	yield (%)	
		3a[b)] [4)]	4a[4)]
-OH	6	0	0
-OMgCl	$1\frac{1}{3}$	< 5	11
-OMgBr	$1\frac{1}{3}$	6	50
-OMgI[c)]	$1\frac{1}{3}$	12	62
-OMgBr	6	10	85

a) The reaction was carried out in refluxing p-xylene.
b) Only one stereoisomer was observed by ^{1}H-NMR.
c) In the case of iodomagnesium salt, longer reaction time resulted in partial decomposition of the reaction products.

As shown in the Table I, the bromomagnesium and iodomagnesium salts gave the superior results to the chloromagnesium salt. And moreover, predominant formation of six-membered δ-lactam 4a should be noted, since it is generally observed that in most of these 1,6-diene type compounds, only five-membered cyclic compounds are formed.[1)] Though it is not clear whether this reaction proceeds via a step-



(A)



(B)

wise mechanism with a zwitterionic intermediate (A) or a concerted mechanism with a polar transition state (B),5) it should be pointed out that magnesium salts, generally regarded as weak Lewis acids, promote the reaction quite effectively.

Next, the reactions of variously substituted acrylic amide derivatives were examined. Expectedly, methacrylic amide 1b and α-ethylacrylamide 1c cleanly gave the corresponding cyclized products 3 and 4 in high yields when they are converted to their bromomagnesium salts. However, crotonamide 1d resulted in complex mixture of products presumably due to the steric hindrance of β-substituted methyl group, and 4d was obtained in only 27% yield. The results are summarized in Table II.

Table II. The ene reaction of 1b, 1c and 1d a)

compound	salt	reaction time (h)	yield (%) 3 b) 4)	 4 b) 4)
1b	-OH	5	trace	0
1b	-OMgCl	5	19	14
1b	-OMgBr	5	35	48
1b	-OMgI	5	39	11
1c	-OH	2.5	0	0
1c	-OMgBr	2.5	11	54
1c	-OMgBr	8	9	89
1d	-OH	24	0	0
1d	-OMgBr	24	0	27

a) The reaction was carried out in refluxing p-xylene.
b) Only one stereoisomer was observed by ^{1}H-NMR.

A general procedure is described for the preparation of 3a and 4a from 1a via bromomagnesium salt of 1a: To a THF solution6) (5 ml) of 1a (0.35 mmol) was added an ether solution of butylmagnesium bromide (0.35 mmol) at -78°C. The solvent was evaporated at room temperature in vacuo and p-xylene (6 ml) was added to the residue. The mixture was refluxed for 6 h, cooled to room temperature and 2 N HCl (15 ml) was added. The organic layer was extracted with ethyl acetate and the combined extracts were dried over anhydrous magnesium sulfate and then evaporated in vacuo. The residue was purified by silica gel thin layer chromatography.

Thus, an efficient method for acceleration of the intramolecular ene reactions by the internal coordination of the magnesium salts is established. Various cyclized products, especially six-membered δ-lactams are obtained in high yields according to the present procedure. Application of this method to the asymmetric ene reaction and natural product synthesis is now in progress.

References

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2) B. B. Snider, Acc. Chem. Res., 13, 426 (1980). For the recent study using alkylaluminum halide as an effective Lewis acid, see the following examples; W. Oppolzer and C. Robbiani, Helv. Chim. Acta., 63, 2010 (1980); B. B. Snider, D. J. Rodini, M. Karras, T. C. Kirk, E. A. Deutsch, R. Cordova and R. T. Price, Tetrahedron, 37, 3929 (1981).

3) T. Mukaiyama, T. Tsuji and N. Iwasawa, Chem. Lett., 1979, 697; T. Mukaiyama and N. Iwasawa, Chem. Lett., 1981, 29.

4) Spectral data of these compounds are as follows; 3a: IR (KBr) 3250, 1660 cm^{-1}; NMR (CDCl$_3$) δ = 1.10 (3H, d, J=7 Hz), 1.70 (3H, s), 2.60 - 3.33 (2H, m), 3.73 - 3.97 (2H, m), 4.76 (1H, s), 4.88 (1H, s), 6.77 - 7.13 (4H, m), 8.57 (1H, s). 4a: IR (KBr) 3050, 1630 cm^{-1}; NMR (CDCl$_3$) δ = 1.77 (3H, s), 1.80 - 2.10 (2H, m), 2.50 - 2.77 (3H, m), 3.67 (2H, d, J=7 Hz), 4.80 (1H, s), 4.87 (1H, s), 6.83 - 7.30 (5H, m). 3b: IR (neat) 3170, 1660 cm^{-1}; NMR (CDCl$_3$) δ = 1.00 (3H, s), 1.27 (3H, s), 1.77 (3H, s), 2.73 (1H, t, J=7 Hz), 3.67 - 3.80 (2H, m), 4.75 (1H, s), 4.88 (1H, s), 6.50 - 7.17 (4H, m), 8.33 (1H, br). 4b: IR (KBr) 3100, 1635, 1620 cm^{-1}; NMR (CDCl$_3$) δ = 1.37 (3H, d, J=7 Hz), 1.77 (3H, s), 1.62 - 2.23 (2H, m), 2.50 - 2.87 (2H, m), 3.60 - 3.75 (2H, m), 4.80 (1H, s), 4.86 (1H, s), 6.77 - 7.23 (5H, m). 3c: IR (neat) 3200, 1655 cm^{-1}; NMR (CDCl$_3$) δ = 0.95 (3H, t, J= 7 Hz), 1.03 (3H, s), 1.65 (2H, q, J=7 Hz), 1.75 (3H, s), 3.00 (1H, t, J=7 Hz), 3.77 (2H, d, J=7 Hz), 4.73 (1H, s), 4.88 (1H, s), 6.80 - 7.07 (4H, m), 8.40 (1H, s). 4c: IR (neat) 3150, 1620 cm^{-1}; NMR (CDCl$_3$) δ = 1.00 (3H, t, J=7 Hz), 1.70 (3H, s), 1.60 - 2.00 (4H, m), 2.20 - 2.77 (2H, m), 3.60 (2H, d, J=7 Hz), 4.73 (2H, s), 6.57 - 7.17 (4H, m), 7.53 (1H, br). 4d: IR (KBr) 3070, 1620 cm^{-1}; NMR (CDCl$_3$) δ = 0.97 (3H, d, J=7 Hz), 1.77 (3H, s), 2.17 - 2.83 (4H, m), 3.40 - 4.07 (2H, m), 4.60 (1H, s), 4.90 (1H, s), 6.73 - 7.23 (4H, m), 7.50 (1H, br).

5) The term "ene reaction" has sometimes been defined to refer only to those reactions which are concerted, but other times to describe a reaction which forms an ene-type product, whether it is obtained by a stepwise or concerted process. In this communication, we use the broader definition, partly because the precise reaction mechanism of this reaction is not clear.

6) When amide 1a was employed, a THF solution gave better yields of 3a and 4a. In other cases, an ether solution was used.

(Received January 28, 1982)