Tetrahedron Letters,Vol.25,No.33,pp 3583-3586,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

INTRAMOLECULAR DIELS-ALDER REACTION OF IMINOTHIOL ESTERS

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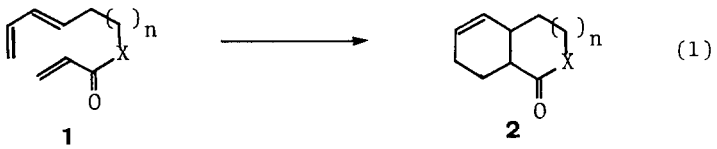
Summary: Diels-Alder reaction of dienyl α-methacrylthioimidates has been investigated under thermal or Lewis acid or protonic acid catalyzed conditions. The utility of the reaction is shown by desulfurative ring contraction of bicyclo[4.4.0] to bicyclo[4.3.0]system.

The intramolecular Diels-Alder reaction[1] of 1 (n = 0, 1, 2, 3; X = CH_2,[2] O,[3] N^4) is a subject of extensive study, because the product 2 possesses desirable structural and functional features for natural product syntheses (eq 1). In this communication we describe results of the systematic investigation of the intramolecular Diels-Alder reaction of dienyl α-methacrylthioimidates 5 (n = 0, 1, 2; R^2 = phenyl, 2,6-dimethylphenyl, and tert-butyl).



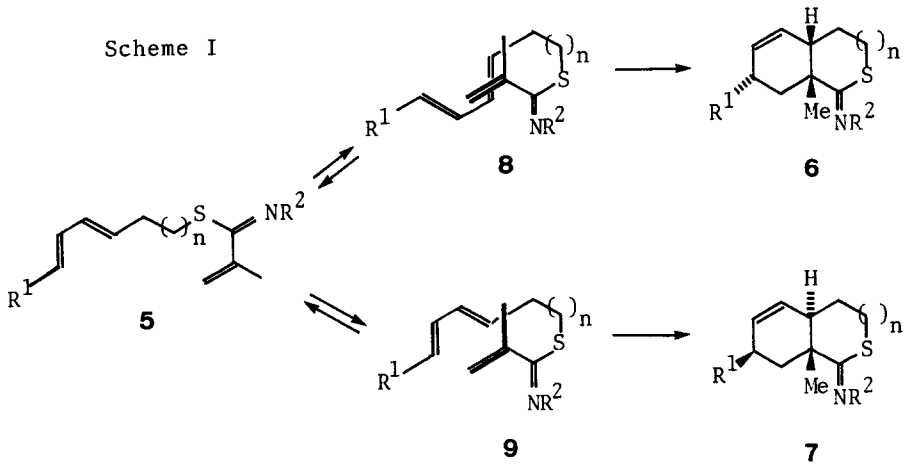
(1)

The requisite dienyl α-methacrylthioimidates 5 were readily prepared by Mitsunobu coupling[5] of dienyl alcohols 4[6] with α-methacrylthioamides 3[7] (R^2 = aryl; 50 - 80% yields; diethyl azodicarboxylate-tri-n-butylphosphine in THF at - 78°C → 0°C). This method was not applicable to the synthesis of 5 (R^2 = tert-butyl), and 5c, 5f, and 5i were prepared by the reaction of dienyl tosylates with the potassium salt of 3 (70 - 80% yields in THF at room temperature, Scheme I).

Results, together with the reaction conditions for the Diels-Alder reaction of 5, are summarized in Table I. All substrates were screened at 160°C in m-dichlorobenzene containing a trace of hydroquinone monomethyl ether under argon atmosphere. Under these or even under lower temperature conditions the iminothiol esters 5 (R^2 = tert-butyl) were consumed to provide a myriad of products. Several interesting points emerge from Table I. First, the reactivity largely depends on the number of methylene units. The iminothiol

esters with n = 0 show the higher reactivity than those with n = 1. No iminothiol esters with n = 2 gave the Diels-Alder products. They resulted in no reactions or decomposed under the enforced conditions (entries 10 - 13). The relative reactivity of 5 (n = 0) to 5 (n = 1) is the reverse of many precedents (X = CH_2)[2] and this may be due to the long C-S bond lengthes, which reduce steric constraint in a transition state leading to a bicyclo[4.3.0] system.[2d] Entropic disadvantage is most likely for the low reactivity of 5g - 5i. The second is the effects of the N-substituents on the stereoselectivity. Despite our expectation that the sterically large R^2 group might destabilize an endo transition state 8 owing to repulsion between R^2 and dienyl moiety, no significant differences in the ratios of 6 to 7 were observed among R^2 groups with large differences in steric bulk. In the reactions providing bicyclo [4.3.0] system, the exo products 7 were formed in slight preference over endo products 6. On the other hand, in the reactions giving bicyclo[4.4.0] system, the endo products were obtained selectively. The selectivity and also the reactivity were dramatically enhanced by the use of Lewis acid catalysts (BF_3-OEt_2 or $ZnCl_2$). Interestingly, however, these catalysts were not effective to promote the reaction of 5a, 5b, 5g, or 5h (e.g., entry 11).

Scheme I



The reaction behavior of 5f is very unique. Although neither thermal nor Lewis acid catalyzed Dield-Alder reaction of 5f was successful, protonic acids nicely catalyzed the reaction. The facile and clean formation of 6f was indicated by monitoring the reaction by means of ^1H NMR (either in $CDCl_3$ or in D_2O in the presence of a stoichiometric amount of p-toluenesulfonic acid). For the preparative purpose, 5f was dissolved in 1.5-N HCl aqueous solution and allowed to stand for 15 h at room temperature. Neutralization ($NaHCO_3$) and extaction with diethyl ether provided pure 6f in 85% isolated yield (entry 8).

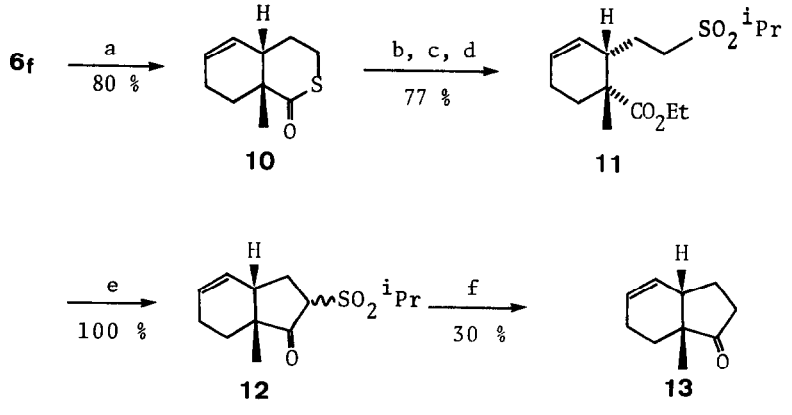
The stereochemistry of 6 and 7 was determined on the basis of the higher field

Table I. Intramolecular Diels-Alder Reaction of Iminothiol Esters 5[a]

entry	iminothiol ester[b]			Diels-Alder conditions[c]	product distribution[d] 6 : 7	% isolated yield
	n	R^1	R^2			
1	5a: 0	Me	Ph	160°C, 3 h in m-$Cl_2C_6H_4$	33 : 67	61
2	5b: 0	Me	Me_2Ph	160°C, 4 h in m-$Cl_2C_6H_4$	40 : 60	50
3	5c: 0	Me	t-Bu	100°C, 15 h in m-$Cl_2C_6H_4$	decomposition of 5c	
4	5d: 1	H	Ph	160°C, 25 h in m-$Cl_2C_6H_4$	79 : 21	70
5	5d:			r.t., 80 h, BF_3-OEt_2 in THF	100 : 0	79
6	5e: 1	H	Me_2Ph	160°C, 13 h in m-$Cl_2C_6H_4$	89 : 11	82
7	5e:			r.t., 40 h, BF_3-OEt_2 in THF	100 : 0	68
8	5f: 1	H	t-Bu	r.t., 15 h, 1.5 N HCl in H_2O	100 : 0	85
9	5f:			110°C, 9 h in m-$Cl_2C_6H_4$		7
10	5g: 2	H	Ph	160°C, 10 h in m-$Cl_2C_6H_4$	no reaction	
11	5g:			60°C, 24 h, BF_3-OEt_2 in THF	no reaction	
12	5h: 2	H	Me_2Ph	220°C, 26 h in tetralin	decomposition of 5h	
13	5i: 2	H	t-Bu	60°C, 6 h, CSA in m-$Cl_2C_6H_4$	decomposition of 5g[e]	

a) For the structures of 5, 6, and 7, see Scheme I. b) Ph = phenyl, Me_2Ph = 2,6-dimethylphenyl, t-Bu = tert-butyl. c) All reactions were undertaken under argon. CSA = 10-camphoresulfonic Acid. d) Ratios were determined on the basis of either area intensities on VPC (entries 1 and 2) or isolated yields (entries 4 - 8). e) Besides many products, the corresponding thiolester was isolated in 42% yield.

Scheme II



a) silica gel - hexane. b) EtONa, EtOH, r.t., 5 h. c) ^{i}PrI, EtOH, r.t., 18 h. d) m-CPBA, $CHCl_3$, 0°C, 30 min. e) tert-BuOK, THF, r.t., 40 min. f) 5% Na(Hg), $NaHPO_4$, dry MeOH, refl., 7 h.

resonances of the angular methyl resonances of 7 compared with those of 6 both in ^{1}H NMR[8] and ^{13}C NMR spectra.[9] The structure of 6f was also confirmed by the desulfurative ring contraction to cis-hydrindenone 13.[2a,2d] (Scheme II): Hydrolysis of 6f was readily accomplished by exposure to silica gel-hexane (1 day) and pure thiolester 10 was isolated by means of column chromatography over silaca gel (80%, benzene). Transesterification of 10 (EtONa, EtOH, r.t., 5 h) followed by alkylation with sec-propyl iodide (r.t., 18 h) were conducted in one flask. The thus obtained crude ester sulfide was oxidized with 2.2 equiv of m-chloroperbenzoic acid ($CHCl_3$, 0°C) to provide 11 in 77% overall yield from 10 after column chromatography (silica gel-hexane-ether). Cyclizatoin (3 equiv of KO^tBu in THF, r.t., 30 min) furnished 12 as a nice crystalline solid (100%, mp 85°C from benzene-hexane). By desulfurization of 12, 13 was obtained as a single product (1.8 equiv of Na(Hg), 4 equiv of $NaHPO_4$ in dry MeOH, reflux 7 h).[10,11]

References and Notes

1) Reviews. (a) W. Oppolzer, Angew. Chem. Int. Ed. Engl., 16, 10 (1977). (b) G. Brieger and J. N. Bennett, Chem. Rev., 80, 63 (1980).
2) For n = 0, see (a) J. J. S. Bajorek and J. K. Sutherland, J. Chem. Soc., Perkin Trans., 1, 1559 (1975). (b) A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, J. Am. Chem. Soc., 102, 6353 (1980). (c,d) M. E. Jung and K. M. Halweg, Tetrahedron Lett., 22, 2735, 3929 (1981). (e) S. A. Bal and P. Helquist, Ibid, 22, 3933 (1981). For n = 1, see (f) J.-L. Gras and M. Bertrand, Tetrahedron Lett., 4549 (1979). (g) D. F. Taber and B. P. Gunn, J. Am. Chem. Soc., 101, 3992 (1979). (h) G. Stork, G. Clark, C. S. Shiner, Ibid, 103, 4948 (1981). (i) L. A. Van Royen, R. Mijngheer, and P. J. De Clercq, Tetrahedron Lett., 23, 3283 (1982). For n = 3, see (j) E. Wedkert, Syn. Commun., 3, 45 (1973). For n = 4, see (k) K. Sakan and B. M. Craven, J. Am. Chem. Soc., 105, 3732 (1983).
3) For n = 0, see a) L. H. Klemm, T. M. McGuire, and K. W. Gopinath, J. Org. Chem., 41, 2571 (1976). b) B. Nader, T. R. Bailey, R. W. Frank, and S. M. Weinreb, J. Am. Chem. Soc., 103, 7573 (1981). c) R. A. Gobao, M. L. Bremmer, and S. M. Weinreb, Ibid, 104, 7065 (1982). For n = 1, see d) M. L. Bremmer and S. M. Weinreb, Tetrahedron Lett., 24, 261 (1983).
4) For n = 0, see (a) H. W. Gschwend and H. P. Meyer, Angew. Chem. Int. Ed. Engl., 11, 294 (1972). (b) H. W. Gschwend, A. O. Lee, and H.-P. Meier, J. Org. Chem., 38, 2169 (1973). (c) S. G. Pyne, M. J. Hensel, S. R. Byrn, A. T. McKenzie, and P. L. Fuchs, J. Am. Chem. Soc., 102, 5960 (1980). (d) S. G. Pyne, M. J. Hensel, and P. L. Fuchs, Ibid, 104, 5719 (1982). (e) S. V. Kessar, I. R. Irehan, T. V. Singh, M. Narula, and N. P. Singh, Tetrahedron Let., 23, 4177 (1982).
5) O. Mitsunobu, Synthesis, 1 (1981).
6) 3,5-Hexadien-1-ol: (a) R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme, J. Am. Chem. Soc., 98, 6317 (1976). (b) S. F. Martin, C. Tu, and T. Chou, Ibid, 102, 5274 (1980). 4,6-Heptadien-1-ol: (c) K. A. Parker and T. Iqbal, J. Org. Chem., 47, 337 (1982).
7) Y. Tamaru, M. Kagotani, and Z. Yoshida, Tetrahedron Lett., 22, 3409 (1981).
8) A. Gaudemer, In "Stereochemistry", H. B. Kagan, Ed., Georg Thieme Verlag, 1977, vol 1.
9) G. C. Levy, R. L. Lichter, and G. N. Nelson,"Carbon-13 NMR Spectroscopy", 2nd Ed., John Wiley & Sons, New York, 1980.
10) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, Tetrahedron Lett., 3477 (1976).

11) We express our gratitude to Doctors K. Oshima (Kyoto University) and T. Takahashi (Tokyo Institute of Technology) for helpful suggestion about desulfurization. We are also grateful for partial support provided by the Ministry of Education, the Japanese Government (Grant in Aid for Special Project Research No. 58110005 and Scientific Research B No. 58470066).

(Received in Japan 12 April 1984)