Pergamon

Tetrahedron Letters, Vol. 37, No. 45, pp. 8073-8076, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01842-4

Polyene Cyclization Promoted by the Cross Conjugated α-Carbalkoxy Enone System

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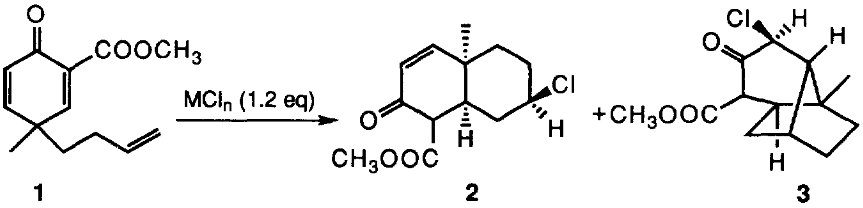
Abstract: The cross conjugated α-carbalkoxy enone system was found to be an excellent promoter for polyene cyclization. Under mild conditions, the reaction occurred efficiently with a high degree of regio- and stereochemical control. Copyright © 1996 Elsevier Science Ltd

Polyene cyclization, also known as cationic cyclization, is a powerful synthetic tool. It has been applied widely for the preparation of polycyclic compounds, and has been the subject of several reviews.[1] In general, the success of the polyene cyclization process depends on the method of initiation, the nucleophilicity of the participating double bond(s), and the process of termination. To facilitate the cyclization, the use of an appropriately positioned functional group as an initiator is a common practice. Previously applied functional groups include epoxide,[2] acetal, allylic alcohol,[1b,3] and α,β-unsaturated carbonyl groups (aldehyde or ketone).[4] These initiators have met with varying degrees of success.

During the course of our synthetic studies on *cis*-clerodanes,[5] enone ester **1**[6] was subjected to Diels-Alder reaction under Lewis acid catalysis. Interestingly, treatment of **1** and *trans*-piperylene in the presence of zinc chloride gave rise to cyclic compounds **2** and **3** instead of the expected Diels-Alder adduct. These observed products were apparently formed *via* intramolecular cyclization promoted by the cross conjugated β-keto ester system. Further investigation showed that this newly observed initiator is highly efficient for the induction of cationic cyclization, and the formation of compounds **2** and **3** could be controlled by the use of different Lewis acids (Scheme 1). When the reaction was carried out at room temperature in ether with zinc chloride, compounds **2** and **3** were formed in 90% yield in 2.6:1 ratio. When zinc chloride was replaced by aluminum chloride, a remarkable enhancement of the reaction rate as well as selectivity was observed. The reaction occurred almost instantaneously (15 min) even at -78°C, and bicyclic compound **2** was produced exclusively in 75% yield. On the other hand, when stannic chloride was used as a catalyst and dichloromethane as a solvent, a rapid cyclization (5 min at -78°C) also took place but giving tricyclic compound **3**, instead of bicyclic compound **2**, as the predominant product (**3**:**2** = 2.5:1; 92% yield). Two other Lewis acids, ethylaluminum chloride and titanium tetrachloride, were also examined. These reagents were found to be also effective, but the product selectivity in favor of bicyclic compound **2** was inferior to aluminum chloride. Compounds **2** and **3** were each obtained as an inseparable mixture of isomers mainly due to the presence of the highly enolizable and epimerizable β-keto ester moiety. The regiochemistry and stereochemistry of these compounds were determined as follows.

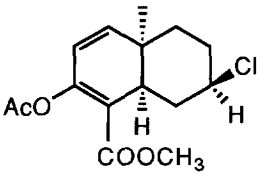


Lewis Acid	Solvent	Temp. (°C)	Time	% Yield	Ratio (**2**:**3**)
$ZnCl_2$	Et_2O	25	3 h	90	2.6:1
$AlCl_3$	Et_2O	-78	15 min	75	1:0
$EtAlCl_2$	CH_2Cl_2	-78	1 h	78	2.1:1
$TiCl_4$	CH_2Cl_2	-78	2 min	86	3:1
$SnCl_4$	CH_2Cl_2	-78	5 min	92	1:2.5

Scheme 1

Treatment of compound **2** with acetic anhydride in pyridine gave rise to the corresponding enol acetate **4** whose structure was confirmed by spectroscopic methods especially nmr spectroscopy with the assistance of nOe experiments. Similarly, acetylation of tricyclic compound **3** afforded enol acetate **5**. Its structure was also verified by spectroscopy.

In addition to its high efficiency, the regio- and stereoselectivity observed for the above cyclization process as well as the unusual mode of termination *via* chloride formation are of considerable interest. A mechanistic rationale is depicted in Scheme 2. It is conceivable that the chloride formation with the specific stereochemistry in both cases **2** and **3** is a result of intramolecular transfer of chloride ion from the metal to the incipient carbocation (**6**→**7** and **8**→**9**). This proposal is in agreement with the following findings. When the zinc chloride induced cyclization (*vide supra*) of enone ester **1** was carried out in the presence of an excess of lithium chloride, neither the yields of products **2** and **3** nor the stereochemical course of the reaction were significantly altered. It is also noteworthy that the formation of tricyclic compound **3** requires the participation of the β-carbon of the conjugated enone system. This is rather unusual, but could be explained by invoking the intermediacy of the allylic carbocation **8**.



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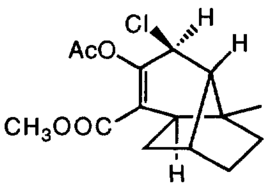

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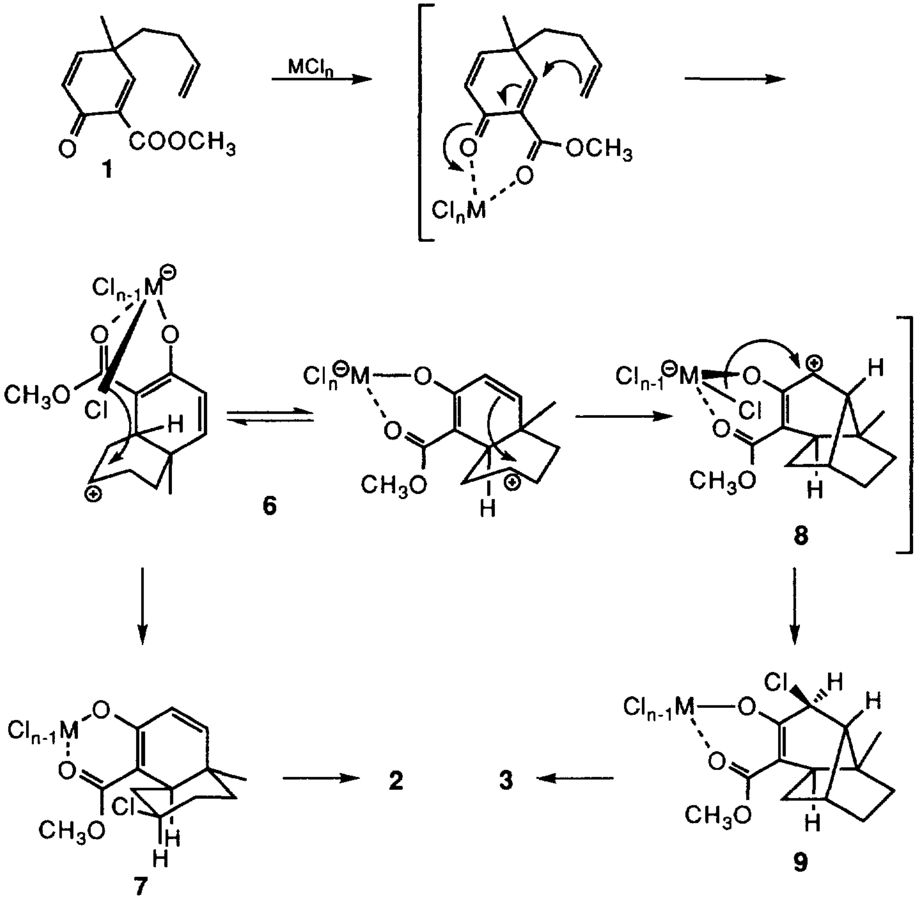
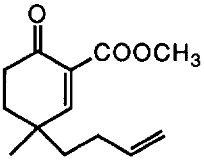
The cyclization of enone ester **10** was also carried out in order to determine the potential influence of the additional double bond present in dienone ester **1** to its cyclization. The ring closure of compound **10** was found to be equally facile. On exposure to stannic chloride (1.2 eq) in methylene chloride at low temperature (-78°C) for a brief period (10 min), compound **10** cyclized readily to give a 91% yield of chloride **11**. For comparison, enones **12** and **13** were subjected to similar treatment with stannic chloride. No reaction was observed for the former compound **12** even after 24 h at room temperature. In the latter case, the starting material was intact at low temperature. At room temperature, a complex mixture was formed upon complete consumption of the starting material which took about 2 h.



Scheme 2

In conclusion, the preliminary results described above illustrate that the cross conjugated β-keto ester system can serve as an excellent promoter for cationic cyclization. This initiator is expected to have broad synthetic utility in light of the following salient features. The cyclization is highly efficient in terms of the yield of product and the high degree of regio- and stereochemical control. In addition, the use of this initiator also increases the degree of functionalization of the product and allows the incorporation of a halogen atom at a predictable position to facilitate further modification based on the rich chemistry of alkyl halides.[7]



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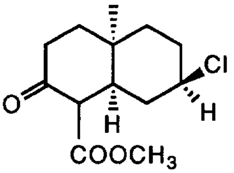

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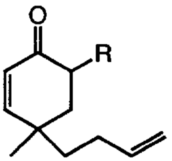

12 R = $COOCH_3$
13 R = H

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6. This compound was prepared from 3-ethoxy-6-methyl-2-cyclohexenone in six steps using a synthetic sequence similar to that described for an analogous compound.[5]
7. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support.

(*Received in USA* 21 *August* 1996; *revised* 6 *September* 1996; *accepted* 10 *September* 1996)