CHEMISTRY LETTERS, pp. 1353-1356, 1992.

The Cationic Diels-Alder Reaction. Facile Formation of Cationic Species from 2-Oxoalkyl Esters

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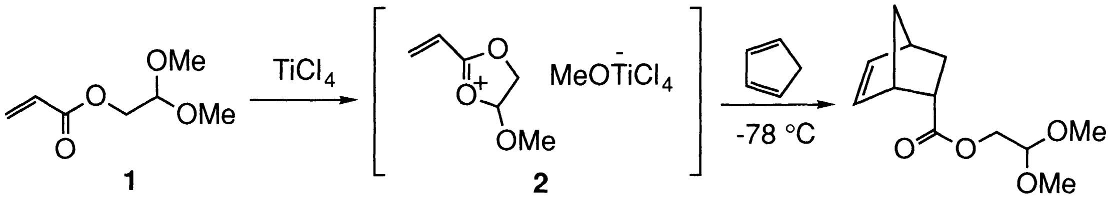
In the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and methoxytrimethylsilane (MeOTMS), 2-oxopropyl acrylate and 2-oxocyclopentyl acrylate readily form cationic intermediates. The cationic moiety works efficiently as an electron-withdrawing group, and accelerates the Diels-Alder reaction under mild conditions.

A carbocation is generally considered to be a highly reactive species, and sometimes exists transitionally. However, by stabilizing it moderately, a cationic species can be handled as a useful intermediate in organic reactions. Several reports have been made so far on the generation of a carbocation stabilized by two oxygen atoms.$^{1)}$ Among them, treatment of an orthoester with a Lewis acid is a reliable method to obtain a cationic intermediate. Although this method is adopted by several groups,$^{1-3)}$ the synthetic route of an orthoester is not always readily accessible. Therefore, another simple and reliable path to a cationic species from a simple substrate is desired in order to broaden its chemistry. Moreover, much attention is recently focused on a cationic species that is preorganized for selective synthetic reactions. As previously reported, by using 2,2-dimethoxyethyl ester as a precursor for the generation of such a cationic intermediate, we have developed several synthetic methods.$^{4,5)}$ For example, in the presence of a Lewis acid, 2,2-dimethoxyethyl acrylate (**1**) was readily converted into cationic key intermediate **2**, which was found to be an excellent dienophile toward various dienes (Scheme 1).$^{5)}$ In this letter, we wish to report a new and easy method for the generation of a cationic species and its application in the Diels-Alder reaction.



Scheme 1.

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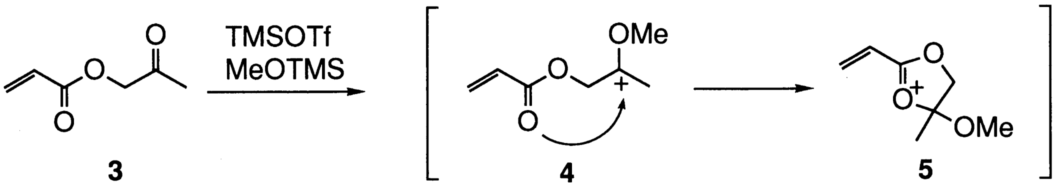
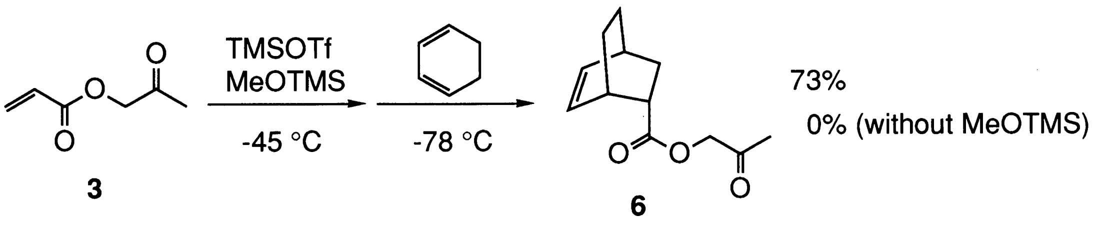
In the course of our investigation to prepare 2,2-dialkoxyalkyl acrylate, we tried acetalization of 2-oxopropyl acrylate (**3**).[6] Considering the polymerizability of the acrylate skeleton, we utilized a mild and efficient acetalization reaction catalyzed by TMSOTf.[7] Under the usual reaction conditions,[7] however, no acetalized product was obtained.

In general, a cationic species like **4** is considered to be formed as an intermediate in this acetalization reaction. If the ester carbonyl group participates to the cationic center as depicted in Scheme 2, more stable cationic intermediate **5** is generated, and consequently further acetalization reaction is difficult to proceed. However, **5** is expected to become an efficient dienophile generated in situ, since **5** has a similar structure as **2.**



Scheme 2.

On the basis of these considerations, we tried the reaction of the intermediate with cyclohexadiene. As shown in Scheme 3, by adding cyclohexadiene into a mixture of equimolar amounts of 2-oxopropyl acrylate (**3**), TMSOTf, and MeOTMS at -78 °C, desired Diels-Alder adduct **6** was obtained in good yield. The Diels-Alder reaction without MeOTMS was also examined as a control experiment, and no adduct was produced. These results indicate that the observed great acceleration of the reaction is not attributed to a usual Lewis acid (TMSOTf) promotion, but to cationic intermediacy.

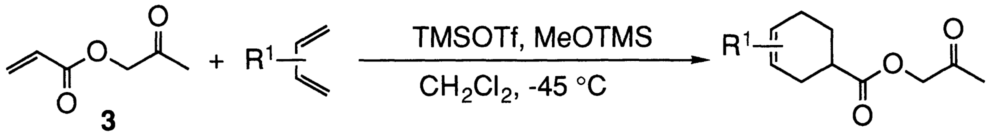


Scheme 3.

We next investigated the efficiency of dienophile **5** toward various dienes.[8] The results are listed in Table 1. In all cases, the desired adducts were obtained in good yields with excellent stereo- and/or regioselectivity under mild conditions. In the case of the reaction with cyclopentadiene, the yield (65%) was somewhat low under the standard conditions due to the competing oligomerization of the diene. However, this problem was overcome by adding cyclopentadiene slowly enough at a lower temperature (-78 °C) in order to prevent the oligomerization (yield: 85%).

From these results, we assumed that a substrate, of which the conformation is favorable for neighboring group participation, would form a cationic intermediate smoothly, and that such an intermediate would be a superior dienophile toward highly polymerizable dienes. On the basis of this consideration, 2-oxocyclopentyl acrylate (**7**) was desinged as a cation precursor.[9]

Table 1. Results of the Diels-Alder Reaction of 2-Oxopropyl Acrylate (**3**) with Dienes



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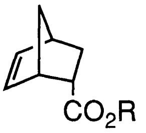
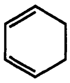
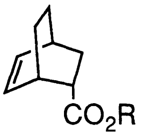
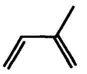
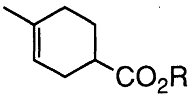
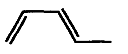
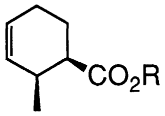
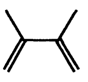
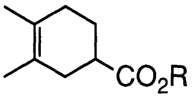
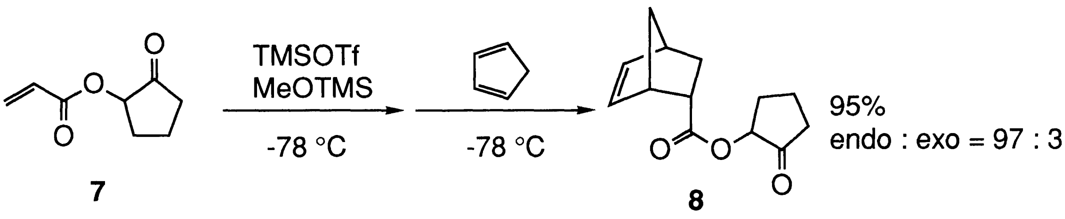
Diene	Reaction time/h	Major product	Yield/%	Selectivity[a)]
	8 14		65 85	endo : exo = 97 : 3 endo : exo = 98 : 2 [b)]
	10		89	endo : exo = >99 : 1
	12		66	para : meta = 98 : 2
	26		61	ortho : meta = >98 : 2 endo : exo = >99 : 1
	14		75	—

(R = 2-oxopropyl)

a) Determined by GLC analysis.

b) Cyclopentadiene was added over the period of 2 h at -78 °C.

As anticipated, the reaction of **7** with cyclopentadiene proceeded quite smoothly even at -78 °C. Monitoring the reaction by TLC just after the addition of cyclopentadiene, we observed neither starting material nor oligomers of cyclopentadiene, and only Diels-Alder adduct **8** was detected. The reaction mixture was easily purified by chromatography to give the adduct in almost quantitative yield (95%) with a high endo-exo selectivity (97 : 3).



7 **8**

Scheme 4.

We developed a facile method to generate cationic intermediates from simple and easily available substrates **3** and **7** by treating them with equimolar amounts of TMSOTf and MeOTMS. Furthermore, the resulting cationic species act as powerful dienophiles and react smoothly with various dienes under mild conditions to give the corresponding Diels-Alder adducts in good yields with excellent selectivities. We are now preparing more elaborate substrates in order to examine the possibility to achieve asymmetric Diels-Alder reactions.

References

1) F. Perron-Sierra, M. A. Promo, V. A. Martin, and K. F. Albizati, *J. Org. Chem.*, **56**, 6188 (1991) and references therein.

2) A. Mekhalfia, I. E. Markó, and H. Adams, *Tetrahedron Lett.*, **32**, 4783 (1991).

3) Gassman and Chavan also reported that α,β-unsaturated orthoesters were converted into cationic dienophiles on the action of a Lewis acid, and that the reaction of the cationic dienophiles with dienes gave Diels-Alder adducts in good yields under mild conditions: P. G. Gassman and S. P. Chavan, *J. Org. Chem.*, **53**, 2392 (1988); P. G. Gassman and S. P. Chavan, *Tetrahedron Lett.*, **29**, 3407 (1988).

4) S. Machida, Y. Hashimoto, K. Saigo, J. Inoue, and M. Hasegawa, *Tetrahedron,* **47**, 3737 (1991); K. Saigo, S. Machida, K. Kudo, Y. Saito, Y. Hashimoto, and M. Hasegawa, *Synth. Commun.*, **20**, 2197 (1990); Y. Hashimoto, S. Machida, K. Saigo, J. Inoue, and M. Hasegawa, *Chem. Lett.*, **1989**, 943.

5) Y. Hashimoto, K. Saigo, S. Machida, and M. Hasegawa, *Tetrahedron Lett.*, **31**, 5625 (1990).

6) 2-Oxopropyl acrylate was prepared from commercially available hydroxyacetone and acryloyl chloride in the presence of triethylamine.

7) T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, **21**, 1357 (1980).

8) A typical procedure is as follows: Under an argon atmosphere, a dichloromethane solution (0.67 ml) of TMSOTf (0.84 mol•l^{-1}) was added dropwise to a stirred solution of 2-oxopropyl acrylate (0.52 mmol) in dichloromethane (3 ml) at -45 °C, and the mixture was stirred for 30 min. MeOTMS (0.78 mmol) in dichloromethane (1 ml) was added dropwise to the mixture. After 30 min, cyclopentadiene (1.7 mmol) in dichloromethane (1 ml) was added dropwise over a period of 10 min. Being stirred for 8 h at -45 °C, the reaction mixture was quenched by adding water under vigorous stirring. The organic layer was separated, and the aqueous phase was extracted by hexane (3 × 5 ml). The combined organic layers were dried over sodium sulfate. After filtration and evaporation, the crude product was purified by flash column chromatography (EtOAc/hexane) to afford the corresponding Diels-Alder adduct (66 mg, 65%). The selectivity was determined by GLC analysis (endo : exo = 97 : 3).

9) 2-Hydroxycyclopentanone was prepared from dimethyl glutarate in two steps; A. Fadel, J.-L. Canet, and J. Salaüm, *Synlett*, **1990**, 89; X. Creary and A. J. Rollin, *J. Org. Chem.*, **42**, 4231 (1977).

(Received May 1, 1992)