Tetrahedron Letters, Vol. 34, No. 46, pp. 7437-7440, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

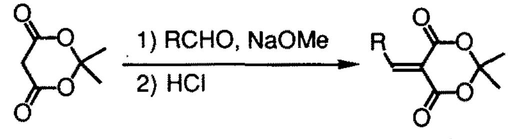
# A Novel Michael Reaction of Silyl Enol Ethers *via* Hetero Diels-Alder Reaction with Alkylidene-Meldrum's Acid

**Shigeo Mizukami, Nobuhiro Kihara,** and **Takeshi Endo***

Research Laboratory of Resources Utilization, Tokyo Institute of Technology,
Nagatsuta-cho, Midori-ku, Yokohama 227, JAPAN

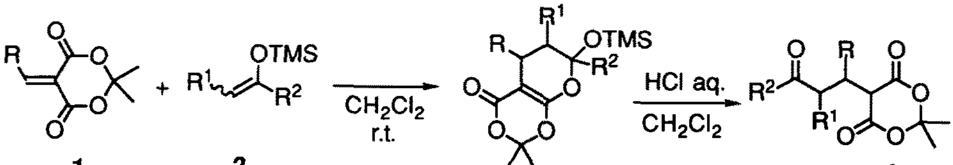
*Abstract:* Alkylidene Meldrum's acid easily reacted with silyl enol ethers without any catalyst to afford hetero Diels-Alder adducts which could be quantitatively hydrolyzed to obtain Michael adducts in good yields. The Michael adducts could be obtained diastereoselectively and could be converted to corresponding δ-ketoesters quantitatively.

Michael reaction of silyl enol ethers is one of the most important tools for C-C bond formation. Although Michael reaction of silyl enol ethers with α,β-unsaturated esters are not successful, Lewis acid-promoted Michael addition of silyl enol ethers to α,β-unsaturated orthoesters[1] and thioesters[2] have been developed.[3] However, Michael reaction in a neutral condition is still desired. Meanwhile, alkylidene Meldrum's acid **1**, which can be readily synthesized from Meldrum's acid[4] and aldehyde,[5,6] is known to be a strong electrophile, and is expected to be a good Michael acceptor. Although the reaction of **1** with vinyl ethers has been reported,[7,8] hetero Diels-Alder adducts are obtained in poor yields and synthetic utility of the adducts has not been examined. Considering that silyl enol ethers are more nucleophilic and more easily available than the corresponding alkyl vinyl ethers, we examined the reaction of silyl enol ethers with **1** to find that hetero Diels-Alder adducts could be obtained and readily hydrolyzed to obtain Michael adduct diastereoselectively in high yield.[9] In this paper, we wish to report a novel two step Michael reaction of **1** and silyl enol ethers **2**.



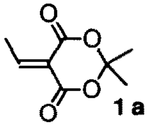
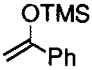
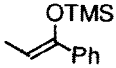
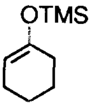
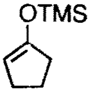
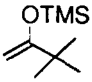
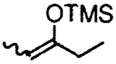
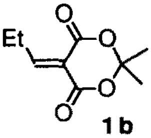
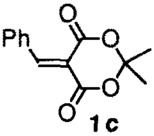
Meldrum's acid **1**

The reaction of **1a** with **2a** proceeded spontaneously at room temperature in $CDCl_3$, and finished within 30 min. $^1H$- and $^{13}C$-NMR spectra of the crude product clearly indicated the formation of hetero Diels-Alder adduct **3aa**.[10] Any product other than **3aa** could not be detected by NMR spectra. Since hydrolysis of **3aa** proceeded during isolation, hydrolysis of the crude product with 1M aqueous HCl was positively carried out to obtain Michael adduct **4aa**[11] instead of **3aa** in 92 % yield. Further, benzyltrimethylammonium fluoride-catalyzed desilylation in the presence of methanol was also carried out to obtain **4aa** in 79 % yield. The reaction of **1a** and **2a** was carried out in some solvent, such as dichloromethane, benzene, toluene, acetonitrile, THF, and DMF,



1 2 3 4

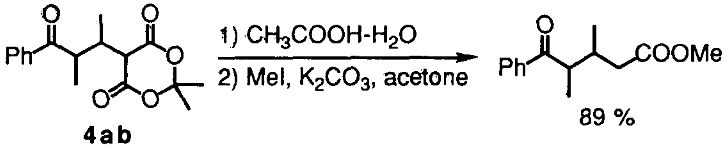
Table 1. Reaction of Alkylidene Meldrum's Acids with Silyl Enol Ethers

| 1 | 2 | Time (h) | Yield of **4**(%) | syn : anti |
|---|---|---|---|---|
|  **1a** |  **2a** | 6 | 92 | - |
| **1a** |  **2b** | 12 | 69 | 14 : 86 a) |
| **1a** |  **2c** | 12 | 83 | 80 : 20 b) |
| **1a** |  **2d** | 12 | 87 | 90 : 10 b) |
| **1a** |  **2e** | 12 | 83 | - |
| **1a** |  **2f** E : Z = 12 : 88<br>E : Z = 67 : 33 | 12<br>12 | 80<br>72 | 24 : 76 b)<br>28 : 72 |
|  **1b** | **2a** | 6 | 96 | - |
|  **1c** | **2a** | 6<br>24 | 51<br>80 | -<br>- |

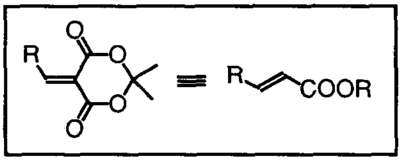
a) determined by HPLC. b) determined by $^1$H-NMR although no notable solvent effect on the yield of **4aa** (80-92 %) was observed except for DMF. Since **1** decomposed in DMF, only 30 % of **4aa** was obtained. Thus, the reaction of **1** and **2** with various substituents was carried out in dichloromethane, and the results are summarized in Table 1. In every case, **4** was obtained in high yield by the hydrolysis with aqueous HCl, and any by-product was not detected. Longer reaction time were required to complete the reaction in the case of less reactive substrates.

A significant feature of this reaction is its high diastereoselectivity.[12] It is noteworthy that silyl enol ethers obtained from cyclic ketones, **2c** and **2d**, afforded mainly *syn* product, while silyl enol ethers obtained from acyclic ketones afforded mainly *anti* product. Interestingly, almost the same diastereo-ratio mixture was obtained using either *Z*-rich **2f** or *E*-rich **2f**. Thus, the diastereo-chemistry of the adduct is independent of the stereo-structure of the starting silyl enol ethers but dependent on the cyclic structure of the starting silyl enol ethers. Although the reason of such an unconventional selectivity is not clear at the present time, we speculated that thermodynamic stability of **3** may determine its stereochemistry. Furthermore, the selectivity was slightly enhanced by the lower temperature reaction (*syn*:*anti* = 7:93 in the case of the reaction of **1a** and **2b** at -45 °C).

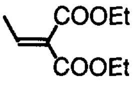
**4** could be readily converted to the corresponding δ-ketoester by the decarboxylative hydrolysis followed by the alkylation in high yield. For example, **4ab** could be converted to δ-ketoester in 89 % yield. Thus, alkylidene Meldrum's acid can be a synthetic equivalent of α, β-unsaturated ester as Michael acceptor.



**4ab**



To demonstrate the specific reactivity of alkylidene Meldrum's acids, the reaction of diethyl ethylidenemalonate **5** with **2a** was also examined although no reaction was observed in spite that **2a** is the most reactive silyl enol ether examined.



**5**

A typical procedure is as follows: To a solution of **2a** (106 mg, 0.55 mmol) in 0.75 mL of dichloromethane was added dropwise a solution of **1a** (85.1 mg, 0.50 mmol) in 0.75 mL of dichloromethane under an argon atmosphere, and the solution was allowed to stand at room temperature for 2h. After the completion of the reaction was checked by TLC analysis, 5 mL of dichloromethane and 5 mL of 1M aqueous HCl were added, and the mixture was stirred vigorously for 10 min. The organic layer was separated out and the aqueous layer was extracted with 10 mL of dichloromethane. The organic layer was combined, washed with water, and dried over $MgSO_4$ before evaporation. 134.0 mg (92 %) of **4aa** was purified by preparative TLC (eluent; hexane/EtOAc, 2/1 (v/v)) as white crystal.

In summary, silyl enol ethers reacted with alkylidene Meldrum's acids without any catalyst to afford the hetero Diels-Alder adducts, which can be easily converted to the corresponding Michael adducts quantitatively. This novel Michael reaction may be applied for a wide variety of organic syntheses since the reaction proceed in neutral condition in high yield with high diastereoselectivity.

## REFERENCES AND NOTES

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2. S. Kobayashi, M. Tamura and T. Mukaiyama, *Chem. Lett.*, **1988**, 91.
3. Lewis acid-promoted Michael reaction of enamines to $\alpha,\beta$-unsaturated 2,2-dimethoxyethyl esters has been reported recently: S. Machida, Y. Hashimoto, K. Saigo, J. Inoue, and M. Hasegawa, *Tetrahedron*, **47**, 3737 (1991).
4. H. McNab, *Chem. Soc. Rev.*, **7**, 345 (1978).
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6. P. Schuster, O. E. Polansky and Wessely, *Mh. Chem.*, **95**, 53 (1964).
7. F. J. Kunz, P. Margaretha, and O. E. Polansky, *Chimia*, **24**, 165 (1970).
8. S. Penades, H. Kisch, K. Tortschanoff, P. Margaretha and O. E. Polansky, *Mh. Chem.*, **104**, 447 (1973).
9. Very recently, Michael reaction of silyl enol ethers to unsaturated cyclic ester-amide which is very resemble to **1** has been reported: M. Sato, N. Kitazawa, S. Nagashima, K. Kano, and C. Kaneko, *Chem. Lett.*, **1992**, 485.
10. $^1$H-NMR (90 MHz, $CDCl_3$) $\delta$ 7.65-7.30 (5H, Ar, m), 3.20-2.10 (3H, $CH_2$ and CH, m), 1.87-1.77 (6H, *gem.* $CH_3$, three singlets), 1.43 and 1.30 (total 3H, two doublets, J=7.2Hz), 0.02 and 0.00 (total 9H, two singlets) ppm.

    $^{13}$C-NMR (22.5MHz, $CDCl_3$) $\delta$ 162.5, 162.1, 142.4, 142.1, 128.4, 128.2, 128.1, 127.9, 124.94, 124.85, 105.3, 105.0, 104.9, 103.9, 84.5, 83.2, 46.4, 43.4, 27.4, 25.7, 24.4, 23.6, 22.7, 22.0, 19.5, 18.6, 1.1, 0.7 ppm.
11. $^1$H-NMR (90 MHz, $CDCl_3$) $\delta$ 8.03-7.92 (2H, Ar, m), 7.65-7.35 (3H, Ar, m), 4.24 (1H, CH, d (J = 2.9Hz)), 3.88-3.08 (3H, CH and $CH_2$, m), 1.78 (3H, *gem.* $CH_3$, s), 1.76 (3H, *gem.* $CH_3$, s), 1.18 (3H, $CH_3$, d (J= 6.8 Hz)) ppm.

    $^{13}$C-NMR (22.5MHz, $CDCl_3$) $\delta$ 200.0, 165.2, 164.8, 136.8, 133.4, 128.7, 128.0, 104.8, 48.8, 41.7, 28.5, 28.4, 26.8, 16.6 ppm.

    IR (KBr) 1782, 1746, 1678, 1598, 1452, 1294, 1264, 1209, 754, 690 $cm^{-1}$.
12. Stereostructure of **4ac** and **4af** were determined by X-ray crystallography of the single diastereo-isomer, and that of the other Michael adducts were estimated by similarity of both $^1$H-NMR spectra and polarity comparing with those of **4ac** and **4af**.

(Received in Japan 20 July 1993)