CHEMISTRY LETTERS, pp. 943-946, 1989.

A Highly *Syn*-selective Michael Reaction of Enamines with α,β-Unsaturated Esters *via* Cationic Intermediates

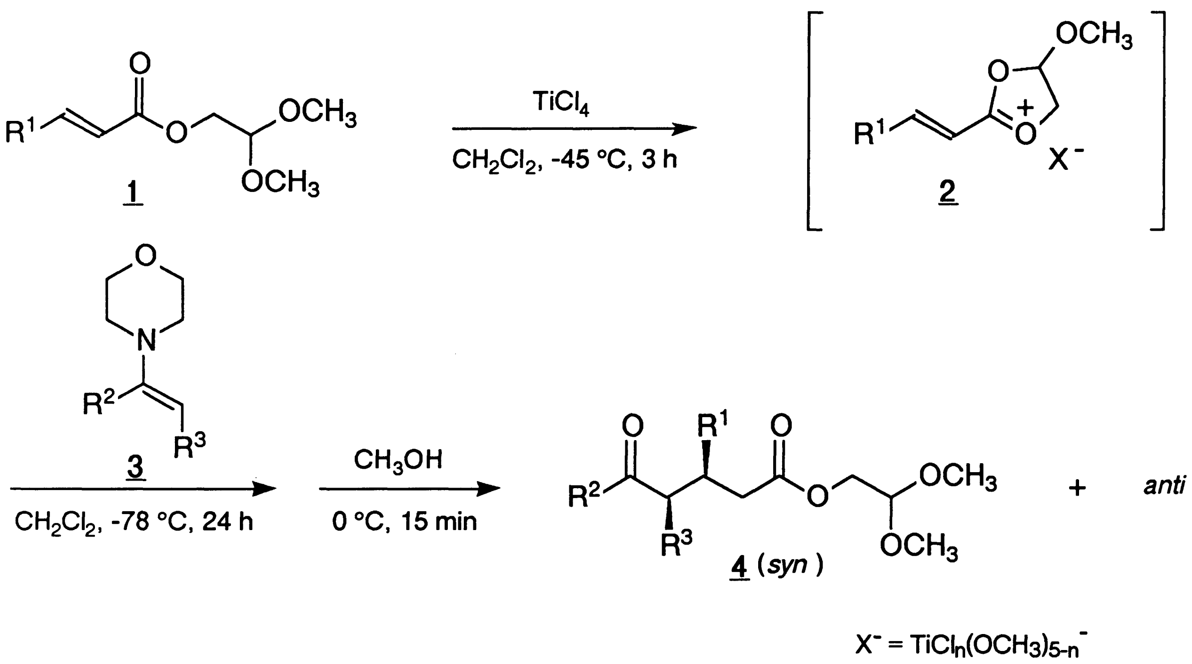
Yukihiko HASHIMOTO, Shigeru MACHIDA, Kazuhiko SAIGO,*
Jun-ya INOUE, and Masaki HASEGAWA
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

An efficient and highly diastereoselective Michael addition of enamines with 2,2-dimethoxyethyl esters of α,β-unsaturated acids was achieved by using titanium(IV) chloride as an activator.

The Michael reaction is one of the most important C-C bond forming reactions, and stereoselective variants have been studied extensively in recent years.1) Generally, the Michael addition of ketone enolate equivalents to α,β-unsaturated esters is thermodynamically disfavored. Enders *et al.*, however, reported that lithiated hydrazones reacted with α,β-unsaturated esters smoothly to give *anti*-adducts.2) In addition, Mukaiyama and his co-workers investigated several Michael acceptors such as orthoesters,3) thioesters,4) and cationic species,5) which are equivalent to α,β-unsaturated esters and reactive enough toward silyl enol ethers; these reactions are also *anti* selective. On the other hand, although diastereoselectivities are not so high, it has been already found that the cationic acceptors, 2-alkenyl-1,3-dithiolan-2-ylium cations, reacted with enamines to give *syn* adducts.6) In this communication, we wish to report a new and *syn*-selective Michael type reaction between modified α,β-unsaturated esters and enamines, based on cationic species chemistry.

We attempted, at first, the generation of moisture-sensitive intermediate cationic species, 1,3-dioxolan-2-ylium salts, from neutral esters *in situ*. As shown in Scheme 1, a 2,2-dimethoxyethyl ester 1 was found to give the corresponding cation 2 in the presence of titanium(IV) chloride under mild conditions (−45 °C, 3 h), which was confirmed by ^{13}C-NMR recorded at a low temperature. Accompanied with the cation formation, the signals of the ester 1 disappeared completely, and the peaks corresponding to the cation 2 appeared. Almost all the signals shifted to low field by 4—28 ppm.

The reaction of this cation 2 with (*E*)-1-morpholino-1-phenylpropene (3, R^2=Ph, R^3=CH_3) proceeded smoothly to give the Michael adduct in a high yield after the methanolic quenching of the reaction, and the predominant formation of *syn* adduct 4 was observed.7) It is noted that, if the corresponding methyl ester was used instead of 2,2-dimethoxyethyl ester 1, the reaction did not occur under the same conditions and only the starting materials were recovered.



Scheme 1.

The reaction conditions were optimized for the reaction of 2,2-dimethoxyethyl crotonate (1, R^1=CH_3) with enamines derived from propiophenone. Among various Lewis acids examined, titanium(IV) chloride was found to be specifically effective, and the morpholino enamine gave the highest *syn*-selectivity.[8] The reaction of esters 1 was carried out with various morpholino enamines 3, and the results are summarized in Table 1. In every case, the reaction proceeded with high *syn*-diastereoselectivity.

Table 1. Reaction of 2,2-dimethoxyethyl esters 1 with enamines 3

R^1	R^2	R^3	Yield/%	*syn* : *anti*[a]
CH_3	Ph	CH_3	82	93 : 7
CH_3	H	CH_3	92	91 : 9
CH_3	C_2H_5	CH_3	83	91 : 9
CH_3	$-(CH_2)_4-$		81	96 : 4
Ph	C_2H_5	CH_3	79	81 : 19

a) Determined by GLC or HPLC.

This stereoselectivity may be explained as follows: On account of interaction between the lone pair of the nitrogen atom in the enamine and the cationic center of the Michael acceptor, this reaction is considered to proceed *via* a six-membered chair like cyclic transition state as shown in Fig. 1 to give *syn* adduct.

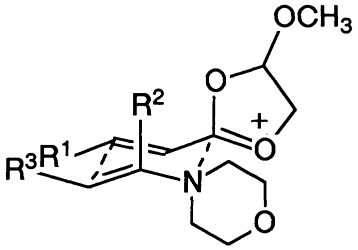


Fig. 1. Chair like transition state leading to *syn* adducts.

The general procedure of this reaction is as follows: To a dichloromethane solution of 2,2-dimethoxyethyl ester 1 (0.5 mmol) was added dropwise a dichloromethane solution of titanium(IV) chloride (0.55 mmol) at −45 °C. The solution was stirred at the temperature for 3 h, and then, cooled down to −78 °C. A dichloromethane solution of enamine 3 (0.6 mmol) was added slowly to the solution, and the mixture was stirred at −78 °C for 24 h. After quenching with excess dry methanol, the solution was warmed up to 0 °C and stirred for 15 min. Then, saturated aqueous sodium hydrogencarbonate solution was added, and the mixture was stirred for further 30 min at room temperature. Insoluble solid mass was filtered off through a Celite pad, and organic materials in the filtrate were extracted with dichloromethane. After the organic layer was dried and concentrated, the residue was purified by silica gel thin layer or column chromatography.

Generally, the Michael reaction using enamines is carried out under relatively drastic conditions, so the stereochemical control of the reaction is rather difficult. Only one exception is the reaction of enamines with nitroalkenes.[9] However, this method cannot be applied to the reaction with ordinary α,β-unsaturated carbonyl compounds. In contrast, using the method reported in this communication, the Michael reaction of enamines with α,β-unsaturated esters proceeds under extremely mild conditions. Also, it should be noted that this reaction is the first example of the *syn*-selective Michael reaction of ketone enolate equivalents with α,β-unsaturated esters. 2,2-Dimethoxyethyl ester is a new and unique function for the activation of ester carbonyls, and further synthetic applications of this function are now under investigation in this laboratory.

References

1) K. Tomioka, K. Yasuda, and K. Koga, Tetrahedron Lett., 27, 4611 (1986); Y. Yamamoto, Acc. Chem. Res., 20, 243 (1987); R. W. Hoffmann, Angew. Chem., Int. Ed. Engl., 26, 489 (1987); Y. Yamamoto, S. Nishii, and T. Ibuka, J. Am. Chem. Soc., 110, 617 (1988); Y. Yamamoto and S. Nishii, J. Org. Chem., 53, 3597 (1988); G. S. Ponticello, M. B. Freedman, C. N. Habecker, M. K. Holloway, J. S. Amato, R. S. Conn, and J. J. Baldwin, *ibid.*, 53, 9 (1988); also see the references cited in Ref. 5.
2) D. Enders, K. Papadopoulos, and B. E. M. Rendenbach, Tetrahedron Lett., 27, 3491 (1986); D. Enders and B. E. M. Rendenbach, Tetrahedron, 42, 2235 (1986); Chem. Ber., 120, 1223 (1987); D. Enders, A. S. Demir, and B. E. M. Rendenbach, *ibid.*, 120, 1731 (1987).
3) S. Kobayashi and T. Mukaiyama, Chem. Lett., 1987, 1183.
4) S. Kobayashi, M. Tamura, and T. Mukaiyama, Chem. Lett., 1988, 91.
5) Y. Hashimoto and T. Mukaiyama, Chem. Lett., 1986, 755, 1623; T. Mukaiyama, Y. Hayashi, and Y. Hashimoto, *ibid.*, 1986, 1627; Y. Hayashi, K. Wariishi, and T. Mukaiyama, *ibid.*, 1987, 1243; Y. Hashimoto, H. Sugumi, T. Okauchi, and T. Mukaiyama, *ibid.*, 1987, 1691, 1695.
6) Y. Hashimoto and T. Mukaiyama, unpublished result.
7) These adducts were easily converted to the corresponding methyl esters, and their stereochemistry was determined by comparison of GLC and NMR with those of the authentic methyl ester prepared from the corresponding thioester having known stereochemistry.[4)]
8) The results with the other enamines were as follows (amine part, yield, *syn*:*anti*): piperidino, 74 %, 86:14; pyrrolidino, 43 %, 68:32; N-methylpiperazino, 18 %, 80:20.
9) D. Seebach and J. Goliński, Helv. Chim. Acta, 64, 1413 (1981); S. J. Blarer, W. B. Schweizer, and D. Seebach, *ibid.*, 65, 1637 (1982); D. Seebach, A. K. Beck, J. Goliński, J. N. Hay, and T. Laube, *ibid.*, 68, 162 (1985).

(Received February 17, 1989)