A Convenient Method for the Lewis Base-catalyzed Synthesis of α,β-Unsaturated Carboxylic Esters Using Trimethylsilylketene Ethyl Trimethylsilyl Acetal and Carbonyl Compounds

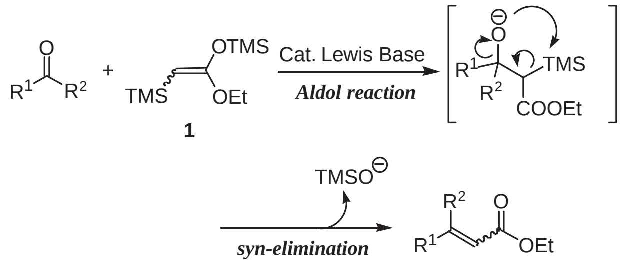
Makoto Michida[1] and Teruaki Mukaiyama*[2]
[1] *Process Technology Research Laboratories, Daiichi Sankyo Co., Ltd., 1-16-3 Kitakasai, Edogawa-ku, Tokyo 134-8630*
[2] *Center for Basic Research, Kitasato University, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*

(Received April 14, 2008; CL-080383; E-mail: mukaiyam@abeam.ocn.ne.jp)

A highly useful method for the synthesis of α,β-unsaturated carboxylic esters from various carbonyl compounds that uses trimethylsilylbetene ethyl trimethylsilyl acetal in the presence of a Lewis base catalyst such as acetate salts was established. This procedure gives the corresponding esters in high yields with excellent E stereoselectivity under mild conditions.

α,β-Unsaturated esters are the building blocks known to be quite useful and they are frequently used in various conjugate addition reactions such as the Michael reaction,[1] the Morita–Baylis–Hillman reaction,[2] or the Diels–Alder reaction.[3] In order to prepare these α,β-unsaturated carboxylic esters, carbonyl olefination is one of the most general and important methods. Among the carbonyl olefination, the Wittig reaction[4] is employed commonly by using phosphorous ylides. However, isolation of the desired product from the co-product in this reaction is often difficult. The Horner–Wadsworth–Emmons reaction[5] and the Peterson reaction[6] are also widely used although an equimolar amount of bases such as n-BuLi or NaH is required. As an alternative method, the Knoevenagel type reaction of malonic acid half esters with aldehydes in the presence of a catalytic amount of DMAP is recently reported.[7] While this method is quite useful and clean for the synthesis of E-α,β-unsaturated carboxylic ester, the substrates employed are limited to aldehydes, and needs long reaction time. Thus, it is required to find more convenient ways for the synthesis of α,β-unsaturated carboxylic esters from carbonyl compounds including ketones.

In our previous papers, it was shown that the nitrogen- or oxygen-containing anions generated from amides, imides, carboxylic acids, or alcohols behaved as effective Lewis-base catalysts in the activation of trimethylsilyl (TMS) derivatives.[8] In order to extend the utility, reaction of carbonyl compounds and trimethylsilylketene ethyl trimethylsilyl acetal **1** was examined so that it may become an useful reagent for the synthesis of α,β-unsaturated carboxylic esters. Namely, the esters would be provided directly from aldehydes by syn elimination via the following aldol-type reaction. Thus, eliminated silanol anion also works as a Lewis base, and generated TMS_2O is removed easily by evaporation (Scheme 1). In addition, the ketene acetal **1** can easily be prepared from commercially available ethyl (trimethylsilyl)acetate.[9] Concerning this type of reaction, Matsuda et al. reported that trimethylsilylketene trimethylsilyl acetals reacted with aldehydes to give the corresponding esters by using an equimolar amount of Lewis acids such as $AlCl_3$ and $TiCl_4$.[10] However, the reaction is applied only to simple aliphatic aldehydes and is hard to apply to the substrates having basic moiety because the reaction is carried out under acidic conditions. In this communication, we would like to report a convenient method for the synthesis of α,β-unsaturated carboxylic esters from carbonyl compounds such as aldehydes and ketones with ketene acetal **1** under mild conditions by using a Lewis base catalysts such as AcOLi or AcONn-Bu$_4$.

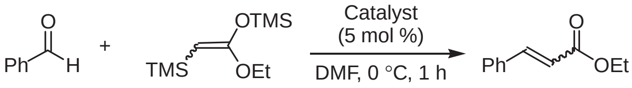


Scheme 1. Lewis base-catalyzed carbonyl olefination.

In the first place, reactions of benzaldehyde with ketene acetal **1** (E:Z = 4:1) were examined in the presence of 5 mol % each of various Lewis bases (Table 1). The reaction did not take place in the absence of the catalyst (Entry 1). Whereas it proceeded smoothly to give the ca. 1:1 mixture of the corresponding E/Z isomers in quantitative yield when AcOLi was used (Entry 2). Then, the same reaction was tried in the different ratio of **1** and the ratios of the product remained almost unchanged (Entry 3). These results indicate that there is no correlation between E/Z stereoselectivity and E/Z ratio of **1**.

Next, in order to investigate effects of the counter anions of Lewis bases, lithium phenoxide was employed and the desired product was obtained in good yield with the same ratio of isomers (Entry 4). Then, effects of the counter cations were further examined, and E stereoselectivities of the products improved as the ionic character increased (Entries 5–8). Thus, it was noted

Table 1. Effects of Lewis bases

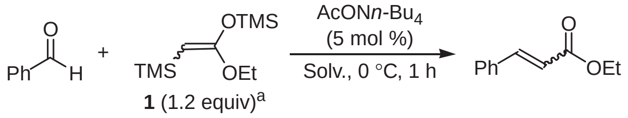


1 (1.2 equiv)[a]

Entry	Catalyst	Yield[b]/%	E:Z[b]
1	None	N.R.	—
2	AcOLi	quant.	47:53
3	AcOLi	quant.	45:55[c]
4	PhOLi	80	47:53
5	AcONa	98	95:5
6	AcOK	96	99:1
7	AcOCs	quant.	>99:1
8	AcONn-Bu$_4$	97	>99:1

[a] Unless otherwise noted, ketene acetal **1** in a ratio of 4:1 (E:Z) was used. [b] Yields and ratios were determined by GC analysis using internal standard. [c] Ketene acetal **1** in a ratio of 1:1 (E:Z) was used.

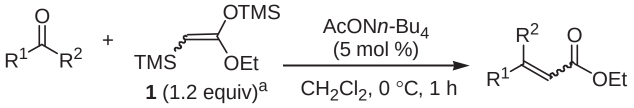
Table 2. Effects of solvents



Entry	Solv.	Yield[b]/%	E:Z[b]
1	Toluene	95	95:5
2	AcOEt	84	98:2
3	Et_2O	94	94:6
4	THF	quant.	97:3
5	CH_2Cl_2	quant.	>99:1
6[c]	DMSO	92	>99:1

[a]Ketene acetal **1** in a ratio of 4:1 (E:Z) was used. [b]Yields and ratios were determined by GC analysis using internal standard. [c]The reaction was carried out at room temperature.

Table 3. Olefination of various carbonyl compounds



Entry	R^1	R^2	Yield[b]/%	E:Z[c]
1	$2\text{-}ClC_6H_4$	H	98	>99:1
2	$3\text{-}ClC_6H_4$	H	94	>99:1
3	$4\text{-}ClC_6H_4$	H	96	>99:1
4	$4\text{-}MeOC_6H_4$	H	quant.	>99:1
5	$4\text{-}MeO_2CC_6H_4$	H	94	>99:1
6	$4\text{-}Me_2NC_6H_4$	H	92	>99:1
7	3-Pyridyl	H	82	>99:1
8	*c*-Hex	H	72	>99:1
9	Ph	Me	4	>99:1
10[d]	Ph	Me	87	47:53
11[d]	$-(CH_2)_5-$		90	—

[a]Ketene acetal **1** in a ratio of 4:1 (E:Z) was used. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^1H NMR analysis. [d]The reaction was carried out in DMF by using 5 mol % of AcOLi.

that the suitable choice of a counter cation was crucial to obtain the adducts in high E stereoselectivity. Next, AcON*n*-Bu$_4$ was chosen on the basis of solubility, and effect of solvents was also examined (Table 2). It was then found that this reaction proceeds smoothly in various solvents (Entries 1–6), and CH_2Cl_2 gave an excellent result in both yield and E stereoselectivity (Entry 5).[11] The observed stereoselectivity indicates that the reaction proceeds via acyclic transition states irrespective of the geometry of the silyl enolate.

Then, reactions of various carbonyl compounds with ketene acetal **1** were examined by using a catalytic amount of Lewis base (Table 3). Aromatic aldehydes having electron-donating or -withdrawing groups reacted smoothly to afford the desired esters in high yields with complete E selectivity (Entries 1–5). Similarly, this reaction is then applied to aldehydes having basic moiety (Entries 6 and 7) and aliphatic aldehydes reacted smoothly as well and afforded the desired adduct in good yields (Entry 8). Next, ketones having α-protons such as acetophenone were tried. As a result, the corresponding ester was obtained only in poor yield and a large amount of silyl enolate was formed (Entry 9). On the other hand, the reaction proceeded smoothly to give the ca. 1:1 mixture of the desired products in high yield in the case when AcOLi was used in DMF (Entry 10). The reaction was also applied to aliphatic ketones such as cyclohexanone in similar fashion (Entry 11).

Thus, a convenient method for the synthesis of *E*-α,β-unsaturated carboxylic esters by using trimethylsilylketene ethyl trimethylsilyl acetal in the presence of a catalytic amount of Lewis base was established. Importantly, in this procedure, only TMS_2O is formed as a co-product which is easily removed by evaporation. This is also applied to the ketones having α-protons as electrophiles. Further studies on this type of reactions are now in progress.

References and Notes

1 a) J. Boyer, R. J. P. Corriu, R. Perz, C. Reye, *Tetrahedron* **1983**, *39*, 117. b) K. Ogura, H. Itoh, T. Morita, K. Sanada, H. Iida, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1216. c) N. Duguet, A. Harrison-Marchand, J. Maddaluno, K. Tomioka, *Org. Lett.* **2006**, *8*, 5745.

2 P. R. Krishna, M. Narsingam, P. S. Reddy, G. Srinivasulu, A. C. Kunwar, *Tetrahedron Lett.* **2005**, *46*, 8885.

3 A. Saito, H. Yanai, T. Taguchi, *Tetrahedron* **2004**, *60*, 12239.

4 a) M. Schlosser, K. F. Christmann, *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126. b) F. Orsini, G. Sello, T. Fumagalli, *Synlett* **2006**, 1717. c) J. P. Bégué, D. B. Delpon, A. Kornilov, *Org. Synth.* **2004**, Coll. Vol. *10*, 703.

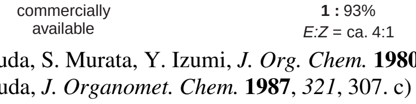
5 a) W. S. Wadsworth, Jr., W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733. b) W. S. Wadsworth, Jr., W. D. Emmons, *Org. Synth.* **1973**, Coll. Vol. *5*, 547. c) D. J. Ager, *Synthesis* **1984**, 384. d) A. Ianni, S. R. Waldvogel, *Synthesis* **2006**, 2103. e) D. J. Schauer, P. Helquist, *Synthesis* **2006**, 3654.

6 a) D. J. Peterson, *J. Org. Chem.* **1968**, *33*, 780. b) M. Iguchi, K. Tomioka, *Org. Lett.* **2002**, *4*, 4329.

7 B. List, A. Doehring, M. T. H. Fonseca, A. Job, R. R. Torres, *Tetrahedron* **2006**, *62*, 476.

8 a) H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2002**, 182. b) H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2002**, 858. c) H. Fujisawa, T. Nakagawa, T. Mukaiyama, *Adv. Synth. Catal.* **2004**, *346*, 1241. d) T. Mukaiyama, T. Nakagawa, H. Fujisawa, *Chem. Lett.* **2003**, *32*, 56. e) T. Mukaiyama, T. Tozawa, H. Fujisawa, *Chem. Lett.* **2004**, *33*, 1410. f) H. Fujisawa, E. Takahashi, T. Nakagawa, T. Mukaiyama, *Chem. Lett.* **2003**, *32*, 1036. g) E. Takahashi, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2004**, *33*, 1426.

9 Ethyl *C*,*O*-bis(trimethylsilyl)ketene acetal **1** is easily prepared in high yield by distillation as a colorless liquid: bp 55–60 °C (3.0 Torr).[10]



10 a) I. Matsuda, S. Murata, Y. Izumi, *J. Org. Chem.* **1980**, *45*, 237. b) I. Matsuda, *J. Organomet. Chem.* **1987**, *321*, 307. c) P. Pellon, Y. L. Ko, P. Cosquer, J. Hamelin, R. Carrié, *Tetrahedron Lett.* **1986**, *27*, 4299.

11 Typical experimental procedure is as follows: To a stirred solution of benzaldehyde (0.50 mmol) and trimethylsilylketene ethyl trimethylsilyl acetal (0.60 mmol) in CH_2Cl_2 (2.5 mL) were added AcON*n*-Bu$_4$ (0.025 mmol) at 0 °C. After the reaction mixture was stired for 1 h, it was quenched with saturated NH_4Claq. The mixture was extracted with AcOEt and organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC to give the desired product as a colorless oil.