Lithium Acetate-catalyzed Mannich-type Reaction between Trimethylsilyl Enolates and Aldimines in a Water-containing DMF

Eiki Takahashi,[†,††] Hidehiko Fujisawa,[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute (TCI), 6-15-5 Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

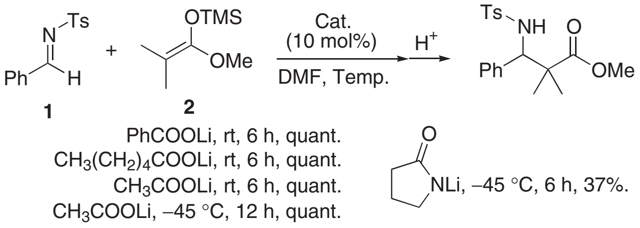
(Received May 13, 2004; CL-040550)

Lithium acetate-catalyzed Mannich-type reaction between trimethylsilyl enolates and aldimines proceeded smoothly in dry or even in a water-containing DMF to afford the corresponding β-amino carbonyl compounds in good to high yields under mild conditions.

The Mannich-type reaction of aldimine with silyl enolate is one of the most important tools for the construction of β-amino carbonyl compounds. Recently, several methods for the catalytic Mannich-type reaction by using Lewis acid catalysts have intensively been studied.[1] Although these acids were generally employed for promotion of the above reaction, deactivation caused by the coordination of a nitrogen atom of the starting aldimines or of the produced amine was considered as a negative problem. On the other hand, it is feasible to use a Lewis base catalyst for the Mannich-type reaction since the catalyst would bring about no undesirable interactions between substrates and catalyst.[2]

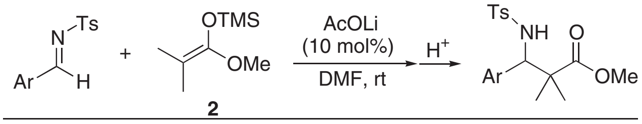
In the course of our investigation for the activation of trimethylsilyl (TMS) enolate with a Lewis base catalyst,[3] nitrogen-containing organic anions generated from amides and imides were found to work effectively as Lewis base catalysts to accelerate the Mannich-type reaction.[4] Accordingly, the carboxylate anion such as lithium acetate were expected to work as an effective Lewis base catalyst as it did in the aldol reaction between aldehydes and TMS enolates.[5] The above anions are readily available, inexpensive and could be used under mild conditions in water-containing solvent because they are weakly-basic and are stable toward water. In addition, they are very useful from an environmental point of view because of their low toxicity and are disposable without any special treatment. Then, in order to further examine the usefulness of organic anions as Lewis bases in organic reactions, the use of oxygen-containing organic anions generated from carboxylic acids was considered. In this communication, we would like to report on the Mannich-type reaction between TMS enolates and aldimines by using a catalytic amount of lithium acetate both in dry or water-containing DMF solvent.

In the first place, reactions between *N*-tosylaldimine **1** and TMS enolate **2** were tried in the presence of 10 mol % of lithium carboxylates such as lithium acetate, benzoate, and hexanoate at room temperature and the corresponding Mannich-adducts were obtained in quantitative yields (Scheme 1). It is interesting to note that the above reaction proceeds smoothly even at −45 °C by using lithium acetate while *N*-lithio-2-pyrrolidone is less effective at the same temperature in spite of weaker nucleophilicity of the lithium carboxylate than that of *N*-lithio-2-pyrrolidone. Because of these results, it was thought that lithium carboxylates would be employed as favorable catalysts of this reaction.



Scheme 1.

Table 1.



Entry	Ar	Time /h	Yield[a] /%
1	p-MeOC$_6$H$_4$	6	quant
2	p-MeC$_6$H$_4$	6	81
3	p-ClC$_6$H$_4$	3	97
4	p-BrC$_6$H$_4$	3	quant
5	p-CNC$_6$H$_4$	3	84
6	p-O$_2$NC$_6$H$_4$	3	96
7	p-Me$_2$NC$_6$H$_4$	6	78
8	4-Pyridyl	3	77

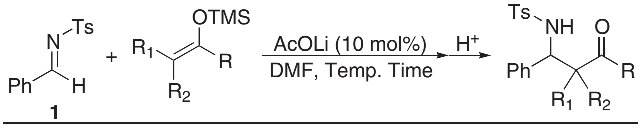
[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

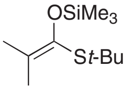
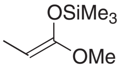
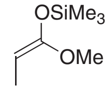
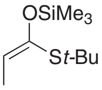
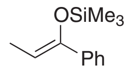
Next, the reactions of TMS enolate **2** with aldimines were tried by using 10 mol % of lithium acetate in DMF (Table 1). Most aromatic aldimines reacted smoothly with **2** to afford the corresponding β-amino esters in high yields. Further, the corresponding Mannich-adducts were afforded in high yields even when aromatic aldimines having either electron-donating or having electron-withdrawing groups were used as their acceptors. It is noteworthy to point out that the corresponding β-amino esters were also obtained in good yields when aldimines having basic part such as dimethylamino- or pyridiyl-function in the same molecule were used (Entries 8 and 9).

The lithium acetate-catalyzed Mannich-type reaction was further tried by using various silyl enolates and the corresponding Mannich-adducts were obtained in good to quantitative yields (Table 2). When two TMS enolates derived from methyl propionate were used, they reacted smoothly at −20 °C to afford the corresponding Mannich-adduct in quantitative yields. Furthermore, the diastereomeric ratio of the *anti* isomer increased with the use of (*E*)-enolate **5** and also the same results were obserbed when silyl enolate **7** was used.

Then, lithium acetate-catalyzed Mannich-type reaction in water-containing DMF solvent was tried. When *N*-tosylaldimine

Table 2.



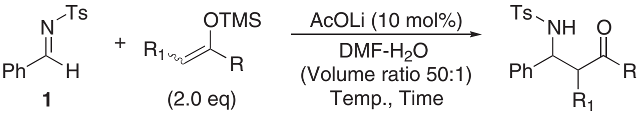
Entry	Silyl enolates	Temp. /°C	Time /h	Yield[a] /%	*anti* : *syn*
1	 **3**	rt	6	quant	—
2	 **4** (*E* : *Z* = 1 : 9)	−20	24	quant	1.6 : 1
3	 **5** (*E* : *Z* = 5 : 1)	rt	6	84	1.6 : 1
4		−20	24	quant	4.2 : 1
5	 **6**	rt	3	quant	3.0 : 1
6		−45	6	85	3.1 : 1
7	 **7**	rt	3	quant	3.0 : 1
8		−20	24	quant	5.4 : 1

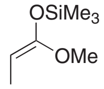
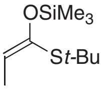
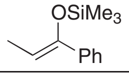
[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

1 and TMS enolate **2** in the presence of 10 mol % of lithium acetate were allowed to react at room temperature for 6 h in DMF/H_2O (50:1), the corresponding β-amino ester was obtained in 65% yield. After screening several reaction conditions, the corresponding Mannich-adduct was obtained in high yield when carried out at −45 °C for 24 h. It is generally known that silyl enolates, especially those generated from carboxylic esters, are sensitive to water and are hydrolyzed easily under acidic conditions. This is the first example of the Lewis base-catalyzed Mannich-type reaction using silyl enolates derived from carboxylic esters in a homogeneous water-containing solvent.[6,7]

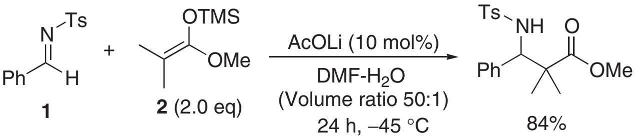
The same reaction in water-containing DMF solvent by using several silyl enolates was studied next, and the diastereoselection of the reaction was found to be influenced by the co-existing water and also by the structures of silyl enolates employed (Table 3). That is, when silyl enolate **5** was employed in water-containing DMF, the yield and ratio of *anti* isomer decreased compared to those in dry DMF whereas the ratio increased when silyl enolate **6** was used.

Table 3.



Entry	Silyl enolates	Temp. /°C	Time /h	Yield[a] /%	*anti* : *syn*[a]
1	 **5**	−20	24	74	1.6 : 1
2	 **6**	−45	6	quant	5.5 : 1
3	 **7**	−20	12	quant	5.8 : 1

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.



Scheme 2.

Thus, the lithium acetate-catalyzed Mannich-type reaction between TMS enolates and aldimines in dry or water-containing DMF solvent was established. This method is quite practical and is applicable to the synthesis of various β-amino carbonyl compounds since its reaction conditions do not have to be strictly anhydrous and mild, readily available yet inexpensive Lewis base catalyst is used. Further development of this reaction is now in progress.

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References

1 I. Ojima, S. Inaba, and K. Yoshida, *Tetrahedron Lett.*, **1977**, 3643; I. Ojima, S. Inaba, and M. Nagai, *Synthesis*, **1981**, 545; T. Mukaiyama, K. Kashiwagi, and S. Matsui, *Chem. Lett.*, **1989**, 1397; T. Mukaiyama, H. Akamatsu, and J. S. Han, *Chem. Lett.*, **1990**, 889; S. Kobayashi, M. Araki, H. Ishitani, and S. Nagayama, *Synlett*, **1995**, 233; M. Shimizu, K. Kume, and T. Fujisawa, *Chem. Lett.*, **1996**, 545; S. Kobayashi, H. Ishitani, and M. Ueno, *J. Am. Chem. Soc.*, **120**, 431 (1998); D. Ferraris, B. Young, T. Dudding, and T. Lactka, *J. Am. Chem. Soc.*, **120**, 4548 (1998); R. Hayakawa and M. Shimizu, *Chem. Lett.*, **1999**, 591; S. Yamasaki, T. Iida, and M. Shibasaki, *Tetrahedron Lett.*, **40**, 307 (1999); H. Ishitani, T. Kitazawa, and S. Kobayashi, *Tetrahedron Lett.*, **40**, 2161 (1999); H. Ishitani, M. Ueno, and S. Kobayashi, *J. Am. Chem. Soc.*, **122**, 8180 (2000); K. Juhl, N. Gathergood, and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, **40**, 2995 (2001); S. Kobayashi, H. Ishitani, Y. Yamashita, M. Ueno, and H. Shimizu, *Tetrahedron*, **57**, 861 (2001); B. M. Trost and L. R. Terrell, *J. Am. Chem. Soc.*, **125**, 338 (2003).

2 K. Miura, K. Tamaki, T. Nakagawa, and A. Hosomi, *Angew. Chem., Int. Ed.*, **39**, 1958 (2000); K. Miura, T. Nakagawa, and A. Hosomi, *J. Am. Chem. Soc.*, **124**, 536 (2002).

3 H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 182; H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 858; T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Helv. Chim. Acta*, **85**, 4518 (2002); T. Mukaiyama, T. Nakagawa, and H. Fujisawa, *Chem. Lett.*, **32**, 56 (2003).

4 H. Fujisawa, E. Takahashi, and T. Mukaiyama, *Chem. Lett.*, **32**, 1036 (2003).

5 T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 462 (2003).

6 T. Akiyama, J. Takaya, and H. Kagoshima, *Synlett*, **1999**, 1045; T. Akiyama, J. Takaya, and H. Kagoshima, *Tetrahedron Lett.*, **42**, 4025 (2001); T. Akiyama, J. Takaya, and H. Kagoshima, *Adv. Synth. Catal.*, **344**, 338 (2002).

7 K. Manabe, Y. Mori, and S. Kobayashi, *Synlett*, **1999**, 1401; T. Akiyama, J. Takaya, and H. Kagoshima, *Synlett*, **1999**, 1426; T. Akiyama, J. Itoh, and K. Fuchibe, *Synlett*, **2002**, 1269.

Published on the web (Advance View) June 26, 2004; DOI 10.1246/cl.2004.936