Lewis Base-Catalyzed Mannich-type Reaction between Aldimine and Trimethylsilyl Enolate

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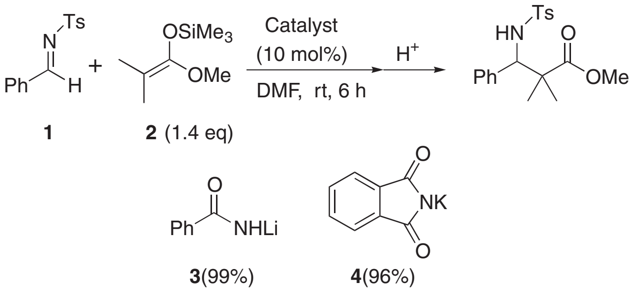
Lithium benzamide- or potassium phthalimide-catalyzed Mannich-type reaction between trimethylsilyl enolates and aldimines proceeded smoothly in a DMF solvent to afford the corresponding β-amino esters in good to high yields.

Mannich-type reaction of silyl enolate with aldimine is one of the most important and versatile tools in constructing β-amino carbonyl compounds. It provides useful routes for the synthesis of β-amino esters which are employed as immediate precursors of β-lactams and β-amino acids. Mannich-type reaction generally proceeds via the electronphilic activation step of Mannich acceptor with Lewis acids[1] such as $TiCl_4$[2] and lanthanoid triflate.[3] On the other hand, it is also known that Mannich-type reaction proceeds via the nucleophilic activation step of nucleophiles such as silyl enolate. For example, Sodeoka and co-workers reported the reactions of imines with nucleophilic transition metal enolate formed by the addition of Pd complex to silyl enolate.[4] In most cases, a Lewis acid activator was often trapped by the nitrogen atom of starting aldimines or that of produced amino esters, and therefore, more than stoichiometric amounts of the Lewis acids are needed to complete the reaction. It was expected then that the reaction would proceed alternatively in the presence of a catalytic amount of Lewis base which would work to activate the silyl enolates and that the above-mentioned undesirable interactions of acids should be eliminated. Recently, Hosomi and co-workers reported that Lewis base-catalyzed Mannich-type reaction was carried out by using dimethyl silyl enolate which readily formed hypervalent silicate with Lewis base such as diisopropylethylamine and calcium chloride.[5] In our previous reports, commonly used trimethylsilyl (TMS) enolate was successfully activated with Lewis bases such as lithium diphenylamide and lithium pyrrolidone, and worked as a strong nucleophile in aldol and Michael reactions.[6] In this communication, we would like to report on a catalytic Mannich-type reaction between TMS enolates and aldimines by using the nitrogen anions generated from amides or imides as Lewis base catalysts.

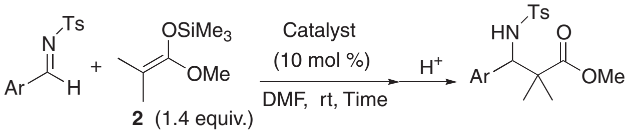
In the first place, a reaction between *N*-tosylaldimine and TMS enolate **2** was tried in the presence of 10 mol % of lithium pyrrolidone at −45 °C in *N*,*N*-dimethylformamide (DMF) and the corresponding β-amino ester was obtained in 37% yield. After screening Lewis bases and reaction conditions, anions generated from lithium benzamide (**3**) and pottasium phthalimide (**4**) turned out to be effective base catalysts in accelerating the present Mannich-type reactions between silyl enolates and aldimines, and the corresponding β-amino ester was afforded in quantitative yields.[7] In the absence of the catalyst, the reaction also proceeded slowly at room temperature, however, the yield of the corresponding β-amino ester was 24% after 6 h. These results indicated that Lewis base such as lithium benzamide **3** or pottasium phthalimide **4** effectively catalyzed Mannich-type reaction between TMS enolates and aldimines.



Scheme 1.

Next, the reactions of TMS enolate **2** with various aldimines were tried by using 10 mol % of **3** or **4** in DMF (Table 1). Various aromatic aldimines smoothly reacted with **2** to afford the corresponding β-amino esters in high yields. When aromatic aldimines having electron-donating groups were used as Mannich acceptors, the reactions proceeded slowly compared with those of using aldimines having electron-withdrawing groups. These results indicated that reaction rates were dependent on the electrophilicity of aldimines. The present Lewis base catalyzed reaction is considered to have a remarkable advantage of forming β-amino esters especially when the aldimines have basic functions in the same molecules. Expectedly, the reactions in the presence

Table 1.



Entry	Ar	Catalyst	Time/h	Yield[a]/%
1	4-ClC_6H_4	**3**	6	95
2	4-ClC_6H_4	**4**	3	quant
3	4-NCC_6H_4	**3**	6	92
4	4-NCC_6H_4	**4**	3	77
5	4-$O_2NC_6H_4$	**3**	6	89
6	4-$O_2NC_6H_4$	**4**	3	80
7	4-$MeOC_6H_4$	**3**	6	87
8	4-$MeOC_6H_4$	**4**	9	92
9	4-MeC_6H_4	**3**	6	91
10	4-MeC_6H_4	**4**	3	84
11	4-$Me_2NC_6H_4$	**3**	6	68
12	4-$Me_2NC_6H_4$	**4**	16	84
13	4-Pyridyl	**3**	6	70
14	4-Pyridyl	**4**	3	81

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

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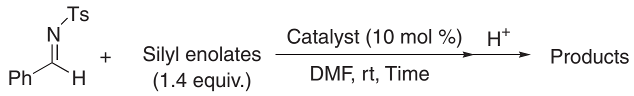
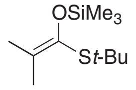
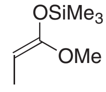
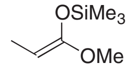
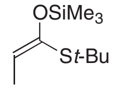
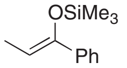
Table 2.



Entry	Silyl Enolates	Catalyst	Time /h	Yield[a] /%	*anti*:*syn*
1		**3**	6	100	-
2		**4**	4	83	-
3	 (*E*:*Z* = 5:1)	**3**	6	70	1.8:1
4		**4**	6	52	1.6:1
5	 (*E*:*Z* = 1:9)	**3**	24	59	1.8:1
6		**4**	24	67	1.6:1
7		**4**	3	80	1.6:1
8		**4**	3	72	2.1:1

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

of **3** or **4** proceeded smoothly at room temperature in DMF to afford the corresponding β-amino esters in high yields (Table 1, Entries 11–14).

Lewis base-catalyzed Mannich-type reaction was further examined by using other silyl enolates (Table 2). When the enolate generated from *S*-*tert*-butyl thioisobutyrate was employed, the corresponding Mannich adduct was obtained in high yield (Entries 1 and 2). Furthermore, the Mannich adducts were obtained in good yields with moderate *anti*-diastereoselectivity irrespective of the geometry of the two isometric silyl enolates derived from methyl propionate (Entries 3–6).[8] The reaction of less reactive *Z* enolate with aldimine proceeded more slowly than that of *E* enolate. The observed *anti*-diastereoselectivities, irrespective of the geometries of silyl enolates, indicated that the present Lewis base-catalyzed Mannich-type reaction proceeded via acyclic transition states.[5,6]

Thus, it is noted that lithium benzamide- or potassium phthalimide-catalyzed Mannich-type reaction between TMS enolates and aldimines proceeded smoothly under weakly basic conditions in DMF. This method is practically applicable for the synthesis of various β-amino esters because the reactions are promoted with such a mild, readily-available, and inexpensive Lewis base catalyst. Further extension of this reaction is now in progress.

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7 Typical experimental procedure is as follows (Scheme 1): to a stirred solution of pottasium phthalimide (3.7 mg, 0.02 mmol) in DMF (0.3 mL) were added successively a solution of silyl enolate **2** (48.9 mg, 0.28 mmol) in DMF (0.4 mL) and a solution of *N*-tosylbenzaldimine **1** (52.0 mg, 0.2 mmol) in DMF (0.7 mL) at 0 °C. After warmed up to room temperature, the mixture was stirred for 6 h, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt. Organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding β-amino ester (69.0 mg, 95%) as a white powder.

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