One-pot Synthesis of β-Lactams from Aldimines and Ketene Silyl Acetals by Tandem Lewis Base-catalyzed Mannich-type Addition and Cyclization

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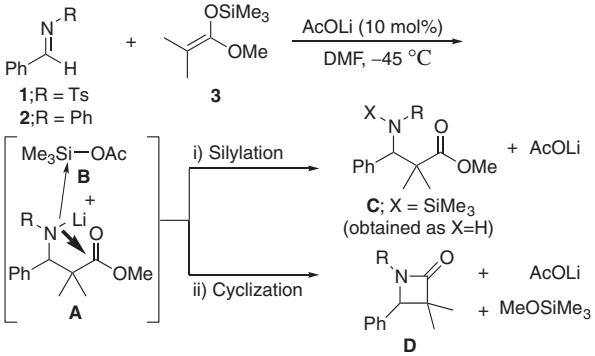
An efficient method for one-pot synthesis of β-lactams from aldimines and ketene silyl acetals by tandem Lewis base-catalyzed Mannich-type addition and cyclization, namely reaction of benzylideneanilines and trimethylsilyl enolates derived from esters or thioesters was established by using a Lewis base catalyst such as lithium acetate, *N*-lithio-2-pyrrolidone, potassium salt of phthalimide or lithium methoxide in DMF at room temperature to afford the corresponding β-lactams in good to high yields with moderate *trans*-selectivities.

β-Lactams are important compounds for their biological activities and various synthetic methods were accordingly developed.[1] Of those developed, a method which is carried out by Mannich-type reaction of aldimines with silyl enolates and cyclization of thus formed β-amino ester is quite useful and affords the corresponding β-lactams by the use of various aldimines and silyl enolates combinations successfully.[2]

In the course of our investigation on the activation of trimethylsilyl (TMS) enolates by Lewis base catalyst,[3,4] nitrogen- or oxygen-containing organic anions generated from amides or carboxylic acids were found to work effective Lewis base catalysts to accelerate the Mannich-type reaction of *N*-tosylaldimines with TMS enolates.[5]

Development of a one-pot synthesis of β-lactams was considered in order to show further applicability of this method. In this communication, we would like to describe a one-pot synthesis of various β-lactams by tandem Lewis base-catalyzed Mannich-type addition and cyclization.

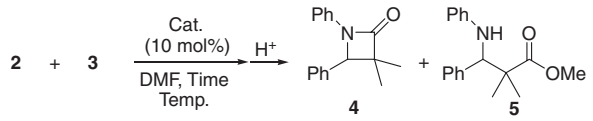


Scheme 1.

The above-mentioned Lewis base-catalyzed Mannich-type reaction was considered to proceed by the following mechanism (Scheme 1): in the presence of a Lewis base, *N*-lithiated Mannich-adduct **A** and silylated Lewis base **B** were formed by nucleophilic addition of TMS enolate to aldimine; thus formed silylated Lewis base **B** worked as a silylating reagent and the corresponding β-amino ester **C** was next formed by a silyl group transfer from **B** to *N*-lithiated Mannich-adduct **A**. An another pathway of forming β-lactam by an intramolecular nucleophilic substitution of **A** was also considered.

In the previously reported Lewis base-catalyzed Mannich-type reaction, no evidence of forming β-lactams was detected when *N*-tosylaldimines were used as Mannich-acceptors. Now, it was interestingly found that the corresponding β-lactam was obtained in 83% yield together with β-amino ester (15% yield) when Mannich-type reaction between benzilideneaniline **2** and TMS enolate **3** was carried out in the presence of 10 mol % of lithium acetate (AcOLi) at −45 °C.

Table 1.



Entry	Cat.	Temp./°C	Time/h	Yield[a]/%	
				4	**5**
1	AcOLi	rt	1.5	95	n.d.[b]
2	AcOLi	−20	6	92	8
3	AcOLi	−45	6	83	15
4	AcOK	rt	3	36	47
5	AcON*n*-Bu$_4$	rt	3	51	44
6	2-pyrrolidone Li[c]	rt	1.5	98	n.d.
7	2-pyrrolidone Li[c]	−45	24	n.d.	trace
8	Phthalimide K[d]	rt	6	98	n.d.
9	Phthalimide K[d]	−45	24	32	49
10	MeOLi	rt	3	quant.	n.d.
11	MeOLi	−45	24	38	22
12	none	rt	6	n.d.	n.d.

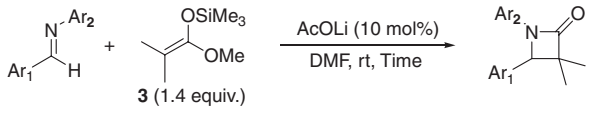
[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]n.d.; not detected. [c]*N*-lithio-2-pyrrolidone. [d]Potassium salt of phthalimide.

Then, reaction conditions were screened in detail in order to develop this method (Table 1). It was found then that the ratio of formation of β-lactam **4** to β-amino ester **5** was influenced by the reaction temperature and the desired β-lactam was afforded selectively at room temperature in the presence of a catalytic amount of AcOLi. Various Lewis bases such as lithium pyrroridone, potassium phthalimide, and lithium methoxide also turned out to be effective when reactions were carried out at room temperature while the ration of **4** was moderate in the case of using potassium acetate or ammonium acetate.

Further, tandem lithium acetate-catalyzed Mannich-type ad-

dition and cyclization was tried by using various aldimines and ketene silyl acetal **3** in DMF (Table 2). Aromatic aldimines smoothly reacted with **3** to afford the corresponding β-lactams in high yields, and in good to high yields in the cases when the aldimines having a basic function within the same molecule were used (Entries 4 and 5).

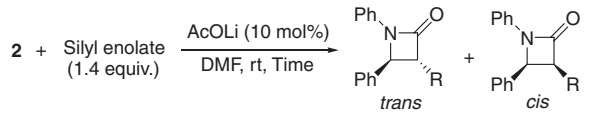
Table 2.

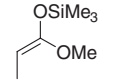
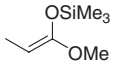
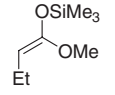
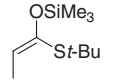
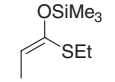
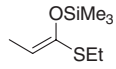


Entry	Ar_1	Ar_2	Time/h	Yield[a]/%
1	p-BrC_6H_4	Ph	6	96
2	p-$O_2NC_6H_4$	Ph	6	73
3	p-$MeOC_6H_4$	Ph	6	80[b]
4	p-$Me_2NC_6H_4$	Ph	24	78
5	3-Pyridil	Ph	4	94[c]
6	Ph	p-ClC_6H_4	6	96
7	Ph	p-$MeOC_6H_4$	6	84

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]3% of β-amino ester was obtained. [c]6% of β-amino ester was obtained.

Table 3.



Entry	Silyl enolate		Time/h	Yield[a]/%	(*trans*/*cis*)
1		**9**	6	62	(78/22)[b,c]
2		**10**	24	85	(66/34)
3		**11**	24	quant.	(75/25)[b]
4		**12**	6	84	(89/11)
5		**13**	6	89	(90/10)[b]
6		**14**	24	93	(92/8)[b]

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]3 equivalents of silyl enolate were used. [c]22% of β-amino ester was obtained as co-product (*anti*/*syn* = 64/36).

Next, tandem lithium acetate-catalyzed Mannich-type addition and cyclization were tried by using various TMS enolates (Table 3). When enolate **9** or **10** was employed, the corresponding β-lactams were obtained with moderate *trans*-selectivity. In the cases of using TMS enolates generated from thioesters such as **12**, **13**, or **14**, however, the corresponding β-lactams were obtained in high yields and good selectivities whose stereochemistry were improved from the case of using enolates of the corresponding carboxylic esters.

It was considered that the Mannich-type reaction proceeded via the acyclic transition states for the corresponding β-lactams were obtained with moderate *trans*-selectivity irrespective of the geometry of the silyl enolates employed (Entries 1, 2, 5, and 6).

Thus, it was found that tandem Lewis base-catalyzed Mannich-type addition and cyclization between TMS enolates and benzilideneanilines proceed smoothly under weakly basic conditions. This method is quite practical and is applicable to the syntheses of various β-lactams in one-pot process. Further development of this reaction is now in progress.

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