Double Nucleophilic Addition of Ketene Silyl (Thio)acetals and Trimethylsilyl Cyanide to α,β-Unsaturated Aldimines Promoted by Aluminum Chloride

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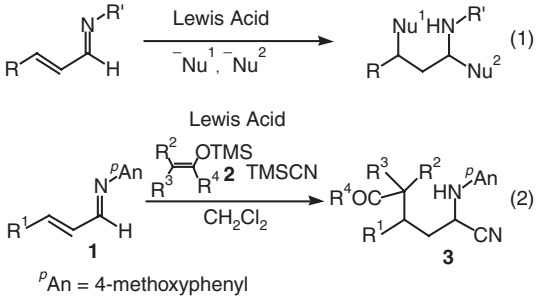
In the presence of $AlCl_3$, a mixture of ketene silyl (thio)acetal and trimethylsilyl cyanide underwent 1,4- and subsequent 1,2-addition, respectively, with α,β-unsaturated imines to give ethyl(*S*-alkyl) 5-amino-6-cyanopentanoates in good yields.

The Strecker reaction is one of the most efficient methods for the synthesis of α-amino nitriles, which are readily converted into α-amino acids.[1] Ojima and co-workers first reported the Lewis acid-catalyzed Strecker reaction of imines with trimethylsilyl cyanide (TMSCN).[2] A variety of asymmetric Strecker reactions have been reported to date.[3] Three component reactions of aldehydes, amines, and TMSCN were also reported to give α-amino nitriles.[4] These reactions do not always need to isolate relatively unstable imines. On the other hand, we have reported double nucleophilic addition reactions of ketene silyl acetals, allylstannanes, and thiols to α,β-unsaturated imines (Eq 1).[5] These reactions proceed via intermediary imino species which are relatively difficult to be isolated and purified.[6] In this paper, we describe the double nucleophilic addition of ketene silyl (thio)acetals **2** and trimethylsilyl cyanide to α,β-unsaturated aldimines **1** (Eq 2).



Scheme 1.

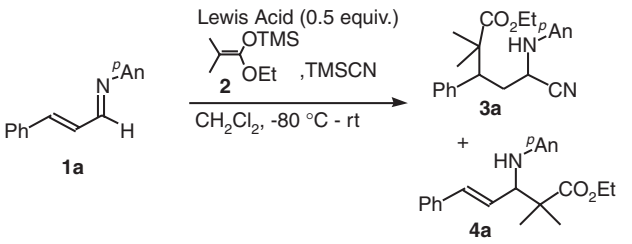
First, the effect of Lewis acids for the double nucleophilic addition to imine **1a** was investigated using ketene silyl acetal **2** ($R^2 = R^3 = Me$, $R^4 = OEt$) and TMSCN, and the results are summarized in Table 1.[7]

Among the Lewis acids tested, most of Lewis acids except for $SnCl_4$ and Et_2AlCl were effective, and especially, $AlCl_3$ and TMSI were found to be efficient promoters (entries 5 and 8). The amount of TMSCN was also examined using $AlCl_3$ as a Lewis acid (entries 8–11). The use of more than 1.5 equivalents of TMSCN gave acceptable yields (entries 10, 11). Under the optimum conditions the use of several imines **1** was investigated, and the results are summarized in Table 2.

Although there is still much room for the improvement of diastereoselectivities, the use of imines having not only an aromatic group but also an aliphatic group worked well (entries 1-3). Imine **1** (R^1 = Ph, $R^2 = CHPh_2$) also gave the desired 1,4-1,2-addtion product **3** (R^1 = Ph, $R^2 = CHPh_2$) in good yield (entry 4). We next examined use of other ketene silyl acetals (Table 3).

In the case of the ketene silyl acetal **5** ($R^1 = R^2 = H$, R^3 = OEt), only 1,2-addtion adduct **4** of the ketene silyl acetal was obtained in 65% yield (entry 1). Use of ketene silyl thioacetals, which were good nucleophiles in the double nucleophilic addition to α,β-unsaturated aldimines, was next examined.[5b] When the ketene silyl thioacetal **5** ($R^1 = R^2 = H$, R^3 = SEt) was used, the reaction proceeded to give the 1,4-1,2-adduct **3** ($R^1 = R^2 =$

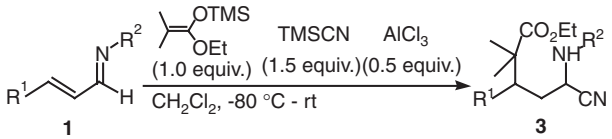
Table 1. Comparison of reaction conditions[a]



Entry	L. A.	**2**/equiv.	TMSCN/equiv.	**3a**/%[b]	(*syn*:*anti*)[c]	**4a**/%[b]
1	$SnCl_4$	1.0	1.0	35	(47:53)	—
2	$TiCl_4$	1.0	1.0	56	(48:52)	5
3	$TiCl_4$	1.0	2.0	65	(46:54)	11
4	$TiCl_4$	1.5	1.5	57	(47:53)	7
5	TMSI	1.0	1.0	74	(56:44)	2
6	$EtAlCl_2$	1.0	1.0	62	(45:55)	7
7	Et_2AlCl	1.0	1.0	47	(35:65)	20
8	$AlCl_3$	1.0	1.0	73	(45:55)	7
9	$AlCl_3$	1.0	1.2	77	(44:56)	4
10	$AlCl_3$	1.0	1.5	84	(47:53)	4
11	$AlCl_3$	1.0	2.0	85	(49:51)	2
12	$AlBr_3$	1.0	1.0	67	(50:50)	5
13	AlI_3	1.0	1.0	61	(48:52)	7

[a]Reaction was carried out according to the typical procedure.[7] [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR. Determination of the relative stereochemistry, see ref. 7.

Table 2. Use of a variety of imines[a]



Entry	R^1	R^2	Yield/%[b]	(*syn*:*anti*)[c]
1	Ph	^{p}An	84	47:53
2	Me	^{p}An	81	49:51
3	^{n}Pr	^{p}An	55	52:48
4	Ph	$CHPh_2$	78	49:51

[a]Reaction was carried out according to the typical procedure.[7] [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR.

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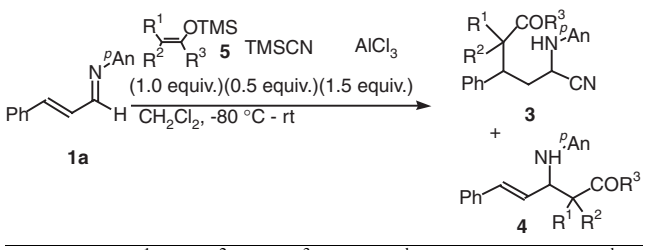
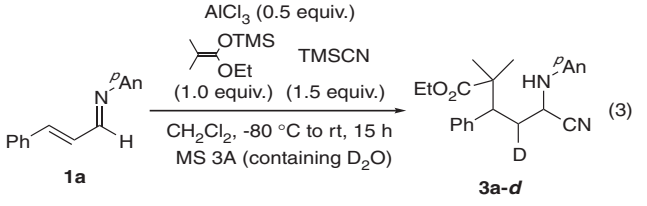
Table 3. Use of a ketene silyl acetal and ketene silyl thioacetals



Entry	R^1	R^2	R^3	**3**/%[b]	Ratio[c]	**4**/%[b]
1	H	H	OEt	0	(-:-)	65
2	H	H	SEt	35	(41:59)	0
3	H	H	SBu^t	53	(51:49)	0
4	H	Me	SEt	21	ND[d]	0
5	Me	Me	SEt	4	(52:48)	0

[a]Reaction was carried out according to the typical procedure.[7] [b]Isolated yield. [c]Isomer ratio determined by ^{1}H NMR. [d]Not determined.

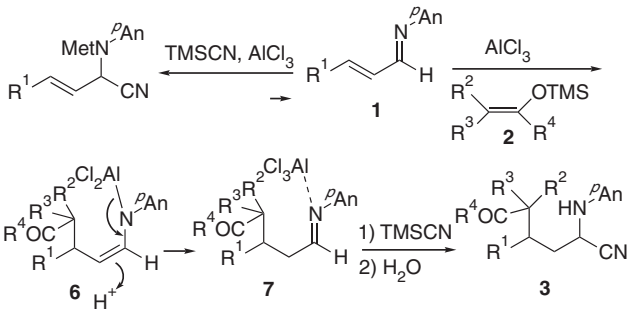
H, R^3 = SEt) in 35% yield (entry 2). A better result was obtained with the ketene silyl thioacetal **5** ($R^1 = R^2$ = H, R^3 = SBu^t), and the reaction gave the desired 1,4-1,2-addtion adduct **3** ($R^1 = R^2$ = H, R^3 = SBu^t) in 53% yield (entry 3). However, tri- or tetra-substituted ketene silyl thioacetal was not a good nucleophile for the present addition reaction (entries 4 and 5). To clarify the reaction mechanism, the reaction of **1a** with **2** ($R^2 = R^3$ = Me, R^4 = OEt) was carried out in the presence of molecular sieves pretreated with D_2O (treated with D_2O and dried) to give the deuterated product **3a–d** in 73% yield with 56% deuterium incorporation (Eq 3). The same reaction conducted in the absence of molecular sieves followed by quenching with CD_3COOD gave the adduct **3a** in 53% yield with only trace of deuterium incorporation. Close examination of the reaction of **1a** with **2** ($R^2 = R^3$ = Me, R^4 = OEt) and TMSCN in the presence of $AlCl_3$ as monitored by TLC revealed that the initial 1,2-addition of TMSCN occurred at -20 °C. A new spot which was assigned to be 1,4-1,2-adduct **3a** gradually appeared at -10 to 0 °C.



73% yield, 56% D-incorporation

From these results, we propose a plausible reaction mechanism as shown in Scheme 2. The initial 1,2-addition of TMSCN occurs, which, however, is a reversible process to regenerate the parent imine **1**. Metalloenamine **6** would be generated via an $AlCl_3$-promoted 1,4-addition reaction of ketene silyl (thio)acetal **2** and reacts with a certain proton source to give imine **7**, which in turn is attacked by TMSCN to afford 1,4-1,2-adduct **3**.

In conclusion, we have found an efficient method for α-amino nitrile synthesis by double nucleophilic addition of ketene silyl acetals and trimethylsilyl cyanide to α,β-unsaturated aldimines. The present reaction has an advantage that α-amino nitriles derived from relatively unstable imines can be obtained due to *in situ* generation of imino species as an intermediate.



Scheme 2.

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6 It has been reported that several 1,4-addition products derived from α,β-unsaturated imines are readily hydrolyzed to the parent carbonyl compounds. See, M. D. Stadnichuk, A. V. Khramchikhin, Y. L. Piterskaya, and I. V. Suvorova, *Russ. J. Gen. Chem.*, **69**, 593 (1999).

7 A typical experimental procedure for the addition reaction: To a suspension of $AlCl_3$ (0.100 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of imine **1a** in CH_2Cl_2 (1.5 mL) at -80 °C and the mixture was stirred at -80 °C for 5 min. A solution of the ketene silyl acetal **2** ($R^2 = R^3$ = Me, R^4 = OEt) (0.200 mmol) in CH_2Cl_2 (1.0 mL) and that of TMSCN (0.300 mmol) in CH_2Cl_2 (1.0 mL) were successively added to the resulting mixture. The mixture was gradually warmed to room temperature during 15 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (15 mL × 3). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give the crude product. Purification on silica gel TLC (hexane : ethyl acetate = 6:1 as an eluent) gave 1,4-1,2-adduct **3a** (64.2 mg, 84%) as a mixture of *syn*- and *anti*-isomers. Further separation of these isomers on activated silica gel TLC (dried in a microwave oven) gave analytically pure samples. ^{1}H NMR (270 MHz, $CDCl_3$) *syn*-isomer: δ = 1.05 (s, 3H), 1.20 (s, 3H), 1.26 (t, J = 7.3 Hz, 3H), 2.13 (dd, J = 13.5 and 13.9 Hz, 1H), 2.46 (dd, J = 13.4 and 13.9 Hz, 1H), 3.32-3.49 (m, 2H), 3.72 (s, 3H), 3.74 (brs, 1H), 4.15 (q, J = 7.3 Hz, 2H), 6.45 (d, J = 8.9 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 7.17-7.34 (m, 5H); *anti*-isomer: δ = 1.10 (s, 3H), 1.18 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H), 2.09 (dd, J = 13.1 and 13.2 Hz, 1H), 2.48 (dd, J = 12.5 and 13.1 Hz, 1H), 3.35-3.51 (m, 2H), 3.68 (brs, 1H), 3.72 (s, 3H), 4.15 (q, J = 7.3 Hz, 2H), 6.48 (d, J = 8.9 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 7.22-7.36 (m, 5H). Each isomer was converted into the corresponding δ-lactam on treatment with trimethylaluminum. Examination of the ^{1}H NMR (NOESY) spectra indicated the relative stereochemistry.

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