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Three-Component or Four-Component Coupling Reactions Leading to δ-Lactams. Facile Synthesis of γ-Acyl-δ-Lactams from Silyl Enolates, α,β-Unsaturated Thioesters, and Imines or Amines and Aldehydes via Tandem Michael-Imino Aldol Reactions

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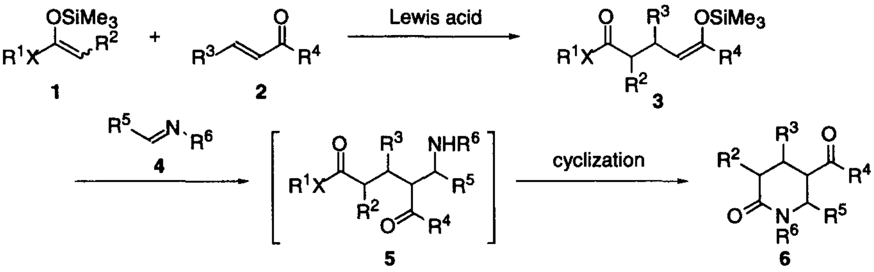
Abstract: *Various γ-acyl-δ-lactam derivatives were prepared on the basis of three-component (silyl enolates, α,β-unsaturated thioesters, and imines) or four-component (silyl enolates, α,β-unsaturated thioesters, amines, and aldehydes) coupling reactions via Lewis acid-catalyzed tandem Michael-imino aldol reactions.* © 1997 Elsevier Science Ltd.

δ-Lactam derivatives are often observed in various natural products, such as strychnine,[1] surugatoxin,[2] matrine,[3] etc., and many of them are of great current interest because of their unique biological activities. Herein we describe a novel route for the synthesis of γ-acyl-δ-lactams via Lewis acid-catalyzed tandem Michael-imino aldol reactions. The route is based on three-component (silyl enolates, α,β-unsaturated thioesters, and imines) or four-component (silyl enolates, α,β-unsaturated thioesters, amines, and aldehydes) coupling reactions under Lewis acidic conditions.

A general scheme for the synthesis of γ-acyl-δ-lactams is shown in Scheme 1. In the presence of a Lewis acid catalyst, silyl enolates derived from ester equivalents (**1**) react with α,β-unsaturated carbonyl compounds (**2**) to afford the corresponding Michael adducts as silyl enolates (**3**).[4] Sequential imino aldol reactions of **3** with imines (**4**) would proceed to give the desired γ-acyl-δ-amino ester derivatives (**5**). If the esters could cyclize in the same reaction pot, the corresponding γ-acyl-δ-lactams (**6**) would be obtained.



Scheme 1. A Synthetic Route to δ-Lactams

On the basis of this scheme, several substrates and reaction conditions were examined. It was concluded that the combination of silyl enolates derived from thioesters, α,β-unsaturated thioesters, and imines was suitable for our purpose. It was already reported that α,β-unsaturated thioesters reacted with silyl enolates to afford the corresponding Michael adducts in high yields with high diastereoselectivities, by using a combined catalyst system, antimony(V) chloride ($SbCl_5$) and tin(II) triflate ($Sn(OTf)_2$).[5] We chose 1-ethylthio-1-trimethylsiloxyethene (**1a**), *S*-ethyl 2-butenethioate (**2a**), and *N*-benzylideneaniline (**4a**) as a model, and several reaction conditions for the three-component reaction were examined. It was found that the first Michael reaction of **1a** with **2a** proceeded smoothly in the presence of 5 mol% each of $SbCl_5$ and $Sn(OTf)_2$ in dichloromethane at -78 °C to afford **3a**, but that the successive reaction of **3a** with **4a** proceeded in only a 43%

yield. In order to improve the lower yield, we examined several reaction conditions and finally found that the desired imino aldol adduct was obtained in a high yield when a second catalyst was added at the stage of the imino aldol reaction. The effect of the Lewis acid catalysts is shown in Table 1. It should be noted that Sc(OTf)$_3$, which was found by us as a new class of an excellent Lewis acid in several aqueous reactions and also in the activation of nitrogen-containing compounds,[6] gave excellent results. The product was isolated as a mixture of an amino ester form (**A**) and a δ-lactam form (**B1**), and each of these was confirmed to be a single stereoisomer by ^{1}H and ^{13}C NMR analyses. It was desirable from an experimental point of view that **A** and **B1** were easily separated by column chromatography on silica gel. Amino ester **A** was treated with mercuric trifluoroacetate (Hg(OCOCF$_3$)$_2$)[7] to give the corresponding δ-lactam (**B2**) quantitatively. The relative stereochemical assignment of **B1** and **B2** was made by ^{1}H NMR analyses. All substituents of lactam **B1** were determined to occupy equatorial positions, which was consistent with the experimental result that lactam **B1** was easily cyclized.

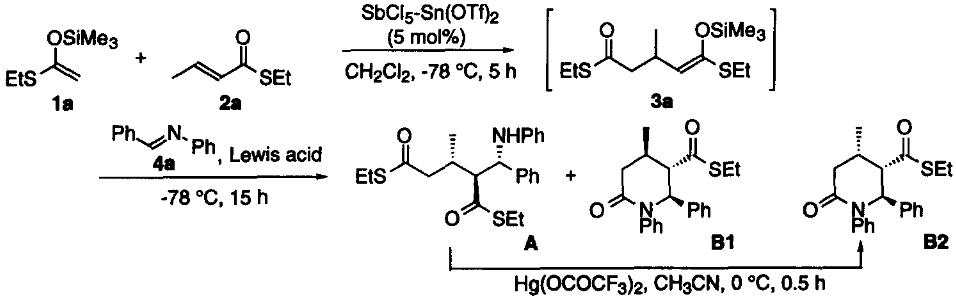


Table 1. Effect of Lewis Acids

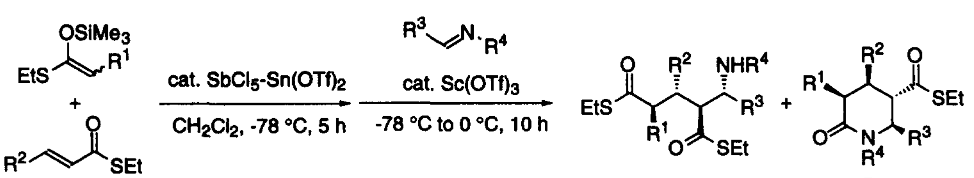
Lewis Acid (mol%)	Yield/%	A/B1
none	43	84/16
TiCl$_4$ (8)	42	86/14
Me$_3$SiOTf (8)	44	82/18
TrSbCl$_6$ (8)	51	80/20
Sc(OTf)$_3$ (8)	62	81/19
Sc(OTf)$_3$ (2.5)	94	81/19[a]

a) Imine (0.5 eq), -78 °C to 0 °C in the imino aldol reaction.

Several examples of the synthesis of γ-acyl-δ-lactams are shown in Table 2, and in all cases, the desired γ-acyl-δ-lactams were obtained (after treatment of Hg(OCOCF$_3$)$_2$ in some cases) in high yields. It is noteworthy that high diastereoselectivities were observed in these reactions. For example, in the reaction of (*Z*)-1-*S*-ethyl-1-trimethylsiloxy-1-propene (**1b**), α,β-unsaturated thioester **2a**, and imine **4a**, two of eight possible stereoisomers were produced in a good yield, and the ratio of the two was 83/17 (Table 2, entry 9).

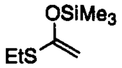
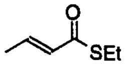
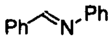
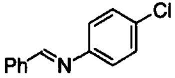
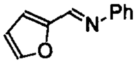
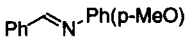
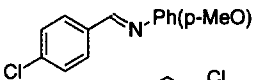
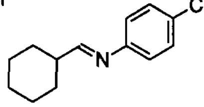
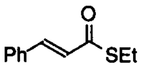
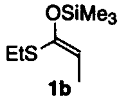
Furthermore, it was found that the present method could be extended to four-component reactions of silyl enolates, α,β-unsaturated thioesters, amines, and aldehydes. According to the scheme shown in Table 3, the desired four-component reactions proceeded smoothly to afford the corresponding adducts in high yields.

A typical experimental procedure is described for the reaction of silyl enolate **1**, α,β-unsaturated thioester **2**, and imine **4**. Antimony(V) chloride (0.025 mmol) and tin(II) triflate (0.025 mmol) were stirred in dichloromethane (1 ml) at room temperature for 30 min, and the mixture was then cooled to -78 °C. A mixture of **1** (0.5 mmol) and **2** (0.5 mmol) in dichloromethane (1 ml) was added and the reaction mixture was allowed to stand for 5 h at the same temperature. Imine **4** (0.25 mmol) in dichloromethane (1 ml) and Sc(OTf)$_3$ (0.013 mmol) were then added and the mixture was further stirred at -78 °C to 0 °C over 10 h. Saturated aqueous



A **B**

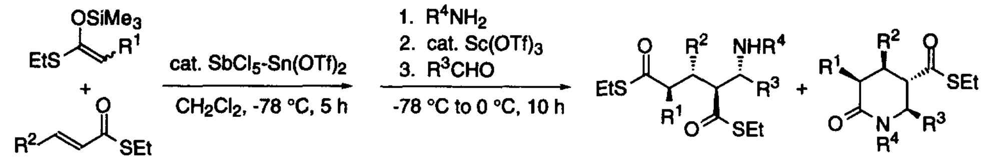
Table 2. Three-Component Reactions of Silyl Enolates, α,β-Unsaturated Thioesters, and Imines

Entry	Silyl Enolate	α,β-Unsaturated Thioester	Imine	Yield/% (A/B)
1	 **1a**	 **2a**	 **4a**	94 (81/19)
2	**1a**	**2a**	 **4b**	90 (71/29)
3	**1a**	**2a**		88 (79/21)
4	**1a**	**2a**		97 (76/24)
5	**1a**	**2a**		88 (76/24)
6	**1a**	**2a**		82 (80/20)
7	**1a**	 **2b**	**4a**	quant. (75/25)
8	**1a**	**2b**	**4b**	98 (74/26)
9	 **1b**	**2a**	**4a**	75 (83/17)[a]
10	**1b**	**2a**	**4b**	65 (77/23)[a]

[a] The major isomer was the δ-lactam and the minor was obtained as the amino ester.

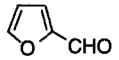
sodium hydrogen carbonate was added to quench the reaction, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford the amino ester and the δ-lactam. The amino ester was quantitatively converted to the corresponding δ-lactam by treating with mercuric trifluoroacetate ($Hg(OCOCF_3)_2$) (2 eq.) in acetonitrile at 0 °C for 30 min. In the four component reaction, Drierite (100 mg) was added in the first Michael reaction, and an amine (0.30 mmol), $Sc(OTf)_3$ (0.013 mmol), and an aldehyde (0.25 mmol) were successively added.

In summary, Lewis acid-catalyzed three-component (silyl enolates, α,β-unsaturated thioesters, and imines) or four-component (silyl enolates, α,β-unsaturated thioesters, amines, and aldehydes) coupling reactions were successfully carried out to afford the corresponding amino ester and γ-acyl-δ-lactam derivatives stereoselectively in high yields. The former was easily converted to the corresponding δ-lactam. Since it is



A **B**

Table 3. Four-Component Reactions of Silyl Enolates, α,β-Unsaturated Thioesters, Amines, and Aldehydes

Entry	Silyl Enolate	α,β-Unsaturated Thioester	Amine	Aldehyde	Yield/% (A/B)
1	**1a**	**2a**	$PhNH_2$	PhCHO	90 (82/18)
2	**1a**	**2a**	$(p\text{-}Cl)PhNH_2$	PhCHO	90 (80/20)
3	**1a**	**2a**	$PhNH_2$		91 (86/14)
4	**1a**	**2b**	$PhNH_2$	PhCHO	81 (80/20)
5	**1a**	**2b**	$(p\text{-}Cl)PhNH_2$	PhCHO	92 (87/13)

now well-recognized that multi-component reactions are useful for the synthesis of libraries,[8] the present three- and four-component reactions would provide a powerful method for the preparation of large numbers of δ-lactam derivatives.

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