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Stereoselective One-Pot Synthesis of β-Lactams by Reaction of 2-Pyridylthioesters with Imines in the Presence of $AlBr_3$ or $EtAlCl_2$

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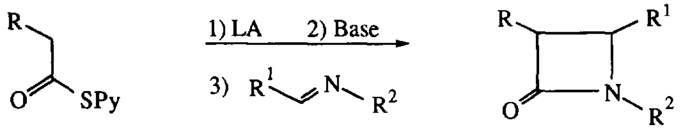
Abstract: The reactions of some 2-pyridylthioesters with imines in the presence of $AlBr_3$ or $EtAlCl_2$ and of a tertiary amine afford β-lactams in a simple one-pot procedure with fair to high *trans* stereoselectivity. The condensation can be also carried out in the absence of base and with sub-stoicheiometric amounts of the Lewis acid. The possible mechanisms of the process are discussed.

In the last few years we have described a convenient one-pot synthesis of β-lactams by the condensation of the titanium,[1] tin,[2] and boron[3] enolates of 2-pyridylthioesters with imines (Eq. 1).[4] The enolates are generated in CH_2Cl_2 by addition of a weak base (generally a tertiary amine) to the thioesters activated by a Lewis acid (LA).



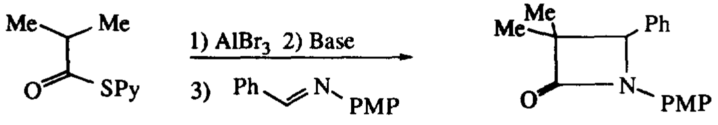
(Eq. 1)

LA = $TiCl_4$, $SnCl_4$, BCl_3

Here we report that $AlBr_3$ and $EtAlCl_2$ can be used to promote this simple β-lactam synthesis,[5] and that, differently from the previous cases,[1-3] the reaction can occur also *without* the base and with sub-stoicheiometric amounts of the LA activator.

The condensations carried out in the presence of $AlBr_3$ were investigated first. Experimental conditions and reagent molar ratios were established studying the reaction of 2-pyridylthio *iso*-butyrate **1** with benzalanisidine **2** to give β-lactam **3** (Table 1, entries 1-11). The use of equimolar amounts of thioester, LA, and imine secured the best results (entries 1-4). The variation of the reaction temperature from -78°C up to room temperature had a small effect (entries 4-6). When CH_2Cl_2 was the solvent better results were obtained than in 1,2-dichloroethane, THF, or toluene (entry 5 *vs* 7-9). Finally, the yields slightly increased when Et_3N was replaced by Et_2NPr-i or pyridine (entries 10 and 11 *vs* 5).

Table 1. Synthesis of β-Lactam **3** from Thioester **1** and Imine **2** in the presence of $AlBr_3$ or $EtAlCl_2$.[a]



1 **2** **3**

Entry	LA (mol. equiv.)	Base[b]	Solvent	Mol. Equiv. of **2**	T°C	Yield %[c]
1	$AlBr_3$ (1.0)	Et_3N	CH_2Cl_2	0.5	-78	85
2	$AlBr_3$ (2.0)	Et_3N	CH_2Cl_2	0.5	-78	68
3	$AlBr_3$ (3.0)	Et_3N	CH_2Cl_2	0.5	-78	36
4	$AlBr_3$ (1.0)	Et_3N	CH_2Cl_2	1.0	-78	77
5	$AlBr_3$ (1.0)	Et_3N	CH_2Cl_2	1.0	0	75
6	$AlBr_3$ (1.0)	Et_3N	CH_2Cl_2	1.0	23	68
7	$AlBr_3$ (1.0)	Et_3N	$(CH_2Cl)_2$	1.0	0	60
8	$AlBr_3$ (1.0)	Et_3N	THF	1.0	0	60
9	$AlBr_3$ (1.0)	Et_3N	Toluene	1.0	0	58
10	$AlBr_3$ (1.0)	Et_2NPr-i	CH_2Cl_2	1.0	0	80
11	$AlBr_3$ (1.0)	C_5H_5N	CH_2Cl_2	1.0	0	77
12	$EtAlCl_2$ (1.0)	Et_3N	CH_2Cl_2	0.5	-78	28
13	$EtAlCl_2$ (2.0)	Et_3N	CH_2Cl_2	0.5	-78	95
14	$EtAlCl_2$ (3.0)	Et_3N	CH_2Cl_2	0.5	-78	60
15	$EtAlCl_2$ (2.0)	Et_3N	CH_2Cl_2	1.0	-78	75
16	$EtAlCl_2$ (2.0)	Et_3N	CH_2Cl_2	1.0	0	70
17	$EtAlCl_2$ (2.0)	Et_3N	CH_2Cl_2	1.0	23	65
18	$EtAlCl_2$ (2.0)	Et_2NPr-i	CH_2Cl_2	1.0	0	73
19	$EtAlCl_2$ (2.0)	C_5H_5N	CH_2Cl_2	1.0	0	68
20	$EtAlCl_2$ (2.0)	Et_3N	$(CH_2Cl)_2$	1.0	0	72
21	$EtAlCl_2$ (2.0)	Et_3N	$CHCl_3$	1.0	0	52
22	$EtAlCl_2$ (2.0)	Et_3N	THF	1.0	0	50
23	$EtAlCl_2$ (2.0)	Et_3N	Toluene	1.0	0	63

[a] PMP = 4-MeOPh. [b] 1 mol. equiv. of base was used. [c] Isolated yields after flash chromatography.

The possibility of exploiting other aluminum LA[6] was then investigated. $EtAlCl_2$ was found to be a suitable promoter for this reaction (Table 1, entries 12-23), but 2 mol. equiv. of LA were required. Otherwise, $EtAlCl_2$ behaved very similarly to $AlBr_3$, the influence exerted on the yields by a variation of the temperature (entries 15-17), of the base (entries 18 and 19), and of the solvent (entries 20-23) being similar for the two promoters.

When the reaction was extended to the thioesters **4-8** and the imines **9-12** to give β-lactams **13t,c-19t,c** as mixtures of *trans* (t) and *cis* (c) diastereoisomers, the two LA gave more different results. Isolated yields and t : c ratios[7] are reported in Table 2. As it is generally observed in the reactions of most metal enolates,[1-3] the *trans* stereoselectivity of the $AlBr_3$ promoted reactions increases with increasing size of the thioester residue R, as can be seen by comparison of the condensations of compounds **4-6** with imine **2**. This effect was not observed when $EtAlCl_2$ was employed, the t : c ratio of β-lactams **13t,c-15t,c** being virtually constant. Remarkably, the use of the relatively weak LA $EtAlCl_2$ allowed the extension of the reaction also to the glycolic acid derived thioesters **7** and **8**, that did not react with imine **2** and $AlBr_3$

In order to minimize the possibility of imine decomposition in the presence of a strong LA such as $AlBr_3$, the reactions of thioester **6** with imines **9-12**, that are less stable then **2**, were carried out at -78°C. The corresponding β-lactams **16t,c-19t,c** were obtained in low to moderate yields. This result does not seem to depend on the decrease in reaction temperature, since **6** reacts with **2** at 0°C or at -78°C with similar yields. As expected, also in the case of β-lactams **16-19** the *trans* products are always obtained in fair to excellent excess over their *cis* counterparts. Extension of the use of $EtAlCl_2$ to the reactions of thioester **6** with other imines was less successful.

Before attempting a mechanistic rationalization of this β-lactam synthesis, some NMR experiments were carried out with the aim of elucidating the mode of activation of the thioester by the LA and the enolization process.

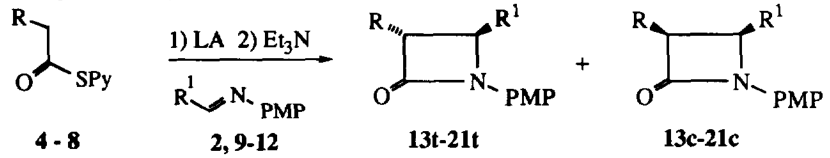
Upon addition of $AlBr_3$ to a CD_2Cl_2 solution of thioester **4** cooled at 0°C, the formation of two species in a roughly 2 : 1 ratio was observed by 300MHz ^1H NMR. On the basis of the shift of the signals, the structure **22** and **23** were assigned to the major and the minor adduct, respectively (Figure 1).[8] When Et_3N was added, a broad peak appeared at 9.30 ppm, and the methylene signal of the base was split. This observation was explained by formation of Et_3NH^+, likely by proton abstraction from the CH_2 group of adducts **22/23**.[9] However, no signals attributable to an enolate such as **24** could be observed,[10] the peaks of the thioester moiety being and remaining very broad in the temperature range from 0°C down to -70°C. In addition to these changes, considerable amounts (ca. 40%) of the starting thioester **4** were detected, likely resulting from displacement of the LA from adducts **22/23** by Et_3N.

Since this displacement should deactivate the thioester toward the enolization and eventually exert a negative effect on the yield of the β-lactam formation, a few condensations of thioester **4** with imine **2** were attempted with reduced amounts of Et_3N. To our surprise, β-lactam **13t,c** was formed even *in the absence* of the base.

The possibility of carrying out the reaction in these conditions with other thioesters was then studied. The results, collected in Table 3, show that the reaction with imine **2** takes place with slightly lower yields and similar stereoselectivities with respect to those carried out with Et_3N. Remarkably, even thioester **7** and **8** afforded the corresponding β-lactams **20** and **21**, albeit in low yields. Furthermore, it was found that also the amount of $AlBr_3$ can be reduced to 0.25 mol. equiv., the yields remaining acceptable. The base could be deleted and the amount of the LA reduced also in the reactions carried out with $EtAlCl_2$ as LA. Thus, β-lactam **3** was obtained from thioester **1** and imine **2** in 57, 35, and 32% yield in the absence of Et_3N and in the presence of 2.0, 1.0, and 0.5 mol. equiv. of this LA, respectively.

Different processes are likely to be involved in this β-lactam synthesis depending on whether the base is present or not in the reaction mixture. In the presence of Et_3N, it is likely that the reaction occurs *via* enolate formation. Since this species was not detected by the NMR experiment and no information about its structure was obtained, the proposal of a model to explain the formation of the products is highly speculative.

Table 2. Synthesis of β-Lactam **13t,c-21t,c** from Thioesters **4-8** and Imines **2, 9-12** in the Presence of AlBr$_3$ or EtAlCl$_2$.[a]



Thioester (R)	LA	Imine (R^1)	β-Lactam	Yield %[c]	t : c ratio[d]
4 (Me)	AlBr$_3$	**2** (Ph)[b]	**13t,c**	54	82 : 18
5 (Et)	AlBr$_3$	**2** (Ph)[b]	**14t,c**	63	93 : 7
6 (Pr-i)	AlBr$_3$	**2** (Ph)[b]	**15t,c**	75	95 : 5
6 (Pr-i)	AlBr$_3$	**2** (Ph)	**15t,c**	81	95 : 5
6 (Pr-i)	AlBr$_3$	**9** (2-Thienyl)	**16t,c**	26	98 : 2
6 (Pr-i)	AlBr$_3$	**10** (2-Furyl)	**17t,c**	19	80 : 20
6 (Pr-i)	AlBr$_3$	**11** (PhCH=CH)	**18t,c**	42	80 : 20
6 (Pr-i)	AlBr$_3$	**12** (C_6H_{11}-c)	**19t,c**	48	98 : 2
4 (Me)	EtAlCl$_2$	**2** (Ph)	**13t,c**	60	91 : 9
5 (Et)	EtAlCl$_2$	**2** (Ph)	**14t,c**	60	90 : 10
6 (Pr-i)	EtAlCl$_2$	**2** (Ph)	**15t,c**	60	92 : 8
7 (MeCOO)	EtAlCl$_2$	**2** (Ph)	**20t,c**	68	71 : 29
8 (PhCH$_2$O)	EtAlCl$_2$	**2** (Ph)	**21t,c**	27	57 : 43
6 (Pr-i)	EtAlCl$_2$	**10** (2-Furyl)	**17t,c**	20	83 : 17
6 (Pr-i)	EtAlCl$_2$	**12** (C_6H_{11}-c)	**19t,c**	12	98 : 2

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[a] Reaction temperature -78°C unless otherwise stated; AlBr$_3$: 1.0 mol. equiv.; EtAlCl$_2$: 2.0 mol.equiv. [b] At 0°C.
[c] Isolated yields after flash chromatography. [d] As determined on the crude reaction products.

However, chair-like cyclic[11] model **25** (Fig. 1) can be used as a working hypothesis to rationalize the formation of *trans* and *cis* β-lactams from an (E)-imine[12] and an (E)- or a (Z)-enolate, respectively.

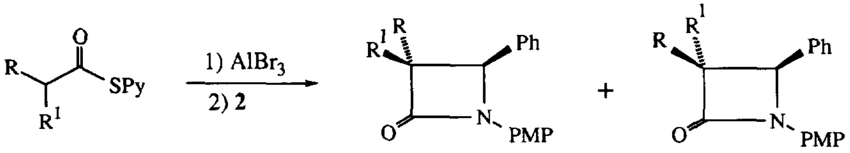
Two different mechanisms can be proposed to explain the condensations carried out in the absence of Et$_3$N (Fig. 1). Upon activation by the LA, the 2-pyridylthioester becomes so reactive that acylation of the imine nitrogen to give the N-acyliminium species **26**[13] is possible. The released 2-pyridylthiolate ion **27** can then act as a base[14] to generate the zwitterion **28**[13], that then undergoes β-lactam ring closure. Alternatively, the imine can play the role of the base[15] giving the enolate and the protonated imine **29**. Reaction of these two species can lead to the final products.[16] Again, ^{1}H NMR experiments were attempted to distinguish between these two mechanisms.

When imine **2** was added to a mixture of thioester **4** and AlBr$_3$ in CD$_2$Cl$_2$ solution at 0°C, the HC=N proton signal of the imine was shifted from 8.48 to 8.95 ppm, a change compatible with the formation of both **26** and **29**. No signal attributable to a C=NH$^+$ proton as in **29** was observed. In two control experiments monitored by

NMR, imine **2** was treated with equimolar amounts of propionyl chloride,[13,17] and of trifluoroacetic acid. The **2** + propionylchloride mixture featured two singlets at 9.00 and at 7.95 ppm[17] (in a *ca.* 1 : 2 ratio), the downfield peak being almost coincident with that of the **4**+$AlBr_3$+**2** mixture (8.95 ppm). On the other hand, the spectrum of the **2**+trifluoroacetic acid mixture featured signals at 16.0 and 8.70 ppm, that were attributed to the $CH=NH^+$ protons of adduct **29**.[18]

These experiments seem to indicate that the **4**+ $AlBr_3$ adduct is as activated as an acid chloride towards nucleophilic attack of the imine nitrogen, and that formation of adduct **26** is indeed possible.[19] The absence of any downfield signal in the spectrum of the thioester+$AlBr_3$+imine mixture seems to rule out the mechanism involving formation of **29**. Remarkably, the proposed mechanism can tolerate sub-stoicheiometric amounts of LA. The Lewis acidity of $AlBr_3$, that is stronger than both $TiCl_4$ and $SnCl_4$,[20] can account for the enhanced reactivity of the thioester+$AlBr_3$ adduct toward imines that was unprecedented with other LA.[10,21]

Table 3. Synthesis of β-Lactams **3**, **13t,c-15t,c**, **20t,c** and **21t,c** from Thioesters **1**, **4-8** and Imine **2**.[a]



1, 4 - 8

3, 13t-15t , 20t, 21t

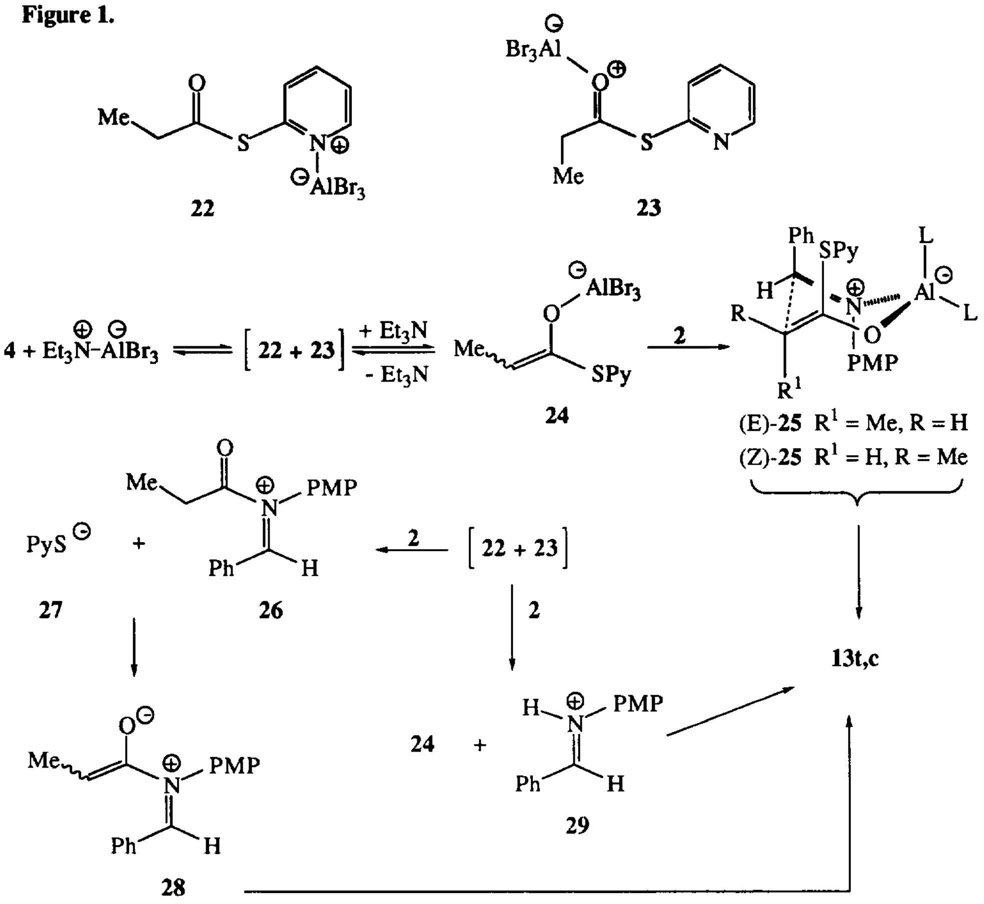
13c-15c , 20c, 21c

Thioester (R, R^1)	Mol. equiv. of $AlBr_3$	Product	Yield%[b]	t : c ratio[c]
1 (R=R^1=Me)	1.0	**3**	72	-
1 (R=R^1=Me	0.5	**3**	68	-
1 (R=R^1=Me)	0.25	**3**	60	-
1 (R=R^1=Me)	0.1	**3**	17	-
4 (R=Me; R^1=H)	1.0	**13t,c**	51	83 : 17
5 (R=Et; R^1=H)	1.0	**14t,c**	43	94 : 6
6 (R=Pr-i; R^1=H)	1.0	**15t,c**	51	97 : 3
6 (R=Pr-i; R^1=H)	0.5	**15t,c**	45	97 : 3
7 (R=MeCOO; R^1=H)	1.0	**20t,c**	30	75 : 25
8 (R=$PhCH_2O$; R^1=H)	1.0	**21t,c**	21	97 : 3

[a] All reactions carried out at 0°C. [b] Isolated yields after flash chromatography. [c] As determined on the crude reaction products.

In conclusion, $AlBr_3$ and $EtAlCl_2$ were shown to be efficient promoters for a simple one-pot synthesis of β-lactams from 2-pyridylthioesters and imines. The reaction can successfully be performed even in the absence of Et_3N and in the presence of sub-stoicheiometric amounts of LA.[22]

Figure 1.



Experimental.

^1H NMR spectra were obtained at 80 and 300 MHz. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent. CH_2Cl_2 and $(CH_2Cl)_2$ were distilled from CaH_2; THF from $LiAlH_4$; toluene from sodium; Et_3N, Et_2NPr-i, and pyridine from KOH. $AlBr_3$ was used as 1M solution in CH_2Br_2; $EtAlCl_2$ as a 1M solution in hexanes.

The imines were prepared by stirring a CH_2Cl_2 solution of freshly distilled aldehyde and 4-methoxyaniline at rt (2 - 12 h) in the presence of $MgSO_4$. Filtration and evaporation of the solvent at rt gave the crude products that were used as such, with the exception of the products derived from benzaldehyde, cinnamaldehyde, and 2-thienylcarbaldehyde that were crystallized before use.[12]

Thioesters **1** and **4-8** were known compounds,[1a,b] as were β-lactams **3**,[2] **13-15**,[1c] **14**,[23] **15**,[23] **16**,[1a] **17**,[24] **20**,[3b] and **21**.[3b]

General Procedure for the Synthesis of β-Lactams. A 1 M CH_2Br_2 solution of AlBr3 (1 mL, 1 mmol) was evaporated to dryness under high vacuum in a 10mL, 2-necked, round-bottom flask. CH_2Cl_2 (2 mL) was added to the flask cooled at -78°C, followed by a solution of thioester (1 mmol) in CH_2Cl_2 (3 mL). After 10 min stirring at -78°C, Et_3N (0.140 mL, 1 mmol) was added and the mixture was stirred for 30 min. A solution of the imine (1 mmol) in CH_2Cl_2 (2 mL) was then added at -78°C, and the reaction was stirred overnight while the temperature was allowed to rise up to room temperature. Work-up involved addition of a sat. aqueous solution of $NaHCO_3$ (10 mL), extraction of the aqueous phase with 3x10 mL portions of CH_2Cl_2, drying of the organic phase over sodium sulphate, filtration, and concentration under vacuum, to give the crude product. ^1H NMR analysis of the residue was then performed to evaluate the *trans/cis* ratio. The product was isolated by flash chromatography with hexanes : Et_2O mixtures as eluant. Yields and diastereoisomeric ratios are reported in the Tables. Evaporation of CH_2Br_2 was necessary to avoid formation of di-(2-pyridylthio)methane by reaction of 2-pyridylthiolate with CH_2Br_2. When $EtAlCl_2$ in hexanes was used instead of AlBr3, the hexanes solution was not evaporated.The reactions performed in the absence of Et_3N were carried out as described above omitting the addition of the base.

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References and Notes.

1. a) Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 8767. b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G. *J. Org. Chem.* **1992**, *57*, 4155. c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Lombardi Borgia, A. *Gazz. Chim. Ital.* **1993**, *123*, 181. d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746. e) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939. f) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 9471. g) Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025. This method of preparation of trichlorotitanium enolates was originally reported by Evans, *et al.* for ketones and 2-oxazolidinones, as described in: Evans, D.A.; Bilodeau, M.T.; Somers, T.C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750, and references therein.

2. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 5821.

3. a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron Lett.* **1995**, *36*, 613.
b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Molteni, V. *Tetrahedron* **1995**, *51*, 8941.

4. Reviews: (a) Hart, D.J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. b) Brown, M.J. *Heterocycles* **1989**, *29*, 2225. c) van der Steen, F.H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

5. To the best of our knowledge, there is a single report in the literature that describes a β-lactam synthesis via Al enolates. These were prepared by transmetalation of ester lithium enolates with Me_2AlCl at -70°C: Wada, M.; Aiura, H.; Akiba, K. *Tetrahedron Lett.* **1987**, *28*, 3377.

6. $AlCl_3$ was found to be poorly soluble in CH_2Cl_2; Et_2AlCl was too weak as LA to promote the reaction.

7. *Trans* : *cis* ratios were determined by 300 MHz ^1H NMR analysis of the crude reaction mixtures. The assignment resided on the value of the β-lactam HC-3/HC-4 coupling constant (J *trans* = 2.0-2.5 Hz; J *cis* = 5.0-6.0 Hz).

8. In addition to adducts **22** and **23**, minor amounts of other species were observed. The chemical shift of the protons of thioester **4**, of adduct **22** (boldface), and of adduct **23** (underlined) were as follows: CH_3: 1.22, **1.45**, 1.00; CH_2: 2.75, **3.00**, 3.10; HC-3 (of pyridine): 7.63, **7.90**, 7.61; HC-4: 7.80, **8.50**, 8.19; HC-5: 7.33, **8.05**, undetermined; HC-6: 8.61, **8.90**, 8.21. Aluminum LA are known to have a maximum co-ordination number of four: Lehmkuhl, H. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 107.

9. Irradiation of the peak at 9.30 ppm converted the CH_2 signal of Et_3N to a quartet. It is interesting to note that the spectrum of a 1 : 1 mixture of Et_3N and $AlBr_3$ does not feature any downfield peak or a splitting of the CH_2 signal.

10. Enolate formation has been studied by NMR also in the case of the $TiCl_4$ and $SnCl_4$ promoted reactions. However, while Ti enolates could be detected (see ref. 1a and 1b), tin enolates could not (ref. 2). In both cases, the addition of Et_3N was necessary for the reaction to occur in good yields.

11. Cyclic models are used to rationalize β-lactam formation by the condensation of imines with metal enolate in general (see ref. 4), and with 2-pyridylthioester enolate in particular (see ref. 1-3).

12. Imines of aromatic aldehydes are known to exist and react in the (E) configuration, while those of aliphatic aldehydes generally exist as mixtures of (E) and (Z) isomers. For a review see: McCarty, C.G. in: *"The Chemistry of the C-N Double Bond"*, Patai, S.; Ed.; Interscience, New York, 1970; chapter 9, pp 363-464. Aromatic imines such as **2** and **8** were shown not to isomerize even in the presence of strong LA (see ref. 1 and 3).

13. For a discussion of N-acyliminium ion formation by reaction of an activated carbonyl compound with imines see: Georg, G. I.; Ravikumar, V. T. in *"The Organic Chemistry of β-Lactams"*, Georg, G. I., Ed.; VCH, New York, 1993, Chapter 6, pp 295 - 368.

14. For the acid/base properties of 2-pyridylthiol see: a) Albert, A.; Barlin, G. B. *J. Chem. Soc.* **1959**, 2384. b) Jones, R. A.; Katrizky, A. R. *J. Chem. Soc.* **1958**, 3610.

15. For a discussion of the basic nature of the imine nitrogen see: a) Weinstein, J.; McIninch, E. *J. Am. Chem. Soc.* **1960**, *82*, 6064. b) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 832. For a review see: Smith, J. W. in: *"The Chemistry of the C-N Double Bond"*, Patai, S.; Ed.; Interscience, New York, 1970; chapter 5, pp 235-253.

16. Ketene formation can be ruled out since the unreacted 2-pyridylthioesters can be recovered from the reaction mixture.

17. For a similar experiment carried out with benzalaniline and acetylchloride see: Bose, A.K.; Spiegelman, G.; Manhas, M.S. *Tetrahedron Lett.* **1971**, *12*, 3167. These authors attributed the singlet at 7.95 ppm to the methine proton of PhCH(Cl)-N(COMe)Ph. No such signal was present in the spectrum of the **4**+$AlBr_3$+**2** mixture.

18. Similar results were obtained by : Olah, G.A.; Kreienbuhl, P. *J. Am. Chem. Soc.* **1967**, *89*, 4756.

19. However, it is interesting to note that the **2**+propionylchloride+$AlBr_3$ mixture does not afford any β-lactam upon standing overnight at room temperature. This confirms the necessity of a base to ensure proton abstraction from adduct 26, and support the hypothesis that is the 2-pyridylthiolate ion that acts as a base in our reaction.

20. The Lewis acidity of MX_n species has been determined quantitatively and found to be in the following order (only Lewis acids relevant to this work are included): BCl_3>$AlBr_3$> $EtAlCl_2$>$TiCl_4$>$SnCl_4$. See: Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. See also: Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750.

21. Also the adduct between thioester **1** and BCl_3 reacts with imine **2** in the absence of Et_3N (unpublished results from these laboratories).

22. An enantioselective synthesis of β-lactam **3** was attempted using $AlBr_3$ or EtAlCl2 as activators and N-methylephedrine as base or chiral LA ligand (see ref. 3a,b). Racemic products were obtained in these reactions.

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