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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**

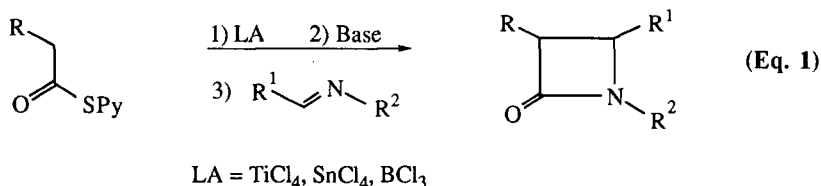
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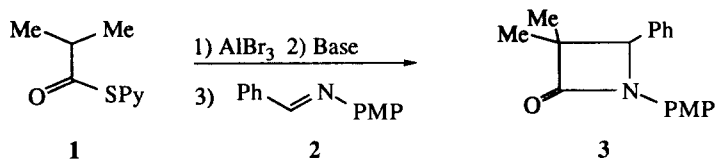
Abstract: The reactions of some 2-pyridylthioesters with imines in the presence of AlBr_3 or EtAlCl_2 and of a tertiary amine afford β -lactams in a simple one-pot procedure with fair to high *trans* stereoselectivity. The condensation can be also carried out in the absence of base and with sub-stoichiometric 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 boron³ 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).



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-stoichiometric 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 $\text{Et}_2\text{NPr-i}$ 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

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	$(\text{CH}_2\text{Cl})_2$	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)	$\text{Et}_2\text{NPr-i}$	CH_2Cl_2	1.0	0	80
11	AlBr_3 (1.0)	$\text{C}_5\text{H}_5\text{N}$	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)	$\text{Et}_2\text{NPr-i}$	CH_2Cl_2	1.0	0	73
19	EtAlCl_2 (2.0)	$\text{C}_5\text{H}_5\text{N}$	CH_2Cl_2	1.0	0	68
20	EtAlCl_2 (2.0)	Et_3N	$(\text{CH}_2\text{Cl})_2$	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 LA⁶ 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 ratios⁷ are reported in Table 2. As it is generally observed in the reactions of most metal enolates,¹⁻³ the *trans* stereoselectivity of the AlBr₃ 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 EtAlCl₂ was employed, the t : c ratio of β -lactams 13t,c-15t,c being virtually constant. Remarkably, the use of the relatively weak LA EtAlCl₂ allowed the extension of the reaction also to the glycolic acid derived thioesters 7 and 8, that did not react with imine 2 and AlBr₃.

In order to minimize the possibility of imine decomposition in the presence of a strong LA such as AlBr₃, the reactions of thioester 6 with imines 9-12, that are less stable than 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 EtAlCl₂ 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 AlBr₃ to a CD₂Cl₂ 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 Et₃N 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 Et₃NH⁺, likely by proton abstraction from the CH₂ 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 Et₃N.

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 Et₃N. 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 Et₃N. 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 AlBr₃ 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 EtAlCl₂ as LA. Thus, β -lactam 3 was obtained from thioester 1 and imine 2 in 57, 35, and 32% yield in the absence of Et₃N 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 Et₃N, 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

^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 cyclic¹¹ model **25** (Fig. 1) can be used as a working hypothesis to rationalize the formation of *trans* and *cis* β -lactams from an (E)-imine¹² and an (E)- or a (Z)-enolate, respectively.

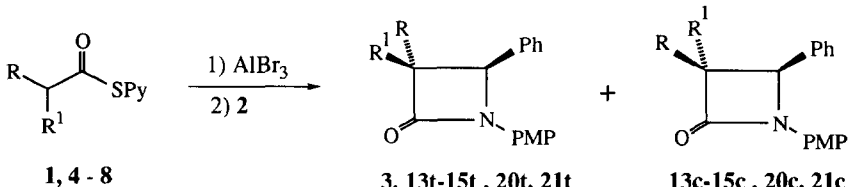
Two different mechanisms can be proposed to explain the condensations carried out in the absence of Et_3N (Fig. 1). Upon activation by the LA, the 2-pyridylthioester becomes so reactive that acylation of the imine nitrogen to give the N-acyliminium species **26**¹³ is possible. The released 2-pyridylthiolate ion **27** can then act as a base¹⁴ to generate the zwitterion **28**¹³, that then undergoes β -lactam ring closure. Alternatively, the imine can play the role of the base¹⁵ giving the enolate and the protonated imine **29**. Reaction of these two species can lead to the final products.¹⁶ Again, ¹H 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_2Cl_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 ppm¹⁷ (in a *ca.* 1 : 2 ratio), the downfield peak being almost coincident with that of the **4**+AlBr₃+**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**+ AlBr₃ 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+AlBr₃+imine mixture seems to rule out the mechanism involving formation of **29**. Remarkably, the proposed mechanism can tolerate sub-stoichiometric amounts of LA. The Lewis acidity of AlBr₃, that is stronger than both TiCl₄ and SnCl₄,²⁰ can account for the enhanced reactivity of the thioester+AlBr₃ adduct toward imines that was unprecedented with other LA.^{10,21}

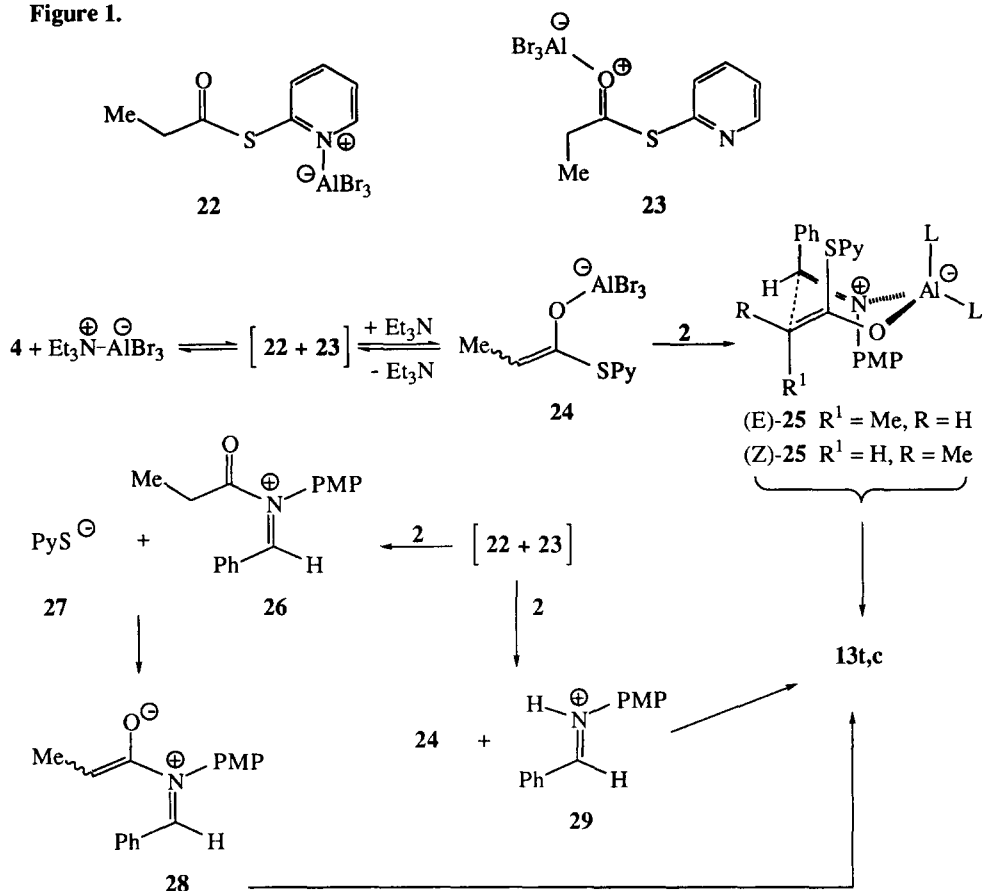
Table 3. Synthesis of β -Lactams **3**, **13t,c**-**15t,c**, **20t,c** and **21t,c** from Thioesters **1**, **4-8** and Imine **2**.^a

				
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 ₂ O; 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, AlBr₃ and EtAlCl₂ 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 Et₃N and in the presence of sub-stoichiometric 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 $(\text{CH}_2\text{Cl})_2$ were distilled from CaH_2 ; THF from LiAlH_4 ; toluene from sodium; Et_3N , $\text{Et}_2\text{NPr-i}$, 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 AlBr_3 (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 3×10 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 AlBr_3 , 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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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 ($J_{\text{trans}} = 2.0\text{--}2.5$ Hz; $J_{\text{cis}} = 5.0\text{--}6.0$ 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 $\text{PhCH}(\text{Cl})\text{-N}(\text{COMe})\text{Ph}$. 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): $\text{BCl}_3 > \text{AlBr}_3 > \text{EtAlCl}_2 > \text{TiCl}_4 > \text{SnCl}_4$. 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 EtAlCl_2 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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