

MILD AND CONVENIENT ONE-POT SYNTHESIS OF β -LACTAMS BY CONDENSATION OF TITANIUM ENOLATES
OF 2-PYRIDYLTHIOESTERS WITH IMINES.

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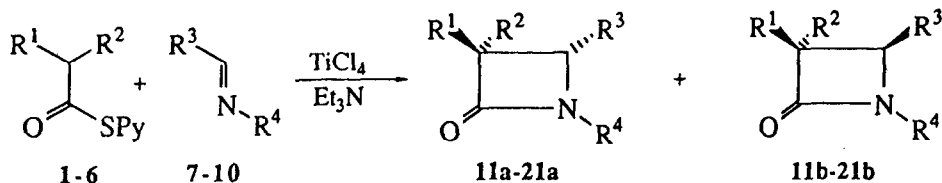
(Received in UK 30 August 1991)

Summary. Treatment of 2-pyridylthioesters with triethylamine in the presence of titanium tetrachloride affords titanium enolates that add to imines to give β -lactams in fair to excellent yields with moderate to good stereoselectivity.

The condensation of ester enolates with imines represents the most popular entry to β -lactams.¹ By this route, these pharmaceutically important compounds² are obtained either stepwise via a β -aminoester, or in one step, depending on the nature of the enolate. The use of thioesters³ allows to avoid strong bases for the enolate generation, but, to the best of our knowledge, there is only a single example of β -lactam one-pot synthesis starting from a thioester.⁴ This is quite surprising, since one of the most efficient way to transform a β -amino acid derivative into a 2-azetidinone exploits activation of the carboxylic group by reaction with a disulphide in the presence of triphenylphosphine.^{5,6}

We here report that simply generated^{7,8} (TiCl_4 triethylamine, -78°C , 0.5 h) titanium enolates⁹ of 2-pyridylthioesters 1-6 readily condense with imines 7-10 to give fair to excellent yields of β -lactams 11-21 in a convenient one pot procedure.

Best reaction conditions were established by reacting S-(2-pyridyl)thiopropionate 1 with benzaldehyde N-benzylimine 7. Thus, treatment of a 0.1 molar solution of 1 in dichloromethane with 1 mol. equiv. of titanium tetrachloride, followed by addition of 1 mol. equiv. of triethylamine (TEA), generated the titanium enolate.¹⁰ This was allowed to react with 7 to produce directly 1-phenylmethyl-3-methyl-4-phenyl azetidin-2-one 11 as a mixture of diastereoisomers. The ratio was determined by 300 MHz $^1\text{H-NMR}$ spectroscopy on the crude product,¹¹ that was purified by flash chromatography.¹² Yields and diastereoisomeric ratios of this reaction, run in different conditions, are collected in Table 1.



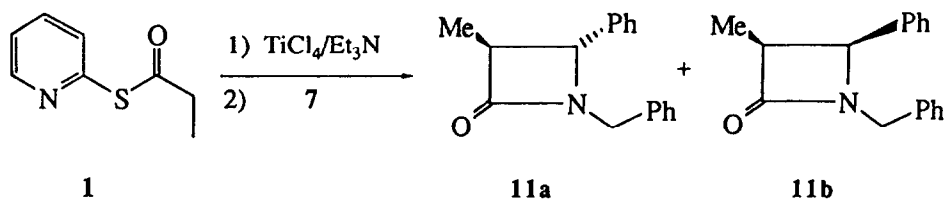
- 1 $R^1 = \text{Me}; R^2 = \text{H}$
 2 $R^1 = \text{Et}; R^2 = \text{H}$
 3 $R^1 = \text{Pr-i}; R^2 = \text{H}$
 4 $R^1 = \text{PhthN}; R^2 = \text{H}$
 5 $R^1 = \text{PhCH}_2\text{O}; R^2 = \text{H}$
 6 $R^1 = \text{Me}; R^2 = \text{Me}$

- 7 $R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 8 $R^3 = \text{Ph}; R^4 = \text{p-MeOPh}$
 9 $R^3 = \text{Pr-n}; R^4 = \text{PhCH}_2$
 10 $R^3 = (\text{E})\text{-HC=CHPh}; R^4 = \text{p-MeOPh}$

- 11 $R^1 = \text{Me}; R^2 = \text{H}; R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 12 $R^1 = \text{Et}; R^2 = \text{H}; R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 13 $R^1 = \text{Pr-i}; R^2 = \text{H}; R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 14 $R^1 = \text{PhthN}; R^2 = \text{H}; R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 15 $R^1 = \text{PhCH}_2\text{O}; R^2 = \text{H}; R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 16 $R^1 = \text{Me}; R^2 = \text{Me}; R^3 = \text{Ph}; R^4 = \text{PhCH}_2$
 17 $R^1 = \text{Me}; R^2 = \text{H}; R^3 = \text{Ph}; R^4 = \text{p-MeOPh}$
 18 $R^1 = \text{Me}; R^2 = \text{H}; R^3 = \text{Pr-n}; R^4 = \text{PhCH}_2$
 19 $R^1 = \text{Me}; R^2 = \text{H}; R^3 = (\text{E})\text{HC=CHPh}; R^4 = \text{p-MeOPh}$
 20 $R^1 = \text{Et}; R^2 = \text{H}; R^3 = (\text{E})\text{HC=CH-Ph}; R^4 = \text{p-MeOPh}$
 21 $R^1 = \text{Pr-i}; R^2 = \text{H}; R^3 = (\text{E})\text{HC=CH-Ph}; R^4 = \text{p-MeOPh}$

^a Only one enantiomer is shown for simplicity; Py = 2-pyridyl; PhthN = phthalimido.

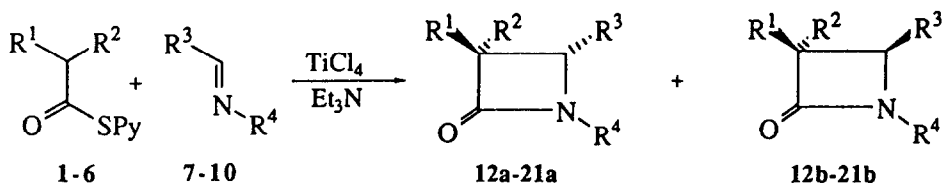
As can be seen from the reported data, virtually quantitative yields are obtained by carrying out the enolization at -78°C and the condensation at 0°C . A higher enolization or a lower condensation temperature led to a decrease in yield. The diastereoselectivity of the reaction was moderate, favouring the trans configured product 11a.¹³ The use of 2 mol. equiv. of thioester per mol. equiv. of imine did not alter substantially the diastereoselectivity, while maintaining excellent chemical yield. The reaction was then

Table 1. Synthesis of β -lactam 11 from thioester 1 and imine 7.

$T^{\circ}\text{C}^{\text{a}}$	Equiv. of 1	$T^{\circ}\text{C}^{\text{b}}$	Yield % ^c	Diastereoisomeric ratio a : b ^d
-78	1	-78	60	60 : 40
-78	1	-40	60	60 : 40
-78	1	0	99	75 : 25
-40	1	-40	78	70 : 30
-40	1	0	78	71 : 29
0	1	0	30	75 : 25
-78	2	0	99 ^e	72 : 28

^aEnolization temperature; enolization time is 0.5 h. ^bCondensation temperature; condensation time is 6.0 h. ^cIsolated yields (see text). ^dBy ¹H-NMR (see text). ^eYield based on the imine.

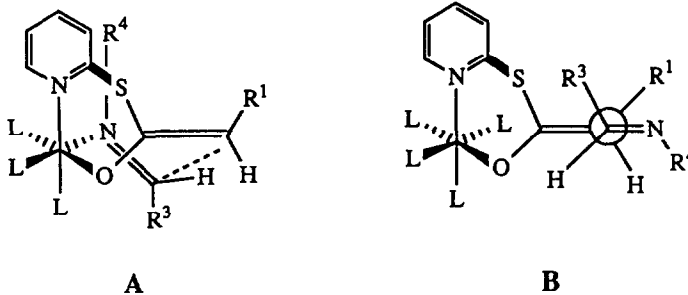
extended to thioesters 2-6 and to imines 8-10. The results are collected in Table 2. These data indicate that the reaction could be successfully applied to enolizable and α,β -unsaturated imines such as 9 and 10. In both cases, however, only the use of 2 mol. equiv. of enolate secured good yield of β -lactam. As for the thioesters, these could feature both α - and β -branching (compounds 3 and 6), and also α -heterosubstituents (compounds 4 and 5). Although in the latter cases the yields were lower, these condensations showed that this method can be applied to the preparation of biologically relevant molecules. For instance, the high yielding synthesis of β -lactams 20 and 21 is remarkably useful, since these products have been converted¹⁴ into carbapenem antibiotic

Table 2. Synthesis of β -lactams 12-21 from thioesters 1-6 and imines 7-10.^a

Thioester	Imine	Product	Yields % ^b	Diastereoisomeric ratio a : b ^c
2	7	12	95	85 : 15
3	7	13	83	92 : 8
4	7	14	40	≥ 98 : 2
5	7	15	64	9 : 91
6	7	16	81	-
1	8	17	99	70 : 30
1	9	18	71	35 : 65
1 ^d	9	18	90	30 : 70
1	10	19	64	60 : 40
1 ^d	10	19	99	60 : 40
2	10	20	76	70 : 30
2 ^d	10	20	91	70 : 30
3 ^d	10	21	52	75 : 25

^aEnolization: -78°C, 0.5 h; condensation: 0°C, 6 h; 1 mol. equiv. of enolate was used unless otherwise e stated. ^bIsolated yield. ^cBy ¹H-NMR on the crude product. ^d2 mol. equiv. of enolate were used.

PS-5 and PS-6.¹⁵ In addition compound 14 opens access to C-3 aminosubstituted 2-azetidinone ring system,² while *cis* configured β -lactam 15b can be considered a highly advanced precursor of (2R*, 3S*)-3-phenyl-isoserine, an intermediate for the synthesis of taxol.¹⁶



In making some comments about the diastereoselectivity of this process, some trends can be pointed out. An increase in the steric requirement of the thioester R^1 group led to a better trans stereoselection, as can be seen from the reaction of esters 1-4 with imine 7, and of 1-3 with 10. The thioester being equal, a large R^3 residue in the imine seems to favour the formation of the trans product, as can be seen by comparing the reaction of 1 with 7, and 10, respectively. In two cases, however, a predominance of a cis configured β -lactam was observed, *i.e.* in the condensation of benzyloxy derivative 5 with imine 7, and of 1 with enolizable imine 9.

A rationalization of the stereochemical outcome seems difficult, since, at least in the case of 1, the diastereoisomeric ratios do not seem to be strictly related to the observed enolate *E/Z* ratio.¹⁰ Moreover, there is the possibility that the reaction can occur *via* a cyclic or an open transition states, thus making any rationale proposal highly speculative at present. However, in the hypothesis that: a) the predominant isomer of the titanium enolates involved in these reactions feature the *Z* configuration;¹⁰ and that b) there is an intramolecular chelation between the pyridine nitrogen and the titanium atom,^{8,10} cyclic model¹⁷ A seems more likely than the acyclic one, B, since A better rationalizes the increase in trans-stereoselection observed when both R^1 and R^3 groups become more sterically demanding. A change in enolate geometry, as in the case of benzyloxy derivative 5,¹⁸ or a diminished bulkiness of the R^3 group, as in the case of imine 9, can account for the preferential formation of a cis configured product.

Work is underway in our laboratory to extend this convenient β -lactam synthesis to enantiomerically pure imines,¹⁹ and to thioesters bearing a chiral pyridyl residue.

Acknowledgments. Partial financial support by MURST-Roma is acknowledged.

Experimental.

NMR spectra were recorded on a Bruker WP-80 or AC-300 instrument using CDCl_3 as solvent; chemical shifts are in ppm downfield from TMS. IR spectra were recorded on a Perkin Elmer 377 instrument. Elemental analyses were obtained on a Perkin Elmer 240 instrument. CH_2Cl_2 was distilled from CaH_2 and Et_3N from KOH.

Thioesters 1²⁰ and 2,²¹ and β -lactams 11,^{3d} 12,²² 13,²³ 15,²⁴ 16,²² 17,²⁵ 18,²⁶ 20,¹⁴ 21,¹⁴ were known compounds.

Synthesis of thioesters. General procedure.²⁰

To a cooled (0°C) 0.5 M solution of thiol (10-50 mmol) and triethylamine (1.1 mol. equiv.) in dry dichloromethane, the acid chloride (1 mol. equiv.) in dichloromethane (2 ml/mmol) was added dropwise. After 30 min stirring at 0°C the reaction mixture was poured into cold water. The organic phase was separated and washed with a cold 5% aqueous solution of sodium hydroxide and with water, dried, and concentrated under reduced pressure. The products were generally pure enough to be used as such. Samples for elemental analysis were prepared by flash chromatography with hexanes:diethylether mixtures as eluant.

S-(2-Pyridyl)-3-methylbutanethioate 3 was obtained as an oil with a 70:30 hexanes:diethylether mixture as eluant. Found: C, 61.38; H, 6.66; N, 7.11. $\text{C}_{10}\text{H}_{13}\text{NOS}$ requires: C, 61.50; H, 6.71; N, 7.17. ¹H-NMR: δ 7.10-8.60 (m, 4H); 2.55 (d, 2H, J 6.0 Hz); 2.10 (m, 1H); 1.00 (d, 6H, J 7.0 Hz). IR: ν 3040, 2950, 1685, 1560, 1420, 1115, 990, 750 cm^{-1} .

S-(2-Pyridyl)-2-(N-phthalimido)ethanethioate 4 was obtained as a solid (m.p. 119-120°C) with diethylether as eluant. Found: C, 60.21; H, 3.50; N, 9.19. $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$ requires: C, 60.39; H, 3.38; N, 9.39. ¹H-NMR: δ 7.15-8.55 (m, 8H); 4.70 (s, 2H). IR: ν 3060, 2960, 1700, 1560, 1410, 1110, 1000, 750 cm^{-1} .

S-(2-Pyridyl)-2-(phenylmethoxy)ethanethioate 5 was obtained as an oil with a 70:30 diethylether:hexanes mixture as eluant. Found: C, 64.99; H, 5.06; N, 5.31. $\text{C}_{14}\text{H}_{13}\text{NO}_2\text{S}$ requires: C, 64.84; H, 5.05; N, 5.40. ¹H-NMR: δ 7.10-8.60 (m, 9H); 4.75 (s, 2H); 4.20 (s, 2H). IR: ν 3040, 2930, 1685, 1560, 1420, 1115, 990, 735 cm^{-1} .

(S)-(2-Pyridyl)-2-methylpropanethioate 6 was obtained as an oil with a 70:30 hexanes:diethylether mixture as eluant. Found: C, 59.74; H, 6.19; N, 7.81. $\text{C}_9\text{H}_{11}\text{NOS}$ requires: C, 59.64; H, 6.11; N, 7.73. ¹H-NMR: δ 7.10-8.60 (m, 4H); 2.85 (m, 1H); 1.15 (d, 6H, J 7.0 Hz). IR: ν 3040, 2960, 1690, 1560, 1420, 1110, 990, 750 cm^{-1} .

Synthesis of β -lactams. General procedure: to a stirred 0.1 M solution of thioester

(0.2-2.0 mmol) in CH_2Cl_2 cooled at -78°C , a 1.0 M solution of TiCl_4 (1 mol. equiv.) was added dropwise over a 1 min period. To the resulting purple solution, TEA (1 mol. equiv.) was added dropwise and stirring was continued at -78°C for 30 min. To this mixture a solution of the imine (1 mol. equiv.) in CH_2Cl_2 was added over a 2 min. period, and the dry ice/methanol bath was replaced by an ice bath. After 6 h stirring at 0°C the reaction was quenched by the addition of a saturated aqueous solution of sodium bicarbonate, and the resulting mixture filtered through celite. The organic phase was separated, washed with water, dried, and evaporated. After $^1\text{H-NMR}$ analysis, the crude product was purified by flash chromatography with hexanes:diethylether mixture as eluant. Yields and diastereoisomeric ratios are collected in Tables 1 and 2. Thioester hydrolysis¹² was performed by stirring a THF solution of the crude product in the presence of a 5 fold mol. excess of 1N aqueous KOH solution for 12 h at RT.

1-(Phenylmethyl)-3-phthalimido-4-phenylazetidin-2-one 14a was obtained as a pale yellow-solid, m.p. $186-188^\circ\text{C}$. Found: C, 75.22; H, 4.67; N, 7.24. $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_3$ requires: C, 75.38; H, 4.74; N, 7.32. $^1\text{H-NMR}$: δ 7.16-7.88 (m, 14H); 5.23 (d, 1H, J 2.0 Hz); 5.00 (d, 1H, J 14 Hz); 4.78 (d, 1H, J 2.0 Hz); 3.90 (d, 1H, J 14 Hz).

1-(4-Methoxyphenyl)-3-methyl-4-[(E)-2-phenylethenyl]-azetidin-2-one 19ab was obtained as a thick oil. Found: C, 77.86; H, 6.47; N, 4.85. $\text{C}_{19}\text{H}_{19}\text{NO}_2$ requires: C, 77.79; H, 6.53; N, 4.77. $^1\text{H-NMR}$ of **19a**: δ 7.00-7.55 (m, 10H); 6.26 (dd, 1H, J 15.0, 7.0 Hz); 4.14 (dd, 1H, J 7.0, 2.0 Hz); 3.72 (s, 3H); 3.05 (dq, 1H, J 7.0, 2.0 Hz); 1.45 (d, 3H, J 7.0 Hz). $^1\text{H NMR}$ of **19b**: δ 7.00-7.55 (m, 10H); 6.36 (dd, 1H, J 15.0, 7.0 Hz); 4.81 (dd, 1H, J 7.0, 5.3 Hz); 3.70 (s, 3H); 3.61 (dq, 1H, J 7.0, 5.3 Hz); 1.25 (d, 3H, J 7.0 Hz). IR: ν 2920, 1715, 1420, 1220, 1110, 960, 820, 730 cm^{-1} .

References and Notes.

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- 6) For a review on the use of thioesters in cyclization reaction see: Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23. For β -lactone formation see: Danheiser, R.L.; Nowick, J.S. *J. Org. Chem.* **1991**, *56*, 1176.
- 7) This procedure was successfully employed for the generation of the titanium enolates

- of ketones, N-acyloxazolidones, and N-acylsultams: Evans, D.A.; Rieger, D.L.; Bilodeau, M.T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, 113, 1047; and references therein.
- 8) For the extension of this procedure to thioesters and α -thiosubstituted esters see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *Tetrahedron*, submitted. Preliminary experiments showed that the titanium enolate of S-phenylpropanethioate condensed with imines **7**, **8**, and **10** to give a predominance of β -aminothioesters in fair to good yields.
 - 9) These compounds are generally obtained by transmetalation from lithium enolates or silylenolethers. Review: Duthaler, R.O.; Hafner, A.; Riedeker, M. *Pure Appl. Chem.* **1990**, 62, 631. Recent report: Nerz-Stormes, M.; Thornton, E.R. *J. Org. Chem.* **1991**, 56, 2489.
 - 10) By monitoring the generation of the enolate of **1** at -78°C by $^1\text{H-NMR}$ in CD_2Cl_2 solution we showed that: a) The enolate is formed rapidly and quantitatively only upon addition of TEA; b) A non-equilibrating 80:20 mixture of Z:E isomeric enolates is obtained, the Z configuration (CIP rules) being tentatively assigned to the major one.
 - 11) Configurational assignment was based on the values of the H-C3/H-C4 coupling constant: for the β -lactams reported here we found J_{trans} ca. 2.0 Hz and J_{cis} ca. 5.0 Hz.
 - 12) The unreacted thioester can be removed by hydrolysis (1N KOH, THF, RT), a procedure that does not alter the diastereoisomeric ratio, as shown by evaluating it on the crude and on the purified product. Moreover, the 2-pyridylthiol is extracted by the basic aqueous phase, and, in the case of quantitative reactions, the chromatographic purification is not necessary.
 - 13) This means that the predominant corresponding β -amino thioester features the anti stereochemistry. It must be remembered that the condensation of the titanium enolate of **1** with aldehydes is either stereorandom or moderately anti stereoselective.
 - 14) Ha, D.-C.; Hart, D.J. *J. Antibiot.* **1987**, 40, 309.
 - 15) It must be remembered that since the reported synthesis of these products is stereodivergent for the trans compound, a highly stereoselection in the α -lactam