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

Mauro Cinquini, Franco Cozzi, Pier Giorgio Cozzi, and Emanuela Consolandi
Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università,
Via Golgi 19, 20133 Milano, Italy

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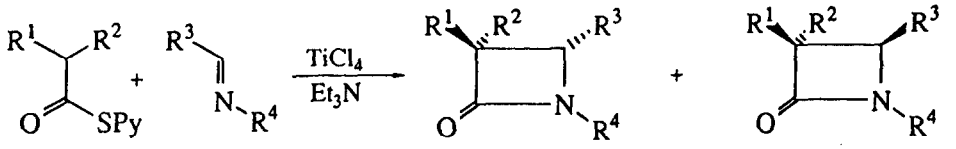
Summary. Treatment of 2-pyridylthioesters with triethylamine in the presence of titanium tetrachloride affords titanium enolates that add to imines to give β-lactams in fair to excellent yields with moderate to good stereoselectivity.

The condensation of ester enolates with imines represents the most popular entry to β-lactams.[1] By this route, these pharmaceutically important compounds[2] are obtained either stepwise via a β-aminoester, or in one step, depending on the nature of the enolate. The use of thioesters[3] 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 enolates[9] 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}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.



1-6 **7-10** **11a-21a** **11b-21b**

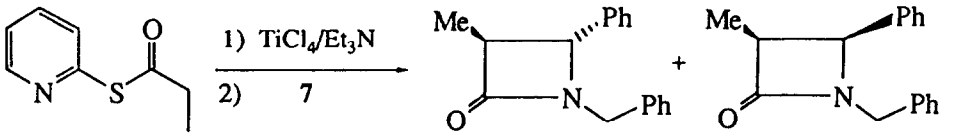
1	R^1 = Me;	R^2 = H	**7**	R^3 = Ph;	R^4 = $PhCH_2$
2	R^1 = Et;	R^2 = H	**8**	R^3 = Ph;	R^4 = p-MeOPh
3	R^1 = Pr-i;	R^2 = H	**9**	R^3 = Pr-n;	R^4 = $PhCH_2$
4	R^1 = PhthN;	R^2 = H	**10**	R^3 = (E)-HC=CHPh;	R^4 = p-MeOPh
5	R^1 = $PhCH_2O$;	R^2 = H			
6	R^1 = Me;	R^2 = Me			

11	R^1 = Me;	R^2 = H;	R^3 = Ph;	R^4 = $PhCH_2$
12	R^1 = Et;	R^2 = H;	R^3 = Ph;	R^4 = $PhCH_2$
13	R^1 = Pr-i;	R^2 = H;	R^3 = Ph;	R^4 = $PhCH_2$
14	R^1 = PhthN;	R^2 = H;	R^3 = Ph;	R^4 = $PhCH_2$
15	R^1 = $PhCH_2O$;	R^2 = H;	R^3 = Ph;	R^4 = $PhCH_2$
16	R^1 = Me;	R^2 = Me;	R^3 = Ph;	R^4 = $PhCH_2$
17	R^1 = Me;	R^2 = H;	R^3 = Ph;	R^4 = p-MeOPh
18	R^1 = Me;	R^2 = H;	R^3 = Pr-n;	R^4 = $PhCH_2$
19	R^1 = Me;	R^2 = H;	R^3 = (E)HC=CHPh;	R^4 = p-MeOPh
20	R^1 = Et;	R^2 = H;	R^3 = (E)HC=CH-Ph;	R^4 = p-MeOPh
21	R^1 = Pr-i;	R^2 = H;	R^3 = (E)HC=CH-Ph;	R^4 = 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 configurated 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**.



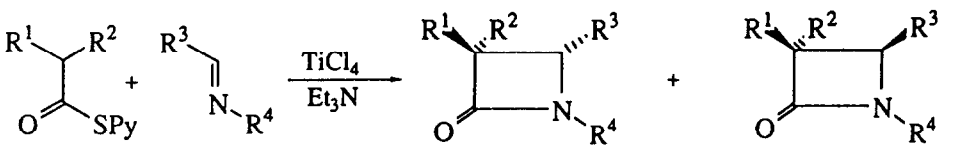
1 **11a** **11b**

T°C[a]	Equiv. of **1**	T°C[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

[a]Enolization temperature; enolization time is 0.5 h. [b]Condensation temperature; condensation time is 6.0 h. [c]Isolated yields (see text). [d]By ^{1}H-NMR (see text). [e]Yield 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 by 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 converted[14] into carbapenem antibiotic

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

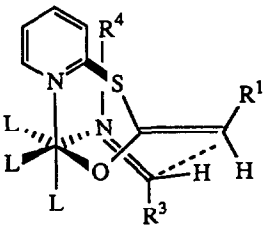


1-6 7-10 12a-21a 12b-21b

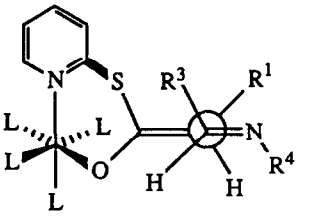
Thioester	Imine	Product	Yields %[b]	Diastereoisomeric ratio a : b[c]
2	7	12	95	85 : 15
3	7	13	83	92 : 8
4	7	14	40	⩾98 : 2
5	7	15	64	9 : 91
6	7	16	81	-
1	8	17	99	70 : 30
1	9	18	71	35 : 65
1[d]	9	18	90	30 : 70
1	10	19	64	60 : 40
1[d]	10	19	99	60 : 40
2	10	20	76	70 : 30
2[d]	10	20	91	70 : 30
3[d]	10	21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

[a]Enolization: -78°C, 0.5 h; condensation: 0°C, 6 h; 1 mol. equiv. of enolate was used unless otherwise e stated. [b]Isolated yield. [c]By ^{1}H-NMR on the crude product. [d]2 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 configurated β-lactam **15b** can be considered a highly advanced precursor of (2R*, 3S*)-3-phenyl-isoserine, an intermediate for the synthesis of taxol.[16]



A



B

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 configurated 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 model[17] **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 configurated 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.

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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 **1**[20] 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. $C_{10}H_{13}NOS$ requires: C, 61.50; H, 6.71; N, 7.17. ^{1}H-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 diethyleher as eluant. Found: C, 60.21; H, 3.50; N, 9.19. $C_{15}H_{10}N_2O_3S$ requires: C, 60.39; H, 3.38; N, 9.39. ^{1}H-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. $C_{14}H_{13}NO_2S$ requires: C, 64.84;, H, 5.05; N, 5.40. ^{1}H-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. $C_9H_{11}NOS$ requires: C, 59.64; H, 6.11; N, 7.73. ^{1}H-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}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 hydrolysis[12] 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°C. Found: C, 75.22; H, 4.67; N, 7.24. $C_{24}H_{18}N_2O_3$ requires: C, 75.38; H, 4.74; N, 7.32. ^{1}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. $C_{19}H_{19}NO_2$ requires: C, 77.79; H, 6.53; N, 4.77. ^{1}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}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}.

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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}H-NMR in CD_2Cl_2 solution[8] we showed that: a) The enolate is formed rapidly and quantitatively only upon adolition 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.[8]

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15) It must be remembered that since the reported synthesis of these products is stereoconvergent for the trans compound, a highly stereoselection in the β-lactam synthesis is not required.

16) For a β-lactam based synthesis of the taxol C-13 side chain, see: Ojima, I.; Habus, I.; Zhao, M.; Georg, G.I.; Jayansighe, L.R. J. Org. Chem. **1991**, 56, 1681.

17) These models must be intended as simple working hypotheses[7] and are not meant to suggest the exact nature of the titanium enolate.

18) In this case benzyloxy group/Ti chelation can occur, thus affecting the enolate configuration. In ancillary experiments[8,10] we showed that the titanium enolates of α-thiosubstituted esters exist as single Z isomer that give rise to highly syn-selective aldol condensation, and that these enolates condense with imine **7** to give syn α-amino esters with 80:20 diastereoselectivity.

19) Preliminary experiments showed that a chiral R^4 group in the imine (R^4=(S)-CH(Me)Ph) did not promote a satisfactory level of diastereofacial control in this reaction. A stereocenter in the R^3 group seems more promising.

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