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Stereoselective Synthesis of β-Lactams by Condensation of Titanium Enolates of 2-Pyridylthioesters with Imines Bearing a Chiral Auxiliary

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Abstract: Addition of the titanium enolates of 2-pyridylthioesters to imines featuring easily removable chiral auxiliaries affords β-lactams in a highly stereoselective fashion.

We recently reported[1] a convenient one-pot synthesis of β-lactams by condensation of titanium enolates[2] of 2-pyridylthioesters with imines.[3] Starting either from chiral alkoxy aldehydes or from a thioester obtained from (*R*)-3-hydroxybutanoic acid, enantiomerically pure compounds were obtained.[4] However, this approach is limited to the preparation of those β-lactams that feature particular substituents at the azetidin-2-one nucleus. A more general synthesis of optically active compounds would require the introduction of a chiral auxiliary on one of the reaction partners. Preliminary results on the use of chiral imines are here reported.[5]

In order to define the best chiral auxiliary, (*S*)-amines **1-5**, that feature an easily removable nitrogen substituent,[5c,d,g,k,o] were screened (Scheme 1). They were reacted with benzaldehyde to give the corresponding (*E*)-imines, that were condensed with non-stereogenic 2-pyridylthioisobutyrate **6** to afford, in poor to good overall yield, β-lactams **7a,b-11a,b** as mixtures of two diastereoisomers.[6] As can be seen from the results collected in Table 1, the reaction proceeded with excellent stereocontrol in the case of imines derived from **1**, **2**, and **5**. Diastereoisomeric ratios were determined by 300 MHz ^{1}H NMR spectroscopy on the crude products, generally exploiting the N-C<u>H</u>(R)Ar signal. The 4*S* configuration of the major isomer of compound **7** (**7a**) was unambigously established by comparison of its ^{1}H NMR data with those reported in the literature.[5j] The common pattern of ^{1}H NMR signals shared by compounds **7a** and **8a** suggested the reasonable extension of the 4*S* configuration also to **8a**. Chemical correlation starting from **11a** (**11a** to *ent*-**7a**: thiocarbonyldiimidazole, 1,2-dichloroethane, reflux, 4h; then tributyltinhydride, AIBN, toluene, reflux, 5h, 52% overall yield. **11a** to **9a**: NaH, benzylbromide, THF, RT, 15h, 63% yield; **11a** to **10a**: t-butyldiphenylsilylchloride, imidazole, DMF, RT, 24h, 80% yield), allowed the attribution of configuration reported in Table 1.

Scheme 1.

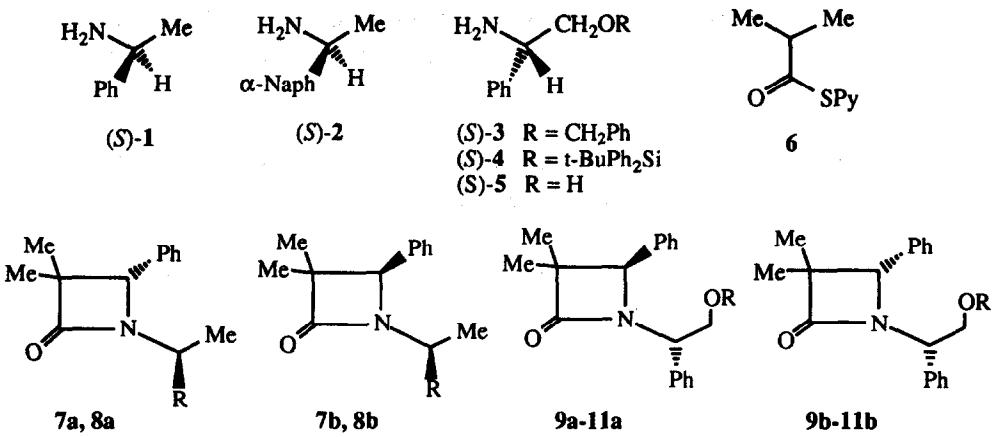


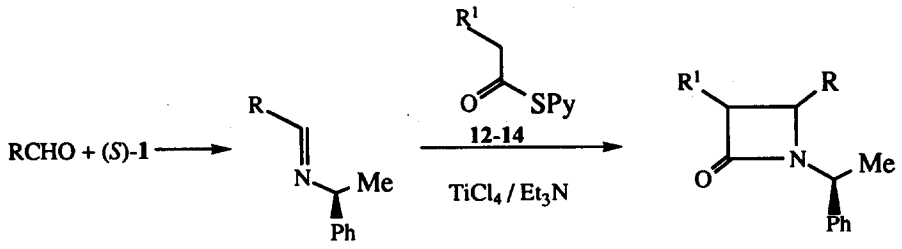
Table 1.Synthesis of β-Lactams **7-11** by Reaction of Thioester **6** with the Benzaldehyde Imines Derived from Amines **1-5**.[a]

Amine	R	Product	Yield%[b]	a : b ratio[c]	C-4 Configuration
1	Ph	**7**	80	96 : 4	*S*
2	α-Naph	**8**	79	95 : 5	*S*
3	$PhCH_2$	**9**	33	80 : 20	*R*
4	t-$BuPh_2Si$	**10**	13	74 : 26	*R*
5	H	**11**	50	>98 : 2	*R*

[a]The reactions were run on a 0.5-5.0 mmol scale in CH_2Cl_2 with a 1.0: 1.0: 1.1: 0.5 ester: $TiCl_4$: Et_3N: imine ratio. Reaction times and temperatures: complexation: 5 min, -78°C; enolization: 30 min, -78°C; condensation: 5 h , 0°C. The reaction were quenched by addition of sat. $NaHCO_3$, the mixture was filtered through celite, the organic phase was separated, dried and concentrated in vacuo, and the crude product analyzed by NMR spectroscopy. [b] Isolated yields after flash chromatography. [c] Determined on the crude products by 300 MHz ^1H NMR spectroscopy. [d] Of the major isomer. [e] A single isomer was detected both by ^1H and ^{13}C (75.4 MHz) NMR analysis.

On the basis of the data reported in Table 1, amine (*S*)-**1** was selected as the chiral auxiliary that seems to promote the β-lactam synthesis with both good chemical yield and high diastereoselectivity.[7] Different imines derived from (*S*)-**1** were therefore reacted with 2-pyridylthioesters **12** (R^1 = Et), **13** (R^1 = i-Pr), and **14** (R^1 = i-Pr_3SiO), to give β-lactams **15-20**.[6] The results are collected in Table 2.

Table 2. Synthesis of β-Lactams **15-20** by Reaction of Thioesters **12-14** with the Imines Derived from Aldehydes RCHO and Amine (*S*)-**1**.[a]



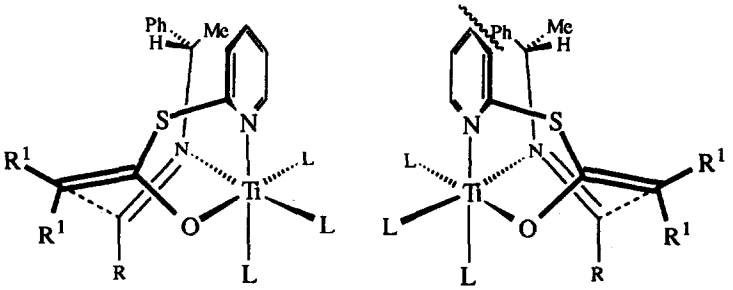
15-20

R	R^1	Product	Yield%[b]	*trans*/*cis* ratio[c]	diastereoisomeric ratio[c]	
					trans	*cis*
Ph	Et	**15**	79	93/7	80/20	-[d]
Ph	Pr-i	**16**	62	93/7	91/9	52/48
Ph	TIPSO[e]	**17**	90	62/38	90/10	84/16
C(Me)=CHPh	Pr-i	**18**	35	>98/2	91/9	-[d]
$CH_2OTBDPS$[f]	Pr-i	**19**	42	80/20	89/11	88/12
C_6H_{11}-c	Pr-i	**20**	60	>98/2	91/9	-[d]

[a-c] See Table 1. [d] Undetermined. [e] TIPS = i-Pr_3Si. [f] TBDPS = t-$BuPh_2Si$.

In principle four products can be obtained from each condensation: two *trans* and two *cis* β-lactams. *Trans* and *cis* compounds were easily recognized on the basis of the HC-3/HC-4 coupling constant value (J_{trans} : 1.5-2.0 Hz; J_{cis} : 5.0-5.5 Hz). In agreement with previous observations,[1,4] the *trans*/*cis* ratios seemed to increase with increasing steric requirement either of the thioester R^1 group or of the imine R substituent. For the predominant *trans* β-lactams the extent of stereocontrol exerted by the chiral auxiliary was constantly satisfactory, while for the minor *cis* ones it was in some cases clearly lower, and in general less predictable. The absolute configuration at C-3 and C-4 of the major isomer of compound *trans*-**15** was established as 3*S*,4*R*, as before by comparison of ^1H NMR data.[5j]

The preference for the attack of the enolate on the *Re* face of the (*E*)-imines derived from (*S*)-**1** can be tentatively rationalized by a model of stereoselection[1,4] as **A**, in which the the imine nitrogen is coordinated to the titanium atom, the H substituent at the stereocenter points toward the enolate, and the Ph group lies in the less sterically crowded position. Attack on the *Si* face of the imine as in **B** should be disfavoured by steric interaction between the Ph group and the pyridine ring of the thioester. Involvement of (*Z*) and (*E*) enolates would account for the formation of major isomers of *trans* or *cis* β-lactams, respectively.[8]



A B

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5. For previous examples of β-lactam synthesis involving chiral auxiliary bearing imines see: for the enolate-imine condensation: (a) Ojima, I.; Inobe, S.I. *Tetrahedron Lett.* **1980**, *21*, 2077, 2081. (b) Overman, L.E.; Osawa, T. *J.Am.Chem.Soc.* **1985**, *107*, 1698. (c) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem.Lett.* **1987**, 293. (d) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J.Org.Chem.* **1987**, *52*, 3498. (e) Brown, M.J.; Overman, L.E. *J.Org.Chem.* **1991**, *56*, 1933. (f) Kleijn, H.; van Maanen, H.L.; Jastrzebski, J.T.B.H.; van Koten, G. *Recl .Trav. Chim. Pays-Bas* **1992**, *111*, 497. (g) van der Steen, F.H.; Kleijn, H.; Britovsek, G.J.P.; Jastrzebski, J.T.B.H.; van Koten, G. *J.Org.Chem.* **1992**, *57*, 3906. For the Staudinger reaction: (h) Just, G.; Liak, T.J. *Can.J.Chem.* **1978**, *56*, 211; (i) Tenneson, S.M.; Belleau, B. *Can.J.Chem.* **1980**, *58*, 1605. (j) Rogalska, E.; Belzecki, C. *J.Org.Chem.* **1984**, *49*, 1397. (k) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (l) Georg, G.I.; Akgun, E.; Mashava, P.M.; Milstead, M.; Ping, H.; WU, Z.J.; Vander Velde, D. *Tetrahedron Lett.* **1992**, *33*, 2111. (m) Farina, V.; Hauck, S.I.; Walker, D.G. *SynLett* **1992**, 761. (n) Bose, A.K.; Manhas, M.S.; van der Veen, J.M.; Bari, S.S.; Wagle, D.R. *Tetrahedron* **1992**, *48*, 4831. For the reaction of a chiral imine in the presence of a chiral catalyst see: (o) Hattori, K.; Miyata, M.; Yamamoto, Y. *J.Am.Chem.Soc.* **1993**, *115*, 1151.
6. All new compounds gave satisfactory analytical and spectral data. Optical rotations ($[\alpha]_D^{23}$, c 0.5 in $CHCl_3$): **7a**, + 91.0; **9a**, - 100.8; **10a**, - 42.1; **11a**, - 120.9.
7. The product of the reaction of (*S*)-5 with benzaldehyde is a > 10:1 mixture of the imine and of the corresponding oxazolidine (see for instance: Fulop, F.; Pihlaja, K.; Neuvonen, K.; Bernath, G.; Argay, G.; Kalman, A. *J.Org.Chem.* **1993**, *58*, 1967; Miao, C.K.; Sorcek, R.; Jones, P.-M. *Tetrahedron Lett.* **1993**, *34*, 2259). This material gave a single *trans* product in the condensation with thioester **13** in 75% yield. However, the reactions of other thioesters with this imine occurred in very low yields.
8. It must be noted that the major products **9a-11a** of the reaction of thioester **6** with the benzaldehyde imines derived from amines **3-5** have the same 4*R* absolute configuration. Since **3-5** feature OR groups of very different chelating ability, addition of the enolate on a chelated conformation of these imines seems unlikely. For an example of a highly stereoselective enolate addition to a chelated imine derived from (*S*)-**3** see ref. 5e.
9. The existence of the co-ordination between the pyridine nitrogen and the titanium atom has been demonstrated spectroscopically ; the importance of this co-ordination in determining the enolate geometry and the stereochemical outcome of the reaction has also been established (see reference 4).

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