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STEREOSELECTIVE ONE-POT SYNTHESES OF *trans*-3-AMINO-β-LACTAMS FROM ZINC ENOLATES OF N-PROTECTED α-AMINOACID ESTERS AND IMINES.

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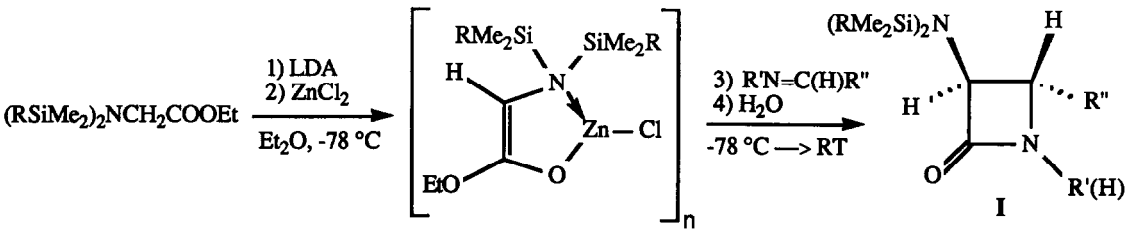
Abstract: A new one-pot synthesis of 3-amino-β-lactams that is based on the condensation of simple imines with zinc enolates of disilyl protected glycine esters is reported. Isolated yields are high and a *trans*-selectivity is observed.

Since 2-azetidinones are useful intermediates for preparing many naturally occurring and synthetic β-lactam antibiotics, such as penicillins, cephalosporins, monobactams and thienamycin,[1] much effort has been spent on the development of short and selective procedures for their preparation.[2] In recent years condensation reactions of imines with metal enolates[3] and silylketene acetals (Lewis-acid promoted)[4] have been shown to be useful for constructing the 2-azetidinone ring. Most of these studies have dealt with the synthesis of thienamycin intermediates, containing a hydroxyethyl side-chain at the 3-position of the 2-azetidinone ring and only little attention has been paid to the synthesis of intermediates containing an amino group at the 3-position. Recently it was reported that the reaction of lithium enolates of protected α-aminoacid esters with N-(cyanomethyl)-amines afforded 3-amino-4-unsubstituted β-lactams in reasonable to good yields[5] and with activated imines afforded predominantly *cis*-β-lactams in reasonable yields.[6] In a previous paper[7] we described a highly selective synthesis of *trans*-3-diethylamino-β-lactams from zinc enolates and imines. We now wish to report a stereoselective synthesis of *trans*-3-amino-β-lactams which are useful intermediates for the synthesis of monobactams.

Scheme 1



The zinc enolates of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethylester (STABASE)[8] and N,N-bis(trimethylsilyl)glycine ethylester[9] were prepared *in situ* from the corresponding lithium enolates, *via* transmetallation with one equivalent of zinc dichloride, and reacted with imines as depicted in Scheme 1. After aqueous workup the almost pure products (**Ia-f**) were purified by either crystallisation or silica-gel column chromatography.

A typical procedure is as follows: STABASE (10 mmol, 2.45 g) was added to a stirred solution of LDA (10 mmol) in 25 ml of diethyl ether at -78 °C. After 10 min at - 78 °C a solution of **dry** $ZnCl_2$ (10 ml, 1.0 M in diethyl ether)[10] was added and after another 15 min at -78 °C N-(benzylidene)methylamine (10 mmol, 1.19 g) was added. The solution was stirred for 1 hour at -78 °C and then allowed to reach room temperature, quenched with saturated aqueous NH_4Cl solution

and extracted with diethyl ether. The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* yielding 3.08 g (97%) of **Ia** as a pale yellow solid. The ^1H NMR spectrum showed the product to be a mixture of *cis*- and *trans*-isomers (*cis*/*trans* ratio 8:92).[11] Recrystallisation from diethyl ether/hexane afforded the pure *trans*-product as colourless crystals.

This standard procedure has been applied to the preparation of a series of β-lactams (**Ia-f**) reported in Table 1.[12] All reactions were carried out as one-pot syntheses on a 10 mmol scale and the reported yields are for the isolated products. These amino-protected 2-azetidinones (**Ia-f**) are easily desilylated by aqueous HCl to afford β-lactams with a free amino function at the 3-position.

A convenient procedure is as follows: To a solution of **Ia-f** in diethyl ether was added aqueous 1N HCl until the pH was ≈2. After 1 hour the solution was washed with diethyl ether, basified with solid KOH to pH was ≈8 and then extracted with dichloromethane. Drying (Na_2SO_4), and concentration *in vacuo* afforded the desilylated products in good yields (85-95%).[13]

Table 1 : Yields of 3-amino-2-azetidinones (**Ia-f**).

Compound	R	R'	R"	yield(%)	cis/trans ratio†
Ia	$-(CH_2)_2-$	CH_2Ph	Me	98	0 : 100
Ib	$-(CH_2)_2-$	Me	Ph	97	8 : 92
Ic	Me	Me	Ph	75	0 : 100
Id	$-(CH_2)_2-$	$SiMe_3$††/ H	Ph	90	30 : 70
Ie	Me	$SiMe_3$††/ H	Ph	70	11 : 89
If	$-(CH_2)_2-$	$SiMe_3$††/ H	$C{\equiv}CSiMe_3$	80	7 : 93

† determined by ^1H NMR integration. †† upon hydrolysis replaced by a proton.

Yields of lactams (**Ia,b,d** and **f**) starting from STABASE are generally high. The lower yields of lactams (**Ic** and **e**) starting from N,N-bis(trimethylsilyl)glycine ethylester are probably caused by the lower stability of the intermediate enolates; the yield appeared to depend on the period between the addition of $ZnCl_2$ (to form the zinc enolate) and subsequent addition of the imine. A short period (5 min) led to reasonable yields (70-75%), whereas a longer period (1 hour) resulted invariably in lower yields (<25%). Such an effect was not observed in the reactions starting from STABASE and we believe that the enolates of STABASE are stabilized due to a favourable entropy effect.

In general these reactions of zinc enolates with imines summarized in Scheme 1 show high *trans*- stereoselectivity. This contrasts with the reactions of lithium enolates with imines.[6] The reactions of the zinc enolates with N-(benzylidene)trimethylsilylamine show a lower *trans*-stereoselectivity than with the other imines. This is probably caused by retroaldolisation during the ring-closure step, as has been observed in reactions of Reformatsky-type enolates

with imines.[14] With N-(benzylidene)- trimethylsilylamine the ring-closure to β-lactam does not take place when warming up to room temperature, but requires additional heating (30 min, 50 °C). We do not yet fully understand, why this is the case for this particular imine.

We believe that the *trans*-stereoselectivity of our synthetic route results from a rigid cyclic chairlike transition-state of a Z-enolate with an E-imine.[15] Preliminary studies[16] on the structures of α-aminoacid ester enolates show that, as a consequence of intramolecular coordination of the nitrogen atom, the enolate anion is chelate bonded to the metal centre, thus fixing the Z-geometry around the central double bond. Additional studies concerning the scope of the presented procedure, elucidation of the mechanism, structures of the intermediate enolates, *etc.* are underway.

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10. It is very important to use **dry** $ZnCl_2$, otherwise the yields and stereoselectivity will be lower. Therefore $ZnCl_2$ was either prepared from Zn and dry HCl in diethyl ether, or commercially available $ZnCl_2$ was dehydrated in refluxing $SOCl_2$.
11. For *trans*-β-lactams $^3J_{3,4}$ is about 2 Hz, while for *cis*-β-lactams this value is about 6 Hz.
12. All products showed satisfactory ^1H NMR, ^{13}C NMR and I.R. spectra.
Selected ^1H NMR data: **Ia** *trans*, δ 7.13 (s, 5H, ArH), 4.59 (d, J=15 Hz, 1H, CH_2-Ph), 3.96 (d, J=15 Hz, 1H, CH_2-Ph), 3.79 (d, J=2.2 Hz, 1H, N-CH-CH-CH_3), 3.24 (dq, J=2.2 and J=6.0 Hz, 1H, N-CH-CH-CH_3), 1.32 (d, J=6.0 Hz, 3H, N-CH-CH-CH_3), 0.74 (s, 4H, Si-CH_2-CH_2-Si), 0.15 (s, 6H, $Si(CH_3)_2$), 0.09 (s, 6H, $Si(CH_3)_2$); **Ib** *trans*, 7.17-7.44 (m, 5H, ArH), 4.10 (d, J=1.8 Hz, 1H, N-CH-CH-Ph), 4.05 (m, 1H, N-CH-CH-Ph), 2.75 (br.s, 3H, N-CH_3), 0.63-0.85 (m, 4H, Si-CH_2-CH_2-Si), 0.12 (s, 6H, $Si(CH_3)_2$), 0.04 (s, 6H, $Si(CH_3)_2$); **Ib** *cis*, 4.74 (d, J=5.6 Hz, 1H, N-CH-CH-Ph), 4.50 (d, J=5.6 Hz, 1H, N-CH-CH-Ph); **Ic** *trans*, 7.08-7.42 (m, 5H, ArH), 4.18 (d, J=1.8 Hz, 1H, N-CH-CH-Ph), 4.09 (m, 1H, N-CH-CH-Ph), 2.73 (br.s, 3H, N-CH_3), 0.20 (s, 18H, $Si(CH_3)_3$; **Id** *trans*, 7.12 (s, 5H, ArH), 6.29 (br.s, 1H, NH), 4.23 (d, J=2.1

Hz, 1H, N-C<u>H</u>-CH-Ph), 3.92 (d, J=2.1 Hz, 1H, N-CH-C<u>H</u>-Ph), 0.70 (s, 4H, Si-C<u>H</u>$_2$-C<u>H</u>$_2$-Si), 0.13 (s, 6H, Si(C<u>H</u>$_3$)$_2$), 0.05 (s, 6H, Si(C<u>H</u>$_3$)$_2$); **Id** *cis*, 4.68 (d, J=5.3 Hz, 1H, N-C<u>H</u>-CH-Ph), 4.42 (d, J=5.3 Hz, 1H, N-CH-C<u>H</u>-Ph); **Ie** *trans*, 7.10 (s, 5H, Ar<u>H</u>), 6.25 (br.s, 1H, N<u>H</u>), 4.25 (d, J=2.0 Hz, 1H, N-C<u>H</u>-CH-Ph), 3.98 (d, J=2.0 Hz, 1H, N-CH-C<u>H</u>-Ph), 0.19 (s, 18H, Si(C<u>H</u>$_3$)$_3$); **Ie** *cis*, 4.64 (d, J=5.2 Hz, 1H, N-C<u>H</u>-CH-Ph), 4.46 (d, J=5.2 Hz, 1H, N-CH-C<u>H</u>-Ph); **If** *trans*, 7.25 (br.s, 1H, N<u>H</u>), 4.48 (d, J=2.1 Hz, 1H, N-C<u>H</u>-CH-C≡C), 3.61 (d, J=2.1 Hz, 1H, N-CH-C<u>H</u>-C≡C), 0.71 (s, 4H, Si-C<u>H</u>$_2$-C<u>H</u>$_2$-Si), 0.15 (br.s, 21H, Si(C<u>H</u>$_3$)$_2$); **If** *cis*, 4.74 (d, J=5.4 Hz, 1H, N-C<u>H</u>-CH-C≡C), 4.54 (d, J=5.4 Hz, 1H, N-CH-C<u>H</u>-C≡C).

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