Tetrahedron Letters, Vol.30, No.6, pp 765-768, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE SYNTHESES OF β-LACTAMS FROM ZINC ENOLATES OF N,N-DISUBSTITUTED α-AMINOACID ESTERS AND IMINES: SUBSTITUENT AND SOLVENT EFFECTS

Fred H. van der Steen, Henk Kleijn, Johann T.B.H. Jastrzebski and Gerard van Koten*.

University of Utrecht, Laboratory of Organic Chemistry, Dept. of Metal-Mediated Synthesis
Padualaan 8, 3584 CH UTRECHT, The Netherlands.

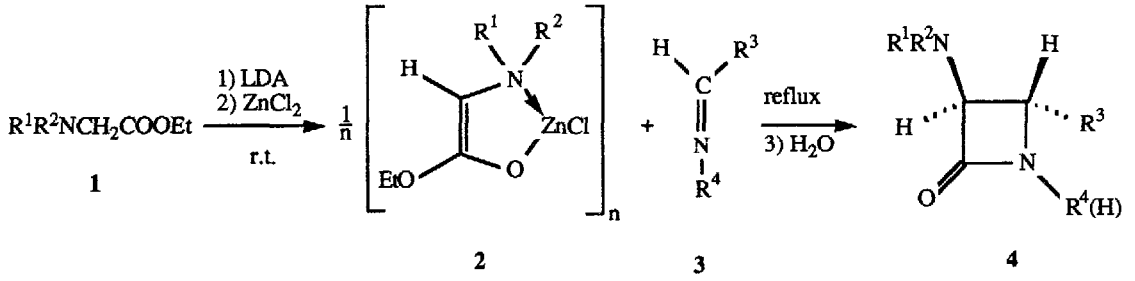
Abstract: A high yield synthesis of 3-(N,N-disubstituted)amino-β-lactams based on the condensation of zinc enolates with imines is reported. With the activated $Me_3SiC{\equiv}C\text{-}C(H){=}NSiMe_3$ (**3b**) exclusively *trans*-β-lactams are formed, whereas with PhC(H)=NMe (**3a**) there are substituent and solvent effects on the product distribution.

The condensation of Reformatsky-type reagents and imines to afford β-lactams was first reported by Gilman and Speeter in 1943.[1] Since this report, considerable attention has been given to the development of new β-lactam syntheses based on this reaction. Because the original reaction was not stereoselective,[2] in most later studies zinc was replaced by other metals, *e.g.* lithium, tin, zirconium, titanium, boron, aluminum and magnesium in order to obtain a stereoselective reaction, although this was not always successful.[3]

Investigations of the reactions of diorganozinc reagents with 1,4-dihetero-1,3-butadiene systems, revealed that diethylzinc reacted with α-iminoesters to form exclusively *trans*-β-lactams *via* intermediate zinc enolates.[4] We further developed this concept by reacting zinc enolates with imines. In previous papers we reported on highly stereoselective syntheses of *trans*-3-diethylamino-2-azetidinones and *trans*-3-amino-2-azetidinones by reacting zinc enolates of N,N-diethylglycine ethylester and disilyl protected glycine ethylesters with imines.[5] This report concerns the extension of the scope of these syntheses to the preparation of 3-(N,N-disubstituted)amino-2-azetidinones and the variation of the product distribution as a function of solvent and reactant substituents. This resulted in new insights into the reaction mechanism and factors which determine the product distribution, thus providing handles for controlling the sterochemistry of aldol-type reactions between metal enolates and aldimines in general.

The starting α-aminoacid esters **1a-f** were prepared from 1-bromoaceticacid ethylester and the appropiate secondary amine. The zinc enolates **2a-f** were prepared *in situ* from the corresponding lithium enolates, *via* transmetallation with one equivalent of zinc dichloride,[6] and reacted with imines **3a** and **3b** at the reflux temperature of the solvents (C_6H_6 or THF) as depicted in Scheme 1. After cooling to room temperature and aqueous work up the 2-azetidinones **4a-i** (Tables 1 and 2) were purified by either crystallization or silicagel column chromatography.[7]

Scheme 1



1 **2** **3** **4**

Table 1 : Reactions of zinc enolates of N,N-disubstituted α-aminoacid ethylesters with PhC(H)=NMe (**3a**).

Entry	Intermediate zinc enolate	R^1	R^2	Solvent	Reaction time (h)†	Product, yield (%)††	Cis / trans ratio†††
1	**2a**	Me	Me	C_6H_6	6	**4a**, 90	47 : 53
2				THF	8	80	70 : 30
3	**2b**	$-(CH_2)_4-$		C_6H_6	3.5	**4b**, 80	53 : 47
4				THF	8	60	73 : 27
5	**2c**	CH_2Ph	CH_2Ph	C_6H_6	8	**4c**, 80	33 : 67
6				THF	8	75	50 : 50
7	**2d**	Et	Et	C_6H_6	0.5	**4d**, 95	23 : 77
8				THF	1.5	90	58 : 42
9	**2e**	t-Bu	Me	C_6H_6	20	**4e**, 90	16 : 84
10				THF	40	70	25 : 75
11	**2f**	Ph	Me	C_6H_6	4	**4f**, 94	2 : 98
12				THF	4	80	18 : 82

† Reflux time, not optimized. †† Yields of the isolated crude products. ††† Determined by ^1H NMR integration of the characteristic proton signals of the crude products.[8]

Reactions of the zinc enolates **2a**-**2f** with N-(benzylidene)methylamine (**3a**) yield mixtures of *cis*- and *trans*-β-lactams. Changing the solvent from benzene to tetrahydrofuran results in lower yields and an increase in the amount of *cis*-β-lactams formed. We believe that the first step in the reaction is activation of the incoming imine *via* coordination of the imino-nitrogen atom to the zinc atom of the enolate, after which C-C bond formation occurs. Because of its strong donor properties tetrahydrofuran will preferentially complete the coordination-sphere around the zinc atom and this implies that coordination of the imine requires prior dissociation of a zinc-THF bond. Furthermore, in tetrahydrofuran the energy difference between the transition states leading to either *cis*- or *trans*-β-lactams is probably smaller than in benzene; this is expressed by the increase in the amount of *cis*-β-lactam formed. Recently we succeeded in isolating pure aluminium enolates of N,N-dimethylglycine methylester (Z-enolates with intramolecular Al-N coordination), which we will use to study the solvent effect in detail.[9]

We assume that the key step (C-C bond formation) of the reaction proceeds *via* cyclic chair or boat transition states, as suggested by other authors.[10] We have ample evidence that the intermediate zinc enolates are formed in one predominant conformation; reactions of the zinc enolates **2** with trimethylsilylchloride at room temperature resulted in the almost exclusive formation of Z-trimethylsilylketene acetals.[11] As a consequence of intramolecular coordination of the nitrogen atom to zinc resulting in chelate bonding of the enolate anion, the Z-isomer is expected to be more stable than the E-isomer. In the absence of Zn-N coordination the latter should be more stable on pure steric grounds.[12] Since the conformation of imines **3a** and **3b** is preferably E, there are two possible transition states for C-C bond formation starting from the Z-enolate: a chair and a boat form, that lead to the formation of *trans*- and *cis*-β-lactams respectively.[14] The energy difference between the two transition states is influenced by steric and electronic effects of the substituents and solvent. A small energy difference will result in low stereoselectivity of the C-C bond formation. The results given in Table 1 suggest that the energy difference is mainly determined by steric factors. The reactions with **2a**, where the two methyl groups on the amino-nitrogen atom are the least sterically demanding, show no selectivity (Entries 1 and 2), whereas the reactions with **2e**, containing a large tertiary-butyl group on the amino-nitrogen atom, show a good stereoselectivity (Entries 9 and 10).

Surprisingly, the reactions with **2f** show an even better stereoselectivity (Entries 11 and 12), although it was expected that the Ph,Me substitution of the nitrogen-donor atom would lead to a lower basicity (*i.e.* weaker chelate coordination) and consequently to stabilization of the E-enolate of **2f**. However, trapping of **2f** with trimethylsilyl chloride showed it to be exclusively the Z-isomer,[11] *i.e.* with the amino-nitrogen atom suitably positioned for chelate

bonding. It is known that the Zn-O bonding is the main bonding component in these zinc enolates, with the weaker Zn-N bonding, depending on the basicity of the nitrogen-donor atom, being prone to association-dissociation processes. It is the influence of the phenyl group on the strenght of the Zn-N bonding that can influence the stereoselectivity of the C-C bond formation. Thus, through delocalization of electron density by the phenyl group in **2f** the amino-nitrogen atom becomes less basic and a longer zinc-nitrogen coordination bond results. Consequently in the boat transition state the methyl and phenyl groups on the amino-nitrogen atom come closer to the phenyl group on the imino-carbon atom , while in the chair transition state these groups move further away from the methyl group on the imino-nitrogen atom, *i.e.* the chair transition state is more stabilized and the boat transition state is further destabilized. This increased energy difference between the transition states when a phenyl group is present on the amino-nitrogen atom is most likely the reason for the observed high stereoselectivity.

It is possibile, although in our opinion not likely, that the formation of *cis*-β-lactams results from retroaldolisation before the ring-closure step.[15] Especially when the ring-closure step is slow and requires prolonged heating, retroaldolisation may take place and this possibility is currently being investigated.

Table 2 : Reactions of zinc enolates of N,N-disubstituted α-aminoacid ethylesters with $Me_3SiC{\equiv}C\text{-}C(H){=}NSiMe_3$ (**3b**).

Entry	Intermediate zinc enolate	R^1	R^2	Solvent	Reaction time (h)†	Product, yield (%)††	Cis / trans ratio†††
1	**2a**	Me	Me	C_6H_6	4	**4g**, 90	<1 : >99
2				THF	4	65	<1 : >99
3	**2d**	Et	Et	C_6H_6	0.5	**4h**, 97	<1 : >99
4	**2f**	Ph	Me	C_6H_6	2	**4i**, 94	<1 : >99

† Reflux time, not optimized. †† Yields of the isolated crude products. ††† *Cis*-isomer not detected with ^1H NMR.[8]

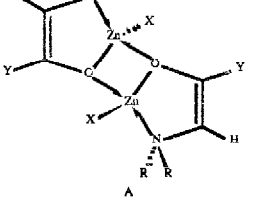
As can be deduced from Table 2, the substituents on the imine also have a great influence on the stereochemical outcome of the reaction. Reactions of zinc enolates **2a**, **d** and **f** with the reactive N-(3-trimethylsilyl-2-propylidene)-trimethylsilylamine (**3b**) resulted in the exclusive formation of *trans*-β-lactams **4g**, **h** and **i**. Even in tetrahydrofuran, there is no formation of *cis*-β-lactam (Entry 2). So with imine **3b** (as with trimethylsilylchloride) the influence of the substituents on the amino-nitrogen atom of the enolate is negligible. Most likely, the energy of activation for the chair transition state is much lower than for the boat transition state and accordingly exclusive formation of *trans*-products results. The reactions with imine **3b** are of particular interest, since the trimethylsilylacetylenic group at the 3-position of the β-lactams offers a good opportunity for further derivatization towards active antibiotics.

Further studies of the mechanism and the syntheses of new β-lactams using metal enolates are underway.

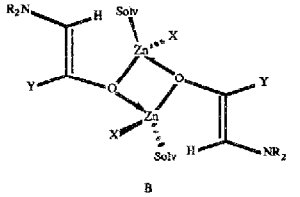
References and notes:

1. H. Gilman, M. Speeter, J.Am.Chem.Soc., 65, 2255 (1943).
2. F. Dardoize, J.L. Moreau, M. Gaudemar, Bull.Soc.Chim.Fr., 1668 (1973).
3. See for example: a) D.J. Hart, C-S. Lee, W.H. Pirkle, M.H. Hyon, A. Tsipouras, J.Am.Chem.Soc., 108, 6054 (1986); b) T. Imori, M. Shibasaki, Tetrahedron Lett., 27, 2149 (1986); c) T. Yamada, H. Suzuki, T. Mukaiyama, Chem.Lett., 293 (1987); d) M. Wada, H. Aiura, K. Akiba, Tetrahedron Lett., 28, 3377 (1987); e) G. Iwasaki, M. Shibasaki, Tetrahedron Lett., 28, 3257 (1987); f) G.I. Georg, J. Kant, H.S. Gill, J.Am.Chem.Soc., 109, 1129 (1987); g) C. Gennari, I. Venturini, G. Gislon, G. Schimperna, Tetrahedron Lett., 28, 227 (1987); h) L.E. Overman, T. Osawa, J.Am.Chem.Soc., 107, 1698 (1985); i) D.A. Burnett, D.J. Hart, J. Lin, J.Org.Chem., 51, 1930 (1986); j) G. Cainelli, D. Giacomini, M. Panunzio, G. Martelli, G. Spunta, Tetrahedron Lett, 28, 5369 (1987); and references cited therein.
4. M.R.P. van Vliet, J.T.B.H. Jastrzebski, W.J. Klaver, K. Goubitz, G. van Koten, Recl.Tr.Chim.Pays-Bas, 106, 132 (1987).

5. a) J.T.B.H. Jastrzebski, F.H. van der Steen, G. van Koten, Recl.Trav.Chim.Pays-Bas, 106, 516 (1987); b) F.H. van der Steen, J.T.B.H. Jastrzebski, G. van Koten, Tetrahedron Lett., 29, 2467 (1988).
6. It is very important to use **dry** $ZnCl_2$, otherwise the yields and stereoselectivity will be lower. Therefore either $ZnCl_2$ was prepared from Zn and dry HCl in diethyl ether, or commercially available $ZnCl_2$ was dehydrated in refluxing $SOCl_2$.
7. All products showed satisfactory ^1H NMR, ^{13}C NMR and I.R. spectra.
Selected ^1H NMR data (200 MHz, C_6D_6): **4a** *trans*, δ 7.15-6.94 (m, 5H, ArH), 4.19 (d, J=2.1 Hz, 1H, N-CH-CH-Ph), 3.43 (br.s, 1H, N-CH-CH-Ph), 2.34 (s, 3H, N-CH_3), 2.20 (s, 6H, N-$(CH_3)_2$); **4a** *cis*, 7.15-7.07 (m, 5H, ArH), 3.90 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 3.37 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 2.27 (s, 3H, N-CH_3), 1.97 (s, 6H, N-$(CH_3)_2$); **4b** *trans*, 7.14-6.93 (m, 5H, ArH), 4.15 (d, J=2.1 Hz, 1H, N-CH-CH-Ph), 3.62 (d, J=2.1 Hz, 1H, N-CH-CH-Ph), 2.35 (s, 3H, N-CH_3), 2.63-2.21 (m, 4H, $NCH_2CH_2CH_2CH_2$), 1.53-1.27 (m, 4H, $NCH_2CH_2CH_2CH_2$); **4b** *cis*, 3.98 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 3.61 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 2.32 (s, 3H, N-CH_3); **4c** *trans*, 7.31-6.74 (m, 15H, ArH), 4.11 (d, J=1.9 Hz, 1H, N-CH-CH-Ph), 4.03 (br.s, 1H, N-CH-CH-Ph), 3.90 (d, J=13.6 Hz, 2H, NCH_2Ph), 3.57 (d, J=13.6 Hz, 2H, NCH_2Ph), 2.29 (s, 3H, N-CH_3); **4c** *cis*, 4.19 (d, J=5.0 Hz, 1H, N-CH-CH-Ph), 3.76 (d, J=5.0 Hz, 1H, N-CH-CH-Ph), 3.75 (d, J=13.6 Hz, 2H, NCH_2Ph), 3.51 (d, J=13.6 Hz, 2H, NCH_2Ph), 2.37 (s, 3H, N-CH_3); **4d** *trans*, 7.15-6.88 (m, 5H, ArH), 4.10 (d, J=1.7 Hz, 1H, N-CH-CH-Ph), 3.86 (br.s, 1H, N-CH-CH-Ph), 2.59 (m, 4H, NCH_2CH_3), 2.34 (s, 3H, N-CH_3), 0.89 (t, 6H, NCH_2CH_3); **4d** *cis*, 4.11 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 4.02 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 2.43 (s, 3H, N-CH_3), 2.43 (m, 4H, NCH_2CH_3), 0.64 (t, 6H, NCH_2CH_3); **4e** *trans*, 7.19-6.91 (m, 5H, ArH), 4.23 (br.s, 1H, N-CH-CH-Ph), 4.16 (d, J=1.8 Hz, 1H, N-CH-CH-Ph), 2.37 (s, 3H, $N(C(CH_3)_3)CH_3$), 2.35 (s, 3H, N-CH_3), 0.85 (s, 9H, $N(C(CH_3)_3)CH_3$); **4e** *cis*, 4.31 (d, J=5.2 Hz, 1H, N-CH-CH-Ph), 3.94 (d, J=5.2 Hz, N-CH-CH-Ph), 2.51 (s, 3H, $N(C(CH_3)_3)CH_3$), 2.10 (s, 3H, N-CH_3), 0.86 (s, 9H, $N(C(CH_3)_3)CH_3$); **4f** *trans*, 7.12-6.36 (m, 10H, ArH), 4.66 (br.s, 1H, N-CH-CH-Ph), 4.00 (d, J=1.8 Hz, 1H, N-CH-CH-Ph), 2.91 (s, 3H, N(Ph)CH_3), 2.31 (s, 3H, N-CH_3); **4f** *cis*, 4.87 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 4.02 (d, J=4.6 Hz, 1H, N-CH-CH-Ph), 2.64 (s, 3H, N(Ph)CH_3), 2.46 (s, 3H, N-CH_3); **4g** *trans*, 6.30 (br.s, 1H, NH), 3.97 (br.s, 1H, N-CH-CH-C≡C), 3.89 (d; J=2.1 Hz, 1H, N-CH-CH-C≡C), 2.09 (s, 6H, N-$(CH_3)_2$), 0.14 (s, 9H, $Si(CH_3)_3$); **4h** *trans*, 6.34 (br.s, 1H, NH), 4.30 (d, J=2.2 Hz, 1H, N-CH-CH-C≡C), 3.86 (d, J=2.2 Hz, 1H, N-CH-CH-C≡C), 2.49 (m, 4H, NCH_2CH_3), 0.89 (t, 6H, NCH_2CH_3), 0.15 (s, 9H, $Si(CH_3)_3$); **4i** *trans*, 7.15 (m, 2H, ArH), 6.80 (m, 3H, ArH), 5.98 (br.s, 1H, NH), 4.96 (br.s, 1H, N-CH-CH-C≡C), 3.62 (d, J=2.2 Hz, 1H, N-CH-CH-C≡C), 2.61 (s, 3H, N-CH_3), 0.16 (s, 9H, $Si(CH_3)_3$).
8. For *trans*-β-lactams $^3J_{3,4}$ is about 2 Hz, while for *cis*-β-lactams this value is about 6 Hz. Ratios were determined with 200 MHz ^1H NMR and checked by comparision with cis/trans mixtures of authentic samples.
9. A publication about the preparation of these aluminum enolates and their reactivity towards imines is in preparation.
10. D.A. Evans, J.V. Nelson, T.R. Taber, In "Topics in Stereochemistry", Vol. 13, "Stereoselective Aldol Condensations", ed. by N.L. Allinger, E.L. Eliel and S.H. Wilen, Wiley, New York (1982).
11. For **2a**, **e** and **f** E/Z ratio's are 5/95, 0/100 and 2/98 respectively. The conformational assignments are based on ^1H NOE difference NMR spectra. Detailed studies concerning the properties of the intermediate enolates and their reactions with trimethylsilylchloride will be published elsewhere.
12. A and B show the main structural features expected for the zinc amino-enolates (Y = OEt) having the Z and E configuration respectively. The dimeric structure A has been proven for Y = Me and X = Et by both NMR and X-ray studies.[13] Note that in the non-coordinate situation the free NR_2 substituent in a Z-isomer represents a group with considerable bulkiness, whereas this steric interference is much lower in the E-isomer. The rate of Z ↔ E equilibrium is under investigation. The role of $HN(i\text{-}Pr)_2$ on this equilibrium is being studied.



A



B

13. M.R.P. van Vliet, G. van Koten, P. Buysingh, J.T.B.H. Jastrzebski, A.L. Spek, Organometallics, 6, 537 (1987).
14. The formation of *trans*-β-lactams starting from the E-enolates is sterically almost impossible. The conformation of the zinc enolate of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-aceticacid ethylester is almost completely E (E/Z = 92/8); however, the reactions with this enolate are carried out under kinetic control. The Z-enolate is apparently far more reactive than the E-enolate, since the reactions with imines showed a fairly good *trans*-stereoselectivity.[5b]
15. J.L. Luche, H.B. Kagan, Bull.Soc.Chim.Fr., 2260 (1971).

Acknowledgement: This research has been financially supported by Gist-brocades n.v., The Netherlands.

(Received in UK 22 November 1988)