Recl. Trav. Chim. Pays-Bas **106**, 516–518 (1987) 0165–0513/87/09516–03$1.25

Selective Formation of 1,3,4-Trisubstituted and 3,4-Disubstituted *Trans*-β -lactams from Zinc Enolates and Imines

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

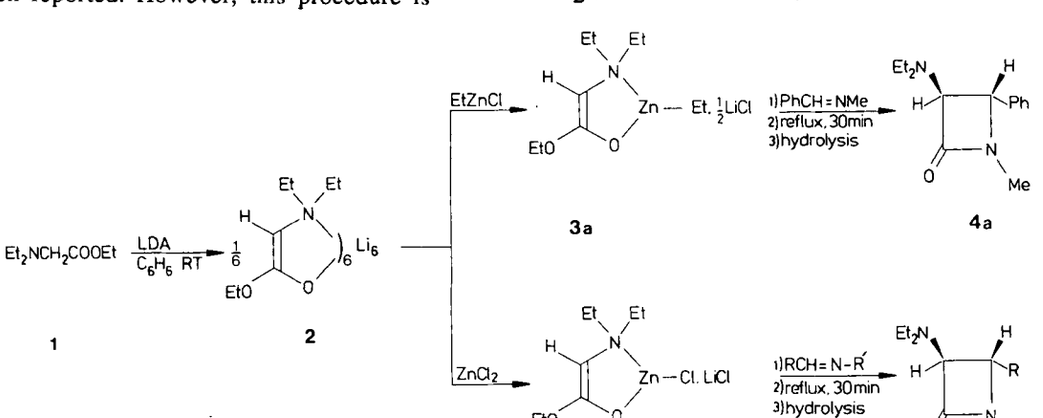
University of Utrecht, Laboratory of Organic Chemistry, Dept. of Metal-Mediated Synthesis Padualaan 8, 3584 CH Utrecht, The Netherlands.

(Received July 22nd, 1987)

Abstract. A new route for the high yield synthesis (better then 90%) of exclusively *trans*-β-lactams (azetidin-2-ones) is reported which involves the 1:1 reaction of an α-aminoacid ester zinc enolate with an appropriate imine. The reaction can be carried out as a 'one-pot' synthesis as has been demonstrated for the synthesis of *trans*-3-diethylamino-4-phenyl azetidin-2-one (93% yield). The novel zinc enolates have most likely a Z-geometry as a result of intramolecular chelate coordination. Evidence has been obtained that in the first step these zinc enolates react with the imine in a highly diastereoselective manner providing the threo aldolate which in a subsequent step undergoes ring closure to the azetidin-2-one.

β-Lactams are the principal building blocks of naturally occurring and synthetic penicillins[1] and therefore much effort has been spent in the development of new and efficient procedures for their preparation.[2] Compared to the large number of studies concerning the aldol condensation,[3] parallel investigations on the condensation of metal enolates with imines, which in principle would lead to β-lactams or β-lactam precursors, have been far less numerous. The stereochemical aspects of the latter reactions have been covered in a review of the Reformatsky reaction.[4] Procedures have been described in which β-lactams are obtained from the reaction of lithium ester enolates with either simple imines[5,6] or secondary N-(cyanomethyl)amines.[7] From these reactions the β-lactams are isolated either as *cis/trans* mixtures or solely as the *cis* stereoisomer. The synthesis of *trans*-3-benzoylamine substituted β-lactams, starting from the dianion of N-benzoyl substituted amino acid esters and imines, have been reported. However, this procedure is limited to the synthesis of 1,4-diaryl substituted β-lactams.[5] We recently found that 1,3,4-trisubstituted *trans*-β-lactams are the exclusive products from the reaction of α-iminoesters with diethylzinc.[8a] In these reactions zinc enolates were proposed as important intermediates. We now report the use of this knowledge for an easy and selective synthesis of 1,3,4-trisubstituted and 3,4-disubstituted *trans*-β-lactams that is based on the condensation reaction of an preformed α-aminoacid ester zinc enolate with an appropriate imine.

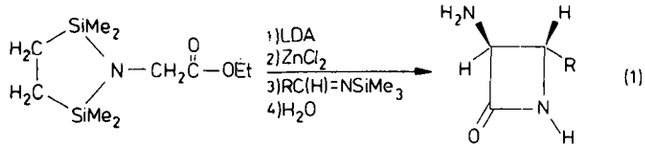
Reaction of a benzene solution of **3a**, the ethylzinc enolate of Et_2NCH_2COOEt (prepared from the reaction of the lithium ester enolate **2** (*vide infra*) with EtZnCl) , with one equivalent of N-methylbenzaldimine (80°C, 1/2 h.) affords in quantitative yield the β-lactam *trans*-1-(N,N-diethylamino)--4-phenylazetidin-2-one, **4a** , and ethylzinc ethoxide as shown in Scheme 1. Under the same conditions **3b**, the chlorozinc enolate of Et_2NCH_2COOEt (prepared from **2** and $ZnCl_2$), reacts with N-methylbenzaldimine to afford the same



	Lactam	Yield	starting imine
4a R=Ph	R'=Me	95%	R'=Me
4b R=Ph	R'=CH_2Ph	98%	R'=CH_2Ph
4c R=Ph	R'=H	93%	R'=$SiMe_3$
4d R=C≡C-Ph	R'=H	98%	R'=$SiMe_3$
4e R=C≡C-$SiMe_3$	R'=H	97%	R'=$SiMe_3$

Scheme 1

trans-azetidin-2-one in high yield. The preparation of this *trans*-β-lactam can be carried out as a facile "one-pot" synthesis as follows. Firstly lithiumdiisopropylamide (LDA) is generated in benzene solution by reaction of diisopropylamine with n-butyllithium, then one equivalent of the N,N-diethylglycine ethylester **1** is added, followed by one equivalent of anhydrous $ZnCl_2$. Finally N-methylbenzaldimine is added, the reaction mixture refluxed for 30 minutes and the product isolated after hydrolysis and work up. This synthesis of *trans*-β-lactams has been extended to a variety of 3,4-disubstituted and 1,3,4-trisubstituted compounds **4a-4e** which have been prepared in high yield, from the appropriate imines . The use of silyl protecting groups is noteworthy since they provide a route to the 3,4-disubstituted *trans*-β-lactams **4c-4e** ; the trimethylsilyl group at the 1 position of the initially formed *trans*-β-lactams is removed by hydrolysis during the aqueous work up. It has been shown that the use of N-silyl protected amino acid esters and trimethylsilyl substituted imines are important starting materials for the synthesis of 1-unsubstituted[15] and 3-amino substituted[16] β-lactams. The potential of this new route is particularly demonstrated by the easy synthesis of *trans*-3-amino-4-substituted azetidin-2-ones (see eqn 1), the principal building blocks of β-lactam antibiotics.

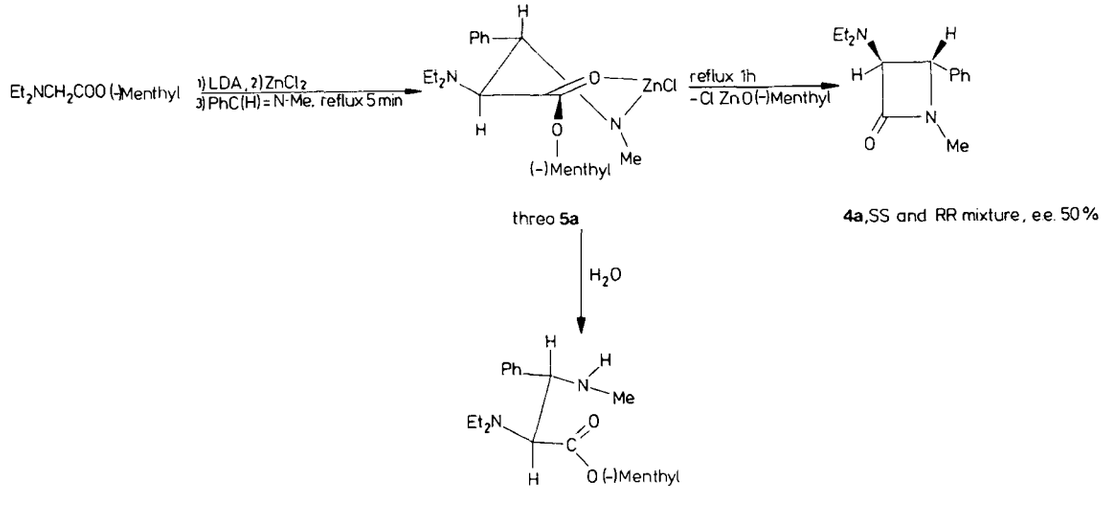


(1)

R=Ph, Yield 80%

the N,N-diethylglycine ethylester **1** is added, followed by one equivalent of anhydrous $ZnCl_2$. Finally N-methylbenzaldimine is added, the reaction mixture refluxed for 30 minutes and the product isolated after hydrolysis and work up. This synthesis of *trans*-β-lactams has been extended to a variety of 3,4-disubstituted and 1,3,4-trisubstituted compounds **4a-4e** which have been prepared in high yield, from the appropriate imines . The use of silyl protecting groups is noteworthy since they provide a route to the 3,4-disubstituted *trans*-β-lactams **4c-4e** ; the trimethylsilyl group at the 1 position of the initially formed *trans*-β-lactams is removed by hydrolysis during the aqueous work up. It has been shown that the use of N-silyl protected amino acid esters and trimethylsilyl substituted imines are important starting materials for the synthesis of 1-unsubstituted[15] and 3-amino substituted[16] β-lactams. The potential of this new route is particularly demonstrated by the easy synthesis of *trans*-3-amino-4-substituted azetidin-2-ones (see eqn 1), the principal building blocks of β-lactam antibiotics.

The *trans*-β-lactams **4a-4e** were characterized by ^1H NMR spectroscopy, melting points and elemental analyses.[9] Preliminary experiments showed that reaction of the enantiomerically pure (-)menthyl ester of N,N-diethylglycine with N-methylbenzaldimine, under the conditions (1 h. reflux) of Scheme 2 , yields the two enantiomers of *trans*-β-lactam **4a** in a 2:1 ratio *i.e.* with an enantiomeric excess of 50%.[11] However , when this reaction mixture was quenched after 5 min. reflux, the non-cyclized product **5b** could be isolated and almost no *trans*-β-lactam had been formed, see Scheme 2. This latter observation indicates that the first step in this reaction is the formation of an aldolate (*i.e.* **5a** , see scheme 2) from the zinc enolate and an E-imine. Moreover, because only *trans*-β-lactams are found this aldolate must be formed in a highly diastereoselective manner and we believe that this species has a threo stereochemistry. The pericyclic transition states involved in this condensation step leading to **5a** are likely to be analogous to those proposed for aldehydes with the extra constraint imposed by the imine geometry.[3] We propose that the zinc enolate involved has a Z-geometry as a result of intramolecular chelate coordination as shown in **3a**



4a,SS and RR mixture, ee. 50%

Scheme 2

5b

and **3b** ; this geometry was established for the lithium enolate **2** by X-ray crystallography.[12] (Others have found that *cis-trans* mixtures of β-lactams result from erythro adducts formed from zinc ester enolates and imines under Reformatsky conditions).[13]

To our knowledge the new route described in this paper for the high-yield synthesis of exclusively *trans*-β-lactams is without precedent and studies regarding its synthetic scope are being carried out. Structural investigations of the enolates are also in progress. Both the ethylzinc enolate **3a** and the chlorozinc enolate **3b** appear to be formed as aggregates with LiCl (1.0 and 0.5 equiv. respectively) as depicted in Scheme 1. These species are soluble in benzene and provide complex temperature dependent 250 MHz. ^{1}H NMR spectra which have not yet been fully interpreted. Results of these investigations into both the applications and mechanism of this new synthetic route will be the subject of forthcoming papers.

Acknowledgement

We are grateful to Gist-Brocades N.V., The Netherlands, for financial support during this research. Thanks are due to Dr. D.M. Grove for critical and stimulating discussions and Mr. H. Kleijn for his experimental assistance.

References and Notes

1. Chemistry and Biology of β-Lactam antibiotics,Vol 1-3, *R.B. Morin,* and *M.Gorman,* Ed.; Academic Press, New York, London, 1982.
2. For a recent comprehensive review of β-lactam syntheses, see: *G.A. Koppel,* In 'Small Ring Heterocycles -Azetidines, β-Lactams, Diazetidines and Diaziridines'; *A.Hassner,* Ed., Wiley, New York, Chapter 2 (1982).
3. *D.A. Evans, J.V.Nelson,* and *T.R.Taber,* In 'Topics in Stereochemistry', Vol 13, 'Stereoselective Aldol Condensations',*N.L.Allinger, E.L.Eliel,* and *S.H.Wilen,* Wiley , New York, 1-115 (1982).
4. *M.Gaudemar* , Organomet. Chem. Rev. A , **8** , 183 (1972).
5. *G.Gluchowski , L.Cooper, D.E.Bergbreiter,* and *M.J.Newcomb,* J.Org .Chem.,**45**, 3413 (1980).
6. *D.J. Hart, K. Kanai, D.G. Thomas,* and *T-K. Yang,* J. Org. Chem., **48**, 289 (1983).
7. *L.E. Overman,* and *T.J. Osawa,* J. Amer .Chem. Soc., **107**, 1698 (1985).
8 a. *M.R.P. van Vliet, J.T.B.H. Jastrzebski, W.J. Klaver, K. Goubitz,* and *G. van Koten,* Recl. Trav. Chim. Pays-Bas, **106**, 132 (1987). b. These enolates are formed in the reaction of $ZnEt_2$ with, for example, the α−iminoketone t-BuN=C(H)C(Me)=O via the formation of the σ-N, σ-O-$ZnEt_2$ iminoketone precursor complex and subsequent migration of an ethyl group from zinc to the imino-N atom, see 8c.c. *M.R.P. van Vliet, G. van Koten, P. Buysingh, J.T.B.H. Jastrzebski,* and *A.L. Spek,* Organometallics, **6**, 537 (1987).
9. ^{1}H NMR spectra in $CDCl_3$ at 60 MHz, δ values in ppm relative to internal $(CH_3)_4Si$. Compound **4a** : ^{1}H NMR : δ 1.15 (t, 6H, NCH_2CH_3), 2.90 (q, 4H, NCH_2CH_3), 2.90 (s, 3H, NCH_3), 4.10 (d, 1H, NCHCHPh, $^3J_{HH}$ 1.6Hz.[10]), 4.60 (d, 1H, NCHCHPh, $^3J_{HH}$ 1.6Hz.[10]), 7.30 (m, 5H, Ph) ; Mp. 70-71°C; Analysis found (calcd.) C 72.13 (72.38), H 8.80 (8.68), N 11.73 (12.06).Compound **4b** : ^{1}H NMR : δ 1.20 (t, 6H, CH_2CH_3), 2.90 (m, 4H, NCH_2CH_3), 3.90 and 5.10 (d, d, 1H, 1H, NCH_2Ph, $^2J_{HH}$ 15 Hz.), 4.20 (d, 1H, NCHCHPh, $^3J_{HH}$ 1.5 Hz.[10]), 4.60 (d, 1H, NCHCHPh, $^3J_{HH}$ 1.5 Hz.[10]), 7.40 (m, 10H, Ph). Compound **4c** : ^{1}H NMR : δ 1.20 (t, 6H, NCH_2CH_3), 2.90 (q, 4H, NCH_2CH_3), 4.15 (d, 1H, NCHCHPh, $^3J_{HH}$ 1.5 Hz[10]), 4.80 (d, 1H, NCHCHPh, $^3J_{HH}$ 1.5 Hz[10]), 6.70 (s, 1H, NH), 7.30 (m, 5H, Ph) ; Mp. 128-130°C; Analysis found (calcd) C 71.29 (71.53), H 8.39 (8.31), N 12.79 (12.83). Compound **4d** : ^{1}H NMR : δ 1.15 (t, 6H, NCH_2CH_3), 2.95 (q, 4H, NCH_2CH_3), 4.45 (s, 2H, NCHCHC≡C and NCHCHC≡C), 6.10 (s, 1H, NH), 7.30 (s, 5H, Ph); Mp. 116-117 °C; Analysis found (calcd) C 74.29 (74.35), H 7.56 (7.49), N 11.57 (11.56). Compound **4e** : ^{1}H NMR : δ 0.30 (s, 9H, $Si(CH_3)_3$), 1.15 (t, 6H, NCH_2CH_3), 2.80 (q, 4H, NCH_2CH_3), 4.25 (d, 1H, NCHCHC≡C, $^3J_{HH}$ 1.5 Hz.[10]), 4.40 (d, 1H, NCHCHC≡C, $^3J_{HH}$ 1.5 Hz.[10]), 6.55 (s, 1H, NH) ; Mp. 108-109°C ; Analysis found (calcd) C 60.07 (60.46), H 9.16 (9.30), N 11.67 (11.75).
10. A value of about 2 Hz for $^3J_{HH}$ is typical for *trans*-β-lactams, for *cis*-β-lactams this value is about 6 Hz.: *H.B. Luche, H.B. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango,* and *C. Zelwer,* Tetrahedron, **24**, 1275 (1968).
11. ^{1}H NMR spectroscopy of a $CDCl_3$ solution of racemic **4a** shows a resonance at 4.60 ppm assigned to the hydrogen atom at the 4-position. On addition of tris[3-trifluoromethylhydroxy -methylene)-d-camphorato]europium(III) one obtains instead two resonances in a 1:1 intensity ratio (separated by about 0.3 ppm) due to the presence of equivalent amounts of the two enantiomers. For the product obtained from the reaction of the enantiomerically pure (-)menthyl ester the intensity ratio of these resonances was 2:1.
12. *J.T.B.H. Jastrzebski, W.F. van de Mieroop,* and *G. van Koten,* J. Organometal. Chem., submitted.
13. Although it has been previously shown that reaction of several zinc ester enolates[14a] with N-phenylbenzaldimine[14b] at temperatures from -10 to -18° C affords exclusively erythro adducts,[14c,e] upon warming *cis-trans* mixtures of β-lactams are obtained from these aldolates . In these cases it was shown that the loss in stereochemistry was due to retroaldolization . In the present study it is most probably the exclusive Z-enolate formation that is crucial for the observed stereoselectivity.
14. a The stereochemistry of these enolates was not established,but for steric reasons these are most likely to have been E. b. The preferred geometry for aldimines is E. c. *J.L. Luche,* and *H.B. Kagan, Bull. Soc. Chim. Fr.,* 2260 (1971). d. *F. Dardoize, J.L. Moreau,* and *M.C. Gaudemar,* R. Acad. Sci., Ser. C, **270**, 233 (1970). e. *F. Dardoize, J.L. Moreau,* and *M. Gaudemar,* Bull. Soc. Chim. Fr., 1668 (1973).
15. *D.A. Burnett, D.J. Hart* and *J. Liu,* J. Org. Chem., **51**, 1929 (1986).
16. *D.J. Hart, K. Kanai, D.G. Thomas* and *T.K. Yang,* J. Org. Chem., **48**, 289 (1983).