Recl. Trav. Chim. Pays-Bas **111**, 497–498 (1992) 0165–0513/92/11497–02$1.00

Preliminary Communication

Diastereo- and enantio-selective synthesis of *trans*-3-phenyl- and *trans*-3-styryl-2-azetidinones via zinc ester enolates and imines.

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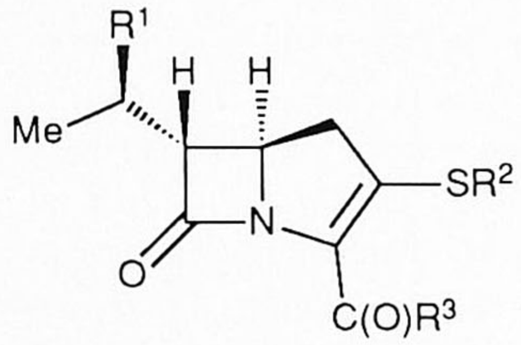
(Received September 24th, 1992)

Abstract: Zinc enolates of phenyl- and *trans*-styryl-acetic acid methyl ester react with excellent diastereoselectivety and good enantioselectivety (e.e. 64 to 91.5%) with imines in high yields to *trans*-2-azetidinones. The corresponding lithium enolates reacted with much lower selectivity and yields.

β-Lactams are the principal building blocks of naturally occurring and synthetic penicillins[1] and therefore continuing interest exists in the development of new and efficient procedures for their preparation[2]. Recently we reported that the zinc-mediated condensation of α-aminoacid ester enolates with imines to 3-amino-substituted β-lactams occurs with excellent conversions and in many cases gives products with excellent diastereo- and enantio-selectivity.[3] Furthermore, we have shown that the zinc-mediated condensation of ester enolates with imines under proper reaction conditions affords exclusively *trans*-β-lactams with conversions >95%,[3,8] in contrast to the lithium-mediated reaction which usually gives *cis* or mixtures of *cis* and *trans*-β-lactams.[2b] Because antibacteriological active 3-alkyl substituted β-lactams, *e.g.* PS5[4], PS6[4] and 3-α-hydroxyethyl substituted β-lactams, such as thienamycin (see Figure 1) all have *trans*-C_3-C_4 stereochemistry, a zinc-mediated synthetic route to these types of compounds looks very promising.

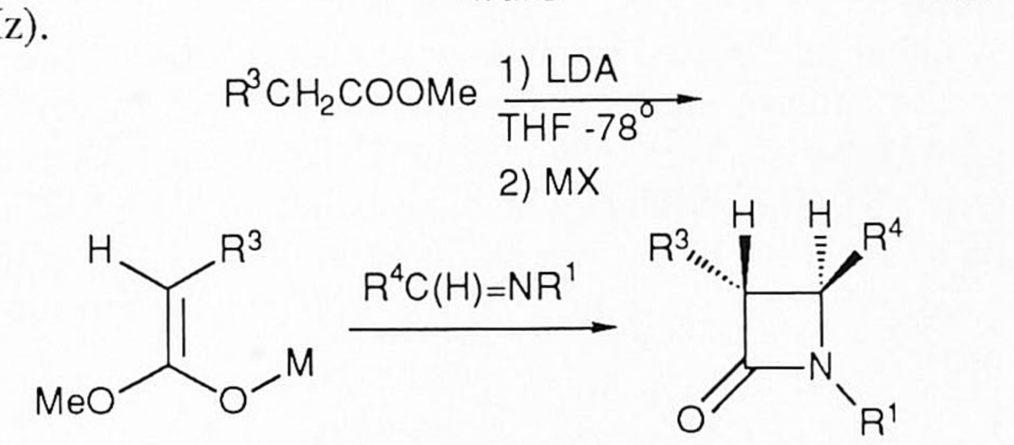


thienamycin R^1= OH, R^2= $CH_2CH_2NH_3^+$, R^3= O^-
(+) PS-5 R^1= H, R^2= CH_2CH_2NHAc, R^3= OH
(+) PS-6 R^1= Me, R^2= CH_2CH_2NHAc, R^3= OH

Fig. 1.

Here we report our first results in the synthesis of 3-hydrocarbon substituted β-lactams *via* the zinc-mediated condensation of ester enolates with imines. As model reactions we studied both the zinc- and lithium-mediated condensation of phenylacetic acid methyl ester and *trans*-styrylacetic acid methyl ester with several selected imines (see Scheme 1).

The reactions were carried out as simple one-pot syntheses in THF. The corresponding esters were deprotonated with LDA at -78°C affording the lithium enolates which were used either as such (entries 1, 3, 5, 7, 9 and 11, Table 1) or as the corresponding zinc enolates formed by transmetallation with one equivalent of $ZnCl_2$. After addition of the imine at -78°C, the reaction mixture was stirred at this temperature for 1h, 12h at -20°C, warmed to room temperature and then quenched with NH_4Cl/H_2O. The products were isolated by extraction with Et_2O/pentane 90/10 followed by evaporation of the solvents. The β-lactams **1**-**5** were obtained as crystalline solids, while **6** was obtained as an oil. All products were characterized by elemental analysis, ^1H and ^{13}C NMR spectroscopy[5] (for the structural assignment the ^1H resonances and coupling constants of the 3- and 4-protons of the β-lactam ring are especially informative, $^3J(HH)_{trans}$ ~2.4 Hz and $^3J(HH)_{cis}$ ~6 Hz).



	R^3	R^4	R^1
1	Ph	2-Furyl	TMS(H)**
2a (3*R*, 4*S*)	Ph	C(H)=NR^{2*}	R^{2*}
2b (3*S*, 4*R*)	Ph	C(H)=NR^{2*}	R^{2*}
3	Ph	C(H)=N*t*-Bu	*t*-Bu
4	*trans*-Styryl	2-Furyl	TMS(H)**
5	*trans*-Styryl	Ph	TMS(H)**
6	*trans*-Styryl	2-Pyridyl	R^{2*}

* R^2= (*R*)-α-methylbenzyl.
** (H) after hydrolysis.

Scheme 1.

Table1: Comparison of the reactions of lithium- and zinc-enolates of R^3CH_2COOMe with $R^4(H)C=NR^1$.

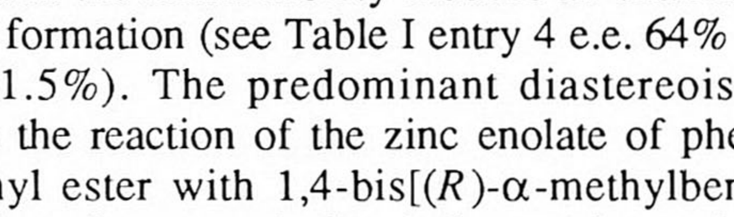
Entry	R^3	R^4	R^1	M	Yield%	*cis/trans*	e.e.%[d]
1	Ph	2-Furyl	TMS(H)	Li	80	7/93	-
2				ZnCl	90	0/100	-
3		$R^{2\,a}$	$R^{2\,a}$	Li	-[b]	-	-
4				ZnCl	94	0/100	64[c]
5		C(H)=N*t*-Bu	*t*-Bu	Li	-	-	-
6				ZnCl	91	0/100	-
7	*trans*-Styryl	2-Furyl	TMS(H)	Li	17	30/70	-
8				ZnCl	90	0/100	-
9		Ph		Li	-	-	-
10				ZnCl	95	0/100	-
11		2-Pyridyl	$R^{2\,a}$	Li	-	-	-
12				ZnCl	97	0/100	91.5

[a] R^2= *(R)*-α-methylbenzyl
[b] Instead of β-lactam, product **7** is formed (see text).
[c] The absolute configuration of the predominant diastereomer **2a** is 3*R*,4*S*
[d] e.e values with respect to the C-C bond formation.

From Table 1 it is obvious that the zinc-mediated route is superior to the lithium-mediated reaction. The zinc-mediated reaction affords the corresponding β-lactams in almost quantitative yields with exclusive *trans* stereochemistry (entries 2, 4, 6, 8, 10 and 12, Table I). When the same reaction was carried out with the lithium enolates, under the same experimental conditions, either no reaction occurs (entries 5, 9 and 11), or *cis/trans* mixtures of β-lactams are formed in low yields, (entries 1 and 7). In this respect it should be noted that others have shown that reaction of the lithium enolate of phenylacetic acid esters with N-phenylbenzaldimine affords the corresponding *trans* β-lactam in 35% yield[6], while reaction with N-methoxycarbonyl-isobutyraldimine affords the C-C coupled product in 82% yield[7].

Furthermore it appeared that the presence of a chiral substituent in the imine moiety induces an enantioselective C-C bond formation (see Table I entry 4 e.e. 64% and entry 12 e.e. 91.5%). The predominant diastereoisomer **2a** formed in the reaction of the zinc enolate of phenylacetic acid methyl ester with 1,4-bis[(*R*)-α-methylbenzyl]-1,4-diaza-1,3-butadiene was isolated diastereoisomerically pure by crystallisation from Et_2O. An X-ray crystal structure determination of **2a** unambiguously revealed a 3*R*,4*S* configuration of the C^3 and C^4 carbon atoms of the β-lactam[5]. A similar configuration for C^3 and C^4 has been found in *trans*-(3*R*,4*S*)-1-{(*R*)-α-methylbenzyl}-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)-2-azetidinone.[8]

A rather unexpected product was obtained from the reaction of the lithium enolate of phenylacetic acid methyl ester with 1,4-bis[(*R*)-α−methylbenzyl]-1,4-diaza-1,3-butadiene (entry 3). This product which, based on the ^1H NMR, could be assigned to be **7**, was obtained in 40% yield, while the expected β-lactam could not be detected in the reaction mixture.



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The formation of a C-N bond in contrast to the initial C-C coupling in the β-lactam formation suggests a mechanism involving the transfer of a radical which is formed *via* prior single electron transfer occurring in the first lithium enolate imine encounter complex. A similar process has been proposed for the transfer of a primary alkyl group from dialkylzinc to one of the nitrogen atoms of 1,4-diaza-1,3-butadienes.[9,10]

These preliminary results show that the zinc-mediated condensation of esters and imines is a useful synthetic method for the synthesis of 3-hydrocarbon substituted β-lactams. However, to obtain useful precursors for β-lactam antibiotics, modifications of the substituent present at the β-lactam are necessary, *e.g.* conversion of the styryl substituent in **4, 5** and **6** to an α-hydroxyethyl group.

These topics are currently under investigation and will be the subject of a forthcoming paper.

Acknowledgement

We are grateful to Gist-Brocades N.V., The Netherlands, for financial support and to Drs. J. Verwey and A. P. G. Kieboom for helpful discussions.

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