Tetrahedron Letters,Vol.23,No.4,pp 379-382,1982 0040-4039/82/040379-04$03.00/0
Printed in Great Britain

SYNTHETIC APPROACHES TO THIENAMYCIN: CARBON-CARBON BOND FORMATION AT C-4 OF AZETIDIN-2-ONES

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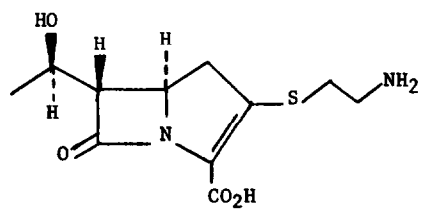
A mild and efficient method of β-lactam alkylation has been achieved using 4-acetoxy-2-azetidinone and a variety of silyl enol ethers.

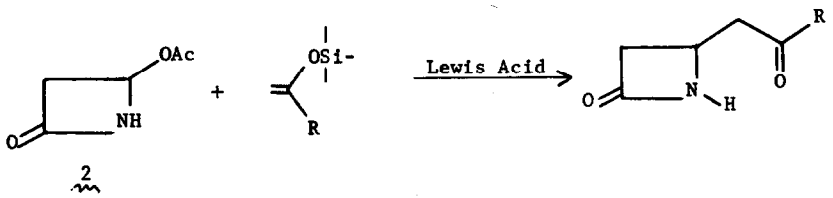
The discovery of thienamycin[1] 1 and analogous 1-carbapenem antibiotics derived from various strains of *Streptomyces* (e.g. Olivanic acid[2], PS-5[3]) has resulted in an intense interest in the synthesis of the novel carbapenem skeleton.

1



The formation of a carbon-carbon bond at the 4-position of an azetidin-2-one opens up a wide variety of synthetic pathways to the carbapenems. Although already demonstrated[4], the known methods suffer from low yields, complex reaction conditions, and functional group limitations. We wish to report a novel conversion of the readily available[5] 4-acetoxyazetidin-2-one (2) into 4-alkylazetidin-2-ones containing useful functionality. This carbon-carbon bond formation occurs under mild conditions, in good yield, and appears to be general.

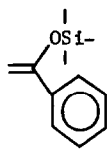
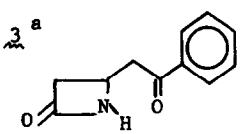
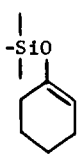
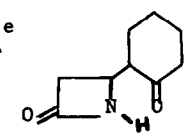
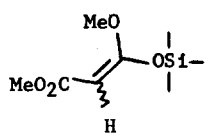
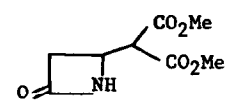
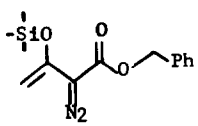
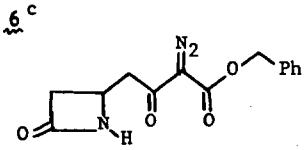
The Lewis acid catalyzed alkylation of ketones as their silyl enol ethers[6] has been well demonstrated[7]. Reetz has recently shown that allylacetates are excellent electrophiles in these reactions using mild Lewis acids[8]. Karady et. al. have demonstrated the $AgBF_4$ mediated reaction of silyl enol ethers with 1-(t-butyldimethylsilyl)-4-chloroazetidin-2-ones in a new synthesis of thienamycin from penicillin[9]. In a logical extension of these observations we wish to report that the use of 4-acetoxyazetidin-2-one (2) as the alkylating agent has resulted in the synthesis of a variety of carbapenem precursors (Equation I).



eq. I

A representative group of substrates successfully alkylated is shown in Table I.

Table I

Entry	Silyl enol ether	Catalyst	Product[d]	m.p.	Yield
A)		ZnI_2	3[a] 	138-140°C	83%
B)		ZnI_2	4[e] 	-	83%
C)		$ZnCl_2$	5[b] 	63-67°C	53%
D)		$ZnCl_2$	6[c] 	100-101°C	54%

Notes:
a) Ref. 4c
b) Ref. 4e
c) Ref. 10
d) all products had physical and spectral properties fully in accord with known or expected values
e) product 4 was isolated as a solid mixture of diastereomers - HPLC indicated 1:1 ratio

A typical experimental procedure is as follows:

A suspension of fused zinc iodide (160 mg, 0.5 mmol) in dichloromethane (3 mL) was treated at room temperature with 4-acetoxyazetidin-2-one (129 mg, 1.0 mmol) and the trimethylsilyl enol ether of acetophenone (384 mg, 2.0 mmol). After 2h, assay by TLC (SiO_2, 1:1 toluene:ethyl acetate, R_f = 0.15) and HPLC (Dupont Zorbax ODS - C_{18}, 25 cm, elution with 65% H_2O: 35% CH_3CN with 0.1% H_3PO_4 at 1 mL/min, R_t = 5.16 min) indicated completion of the reaction. The reaction mixture was diluted with ethyl acetate (50 mL) washed with saturated $NaHCO_3$ (50 mL), brine (50 mL), and dried over $MgSO_4$. Removal of the solvent gave the 4-Phenylcarbonylmethyl-2-azetidinone (3) as a solid contaminated with acetophenone. Recrystallization from benzene gave crystalline product (m.p. 138-140°C, lit[4c] m.p. 141-143°C) in 83% yield (157 mg).

It should be noted that, as in the case described by Karady, use of the silyl enol ether of benzyl diazoacetoacetate[9] (see Table I, entry D) allows the direct introduction of a four carbon synthon[4b] onto a β-lactam. This diazoketoester 6 has been cyclized[10] with rhodium (II) acetate to give the 1-carbapenem structure in near quantitative yield.

The incorporation of this chemistry into an efficient asymmetric synthesis of thienamycin will be reported shortly.

Acknowledgements

We would like to thank Dr. Sandor Karady and Mr. Joseph Amato of these laboratories for many helpful discussions. We are grateful for the many intermediates and procedures they supplied.

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(Received in USA 30 October 1981)

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