Pergamon

Tetrahedron Letters 40 (1999) 1025–1026

TETRAHEDRON LETTERS

Functionalization of a β-Lactam Ring *via* Nucleophilic Displacement of a 4-Vinyloxy Substituent

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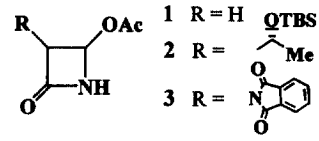
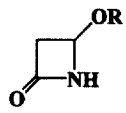
Received 2 October 1998; revised 17 November 1998; accepted 23 November 1998

Abstract : A vinyloxy group at C-4 of an azetidin-2-one can be easily displaced by nucleophiles in the presence of a Lewis acid catalyst.

Keywords : azetidinones ; cyclisation

Nucleophilic displacement at C-4 of an azetidin-2-one ring by C, O, or S nucleophiles is a crucial step in many syntheses of β-lactam antibiotics [1, 2, 3]. For example, 4-acetyloxyazetidin-2-ones **1-3**, are widely used as β-lactam building blocks because the acetoxy group readily undergoes nucleophilic substitution. Other groups at C-4 of the azetidin-2-one, like benzoyloxyl [1, 2], sulphonyl [1, 5, 6, 7] , oxazolinyl [1, 8], or chlorine [1, 9] can also be displaced by nucleophiles.





4 R = CH_2Ph
5 R = $CH{=}CH_2$

Recently, we have presented a new approach for the synthesis of 1-oxacephams from 4-benzyloxy- and 4-vinyloxazetidinones **4** and **5**, which are stable under basic conditions [10, 11, 12]. In the course of our studies leading to 1-oxacephams we focused attention on the selection of a β-lactam building block, which can be *N*-alkylated and subsequently the C-4 substituent can be transformed into a group suitable for nucleophilic displacement.

Unexpectedly, we noticed that the 4-vinyloxy residue, readily undergoes nucleophilic substitution in the presence of a Lewis acid catalyst in the same way that an acyloxy group does. For example, **6a**[1] having the electron rich benzyl ether residue at the terminal of the side chain, when treated with BF_3 etherate, afforded 1-oxacepham **7** and the C-benzylated acetaldehyde **8a** (Scheme 1). Alternatively, ozonolysis of the vinyl double bond in β-lactam **6a** gave formate **6b** which in the presence of BF_3 etherate afforded **7** and benzyl formate **8b**. Yields of the oxacepham **7** formation *via* both 4-vinyloxy- and 4-formyloxyazetidin-2-ones (**6a** and **6b**) were similar, (*ca.* 50%). Moreover, the *N*-unsubstituted β-lactam **5** undergoes condensation with alcohols in the same manner as 4-acetoxyazetidin-2-one.

1. All new compounds were fully characterised by spectroscopic data and microanalysis and/or HRMS.

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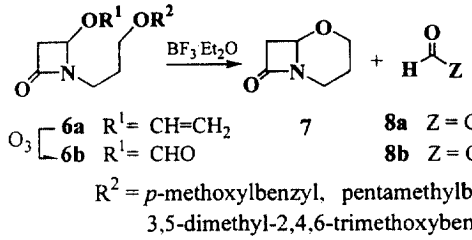
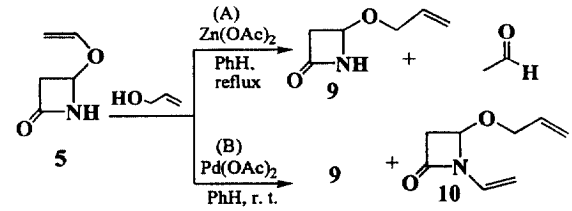
PII: S0040-4039(98)02516-7



Scheme 1



Scheme 2

Thus **5** when treated with allyl alcohol in the presence of zinc acetate in refluxing benzene afforded the 4-allyloxy derivative **9** [13] in 60% yield (Scheme 2, reaction A). The reaction (B) carried out at room temperature and catalysed with palladium acetate proceeded in more complicated way, because the product **9** was accompanied by *N*-vinylazetidin-2-one **10** (10-30% depending on the reaction time). Formation of the compound **10** is the result of the known condensation [14] of **9** with acetaldehyde liberated from **5** by the Lewis acid. We did not observe formation of the product **10** in the reaction (A) because acetaldehyde was continuously removed from the reaction mixture.

Ring openings of the highly strained oxapenem ring system by N or S nucleophiles [15, 16] are, to the best of our knowledge, the only examples of the substitution of an enol ether residue at C-4 of the azetidin-2-one. The substitution of a vinyloxyl substituent has gathered attention recently, as an alternative to that of the acyloxy group. For example, Rabiller *et al* [17] have presented enzymatic syntheses of disaccharides using vinyl-β-D-galactoside as a new type of sugar donor. In the opinion of the authors, the use of vinyl glycosides avoids the reverse transglycosylation reaction in a manner similar to vinyl acetate in lipase catalysed transesterification. Our results correspond well with this observation.

In conclusion, we have shown that a vinyloxy substituent at the C-4 carbon of a β-lactam ring undergoes a nucleophilic displacement in the presence of a Lewis acid in the same manner as an acyloxyl group does.

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