The Addition of Chlorosulphonyl Isocyanate to an Allenyl Acetate. The Preparation of a Versatile Intermediate for Antibiotic Synthesis

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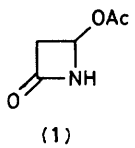
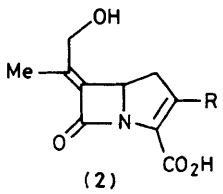
Chlorosulphonyl isocyanate and 1-acetoxy-3-methylbuta-1,2-diene react to form 4-acetoxy-3-(1-methylethylidene)azetidinone, a useful precursor to the skeletons of several antibiotics.

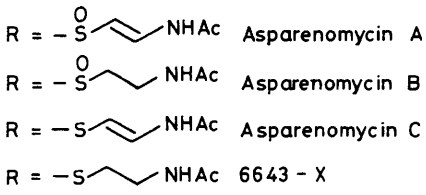
4-Acetoxyazetidinone (**1**), prepared by the addition of chlorosulphonyl isocyanate (CSI) to vinyl acetate,[1] is an extremely useful intermediate for the preparation of molecules containing the β-lactam moiety. Its versatility results from the ease with which the acetoxy substituent is substituted by a number of different heteroatom and carbon nucleophiles. The use of more highly substituted alkenes could, theoretically, introduce additional functionality at C-3 of the azetidinone. Unfortunately, CSI is reactive towards a wide variety of functional groups[2] and such a process is not usually feasible.

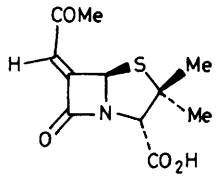


(1)



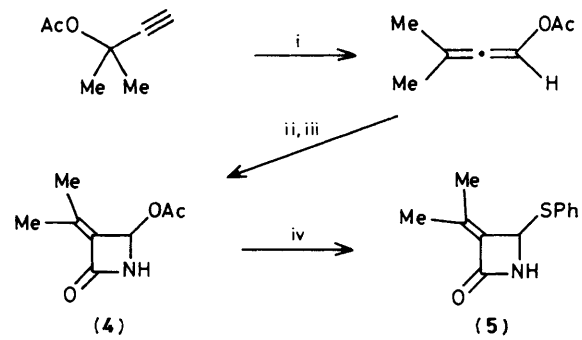
(2)





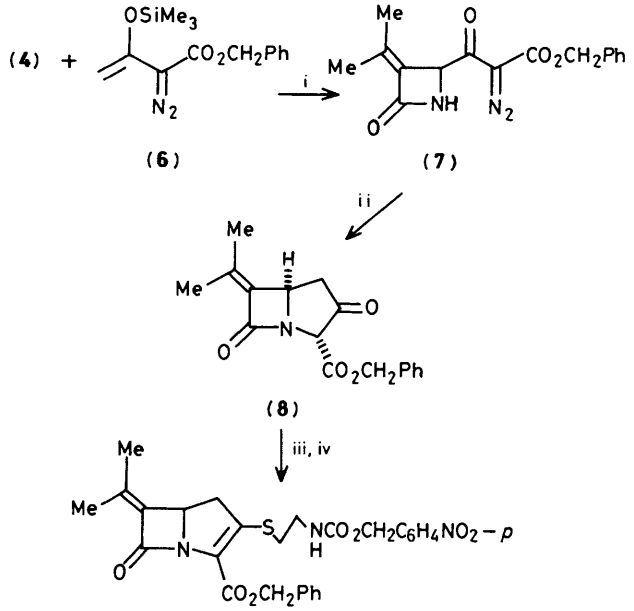
(3)

We have recently explored the reactions of CSI with allenes with the goal of producing useful intermediates for the synthesis of ene-type β-lactam antibiotics such as the asparenomycins[3] (**2**) and Ro 15-1903[4] (**3**). These compounds have been shown to possess potent β-lactamase inhibitory activity. The reaction of CSI with simple allenes has been explored by Moriconi and Kelly.[5] In an effort to produce a highly versatile intermediate, we decided to explore the reaction of CSI with allenyl acetates available from the silver-catalysed rearrangement of propargylic acetates.[6]



(4) (5)

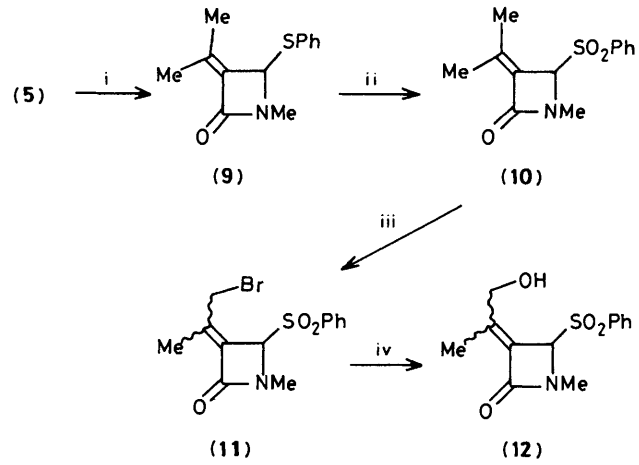
Scheme 1. i, 2.5 mol% $AgClO_4$; ii, CSI; iii, Na_2SO_3; iv, PhS^-Na^+.



Scheme 2. i, $ZnCl_2$; ii, $Rh(OAc)_2$; iii, $(PhO)_2POCl$, Pr^i_2NEt; iv, $HS[CH_2]_2NHCO_2CH_2C_6H_4NO_2$-*p*.

CSI was added to 1-acetoxy-3-methylbuta-1,2-diene at −23 °C in diethyl ether, followed by stirring at 0 °C for 2 h. After reductive work-up (Na_2SO_3, K_2HPO_4) and careful (<0 °C) concentration, a white solid was isolated to which we assigned the structure (**4**). When this material was treated with sodium thiophenoxide in methanol at 0 °C, the stable sulphide (**5**) [^{1}H n.m.r., δ 1.86 (s, 3H), 1.96 (s, 3H), 5.31 (s, 1H), 6.56 (br. s, 1H), 7.14—7.44 (m, 5H)] was isolated in 44% overall yield from the allene (Scheme 1). Addition of the trimethylsilyl enol ether (**6**) to (**4**) in the presence of $ZnCl_2$[7] resulted in the formation of the carbapenem precursor (**7**) [^{1}H n.m.r., δ 1.70 (s, 3H), 2.02 (s, 3H), 2.94 (dd, *J* 18, 10 Hz, 1H), 3.54 (dd, *J* 18, 3 Hz, 1H), 4.41 (br. d, *J* 10 Hz, 1H), 5.32 (s, 2H), 6.70 (br. s, 1H), 7.43 (s, 5H)] in 23% yield. Compound (**7**) was readily cyclized to (**8**) [^{1}H n.m.r., δ 1.80 (s, 3H), 2.09 (s, 3H), 2.37 (dd, *J* 19, 7 Hz, 1H), 2.87 (dd, *J* 19, 7 Hz, 1H), 4.60 (t, *J* 7 Hz, 1H), 4.69 (s, 1H), 5.27 (s, 2H), 7.44 (s, 5H)] which was elaborated as shown in Scheme 2.

We then methylated the sulphide (**5**) and oxidized the



Scheme 3. i, MeI, KOH; ii, 2 equiv. *m*-$ClC_6H_4CO_3H$; iii, NBS, azoisobutyronitrile; iv, H_2O, $NaHCO_3$.

product, the *N*-methyl sulphide (**9**), to the corresponding sulphone (**10**) in 39% overall yield. This sulphone was allylically brominated by *N*-bromosuccinimide (NBS) to produce a 3:1 mixture of *E*- and *Z*-allylic bromides (**11**) in 68% yield (Scheme 3). These bromides were hydrolysed to (**12**) on treatment with aqueous diglyme containing $NaHCO_3$ at 50 °C for 24 h (54%). These materials should allow the design of a wide variety of β-lactamase inhibitors.

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