A Stereospecific Synthesis of (4*R*)-Alkoxyazetidin-2-ones

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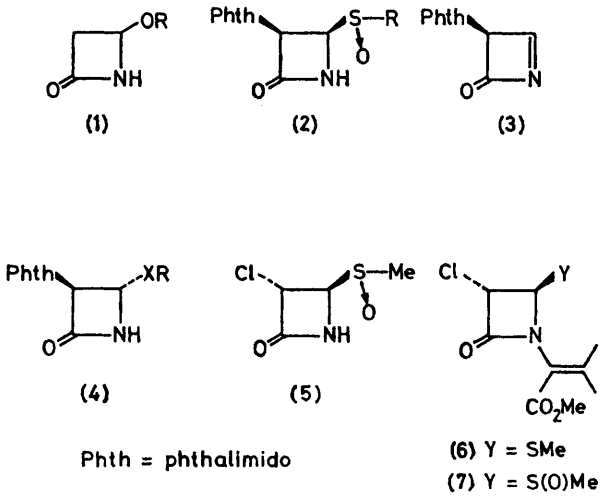
Summary (4*R*)-4-Alkoxyazetidin-2-ones have been obtained in highly stereospecific reactions of (3*S*,4*R*)-3-chloro-4-methylsulphinylazetidin-2-one and alcohols.

4-ALKOXYAZETIDIN-2-ONES of type (**1**)[1–3] have been used in the synthesis of clavam[2] and oxacepham[3] derivatives which are of interest as β-lactamase inhibitors and antibiotic agents. In these syntheses the 4-alkoxyazetidin-2-ones were obtained by displacement of the acetoxy-group in the readily available 4-acetoxy-azetidin-2-one in an acid- or base-catalysed reaction with the required hydroxy-compound. The yield in this reaction is highly influenced by steric elements in the nucleophile, being high with primary-, moderate with secondary-, and low with tertiary-hydroxy-compounds. Furthermore, while the (4*R*)-enantiomer is required for the synthesis of β-lactam antibiotics and β-lactamase inhibitors, the reported syntheses yielded racemic mixtures. A substitute for the 4-acetoxyazetidin-2-one which may serve as a suitable precursor for the efficient preparation of enantiomerically pure (4*R*)-4-alkoxyazetidin-2-ones was therefore sought. We have observed that (3*R*,4*R*)-3-phthalimido-4-alkylsulphinylazetidin-2-ones (**2**) undergo a facile thermal elimination of alkylsulphenic acid to give a highly reactive intermediate, presumably an azetinone (**3**), which reacted spontaneously with nucleophiles RXH to give *trans*-β-lactams of type (**4**).[4] The extension of the scope of this highly stereospecific transformation for the preparation of the title compounds is now described.

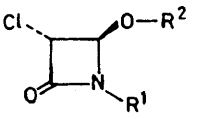


The (3*S*,4*R*)-3-chloro-4-methylsulphinylazetidin-2-one (**5**) was chosen as a substrate for the study of the C-4 alkoxylation with a secondary and a tertiary alcohol. The

chlorine atom in the α-configuration was considered to be sufficiently bulky to direct the attacking alcohol to the β-side and to be readily removable when desired. The starting material for its preparation was the optically active methylthioazetidinone (**6**) which was prepared according to the method of Thomas.[5] The methylthioazetidinone (**6**) was oxidized to the sulphoxide (**7**) (1 : 1 mixture of epimers) with sodium metaperiodate in methanol–water. The *N*-methoxycarbonylmethylpropenyl group was removed by ozonolysis in methylene dichloride at −78 °C followed by methanolysis at −10 °C to give the desired azetidinone (**5**).[6]

Heating the azetidinone (**5**) with an excess of 2-methylbut-3-yn-2-ol at 90 °C for 20 h afforded the (3*S*,4*R*)-3-chloro-4-alkoxyazetidinone (**8**) (68%), m.p. 63–64 °C, $[\alpha]_D^{26}$ + 31° (*c* 0·5, $CHCl_3$).† Reasonably, the reaction proceeded through the intermediacy of the (3*R*)-3-chloro-azetin-2-one (**11**) to which the tertiary alcohol added exlusively from the less hindered β-side. A similar alkoxylation of the azetidinone (**5**) with pentan-3-ol (100 °C; 9 h) gave the (3*S*,4*R*)-3-chloro-4-(1-ethylpropoxy)azetidin-2-one (**9**) (59%), $[\alpha]_D^{20}$ + 54 ° (*c* 1·4, $CHCl_3$).† The yield of the azetidinone (**9**) was considerably increased when a trapping agent for the methanesulphenic acid was added to the reaction mixture. For example, when a solution of the azetidinone (**5**), pentan-3-ol (excess), and methyl propiolate (5 equiv.) was heated under reflux for 7 h, the *trans*-product (**9**) was isolated in 86% yield. In this case, however, it was accompanied by the *cis*-product (**12**) (7%), m.p. 80—81 °C, $[\alpha]_D^{20}$ + 15·6 ° (*c* 0·9, CH_2Cl_2). The adduct (**13**) of methanesulphenic acid and methyl propiolate was isolated in 85% yield.[7]

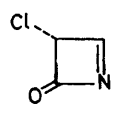
The chlorine atom, which functioned as a steric control element, was removed from the 3-chloroazetidinone (**9**) with Bu^n_3SnH. Thus, protection of the azetidinone nitrogen



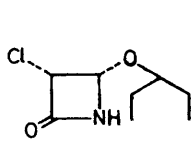
(**8**) R^1 = H, R^2 = $Me_2C(C{\equiv}CH)$

(**9**) R^1 = H, R^2 = Et_2CH

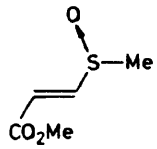
(**10**) R^1 = Me_2SiBu^t, R^2 = Et_2CH



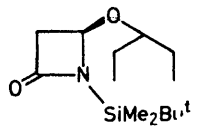
(**11**)



(**12**)



(**13**)



(**14**)

atom with Bu^tMe_2SiCl (dimethylformamide, diisopropylethylamine) gave the azetidinone (**10**) (87%) which on treatment with Bu^n_3SnH and a catalytic amount of azobisisobutyronitrile in toluene (90 °C; 1 h) afforded the enantiomerically pure (4*R*)-alkoxyazetidinone (**14**) (80%), $[\alpha]_D^{20}$ −125 ° (*c* 1·2, CH_2Cl_2).

The use of the described synthetic method for the preparation of β-lactamase inhibitors and β-lactam antibiotics is now in progress.

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† Satisfactory spectroscopic data were obtained for all new compounds.

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