Observations on the Reaction of Cephalosporin V Esters with Hypervalent Iodoarene Dihalides

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Reaction of cephalosporin V esters with 4-t-butyl iodobenzene difluoride is solvent dependent yielding the oxazoline (**5**) in acetonitrile and the fluoroazetidinone (**6**) in dichloromethane; in contrast, the iodoarene dichloride gives the rearranged isothiazole (**9**).

The increasing use of hypervalent iodine reagents for organic synthesis is an appropriate testimonial to their ability to act as a super nucleofuge in a variety of displacement reactions.[1] Particularly noteworthy are reactions in which normally non-nucleophilic groupings such as tosylate, triflate, and trifluoroacetate are introduced.

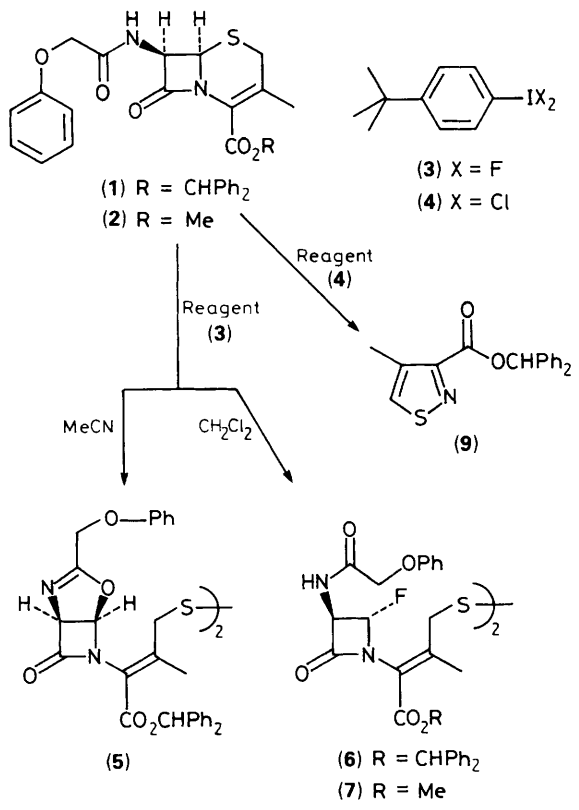
In view of the long known affinity of iodobenzene dichloride for the sulphur atom of penicillin derivatives during conversion to the corresponding sulphoxide in aqueous pyridine,[2] and as a continuation of our interest in the use of readily accessible[3] hypervalent iodoarene difluorides as effective reagents for regio- and stereo-selective fluorination,[4] we have examined the behaviour of cephalosporin V esters (**1**) and (**2**) with crystalline 4-t-butyl iodobenzene difluoride (**3**) and the corresponding dichloride (**4**). The results of this investigation are summarised in Scheme 1.

Thus, treatment of the benzhydryl ester (**1**) with one equivalent of reagent (**3**) in dry acetonitrile afforded the oxazoline derivative (**5**) (33%), presumably as a result of the precedented[5] participation of the side chain amide following stereoelectronically assisted ring opening of an initially formed sulphonium ion by the lone pair of the azetidinone nitrogen atom (Scheme 2).

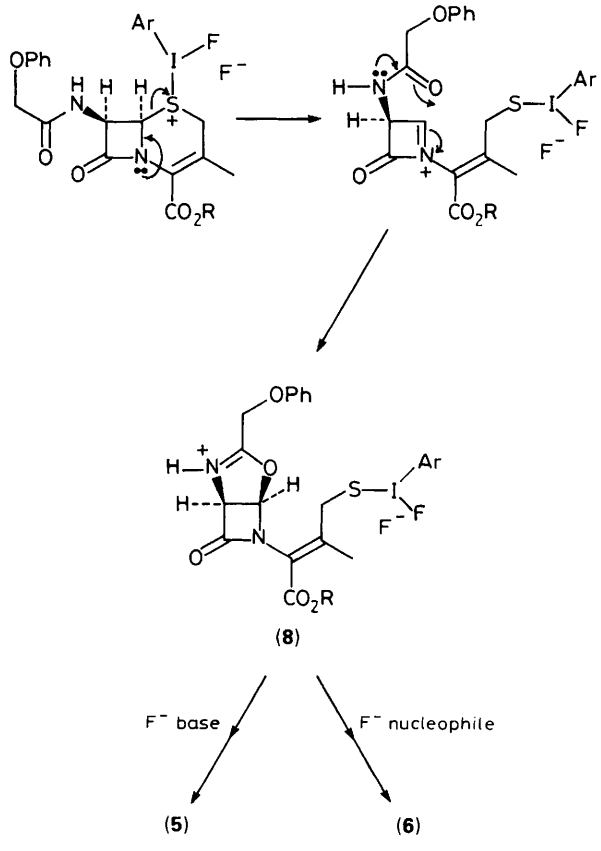
In contrast, the reaction with dichloromethane as solvent led to isolation of the chromatographically unstable fluoroazetidinone disulphide (**6**) in up to 30% yield. The indicated stereochemistry was readily deduced from the proton and fluorine n.m.r. spectra which indicated the absence of *cis* vicinal coupling between the azetidinone ring protons. The methyl ester (**2**) led to the analogous derivative (**7**) in similar yield.

The simplest mechanistic rationale for this solvent dependent divergence of behaviour (Scheme 2) is that the increased basicity of fluoride ion in acetonitrile[6] leads to deprotonation of intermediate (**8**) whereas use of dichloromethane permits nucleophilic attack.

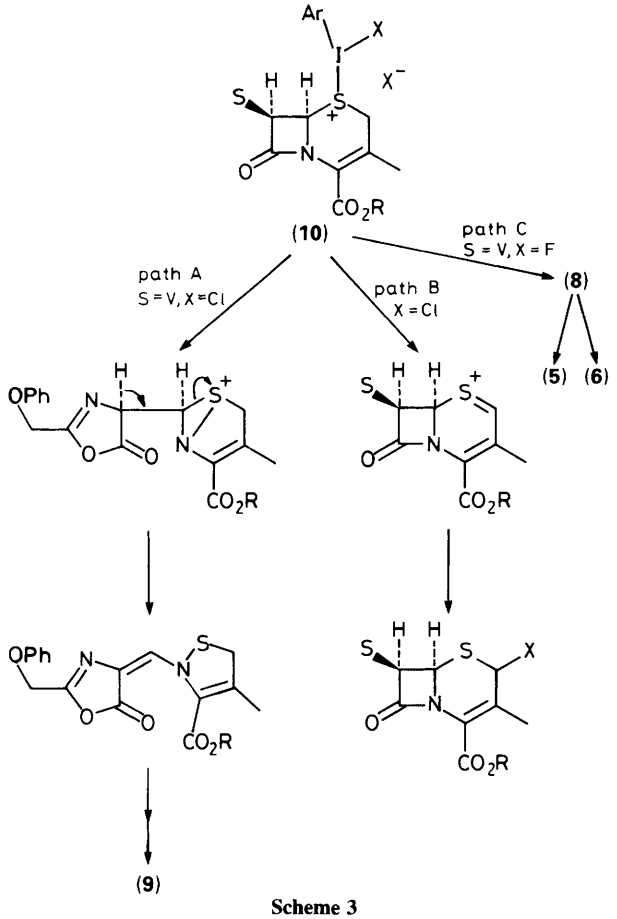
We have also studied the behaviour of cephalosporin (**1**) with the iodoarene dichloride (**4**) under anhydrous conditions, which leads to the rearranged isothiazole (**9**) (31%), whose structure was unambiguously determined by single crystal



Scheme 1



Scheme 2



Scheme 3

X-ray diffraction. Isothiazole formation has also been observed in the reaction of similar cephalosporin derivatives with *N*-chlorosuccinimide,[7] and an analogous mechanism involving initial oxazolone participation, a common occurrence in the acid catalysed cleavage of penicillins,[8] is likely in this instance (Scheme 3).

The striking contrast in behaviour of the iodoarene difluoride and corresponding chloride provides some indication of the relative leaving group ability of the initially formed halogenoiodoarene sulphonium salt (**10**) or the halogenosulphonium salt derived therefrom (Scheme 3). Thus the chlorosulphonium salt, as demonstrated by sulphoxide formation,[2] must be considered as a relatively long lived entity, capable in the absence of water of evolution either towards isothiazole formation (path A) or, in the absence of side chain participation,[7] towards Pummerer products (path B). The absence of such products in reactions of the iodoarene difluoride is accordingly indicative of a rapid cleavage of the C-6–S bond triggered by a superior leaving group (path C).

Interestingly, previous preparations of 4-fluoroazetidinone derivatives[9] led to the β-isomer as either the major or exclusive product. The present reaction therefore provides a mild method for regio- and stereo-specific obtention of the less common α-isomer.

One of us (J. J. E.) wishes to acknowledge the receipt of an S.E.R.C. CASE studentship in collaboration with ICI Pharmaceuticals. We are also grateful to Dr. D. J. Williams and Ms. A. M. Z. Slawin for the crystal structure determination which will be reported in the full paper.

Received, 31st May 1989; Com. 9/02262G

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