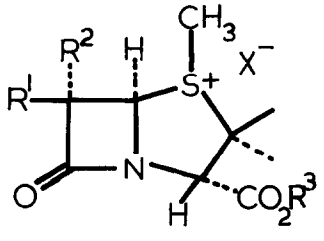
Tetrahedron Letters,Vol.27,No.27,pp 3199-3202,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

4-FLUOROAZETIDINONE DERIVATIVES FROM SECOPENICILLANATE SULPHONIUM TETRAFLUOROBORATES

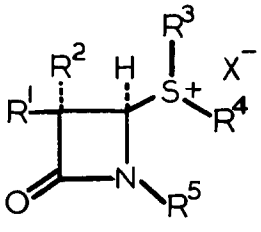
by John Brennan*, Faiq H.S. Hussain and Pedro Virgili
Department of Chemistry, UMIST, Manchester, M60 1QD, U.K.

Abstract: Reaction of certain secopenicillanate esters with trimethyloxonium tetrafluoroborate yielded 4-fluoroazetidinone derivatives presumably via the intermediacy of secopenicillanate sulphonium tetrafluoroborate salts.

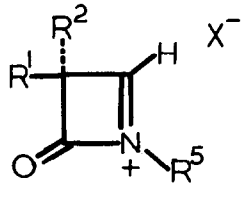
The chemistry of penicillanate methylsulphonium salts **(1)** has been studied in detail and such compounds have been shown to be capable of S-C(2) or S-C(5) cleavage depending upon reaction conditions and structural effects.[1] The chemistry of secopenicillanate sulphonium salts **(2)** has not been widely reported and the absence of a bicyclic structure in these would limit the potential modes of decomposition and ought to favour formation of azetidinium ion intermediates **(3)** by azetidinone C(4)-S heterolysis.



(1)

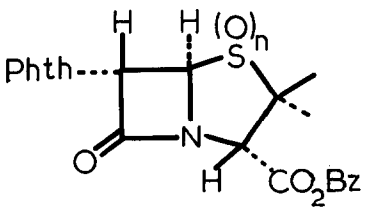


(2)

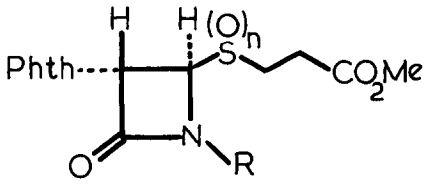


(3)

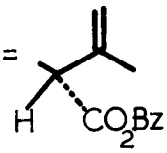
In order to test this hypothesis we synthesised a number of secopenicillanate derivatives and attempted to convert them into their sulphonium salts. Thus benzyl 6β-phthalimidopenicillanate was isomerised with DBU to the 6α-compound **(4)** and this was subjected to m-chloroperoxybenzoic acid oxidation[2] to yield S-oxides **(5)** which subsequently underwent thermolytic ring opening to **(6)** in refluxing methyl acrylate[3]; deoxygenation of **(6)** to **(7)** was accomplished with phosphorus tribromide[4] and reduction (H_2-Pt) of **(7)** yielded secopenicillanate derivative **(8)** in 68% overall yield from benzyl 6β-phthalimidopenicillanate.[5]



(4) n=0
(5) n=1



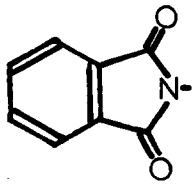
(6) n=1 R=



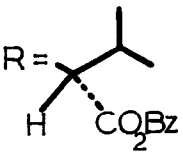
Bz = CH_2Ph

(7) n=0 R as (6)

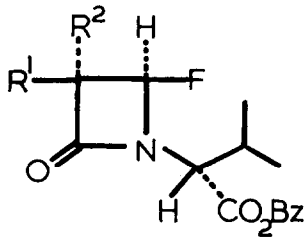
Phth =



(8) n=0 R=



Reaction of **(8)** with trimethyloxonium tetrafluroroborate in acetonitrile (-15° to 0°) led to the disappearance of starting material (as indicated by t.l.c.) and the appearance of a more polar intermediate which was assumed to be the corresponding sulphonium salt. Addition of a catalytic quantity of DBU resulted in rapid decomposition of the polar intermediate. Chromatography (silica-toluene/EtOAc 9:1) of the products yielded one major fraction ($[\alpha]_D^{20}$ = + 106°, C=0.06) which on the basis of its spectroscopic and analytical properties was assigned the structure **(9)**, and was isolated in 40% yield.



(9) R^1= H R^2= Phth

(10) R^1= Phth R^2= H

The i.r. spectrum of this compound showed strong C=O absorptions at 1800, 1795, 1780 and 1735 cm^{-1} and an absorption at 1035 cm^{-1} assigned to a C-F stretch. Proton nmr showed the absence of the original azetidinone C(4) substitution but the continued presence of the N(1) and C(3) substitutents; two doublets of doublets at δ 5.34 (1 H, J = 6.5, 1.0 Hz) and δ 6.39 (1 H, J = 72.5, 1.0 Hz) were assigned to the C(3) and C(4) protons respectively and suggested that these protons were in a trans configuration and that a fluoro substituent was present. Coupling constants of 72.3 and 6.2 Hz observed in the ^{19}F nmr were in accord with this (δ = -66.7 relative to CF_3CO_2H).[6]

A second compound which was isolated in low yield (ca. 2%) was assigned the isomeric 3β-phthalimido-4β-fluoro structure **(10)** on the basis of ^{1}H and ^{19}F nmr data while longer exposure of the crude reaction mixture to DBU increased the ratio of **(10)** to **(9)** to 1:1 (as observed by ^{19}F nmr), which suggested base catalysed isomerisation at C(3); the alternative assignment of this compound as the 3α, 4a-α diastereoisomer of **(10)** was rejected on the basis that epimerisation at C(3) would not be consistent with such a product.

The products observed in this reaction would be consistent with decomposition of the sulphonium salt to an azetidinium ion followed by approach by a tetrafluoroborate ion from the less hindered β-face and fluoride ion transfer; the failure to observe by h.p.l.c. or n.m.r. either of the two other possible diastereoisomeric 4α-fluorides was consistent with this proposal. Methanolysis and ethanolysis of 6α-chloropenicillanate sulphonium salts have been shown to yield products resulting from, respectively, predominant and exclusive attack upon the β-face[1]. While the role of DBU in this reaction is not clear, the formation of the same products was observed in its absence although more slowly and in lower yields.

Analogous results were obtained for the reaction between secopenicillanate **(7)** and trimethyloxonium tetrafluoroborate, but after conjugation of the double bond in **(7)**, attempts to effect the reaction under a variety of conditions were unsuccessful and resulted in degradation of the β-lactam system.

While the synthesis of 4-chloroazetidin-2-ones has been widely reported and their chemistry has been extensively studied,[7] routes to the corresponding 4-fluoro compounds are far fewer[8,9] and, perhaps as a result, their chemistry has received much less attention.

We thank the University of Salahaddin (Iraq) for a studentship to F.H.S.H. and the C.V.C.P. (U.K.) for an O.R.S. award to P.V.

References

1. P.M. Denerley and E.J. Thomas, J. Chem. Soc., Perkin Trans. I, 1979, 3175.
2. R.D.G. Cooper, P.V. De Marco and D.O. Spry, J. Amer. Chem. Soc., 1969, **91**, 1528.
3. M.D. Bachi, O. Goldberg, A. Gross and J. Vaya, J Org. Chem., 1980, **45**, 1477.
4. I. Ager, D.H.R. Barton, D.G.T. Greig, G. Lucente, P. G. Sammes, M.V. Taylor, G.H. Hewitt, B.E. Looker, A. Mowatt, C.A. Robson and W.G.E. Underwood, J. Chem. Soc., Perkin Trans I, 1973, 1187.
5. All compounds had satisfactory ir and nmr spectroscopic data and acceptable microanalytical or high resolution mass spectroscopic data.
6. Full data: nmr δ_H ($CDCl_3$, Me_4Si standard), 0.85 (3 H, d, J=6.5 Hz, CH_3), 0.93 (3 H, s, J=6.5 Hz, CH_3), 2.21 (1 H, m, $C\underline{H}(CH_3)_2$), 4.22 (2 H, dd, J=8 and 1.8 Hz, CHF-N-C$\underline{H}$) 5.15 and 5.24 (each 1 H, d, J=12 Hz, CH_2Ph), 5.34 (1 H, dd, J=6.5 and 1 Hz, C(3)H), 6.39 (1 H, dd, J=72.5 and 1 Hz, C(4)H), 7.29 (5 H, s, Ph), 7.67-7.82 (4 H, m, Phth).
   δ_F($CDCl_3$, CF_3CO_2H standard),-66.7 (dd, J=72.8 and 6.2 Hz), broadened resonances J $<$ 2 Hz unresolved. I.r. ($CHCl_3$), 1800, 1795, 1780, 1735, 1035 cm^{-1}. M.p. 92-94° Microanalysis found: C, 64.9; H, 4.8, N, 6.5; F, 4.6. $C_{23}H_{21}FN_2O_5$ requires C, 65.1; H, 4.9; N, 6.6; F, 4.5%.
7. See e.g. P.G. Sammes, "Recent Chemistry of the β-Lactam Antibiotics", Chem. Rev., 1976, **76** 113.
8. W. A. Spitzer, T. Goodson, S.R. Lammert and S. Kukolja, J. Org. Chem. 1981, **46**, 3568.
9. M. Taisuki, M. Hirotomo, N. Noriyoshi and M. Ochiai, Eur. P. Appl. 81110154.2 (1981).

(Received in UK 8 May 1986)