Tetrahedron Letters, Vol.22, No.21, pp 2025 - 2028, 1981
Printed in Great Britain

0040-4039/81/212025-04$02.00/0

AN EFFICIENT SYNTHESIS OF 2-ETHOXYCARBONYLCARBAPEN-1-EM-3-CARBOXYLIC ACID

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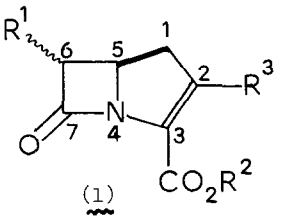
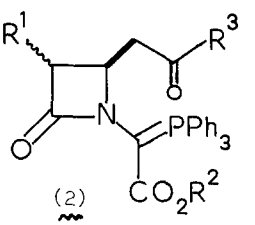
Summary: The title compound, as its sodium salt, has been prepared by a five-step sequence from 4-vinylazetidin-2-one.

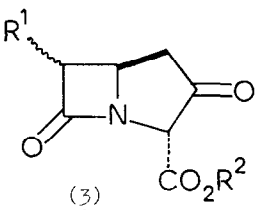
The potent antibacterial properties of thienamycin and its relatives,[1] members of the β-lactam group of antibiotics, have provoked considerable interest in the synthesis of carbapen-2-ems[2] of type (1). Two strategies have been particularly successful in this endeavour. The one relies upon constructing the 2,3-bond of the bicycle by the intramolecular Wittig reaction[3,4] and requires precursors of type (2). The other involves manipulation of carbapenams of type (3), prepared by a 3,4-bond closure involving an intramolecular carbene reaction;[5] diazo-compounds of type (4) serve as precursors in this route.



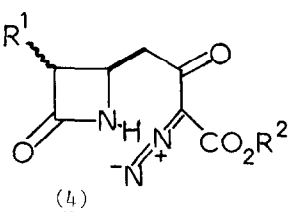
(1)



(2)



(3)

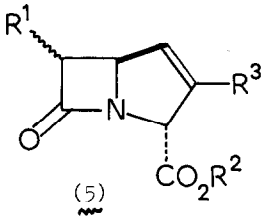


(4)

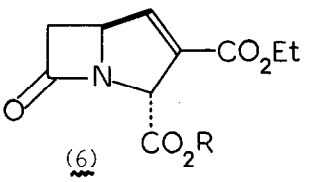
In contrast to carbapen-2-ems, carbapen-1-ems of type (5) have received only scant study. In principle, such compounds are convertible into carbapen-2-ems of type (1). Indeed, the first thienamycin synthesis depended upon effecting such an isomerisation; unfortunately,

in this instance, which was thermodynamically controlled and involved a substrate of type (5; R^3 = S·CH_2·CH_2·NH·CO_2·$C_6H_4NO_2$-p), the carbapen-1-em predominated.[3] In the hope of devising an effective isomerisation method, we have been interested in the efficient preparation of carbapen-1-ems of type (5). We are prompted to present our results, involving the synthesis of compounds of type (6), in view of the recent publications of Durst and his co-workers[6] and of Hirai and his co-workers[7] which are concerned with a similar objective.

In common with the Canadian workers,[6] our strategy for the construction of carbapen-1-ems of type (6) hinged upon forming the 1,2-double bond by the intramolecular Wittig reaction; this approach defined phosphoranes of type (7; X = O) as possible precursors.



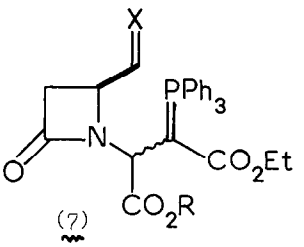
(5)



(6)

a; R = Bu^t c; R = H

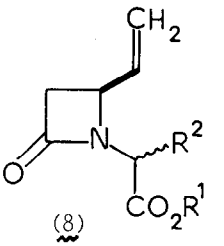
b; R = CH_2·C_6H_4·NO_2-p, d; R = Na



(7)

a; R = Bu^t, X = CH_2

b; R = CH_2·C_6H_4·NO_2-p, X = CH_2



(8)

a; R^1 = Bu^t, R^2 = OH c; R^1 = CH_2·C_6H_4·NO_2-p, R^2 = OH

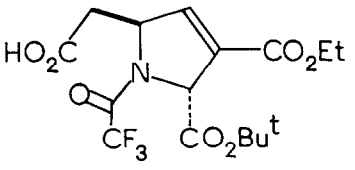
b; R^1 = Bu^t, R^2 = Cl d; R^1 = CH_2·C_6H_4·NO_2-p, R^2 = Cl

Treatment of 4-vinylazetidin-2-one[8] with t-butyl glyoxylate (5 mol·equiv.) and triethylamine (1 mol equiv.) in dry tetrahydrofuran[9] gave the carbinol (8a)[10] (80% after SiO_2 chromatography) as a 1 : 1 mixture of isomers. The carbinol (8a) was converted with lutidine-

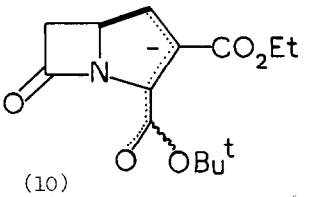
thionyl chloride[9] (each 1 mol equiv., tetrahydrofuran, -20°C) into the chloride (8b), which was immediately treated with ethoxycarbonyltriphenylphosphorane[11] (2 mol equiv., EtOAc); following silica gel chromatography, the phosphorane (7a) was isolated (44%). Ozonolysis[12] of the phosphorane (7a) (CH_2Cl_2-CF_3CO_2H, -78°C), reduction of the ozonide (Me_2S), and neutralisation ($NaHCO_3$) afforded the carbapen-1-em (6a)[10] (89% after SiO_2 chromatography), m.p. 61-62°C, as a single isomer.[13]

Similarly 4-vinylazetidinone was transformed into the carbinol (8c)[10] (80% after SiO_2 chromatography) and thence via the chloride (8d) into the phosphorane (7b)[10] (50% after SiO_2 chromatography). Ozonolysis of the phosphorane (7b) and work-up as before gave the carbapen-1-em (6b)[10] (87% after SiO_2 chromatography), as a single isomer.[13]

An attempt to convert the ester (6a) into the acid (6c) by the action of trifluoroacetic acid was unrewarding; cleavage of the β-lactam occurred prior to the loss of the t-butyl ester function and compound (9)[10] was isolated (80%). Hydrogenolysis (H_2, Pd/C) of the ester (6b) in the presence of sodium hydrogen carbonate, however, proved to be successful and afforded the salt (6d)[10] (73%) as a white solid. The salt, which showed no signs of decomposition in deuterium oxide over a 12 h period, showed no antibacterial activity.[14]



(9)



(10)

There was no evidence for the formation of the Δ^2-isomer when the carbapen-1-em (6a) was treated with 1,5-diazabicyclo[4.3.0]non-5-ene in deuteriochloroform. However, in the presence of deuterium oxide, exchange of the 3-proton was completed without any detectable exchange of the 1-proton. Presumably, the intermediate carbanion (10) shows a strong kinetic preference to protonate at position 3.

We thank Sandoz Forschungsinstitut, Vienna, for financial support and for the biological testing of the salt (6d).

References and Footnotes

1. R.D.G. Cooper in 'Topics in Antibiotic Chemistry', Vol. 3, ed. P.G. Sammes, Ellis Horwood Ltd., Chichester, 1979, p. 41.
2. The trivial name 'carbapenam' has been proposed for 7-oxo-1-azabicyclo[3.2.0]heptane (S.M. Schmitt, D.B.R. Johnston, and B.G. Christensen, J.Org.Chem., 1980, 45, 1135); this system is numbered in the same way as a penicillin [i.e. (1)].
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9. R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R.B. Woodward, Helv.Chim.Acta, 1972, 55, 408; J. Finkelstein, K.G. Holden, and C.D. Perchonock, Tetrahedron Lett., 1978, 1629.
10. This compound, obtained as a racemate, was characterised by its spectral properties.
11. A.H. Shingler and N.G. Weir in 'Recent Advances in The Chemistry of β-Lactam Antibiotics', eds. J. Elks, Special Publication No. 28, The Chemical Society, London, 1977, p. 153.
12. R.B. Woodward in 'Recent Advances in the Chemistry of the β-Lactam Antibiotics, ed. J. Elks, Special Publication No. 28, The Chemical Society, London, 1977, p. 167.
13. The relative configuration of the 3- and 5-positions of this compound was inferred by n.m.r. spectroscopy. Thus the C-3 proton appeared as a doublet of doublets (J 3 and 3 Hz) at ca. δ 5.25 (see the ref. quoted in footnote 2).
14. The Δ^1-isomer of thienamycin has been claimed to be a bactericide (U.S. 4 146 633; Chem.Abst., 1979, 91, 5109).

(Received in UK 11 March 1981)