

The Synthesis of a New Phosphorus-containing Bicyclic β -Lactam

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New phosphonites were shown to give Arbusov type reactions with 4-acetoxazetidin-2-one, and the synthesis of a novel 1-phosphinoceph-3-em is described.

Arbusov reactions of phosphites with 4-acetoxazetidin-2-one (**1**) have been shown¹ to afford an efficient route into a range of aminophosphonic acids and derived peptides. This reaction type has now been extended to include the synthesis of novel phosphorus analogues of the β -lactam antibiotics.

A range of phosphonites including (**2**)–(**8**) have been synthesised. Acetylenes (**2**),² (**3**),[†] and (**4**)[†] were prepared in good yields by the reactions of the lithium acetylides with diethyl phosphorochlorodite whereas we found that the alkenes (**5**)–(**8**)[†] were best prepared by reaction of the alkenyl Grignard reagents.³ All gave Arbusov reactions with (**1**), leading to potentially useful precursors of phosphorus containing bicyclic β -lactams. To illustrate a new bicyclic heteroannulation sequence, the reaction of (**6**) with 4-acetoxazetidin-2-one (**1**) is described.

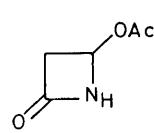
Dimethyl but-4-enylphosphonite (**6**) reacted with (**1**) at 110°C to give the phosphinate (**9**)[†] (80%) as a mixture of diastereoisomers which, although separable, were progressed as a mixture through the synthesis. Ozonolysis of (**9**) (CH_2Cl_2 , -78°C ; PPh_3 , then chromatography) gave the bicyclic β -lactams (**10**)[†] (72%) which existed in equilibrium (CDCl_3) with the aldehydes (**11**) (ratio 9:1).

Dehydration of (**10**) could be effected by base catalysed elimination of the methanesulphonate, but a more convenient process was by refluxing in toluene containing a trace of *p*-toluenesulphonic acid, giving the diastereoisomers (**12**)[†] in 36% yield. Nuclear Overhauser effect difference spectra at 400 MHz indicated the Δ^2 structures (**12**) rather than the Δ^3 isomers, although this assignment should be regarded with some caution. The problem of diastereoisomerism at phosphorus was resolved by deprotection (thiourea-methanol reflux⁴) (90%) to give the hygroscopic methyl isothiuronium salt (**13**), i.r. (KBr), 1770, 1660 cm^{-1} ; u.v. (EtOH), λ_{max} 243, (ϵ 5 200); ^1H n.m.r. (CD_3OD) 400 MHz, 7.14 [4H, br.s., (NH_2)₂], 6.45 (1H, dd, 4-H), 5.14 (1H, ddd, 3-H), 3.85 (1H, m, 6-H), 3.30 (1H, m, 7 β -H), 3.15 (1H, m, 7 α -H), 2.65 (3H, s, SMe), 2.48 [1H, m, $J(2\beta\text{-H}-2\alpha\text{-H})$ 18 Hz, 2 β -H], 2.13 [1H, m, $J(2\alpha\text{-H}-2\beta\text{-H})$ 18 Hz, 2 α -H]; the 2D J -resolved spectrum allowed assignment of ^{31}P - ^1H couplings, e.g. $J(2\beta\text{-H}-^{31}\text{P})$ 14.7 Hz, [M^-+1 (FAB)263, $\text{C}_8\text{H}_{14}\text{N}_3\text{O}_3\text{PS}$ requires M^-+1 , 263].

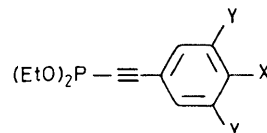
It is apparent from the 400 MHz spectrum with 2D J -correlation and 2D J -resolved analyses that the Δ^3 , rather than the Δ^2 structure, is favoured for the deprotected bicyclic β -lactam. Further studies will be reported.

We thank S.E.R.C. for postdoctoral support (S. J. M., P. M. W.) and for a grant towards the mass spectrometer, and

[†]New compounds gave satisfactory spectral data and elemental analysis or high resolution mass measurement, although (**13**) was analysed by negative ion low resolution fast atom bombardment (FAB) mass spectrometry.



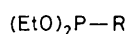
(1)



(2) X = Y = H

(3) X = OMe, Y = H

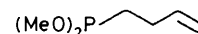
(4) X = Y = OMe



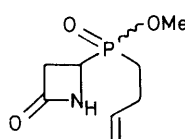
(5) R =

(7) R =

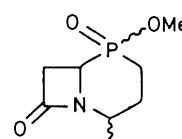
(8) R =



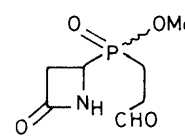
(6)



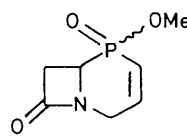
(9)



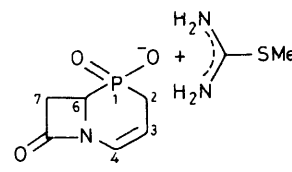
(10)



(11)



(12)



(13)

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