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-acetoxyazetidin-2-one, and the synthesis of a novel 1-phosphinoceph-3-em is described.

Arbusov reactions of phosphites with 4-acetoxyazetidin-2-one (**1**) have been shown[1] 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 heteroannelation sequence, the reaction of (**6**) with 4-acetoxyazetidin-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 reflux[4]) (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, 7β-H), 3.15 (1H, m, 7α-H), 2.65 (3H, s, SMe), 2.48 [1H, m, J(2β-H–2α-H) 18 Hz, 2β-H], 2.13 [1H, m, J(2α-H–2β-H) 18 Hz, 2α-H]; the 2D *J*-resolved spectrum allowed assignment of ^{31}P–^1H couplings, *e.g.* J(2β-H–^{31}P) 14.7 Hz, [M^-+1(FAB)263, $C_8H_{14}N_3O_3PS$ 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.

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† 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.

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