A Novel Rearrangement of 3-Phenylacetamido-1-hydroxyazetidin-2-one

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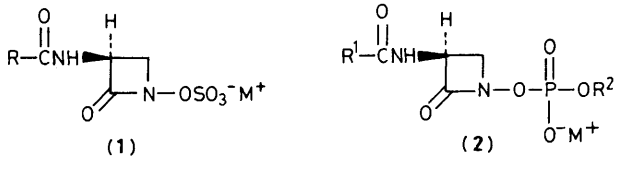
Reaction of 3-phenylacetamido-1-hydroxyazetidin-2-one (**3**) with methyl dichlorophosphate followed by quenching with water and work-up provided the hydroxyimidazolidinone (**4**), the structure of which has been determined by *X*-ray crystallography.

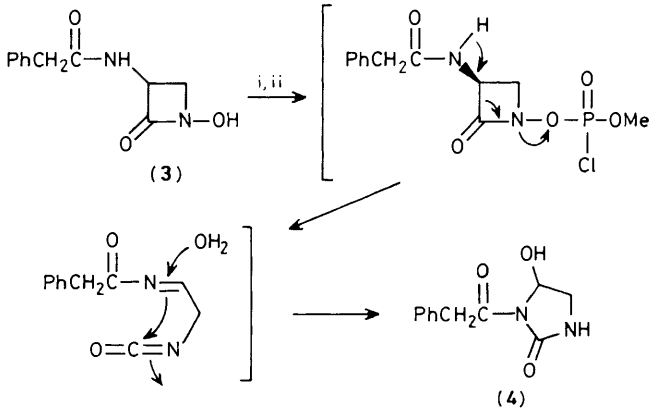
The recent synthesis and study of the biologically active monosulfactams (**1**)[1] encouraged us to investigate the synthesis of the corresponding *N*-phosphorylated-β-lactams (**2**). During this work we observed an unusual rearrangement of the 3-phenylacetamido-1-hydroxyazetidin-2-one (**3**) to 1-phenylacetyl-5-hydroxyimidazolidin-2-one (**4**).

A solution of compound (**3**)[2] and *N*-methylmorpholine in acetonitrile at 0 °C was treated with methyl dichlorophosphate. After 1 h water was added, followed by an additional equivalent of *N*-methylmorpholine in the expectation that the phosphate salt (**2**) would be formed. The mixture was then poured into EtOAc, washed twice with H_2O, dried, and evaporated. Chromatography, followed by recrystallization (EtOAc–hexanes), gave the rearranged imidazolidinone derivative (**4**) in 36% yield; m.p. 146—148 °C; i.r (KBr) 3325 (br.), 1720, and 1670 cm^{-1}; n.m.r. (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 5.94 (d, 1H), 5.73 (s, 1H), 4.44 (s, OH), 4.28 (s, 2H), 3.62 (dd, 1H), and 3.29 (d, 1H). The structure of (**4**) was also confirmed by *X*-ray crystallography (Figure 1).† Examination of the aqueous extracts indicated only further decomposed materials with no recovered β-lactam (**3**) nor the phosphorylated derivative (**2**).

Interestingly, under similar phosphorylation conditions, the azetidinone (**5**), in which the 3-amino group is fully protected,[3] gave the phosphorylated β-lactam (**6a**)‡ cleanly in 83% isolated yield (Scheme 2). Treatment of (**5**) with diethyl chlorophosphate gave (**6b**)‡ in 98% yield. Thus, the rearrangement of (**3**) to (**4**) may involve the phenylacetamido side chain and proceed as shown in Scheme 1. This type of rearrangement might also account for the low overall yields and instability of the intermediates in the preparation of the related β-lactams (**7**) reported by the Squibb group.[4]

The novel rearrangement of the azetidinone (**3**) provides a further indication of the chemical reactivity of *N*-hydroxy-β-lactams and complements their known thermal reactivity.[5]





Scheme 1. *Reagents:* i, *N*-methylmorpholine (1.1 equiv.), $Cl_2P(O)OMe$ (1.1 equiv.), MeCN, 0 °C; ii, *N*-methylmorpholine (1.1 equiv.), H_2O.

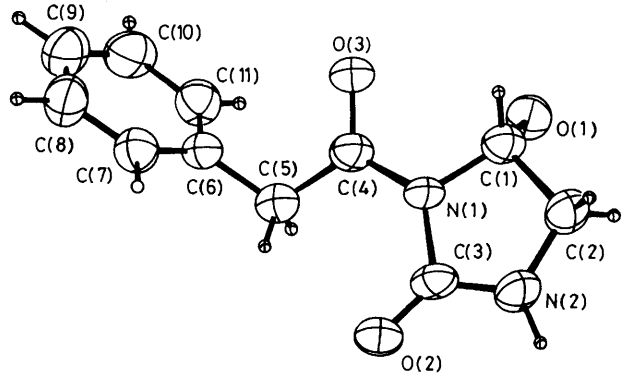
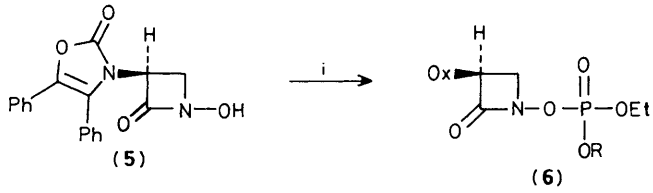


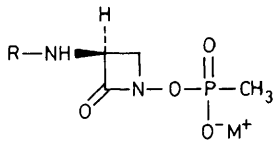
Figure 1. ORTEP plot of compound (**4**) (only one molecule, of three in the asymmetric unit is shown) with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms are unlabelled for clarity.



Scheme 2. *Reagents:* (**6a**) i, Et_3N (1.0 equiv.), $Cl_2P(O)OEt$ (1.0 equiv.), tetrahydrofuran, 0 °C; then H_2O. (**6b**) i, Et_3N (1.0 equiv.), $ClP(O)(OEt)_2$ (1.0 equiv.), tetrahydrofuran, 0 °C.

† *Crystal data:* $C_{11}H_{12}N_2O_3$, monoclinic, space group $P2_1/n$, a = 9.706(1), b = 12.534(2), c = 26.154(3) Å, β = 95.49(1)°, U = 3167.2 Å^3, Z = 12, D_c = 1.390, D_m = 1.390 g cm^{-3}; λ(Cu-K_α) = 1.541 84 Å; μ(Cu-K_α) = 8.1 cm^{-1}. Enraf-Nonius CAD4 diffractometer; graphite monochromated Cu-K_α radiation; θ–2θ scan to 2θ = 150°; 6519 unique reflections out of 7380 measured, 4446 with $F_o^2 > 3\sigma(F_o^2)$ used in solution; Lorentz–polarization correction; direct methods (MULTAN); C, N, O anisotropic; R = 0.050; R_w = 0.069. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

‡ (**6a**): i.r. ($CDCl_3$) 1800 and 1755 cm^{-1}; n.m.r. (90 MHz, $CDCl_3$) δ 10.78 (br. s, 1H), 7.51 (m, 5H), 7.17 (s, 5H), 4.62 (m, 1H), 4.15 (m, 3H), 3.72 (t, 1H), and 1.28 (dt, 3H); (**6b**): i.r. ($CDCl_3$) 1805 and 1760 cm^{-1}; n.m.r. (90 MHz, $CDCl_3$) δ 7.53 (m, 5H), 7.20 (s, 5H), 4.71 (m, 1H), 4.25 (dq, 4H, overlapping m, 1H), 3.93 (t, 1H), and 1.33 (dt, 6H).



(7)

a; R = $PhCH_2CO$

b; R = Bu^tOCO

The utility of this and related rearrangements of substituted *N*-hydroxyazetidin-2-ones for the synthesis of heterocyclic systems merits further study.[6]

M. M. is a Fellow of the Alfred P. Sloan Foundation (1981—1985), and recipient of an N.I.H. Research Career Development Award (1983—1988). We are grateful for support by the N.I.H., Eli Lilly and Company, and a Reilly Fellowship for M. K. The 300 MHz n.m.r. instrument was obtained by grants from the N.I.H. and the University of Notre Dame. *X*-Ray crystallography was performed by Dr. Charles Eigenbrot.

Received, 5th June 1985; Com. 778

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