NEW SYNTHETIC APPLICATIONS OF 4-ACETOXYAZETIDIN-2-ONE: CARBOXYLATE AND NITROGEN NUCLEOPHILE DISPLACEMENTS

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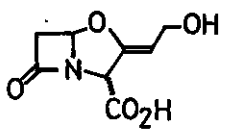
Abstract : Reaction conditions for displacement of the acetate group in 4-acetoxyazetidin-2-one by carboxylate and nitrogen nucleophiles have been studied, giving firstly, a 4-malonyloxyazetidin-2-one from which was synthesized the clavulanic acid degradation product benzyl 3,7-dioxo-4-oxa-1-aza[3.2.0.]bicycloheptan-7-one 2-carboxylate, and secondly, new routes to 4-aza substituted azetidin-2-ones.

1-Oxa analogues of the penicillin antibiotics currently attract considerable attention[1], particularly in the search for drugs with superior antibiotic activity or with β-lactamase inhibitory properties. Clavulanic acid (1)[2], although only a weak antibiotic, inhibits β-lactamase enzymes and strikingly enhances the potency of a range of antibiotics against resistant organisms. We have been concerned with further exploitating the synthetic utility of 4-acetoxyazetidin-2-one (2)[3] in the preparation of analogues. Although many displacements of the acetate group by heteronucleophiles are now known, carboxylate nucleophiles[3] and nitrogen nucleophiles have received relatively little attention, and we now report new reactions and rearrangements in this area.

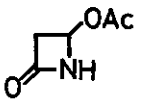
Benzyl malonic acid (3) reacted as its sodium salt with (2) in a range of conditions to give only very low yields of the desired adduct (4). However, the copper salt of (3) in tetrahydrofuran gave an equilibrium mixture from which a 25% yield of crystalline (4)† (m.p. 57-59°) could readily be obtained together with recyclizable (2). Product (4), in common with derived β-dicarbonyls in this study, was extremely susceptible to elimination reactions and required very rapid, short-path chromatography for purification. Hydrogenolysis of (4) (Pd-C) gave the stable carboxylic acid (5).† This type of displacement was further illustrated by the reaction of (L-)-N-benzyloxycarbonyl alanine, this time reacting only as the sodium salt and in a two phase system (ethyl acetate-water), to give the unstable and inseparable diastereoisomers (6) (41%) which could be deprotected by hydrogenolysis without β-lactam cleavage to give the L-alanine derivatives (7).† No trace of nucleophilic displacement by alanyl nitrogen was detected, unlike the cases described later.

In an investigation of the synthesis of bicyclic systems from precursors such as (4), diazo exchange reactions of the malonyl methylene unit were investigated, and, not surprisingly, most base-catalysed reactions led to immediate elimination of the malonate

† New compounds were characterised by elemental analysis and/or high resolution mass spectrometry, together with i.r. and n.m.r. spectroscopy.



(1)



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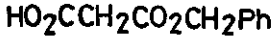

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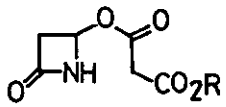
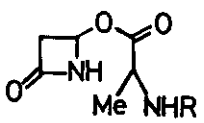


(4) R = CH_2Ph

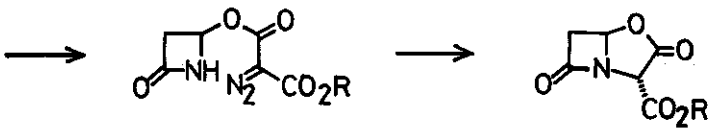
(5) R = H



(6) R = $PhCH_2OCO$

(7) R = H

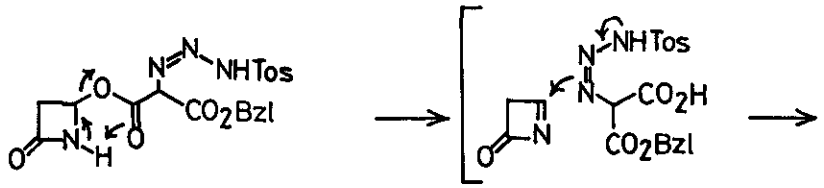
and β-lactam cleavage. The mild reagent, N-ethyl 2-azidobenzthiazolium fluoroborate[4] however, in ethanol-sodium acetate gave the diazomalonate (8) in variable yield together with the principal by-product, benzyl diazoacetate. Rhodium acetate catalysed the intramolecular coupling[5] to give the racemic 1-oxa-2-oxopenam (9) in 30% yield from (8), spectroscopically identical to the chiral product obtained by oxidative degradation of clavulanic acid[6].

(4) 

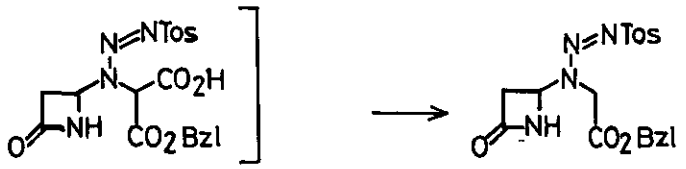
(8) (9)

During the diazo transfer studies on (4) a novel rearrangement was uncovered. Diazo exchange with toluene-p-sulphonyl azide in methylene chloride with ethyl diisopropylamine as base did not give (8), but instead, heating and concentration of the reaction solution resulted in evolution of CO_2 and gave the unexpected product (12)† in 35% yield. The alternative structure (13) cannot rigorously be excluded at this stage, but the base peak in the mass spectrum corresponding to loss of $C_7H_7SO_2N_2$ is more readily accommodated by structure (12). Presumably the diazo intermediate (8) is trapped by toluene-p-sulphonamide to give N-tosyltriazine (10). Geometrical constraint may preclude intramolecular displacement of the carboxylate through a five-membered spiroelimination process, and the reaction could therefore occur by dissociation of (10) and recombination by N-tosyltriazinyl attack at C(4) of an

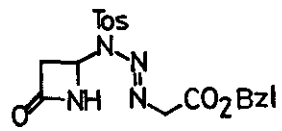
azetinium intermediate. Decarboxylation of the resultant acid (11) would then give (12). Nitrogen nucleophile reactions at C(4) are relatively uncommon,[††] and it was thus of interest to examine briefly the implications of this new displacement. Thus, methyl N-(toluene-p-sulphonyl) glycinate as its sodium salt in tetrahydrofuran gave in good yield the product (14), whereas methyl N-(benxyloxycarbonyl) glycinate led to cleavage of the β-lactam in a range of reactions.



(10)



(11) (12)



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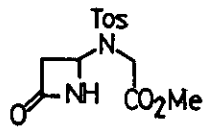

(14)

The racemic 1-oxa-2-oxopenam carboxylic acid derived from (9) (10% Pd/H_2, quant.) was active as an antibiotic against a range of organisms and also exhibited synergy with ampicillin. The alanine derivative (7) was inactive.

[††] Azide and phthalimide effect displacement[3]. Intramolecular displacement is also known[7].

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Note Added: A very recent publication describes related reactions of crotonates, leading to 1-oxa-2-oxocephems; K. Prasad, H. Hamberger, P Stütz and G. Schultz, Heterocycles, 1981, 16 (2), 243.

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