Facile Entry into the 7-Oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene Ring System

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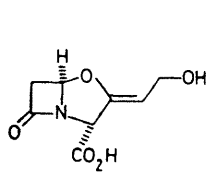
Summary Rhodium(II) acetate-catalysed addition of ethyl diazoacetoacetate to (±)-4-acetoxyazetidin-2-one results in the formation of ethyl 7-oxo-4-oxa-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate.

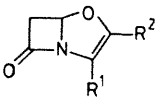
DURING the last five years, considerable interest in novel natural β-lactamase inhibitors[1] has been evident, and this has culminated in several[2] total syntheses of clavulanic acid (**1**) and structurally related analogues.[3] In particular, Bentley and co-workers have used an approach[2a] based upon

the isomerisation of 7-oxo-4-oxa-1-azabicyclo[3 2 0]hept-2-enes (**2**, $R^1 = CO_2Me$, $R^2 = CH_2Ph$) to clavulanic acid derivatives

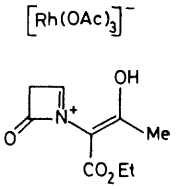
Although some interest has been shown[4] in derivatives of (**2**), most of the published methods† leading to (**2**) involve several steps and give low overall yields



(1)

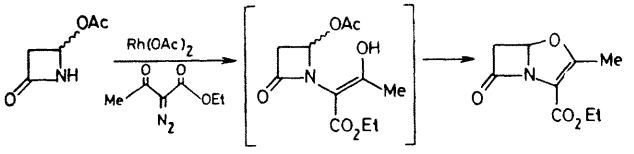


(2)



(3)

In an attempt to effect a synthesis of the 4-oxa-1-azabicyclo[3 2 0]hept-2-ene ring system, we decided to take advantage of the rhodium(II) acetate-catalysed insertion of a carbene derived from a diazo-β-keto-ester into the N–H bond of 4-acetoxyazetidin-2-one to provide a suitable *N*-alkylated species (Scheme) for subsequent cyclisation In practice, the intermediate *N*-alkylated product was not observed, but the cyclisation proceeded spontaneously to yield (**2**, $R^1 = CO_2Et$, $R^2 = Me$)



SCHEME

Dropwise addition of ethyl diazoacetoacetate (4 mmol) to a solution of (±)-4-acetoxyazetidin-2-one[5] (4 mmol) and rhodium(II) acetate (5 mg) in toluene (10 ml) over 1 h, followed by stirring the resultant solution at room temperature for 16 h resulted in the disappearance of the diazo-ester (i r) with the concomitant formation of two products These were separated‡ by rapid chromatography through a silica column to yield ethyl 7-oxo-4-oxa-1-azabicyclo-[3 2 0]hept-2-ene-2-carboxylate (**2**, $R^1 = CO_2Et$, $R^2 = Me$) (0 220 g, 28%), as an oil, ν_{max} ($CHCl_3$) 1800 and 1705 cm^{-1}, ^1H n m r δ($CDCl_3$) 1 4 (3H,t,*J* 7 Hz), 2 20 (3H,s), 3 2 (2H,m), 4·2 (2H,q,*J* 7 Hz), and 6 2 (1H,m), *m/e* 197 0699 (M^+), (calc 197 0689) The second product was shown to be ethyl 2-acetoxy-3-oxobutanoate, presumably formed by the reaction of the acetic acid liberated during the reaction with the carbenoid derived from the diazo-ester

The principal advantage of this reaction is that it offers a direct, one-step synthesis of the 7-oxo-4-oxa-1-azabicyclo-[3 2 0]hept-2-ene-2-carboxylate ring, and to our knowledge this appears to be the first example of a direct intramolecular displacement with the acetate functioning as the leaving group in the intermediate *N*-alkylated 4-acetoxyazetidin-2-one Howarth and co-workers[6] have used the zinc acetate-catalysed displacement of the acetate group in an intermolecular reaction between 4-acetoxyazetidin-2-one and benzyl 2-bromo-3-hydroxy-3-methylbutanoate, and it seems probable that the rhodium(II) acetate not only serves to catalyse carbenoid formation from the diazo-ester, but also aids ring closure to the bicyclic product, possibly by way of an azetidinium complex *e g* (**3**)

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† An obvious exception to this statement can be found in the work of E Hunt, *J Chem Soc, Chem Commun*, 1979, 688, but the derived 7-oxo-4-oxa-1 azabicyclo[3 2 0]hept-2-ene has lost the important C 2 carboxy function

‡ The 7-oxo-4-oxa-1-azabicyclo[3 2 0]hept-2-ene ring is known to be unstable, and extensive decomposition occurs unless the chromatographic separation is extremely rapid, see *e g* ref 2b

[1] T T Howarth, A G Brown, and T J King, *J Chem Soc, Chem Commun*, 1976, 266

[2] (a) P H Bentley, P D Berry, G Brooks, M L Gilpin, E Hunt, and I I Zomaya, *J Chem Soc, Chem Commun* 1977, 749, (b) P H Bentley, G Brooks, M L Gilpin, and E Hunt, *ibid*, 1977, 906, (c) P H Bentley, G Brooks, M L Gilpin, and E Hunt, *Tetrahedron Lett*, 1979, 1889

[3] E Hunt, P H Bentley, G Brooks, and M L Gilpin, *J Chem Soc, Chem Commun*, 1977, 906, P H Bentley and E Hunt, *ibid*, 1978, 518

[4] A J Eglinton, *J Chem Soc, Chem Commun*, 1977, 720

[5] K Clauss, D Grimm, and G Prossel, *Liebig's Ann Chem*, 1974, 539

[6] A G Brown, D F Corbett, and T T Howarth, *J Chem Soc, Chem Commun*, 1977, 359