Tetrahedron Letters,Vol.24,No.26,pp 2693-2696,1983 0040/4039/83 $3.00 + .00
Printed in Great Britain

THE CHEMISTRY OF CLAVULANIC ACID: SOME REACTIONS OF ESTERS UNDER NEUTRAL, ACIDIC AND BASIC CONDITIONS

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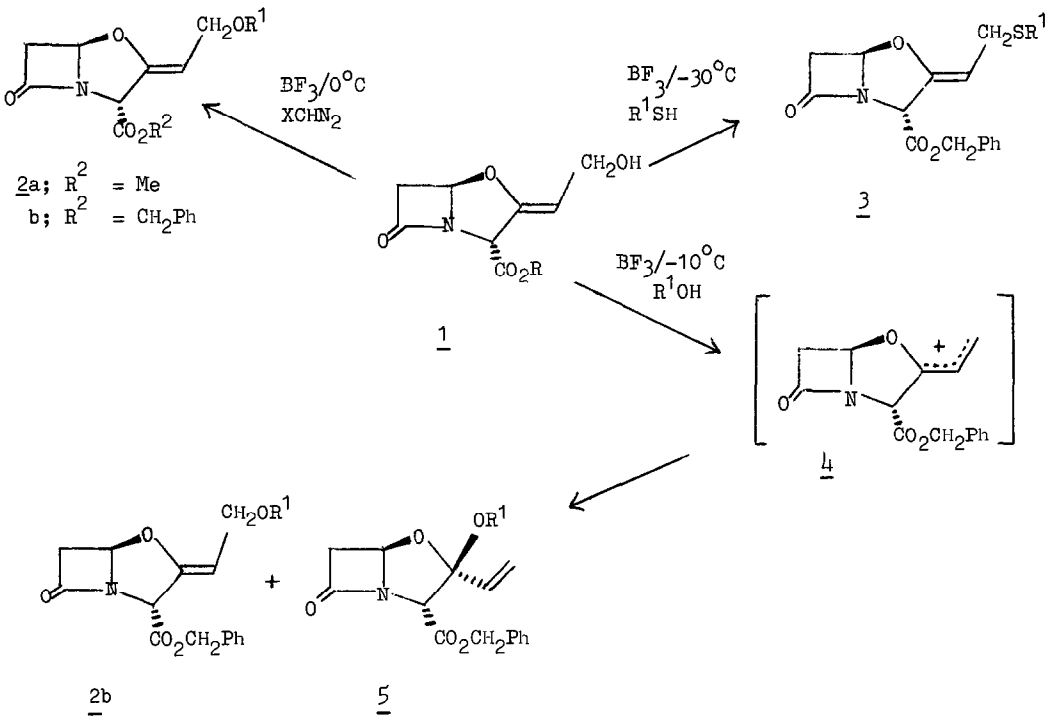
Summary: Investigations into the chemistry of benzyl clavulanate under a variety of reaction conditions has led to acid catalysed one-step conversion to ether and thioether derivatives. Generation of nitrogen-containing displacement products proceeds via the reactive dichloroacetate (6). Several products arising from these reactions by rearrangement or ring cleavage have been identified and characterised.

Clavulanic acid (1; R = H) is a naturally occurring β-lactamase inhibitor which has undergone intensive study over recent years. Following its isolation[1] a programme of structural modification was undertaken with the aim of deriving new and more potent analogues. One of our targets was to develop simple one-step conversion of clavulanic acid esters to new derivatives that could be cleaved readily to provide biologically active salts. To this end an investigation of the chemistry of clavulanic acid esters under neutral, mild acid and basic conditions was carried out.



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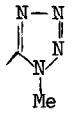
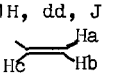
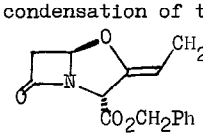
Observations on the esterification of clavulanic acid using ethereal diazomethane at 0°C showed that the methyl ether (2a; R^1 = Me) could be isolated[2]. Treatment of benzyl clavulanate (1; R = CH_2Ph) in dichloromethane with a solution of ethereal diazomethane using a catalytic amount of BF_3 etherate at 0°C led to a 30% yield of methyl ether (2b; R^1 = Me) isolated as an oil after chromatography on silica gel $[\alpha]_D$ + 50° (MeOH) ν_{max} ($CHCl_3$) 1800, 1745, 1695 cm^{-1}; δ($CDCl_3$), inter alia, 3.10(1H, d, J 17Hz, 6β-CH), 3.55 (3H, s, OCH_3), 3.60 (1H, dd, J 17, 2.5 Hz, 6α-CH), 4.12 (2H, d, J 8Hz, $\underline{CH_2}OCH_3$), 4.94 (1H, t, J 8Hz,=CH-), 5.24 (1H, br. s, 3-CH), 5.82 (1H, d, J 2.5Hz, 5-CH). Similar reaction using diazotoluene led to the benzyl ether (2b; R^1 = CH_2Ph) (12%).

Using BF_3 etherate and the appropriate thiol in methylene chloride at -30°C a one-step conversion to thioethers (3) could also be demonstrated[3]. Treatment of benzyl clavulanate with benzyl mercaptan gave the benzyl thioether (3; R^1 = CH_2Ph) (25%) exclusively in the Z-configuration $[\alpha]_D$ + 29.7° (MeOH) ν_{max} ($CHCl_3$) 1800, 1745, 1690 cm^{-1} δ($CDCl_3$) inter alia, 3.00 (1H, d, J 17 Hz, 6β-CH), 3.52 (1H, dd, J 17, 2.5 Hz, 6α-CH), 3.20 (2H, d, J 8Hz,=CH-$\underline{CH_2}$), 3.77 (2H, s, SCH_2Ph) 4.77 (1H, t, J 8Hz,=CH-), 5.18 (1H, br.s, 3-CH), 5.72 (1H, d, J 2.5Hz, 5-CH). The generality of the reaction could also be shown since (1; R = CH_2Ph) on treatment with thiophenol provided (3; R^1 = Ph) (20%) and with 1-methyl-1,2,3,4 tetrazol-5-thiol, gave the thioether (3; R^1 = ) (20%).

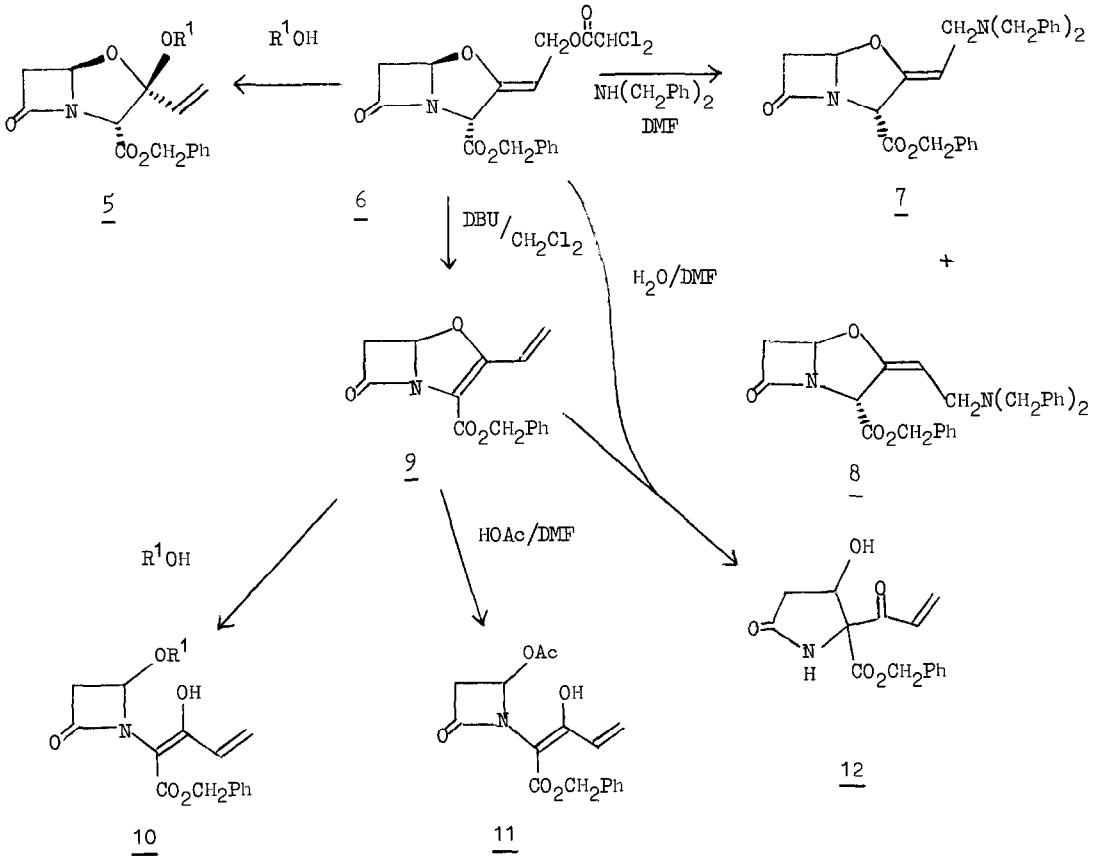
The reaction of benzyl clavulanate under BF_3 etherate conditions using benzyl alcohol as the external nucleophile produced a complex mixture of products including the benzyl ether (2b; R^1 = CH_2Ph) (4%) and rearranged ether (5; R^1 = CH_2Ph)[4] (2.5%) $[\alpha]_D$ -8° (MeOH) ν_{max} ($CHCl_3$) 1795, 1745 cm^{-1}. δ($CDCl_3$), inter alia, 2.87 (1H, dd, J 17, 1Hz, 6β-CH), 3.35 (1H, dd, J 17, 2.5Hz, 6α-CH), 4.47 and 4.65 (2H, ABq, J 13 Hz, OCH_2Ph), 4.89 (1H, s, 3-CH), for  5.30 (1H, dd, J10, 2.5 Hz, Hb), 5.61 (1H, dd, J 17, 2.5 Hz, Ha) 5.84 (1H, dd, J 17, 10 Hz, Hc), 5.76 (1H, m, 5-CH), presumably generated via the carbonium ion (4). Other products included those formed by condensation of two molecules of benzyl clavulanate e.g.

(2b and 5; R^1 = ).

In order to effect displacement with nitrogen-containing nucleophiles it was found preferable to proceed via the reactive dichloroacetate (6) which is readily prepared from benzyl clavulanate (1; R^1 = CH_2Ph) using dichloroacetic acid and DCCI/pyridine at 0°C (63%) $[\alpha]_D$ + 23° (MeOH) ν_{max} ($CHCl_3$) 1805, 1750, 1700 cm^{-1}. δ($CDCl_3$) inter alia, 3.10 (1H, d, J 17 Hz, 6β-CH) 3.60 (1H, dd, J 17, 2.5Hz,6α-CH), 4.93 (3H, m, CH_2O and =CH-), 5.21 (1H, s, 3-CH), 5.82 (1H, d, J 2.5Hz, 5-CH), 6.02 (1H, s, $CHCl_2$).

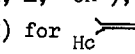
Treatment of the dichloroacetate (6) with methanol over 48 hours led to the vinylic ether (5; R^1 = Me) (63%) $[\alpha]_D$ +32°(MeOH) and with non-nucleophilic base (DBU) to the diene (9)[5,6] (60%). Reaction of the dichloroacetate (6) with dibenzylamine (2 equivs./R.T./5 mins) in DMF gave a 1:1 mixture of displacement products (7) and (8) (30%) ν_{max} ($CHCl_3$) 1800, 1750, 1700 cm^{-1}.

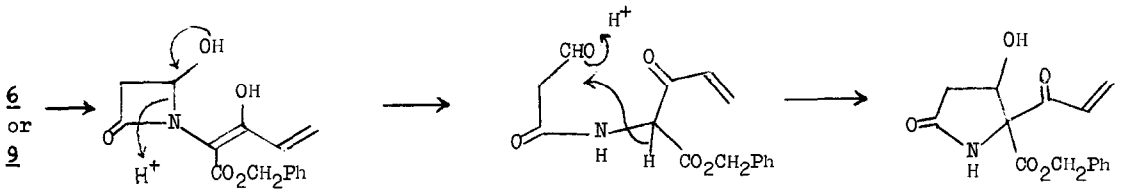
$\delta(CDCl_3)$, inter alia, 2.98 (1H, d, J 17Hz, 6β-CH), 3.07 and 3.22 (2H, 2xd, J 8Hz, =CH-$\underline{CH_2}$- for two isomers) 3.49 (1H, 2xbr. d, J 17, 2.5Hz, 6α-CH), 4.85 and 5.29 (1H, 2xbr. t, J 8 Hz, =CH- for two isomers) 5.19 and 5.29 (3H, 2xs, 3-CH and CO_2CH_2Ph for two isomers) 5.72 (1H, d, J 2.5 Hz, 5-CH). Also isolated from the reaction mixture was the diene (9) in 6% yield.



Alcoholysis of the diene (9) gave a different product to that derived from (6) in that ring cleavage occurred, e.g. treatment of (9) with methanol gave (10; R^1 = Me) (62%) ν_{max} ($CHCl_3$) 3500, 1765, 1660 cm^{-1} $\delta(CDCl_3)$, inter alia, 2.76 (1H, dd, J 17, 2Hz, 3β-CH) 3.09 (1H, dd, J 17, 3.5 Hz, 3α-CH) 3.30 (3H, s, OCH_3) 5.00 (1H, dd, J 3.5, 2Hz, 4-CH) for Hc(Ha)=C(Hb)- 5.78 (1H, dd, J 11, 2Hz, Hb) 6.28 (1H, dd, J 17, 2Hz, Ha) 6.81 (1H, dd, J 17, 11Hz, Hc).

Similar treatment of the diene (9) with glacial acetic acid in DMF gave the 4-acetoxy azetidinone (11) (60%) ν_{max} ($CHCl_3$) 3500, 1780, 1760, 1660 cm^{-1}. $\delta(CDCl_3)$, inter alia, 2.00 (3H, s, $OC(=O)$-Me) 2.91 (1H, dd, J 17, 2Hz, 3β-CH), 3.28 (1H, dd, J 17, 4Hz, 3α-CH), 6.20 (1H, dd, J4, 2Hz, 4-CH). For Hc(Ha)=C(Hb)- 5.79 (1H, dd, J10, 2Hz, Hb), 6.29 (1H, dd, J17, 2Hz, Ha), 6.78 (1H, dd, J17, 10Hz, Hc).

Degradation of both the dichloroacetate (6) and the diene (9) in aqueous DMF led to a non-β-lactam containing product (12) as a mixture of diastereoisomers (60% ν_{max} ($CHCl_3$) 3300, 1730, 1700, 1610 cm^{-1}. δ($CDCl_3$) 2.33 (1H, d, J 17 Hz, 3 β-CH), 2.66 and 2.80 (1H, 2xdd, J 17, 6Hz, 3α-CH), 5.04 (1H, m, -CH-), 5.18 and 5.23 (2H, s, CO_2CH_2Ph for two isomers), 5.10 (1H, br. s, exchangeable, OH) for  5.72 and 5.78 (1H, 2 xdd, J 10, 2Hz, Hb) 6.31 and 6.36 (1H, 2xdd, J 17, 2Hz, Ha) 6.54 and 6.68 (1H, 2 x dd, J 17, 10 Hz, Hc) 7.28 (5H, s, CO_2CH_2Ph) 7.88 and 7.98 (1H, 2 x s, exchangeable, NH). Separation of the diastereoisomers and assignment of absolute stereochemistry was not attempted but formation of similar products with defined stereochemistry is not unprecedented in the penicillin field[7]. The product (12) conceivably arises by formation of the diol (13). (13) May then lead to the ketoaldehyde (14) which could recyclise to the hydroxy γ-lactam (12).



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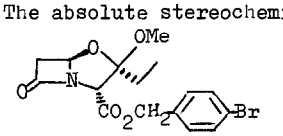
References and Notes

1. A.G. Brown, D. Butterworth, M. Cole, G. Hanscombe, J.D. Hood, C. Reading and G.N. Rolinson, J. Antibiotics, 29, 668, (1976).

2. British Patent No. 1,565,209 (Beecham Group).

3. An alternative procedure for preparation of thioethers has been described by P.C. Cherry, G.I. Gregory, C.E.Newall, P. Ward and N.S. Watson, J.C.S. Chem. Commun. 476, (1978).

4. The absolute stereochemistry was determined by X-ray analysis of a related analogue,  prepared by hydrogenation of (5; R^1 = Me) (10% Pd/C/tetrahydrofuran) and esterification by using p-bromobenzyl bromide. The X-ray determination was kindly carried out by courtesy of Professor Professor T.J. King, University of Nottingham.

5. D.F. Corbett, T.T. Howarth and I. Stirling, J.C.S. Chem. Commun. 905 (1977).

6. P.C. Cherry, C.F. Newall and N.S. Watson, J.C.S. Chem. Commun. 469 (1978).

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(Received in UK 6 April 1983)