Tetrahedron Letters,Vol.25,No.27,pp 2919-2922,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

BORON TRIFLUORIDE CATALYSED REACTIONS OF 2,2,2-TRICHLOROETHYL-6-DIAZOPENICILLANATE WITH KETONES: PREPARATION OF NOVEL 6β-ACYL-6α-ALKYL(ARYL) PENICILLANATES.

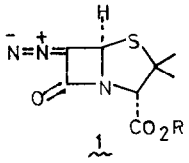
V.J. Jephcote and D.I. John*

Department of Chemistry, University of London King's College,
Strand, London WC2R 2LS.

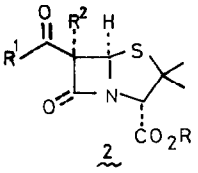
Abstract. The $BF_3.Et_2O$ catalysed reactions of the diazopenicillanate 1 with ketones provide novel 6-acyl-6-alkyl(aryl)penicillanates 2, together with thiazolooxazinones 6 formed via penam C(5)-C(6) cleavage reactions.

Since the discovery of thienamycin[1] and olivanic acid[2] there has been considerable interest in the preparation of penicillanate derivatives bearing carbon substituents at C-6. Many such derivatives have been generated *via* 6-diazopenicillanates,[3-5] e.g. 1, and the reactions of these versatile synthetic intermediates with aliphatic aldehydes[4,5] have provided useful 6-acylpenicillanates. Analogous 6-acylpenicillanates bearing additional alkyl-(aryl) substituents at C(6) have not yet been reported. Ketones under BF_3 catalysed conditions are known to react with diazoalkanes to yield homologated ketone products,[6] however such reaction of acetone with 1 is reported[4] to have failed to provide β-lactam containing products. Contrary to the latter report we have found that acetone, and several other ketones, undergo reactions with 1, in the presence of $BF_3.Et_2O$, to provide novel 6-acyl-6-alkyl(aryl)penicillanates as well as other interesting rearrangement products derived *via* penam C(5)-C(6) cleavage reactions.

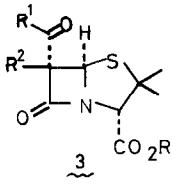
Thus, when an equimolar solution of 1 and dry acetone in CH_2Cl_2 at 0° was treated with a catalytic quantity of $BF_3.Et_2O$, the 6β-acetyl-6α-methylpenicillanate 2a was isolated (35%), after silica chromatography. Spectroscopic and analytical data[7] were consistent with the overall structure of 2a, while NOE studies[8] revealed the 6α-methyl configuration. No evidence for the presence of the epimeric penicillanate 3a was detected. Many attempts to improve the yield on this reaction were surprisingly unsuccessful, and a change of catalyst to $AlCl_3$ only led to similar yields. Our previous observations[9] suggested a probable explanation to be rearrangement of the 6-acylpenicillanate product *via* C(5)-C(6) bond cleavage. The reaction was therefore repeated on a larger scale under the same conditions. On this occasion a second product of similar polarity (tlc) to that of 2a was observed. Although possible, no attempt to effect separation by chromatography was made at this stage. Instead, the reaction mixture, following removal of solvent, was treated with $NaBH_4$ in dioxan-phosphate buffer (pH 7) to effect ketone reduction of the 6-acylpenicillanate 2a. The resultant reaction mixture, after work up and silica chromatography, then provided the expected 6β-(2'-hydroxyethyl)-6α-methylpenicillanate 4 (mixture of 2'-epimers,2·3:1) (59%)



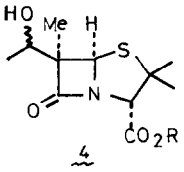
1



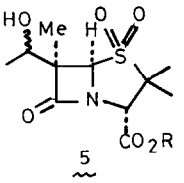
2



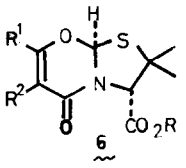
3



4



5



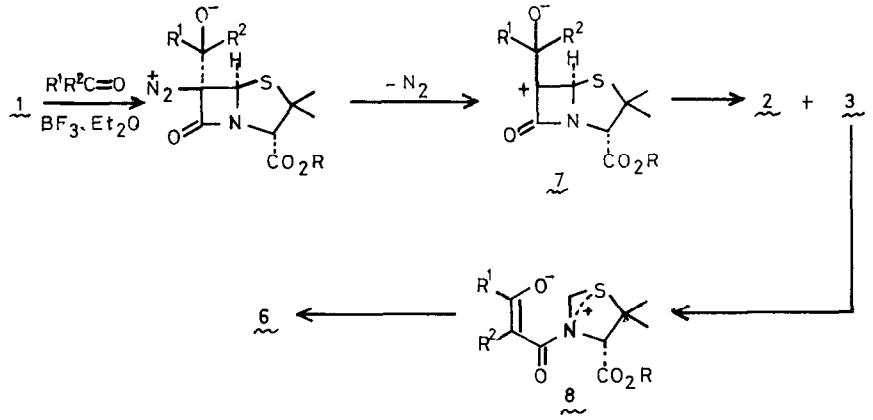
6

R = CH_2CCl_3

2, 3 and 6 a $R^1 = R^2 =$ Me. e R^1 = Me, R^2 = Ph.
b $R^1R^2 = (CH_2)_4$. f R^1 = Ph, R^2 = Me.
c R^1 = Me, R^2 = Et. g R^1 = Me, R^2 = H.
d R^1 = Et, R^2 = Me.

along with the 2,3-dihydrothiazolooxazinone 6a (18.4%) arising from a 6-acylpenicillanate intermediate by C(5)-C(6) ring opening and recyclisation. Spectroscopic data[7] for 6a was consistent with the proposed structure and comparable with that obtained for the analogous thiazolooxazinones derived from the corresponding reactions of aromatic aldehydes with 1 previously reported.[9] Similar reaction of cyclopentanone with 1 provided the 6,6-spiro-cyclohexanonepenicillanate 2b (20.5%) and the tricyclic oxazinone 6b (12.6%) after silica chromatography. The 6β-acyl configuration for 2b is proposed by comparison with 2a, and with 2e and 2f below. No evidence for the presence of the epimer 3b was detected.

As expected, the reactions of unsymmetrical ketones with 1 under the same conditions provided mixtures of crossed homologation products together with penam C(5)-C(6) cleavage products. Thus, ethyl methyl ketone gave an inseparable mixture of mainly the 6β-acetyl- and 6β-propanoyl-penicillanates 2c and 2d, as observed by ^{1}H nmr, with no trace of the epimers 3c and 3d, and oxazines 6c and 6d being detected. In contrast, however, the similar reaction of acetophenone with 1 gave a mixture of products from which, after silica chromatography, the 6β-acetyl-6α-phenyl- and 6β-benzoyl-6α-methyl-penicillanates 2e (11.2%) and 2f (3.8%) were isolated, as well as an oxazinone product (4.6%) which is tentatively assigned the structure 6e, rather than 6f. Spectral and analytical data[7] for all these products was consistent with the proposed overall structures, while NOE difference spectroscopy[8] revealed the 6β-acetyl- and 6β-benzoyl configuration for 2e and 2f. Attempted reactions of the unsaturated ketones, methyl vinyl ketone and mesityl oxide with 1 under $BF_3.Et_2O$ catalysed conditions failed to provide any penicillanates arising from homologation of the ketones, and gave no conclusive results.



Scheme

Significantly, the 6β-acylpenicillanates 2a, 2e, and 2f, unlike the analogous 6-formyl derivatives previously reported,[9] failed to undergo rearrangement to the corresponding thiazolooxazinones 6, neither under the conditions of the initial ketone reactions with 1 nor under more prolonged or thermal treatment with BF_3Et_2O or silica.[9] This, together with the distinct absence of any 6α-acylpenicillanate products 3 from the ketone reactions, would suggest that the oxazinones 6 are formed *via* the unstable 6α-acyl epimers 3 and that these epimers undergo a *trans* elimination type cleavage of the C(5)-C(6) bond to the intermediate thiazolinium-enolate 8 through participation of the sulphur electrons. The unstable 6α-acetylpenicillanate 3g has been obtained from the $BF_3.Et_2O$ catalysed reaction of 1 with acetaldehyde,[4] but in this case its instability has been attributed to facile proton loss from C(6). Like the formation of both C(6)-acetyl epimers 2g and 3g in the latter reaction, the derivation of the products in the corresponding ketone reactions is envisaged to occur *via* initial attack of 1 from the less hindered α-face, followed by nitrogen loss to give an intermediate carbonium ion 7, which subsequently undergoes substituent migration to provide both 6α- and 6β-acyl epimers 2 and 3. (Scheme)

De-protection (Zn/acetic acid[9]) of the esters 2a, 2b and 6, and the sulphone ester 5 obtained by m-chloroperbenzoic acid oxidation of 4, gave the corresponding acids[7] which showed no significant β-lactamase inhibition or antibacterial activity.

Acknowledgements

We should like to thank the SERC for a CASE Award (to VJJ) and Beecham Pharmaceuticals for their generous support, and Mrs. J. Elliott for recording nmr spectra.

References, Notes and Spectral Data

1. G. Albers-Schönberg et al., J. Amer. Chem. Soc., 1978, 100, 6491.
2. D.F. Corbett, A.J. Edlington, and T.T. Howarth, J. Chem. Soc., Chem. Commun., 1977, 953.
3. S.A. Matlin and L. Chan, Tetrahedron Lett., 1981, 1627, 4025, J. Chem. Soc., Chem. Commun., 1981, 10, and references cited therein.
4. J.C. Sheehan, E. Chacko, Y.S. Lo, D.R. Ponzi, and E. Sato, J. Org. Chem., 1978, 43, 4856.
5. S. Karady, J.S. Amato, R.A. Reamer, and L.M. Weinstock, J. Amer. Chem. Soc., 1981, 103, 6765.

6. E. Eistert, M. Regitz, G. Heck, and H. Schwall, in 'Methoden Der Organischen Chemie (Houben-Weyl)', Thieme Verlag, Stuttgart, 1968, Vol 10/4; G.W. Cowell and A. Ledwith, Quart. Rev., Chem. Soc., 1970, 24, 119.

7. Satisfactory spectroscopic and analytical data was obtained for all new compounds. Selected data are as follows:

2a M.p. 129-130°; $\nu_{max}(CHCl_3)$, 1780, 1770, and 1710 cm^{-1}; $\delta(CDCl_3)$ 1.54 and 1.67 (each 3H, s, CMe_2), 1.77 (3H, s, 6-Me), 2.30 (3H, s, COMe), 4.48 (1H, s, 3-H), 4.71 and 4.87 (each 1H, d, J=11.95Hz, CH_2CCl_3), 5.13 (1H, s, 5-H); m/e Found 386.9857(M^+) $C_{13}H_{16}{}^{35}Cl_3NO_4S$ requires 386.9865.

2b M.p. 175-7° dec.; ν_{max} 1780, 1760, and 1710 cm^{-1}; $\delta(CDCl_3)$ 1.53 and 1.65 (each 3H, s, CMe_2), 1.67-2.66 (8H, br.m, cyclohexanone-H), 4.77 (1H, s, 3-H), 4.73 and 4.84 (each 1H, d, J=12.1Hz, CH_2CCl_3), 5.20 (1H, s, 5-H); m/e Found 413.0005(M^+) $C_{15}H_{18}{}^{35}Cl_3NO_4S$ requires 413.0022.

2e M.p. 139-140°; $\nu_{max}(CHCl_3)$ 1780, 1770, and 1710 cm^{-1}; $\delta(CDCl_3)$ 1.53 and 1.73 (each 3H, s, CMe_2), 2.24 (3H, s, COMe), 4.54 (1H, s, 3-H), 4.68 and 4.86 (each 1H, d, J=12.13Hz, CH_2CCl_3), 5.45 (1H, s, 5-H), 7.38-7.50 (5H, m, Ph); m/e Found 449.0051(M^+) $C_{18}H_{18}{}^{35}Cl_3NO_4S$ requires 449.0020.

2f M.p. 160-62°; $\nu_{max}(CHCl_3)$ 1785, 1770, and 1715; $\delta(CDCl_3)$ 1.52 and 1.61 (each 3H, s, CMe_2), 1.99 (3H, s, 6-Me), 4.53 (1H, s, 3-H), 4.72 and 4.89 (each 1H, d, J=11.8Hz, CH_2CCl_3) 5.43 (1H, s, 5-H), 7.48-7.61 and 7.98-8.01 (5H, m, Ph); m/e 449(M^+).

6a Oil, $\nu_{max}(CHCl_3)$ 1760 and 1660 cm^{-1}; ^1H $\delta(CDCl_3)$ 1.54 and 1.79 (each 3H, s, CMe_2), 1.82 and 2.03 (each 3H, s, 6-Me and 7-Me), 4.80 (2H, s, CH_2CCl_3), 4.90 (1H, s, 3-H), 6.64 (1H, s, 8a-H); ^{13}C $\delta(CDCl_3)$ inter alia 93.74 (d, 8a-C) 161.87, 162.45, and 167.40 (each s, 5-C, 7-C and ester C=O); m/e Found 386.9855(M^+) $C_{13}H_{16}{}^{35}Cl_3NO_4S$ requires 386.9865.

6b M.p. 122-4°; $\nu_{max}(CHCl_3)$ 1760 and 1660 cm^{-1}, ^1H $\delta(CDCl_3)$ 1.55 and 1.80 (each 3H, s, CMe_2), 1.58-1.84 and 2.20-2.34 (8H, m, cyclohexyl-H), 4.80 (2H, s, CH_2CCl_3), 4.90 (1H, s, 3-H), 6.68 (1H, s, 10a-H); ^{13}C $\delta(CDCl_3)$ inter alia 93.98 (d, 10a-C) 162.12, 164.00 and 167.49 (each s, 5-C, 9a-C, ester C=O); m/e Found 413.0019(M^+) $C_{15}H_{18}{}^{35}Cl_3NO_4S$ requires 413.0022.

6e M.p. 155-7°; $\nu_{max}(CHCl_3)$ 1760 and 1660 cm^{-1}; $\delta(CDCl_3)$ 1.57 and 1.86 (each 3H, s, CMe_2), 1.98 (3H, s, 7-Me), 4.77 (2H, s, CH_2CCl_3), 4.96 (1H, s, 3-H), 6.86 (1H, s, 8a-H), 7.27-7.40 (5H, m, Ph); m/e Found 449.0026(M^+) $C_{18}H_{18}{}^{35}Cl_3NO_4S$ requires 449.0020.

8. NOE difference spectroscopy showed strong enhancements of the 6α-methyl signals of 2a and 2e as well as the 6α-phenyl signals of 2f on irradiation of the 5α-H resonances of these compounds. In each case, the 5α-H configuration was confirmed by enhancement of only this signal on irradiation of the upfield 2α-methyl resonance, while irradiation of the downfield 2β-methyl resonance produced enhancement of only the 3β-H signal.

9. V.J. Jephcote and D.I. John, preceding Communication; D.I. John, N.D. Tyrrell, E.J. Thomas, P.H. Bentley, and D.J. Williams, J. Chem. Soc., Chem. Commun., 1982, 76.

10. J.C. Sheehan, T.J. Commons, and Y.S. Lo, J. Org. Chem., 1977, 42, 2224.

(Received in UK 17 April 1984)