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A NEW ROUTE TO OPTICALLY ACTIVE 4-ACYLOXY AZETIDIN-2-ONES

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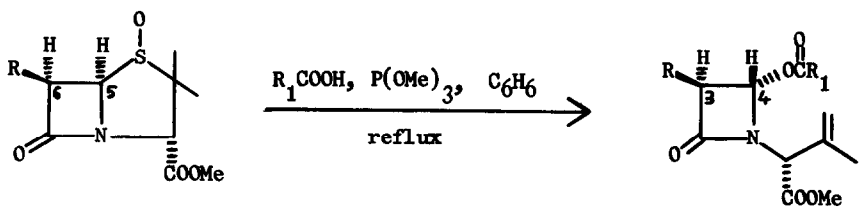
No efficient preparation of 4-acyloxy monocyclic azetidinones from penicillins has been reported in the literature. Before our work, only few examples of this class of compounds have been described,[1a-e] while their potential use as a starting material for the synthesis of, e.g., novel 1-oxa-1-dethiapenam derivatives has been pointed out recently.[2a,b] Since synthetic projects under way in our laboratory require the facile conversion of penicillins into optically active functionalised azetidinones, we sought a general entry into this class of synthons.

We have found that when a methyl penicillinate 1-oxide (12 mmole) was refluxed with a carboxylic acid R_1COOH (45 mmole) in C_6H_6 or C_6H_6-THF (300 ml) in presence of trimethylphosphite (8 ml) during 4-6 hours an 65-86% yield of the azetidinone 1 was obtained.[3]

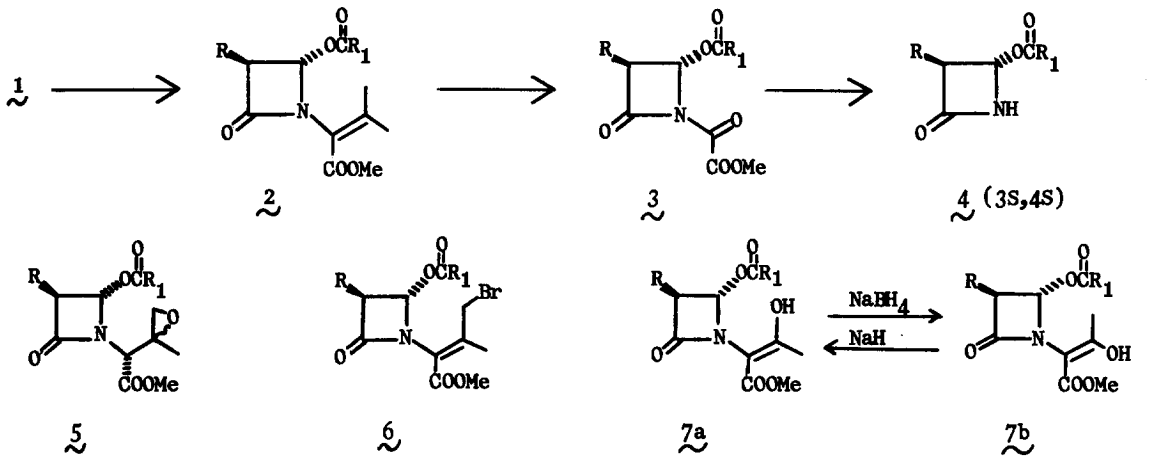


(5R, 6R) 1 (3S, 4S)

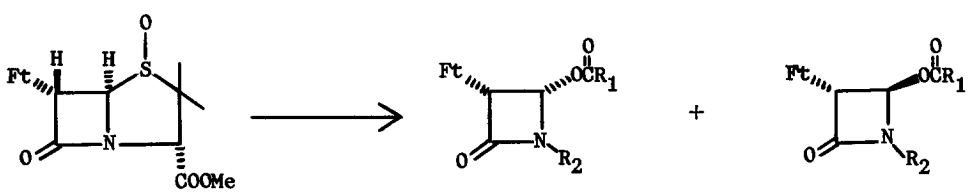
This novel opening of the thiazolidine ring by which the sulphur atom is replaced by an acyloxy group, with inversion of configuration at C-4, whereas the nitrogen atom remains linked to the useful β,γ-unsaturated appendage[4] is of general applicability. We have prepared, in fact, 4-acyloxy azetidinones starting from both phthalimido and phenoxyacetamido[5] penicillinate using a wide variety of carboxylic acids. The acetic, the benzoic, the p- and o-chlorobenzoic acids allow further manipulation at C-4, by introducing good leaving groups.

The fate of the nitrogen appendage is two-fold. The well known chain degradation process via the α,β-unsaturated ester 2 (Et_3N, CH_2Cl_2, r.t.)[6] followed by the oxidative cleavage (O_3, CH_2Cl_2, -78°C) of the olefinic bond to give the oxalylamide 3[7] afforded, after removal of the appendage (MeOH, MeO^-), a 60-80% overall yield of the azetidinone 4[8], which has been proven a useful starting material for the building of a second fused ring.[2a,b,9a-f]

Alternatively, further functionalisation of the isopropylidene moiety afforded the epoxides 5,[10] the allylic bromide 6[11] and the enol 7a[12] which lend themselves to be cyclised to 1-oxacephem systems as shown by other workers with similar compounds.[13a-c] Interestingly, we could isolate from the enol 7a its geometrical isomer 7b[12] ($NaBH_4$, i-propanol, r.t.) which gave 7a back on basic treatment (NaH, THF, 0°C).



On turning our attention to 6-epi-penicillins, we found that the thiazolidine ring of, e.g., methyl 6-epi-phthalimido penicillinate 1-oxide opens similarly in the aforementioned conditions but to give the separable mixture of the two epimeric azetidinones 8a and 8b,[14] from which compounds 9a, 9b,[15] 10a, 10b, 11a and 11b[16] were obtained as described before and characterised. Enantiomeric and diastereoisomeric analogs of 5, 6, 7a and 7b were also prepared. The 8a/8b ratio was found to be dependent upon the bulkiness of the R_1 group and it increased in favour of 8b as the size of the R_1 group increased. The fact that both 8a and 8b remained unchanged when individually treated under the reaction conditions was indicative of absence of an equilibrium between the two. On the other hand the catalytic action of a mild Lewis acid (C_6H_6, reflux) transformed readily the azetidinone 11a into the more stable isomer 11b, conceivably via the imine 12,[17] whereas it was ineffective on the N-substituted azetidinones 8a and 9a.



8, R_2 =  9, R_2 =  10, R_2 =  11, R_2 = H

Transformation at C-4 was then briefly investigated. As it was reported[1e] that the bulky phthalimido group exerts a certain degree of steric control upon substitution reactions at C-4, we treated the azetidinones 4, 11a and 11b (R = Ft, R_1 = CH_3 or p-ClC_6H_4) with mercaptans (NaOH, H_2O, Me_2CO) or carbinols ($Zn(OAc)_2$, C_6H_6, reflux). In both cases we isolated (80-90% yield) only optically active trans substituted β-lactams, each enantiomer coming solely from

4 or from either 11a and 11b. These results suggest that displacement reactions on these substrates may proceed via the imine 12[17] (R = Ft) to which the nucleophilic specie approaches from the less hindered side.

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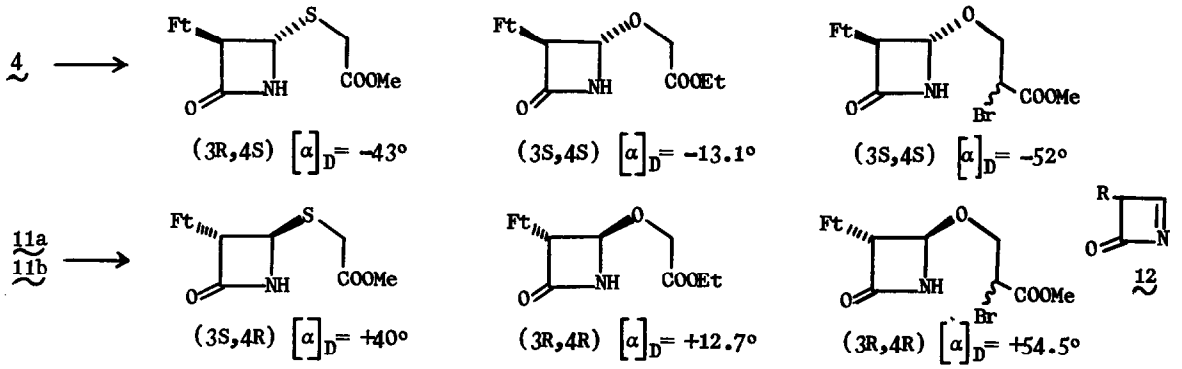

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1. (a) E.G. Brain, A.J. Eglington, J.H.C. Nayler, M.J. Pearson, and R. Southgate, J.C.S. Chem. Comm., 1972, 229; (b) K. Heusler, Helv., 55, 388 (1972); (c) R.J. Stoodley and N.R. Whitehouse, J.C.S. Perkin I, 1973, 32; (d) J.C. Sheehan, D. Ben-Ishai, and J.U. Piper J. Amer. Chem. Soc., 95, 3064 (1973); (e) S. Wolfe and M.T. Goeldner, Tetr. Letters, 1973, 5131.

2. (a) A.G. Brown, D.F. Corbett, and T Trefor Howarth, J.C.S. Chem. Comm., 1977, 359; (b) R.G. Alexander and R.Southgate, J.C.S. Chem. Comm., 1977, 405.

3. R = Ft, R_1 = CH_3 δ 2.01 (3H,s) 2.12 (3H,s) 3.76 (3H,s) 4.98, 5.08 and 5.21 (3H,3s) 5.32 and 6.36 (2H,2d, J = 1.5 Hz) 7.78 (4H,br); ν_{max} 1780, 1750, 1730 cm^{-1}; m/e 386, 358, 327, 231, 189. R = Ft, R_1 = p-ClC_6H_4 δ 2.05 (3H,s) 3.77 (3H,s) 5.10 (2H,s) 5.13 (1H,s) 5.48 and 6.53 (2H,2d, J = 1.5 Hz) 7.40 and 8.03 (4H,2d, J = 9 Hz) 7.77 (4H,br). R = Ft, R_1 = C_6H_5 δ 2.06 (3H,s) 3.76 (3H,s) 5.11, 5.19 and 5.27 (3H,3s) 5.50 and 6.61 (2H,2d, J = 1.5 Hz) 7.40 - 8.20 (9H,m). R = $C_6H_5OCH_2CONH$, R_1 = CH_3 δ 1.94 (3H,s) 2.10 (3H,s) 3.78 (3H,s) 4.52 (2H,s) 4.82 (1H,dd, J = 10 Hz, J = 1.5 Hz) 4.85, 5.07 and 5.21 (3H,3s) 6.21 (1H,d, J = 1.5 Hz) 6.80 - 7.45 (6H,m); ν_{max} 3440, 1785, 1750, 1690 cm^{-1}. R = $C_6H_5OCH_2CONH$, R_1 = p-ClC_6H_4 δ 1.95 (3H,s) 3.73 (3H,s) 4.53 (2H,s) 4.79 (1H,dd, J = 10 Hz, J = 1.5 Hz) 4.96, 5.02 and 5.16 (3H, 3s) 6.41 (1H, d, J = 1.5 Hz) 7.40 and 8.09 (4H, 2d, J = 9 Hz) 6.80 - 7.45 (6H, m). R = $C_6H_5OCH_2CONH$, R_1 = o-ClC_6H_4 δ 1.93 (3H,s) 3.68 (3H,s) 4.47 (2H,s) 4.91 (1H, dd, J = 8 Hz, J = 1.5 hz) 4.93, 5.07 and 5.13 (3H, 3s) 6.48 (1H, d, J = 1.5 hz) 6.75 - 7.97 (10H, m).

4. Previously known examples bore the α,β-unsaturated appendage and deconjugation was accomplished by extra two steps. See ref. 13b.

5. Methyl phenylacetamido penicillinate 1-oxide turned unstable in these conditions.

6. R = Ft, R_1 = CH_3 δ 2.12 (3H,s) 2.12 and 2.29 (6H,2s) 3.85 (3H,s) 5.35 and 6.52 (2H,2d, J = 1.5 Hz); ν_{max} 1780, 1730 cm^{-1}; $[\alpha]_D$ = -57°. R = Ft, R_1 = p-ClC_6H_4 δ 2.09 and 2.23 (6H,2s) 3.74 (3H,s) 5.46 and 6.67 (2H,2d, J = 1.5 Hz) 7.15 - 7.90 (8H,m).

7. R = Ft, R_1 = CH_3 δ 2.16 (3H,s) 3.94 (3H,s) 5.48 and 6.72 (2H,2s, J = 2Hz) 7.82 (4H,br). R = Ft, R_1 = p-ClC_6H_4 ν_{max} 1830, 1780, 1750, 1725 cm^{-1}.

8. R = Ft, R_1 = CH_3 δ 2.12 (3H,s) 5.37 and 6.12 (2H,2d, J = 1.5 Hz) 6.74 (1H,br) 7.75 (4H,br); $[\alpha]_D$ = -57.1°. R = Ft, R_1 = p-ClC_6H_4 δ 5.55 and 6.43 (2H,2d, J = 1.5 Hz) 7.20 - 8.10 (9H,m).

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10. R = Ft, R_1 = CH_3 δ (mixture of epimers) 1.58 (3H,s) 2.14 (3H,s) 2.77, 3.02 (2H,m) 3.80, 3.83 (3H,s) 4.27, 4.45 (1H,s) 5.36, 5.43 (1H,d, J = 1.5 Hz) 6.57, 6.77 (1H,d, J = 1.5 Hz) 7.82 (4H,m).

11. G. Franceschi, M. Foglio, P. Masi, A. Suarato, G. Palamidessi, L. Bernardi, F. Arcamone, and G. Cainelli, J. Amer. Chem. Soc., 99, 248 (1977).

12. 7a (R = Ft, R_1 = CH_3) δ 2.09 (3H, s) 2.25 (3H,s) 3.88 (3H,s) 5.38 and 6.48 (2H,2d, J = 1.5 Hz) 7.60 (4H,br) 11.30 (1H,s). 7b (R = Ft, R_1 = CH_3) δ 2.10, 2.19, 3.87, 5.33, 6.64, 7.82, 11.41.

13. (a) S. Wolfe, W.S. Lee, G. Kannengiesser, and J.B. Ducep, Can. J. Chem., 50, 2894, 2898, 2902 (1972); (b) S. Wolfe, J.B. Ducep, K. Chung Tin, and S. Lung Lee, Can. J. Chem., 52, 3996 (1974); (c) S. Wolfe, Offenlegungsschrift 2356862, US Patent 4,013,653.

14. 8a (R_1 = CH_3) δ 1.95 (6H,s) 3.78 (3H,s) 4.78, 5.09 and 5.14 (3H,3s) 5.53 and 6.27 (2H,2d, J = 4.5 Hz) 7.71 (4H,br); ν_{max} 1795, 1745,1730 cm^{-1}. 8a (R_1 = p-ClC_6H_4) δ 1.96 (3H,s) 3.75 (3H,s) 4.88 and 5.10 (3H,2s) 5.70 and 6.58 (2H,2d, J = 4 Hz) 7.12 - 7.90 (8H,m). 8b (R_1 = CH_3) δ 1.94 (3H,s) 2.10 (3H,s) 3.80 (3H,s) 4.98, 5.10 and 5.12 (3H,3s) 5.28 and 6.54 (2H, 2d, J = 1.5 Hz) 7.72 (4H,br); ν_{max} 1785, 1750, 1730 cm^{-1}. 8b (R_1 = p-ClC_6H_4) δ 1.94 (3H, s) 3.80 (3H,s) 5.02 and 5.10 (3H,2s) 5.41 and 6.79 (2H,2d, J = 2 Hz) 7.28 - 7.90 (8H,m).

15. 9a (R_1 = CH_3) δ 1.94 (3H,s) 2.26 and 2.30 (6H,2s) 3.81 (3H,s) 5.64 and 6.42 (2H,2d, J = 4 Hz) 7.75 (4H,br); $[\alpha]_D$ = -24.5°. 9b (R_1 = CH_3) δ 2.09 (6H,s) 2.29 (3H,s) 3.82 (3H,s) 5.38 and 6.51 (2H,2d, J = 2 Hz) 7.75 (4H,br); $[\alpha]_D$ = +58.5°.

16. 11a (R_1 = CH_3) δ 1.97 (3H,s) 5.51 and 6.02 (2H,2d, J = 4 Hz) 6.90 (1H,br) 7.75 (4H,br); $[\alpha]_D$ = -133°. 11b (R_1 = CH_3) δ 2.14 (3H,s) 5.38 and 6.16 (2H,2d, J = 1.5 Hz) 6.92 (1H,br) 7.77 (4H,br); $[\alpha]_D$ = +55°.

17. J.C. Sheehan, US Patent 3,487,074; 3,487,079.

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