

Use of the Allylic Sulphoxide–Sulphenate Ester Rearrangement for the Synthesis of a 2-Thiacephem and a Penem

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A 2-thioxopenam is synthesised from an acetylthio substituted penem and 2-thiacephem; the latter compound was prepared through the intramolecular nucleophilic capture of an allylic sulphenate ester, generated thermally from the corresponding sulphoxide (1).

Although the mild thermal interconversion of an allylic sulphoxide with a sulphenate ester is well established^{1,2} (Scheme 1) its use as a sulphenic acid equivalent in β -lactam chemistry has not yet been explored.

In this communication we describe the synthesis of the bis-(acetylthio)allylsulphinyl substituted azetidinone (1) and its facile transformation through the intermediacy of an allylic sulphenate ester into the new 3-acetylthio-2-thiacephem ring system (2). We further describe the phosphine mediated ring contraction of (2) to the corresponding 2-acetylthiopenem (3) and its transformation into the 2-thioxopenam (4).

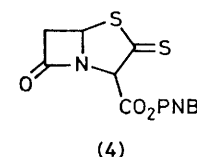
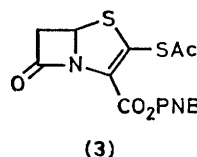
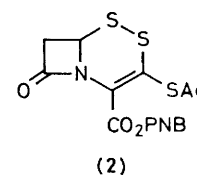
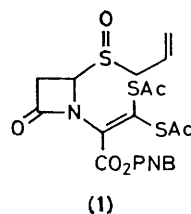
The bis(acetylthio) compound (1),[†] which was synthesised as shown in Scheme 2,³ possesses both a latent sulphenate ester and a masked thiol. The transformation of (1) into the 2-thiacephem would require the controlled release of both groups in such a way that cyclisation could take place.

Thermolytic treatment of (1) in a variety of solvents, however, failed to afford the desired 2-thiacephem (2) even in trace amounts. The well defined role of acid catalysis in the Morin–Jackson rearrangement⁴ of penicillin sulphoxides to cephems led us to incorporate an acid in the thermolysis.



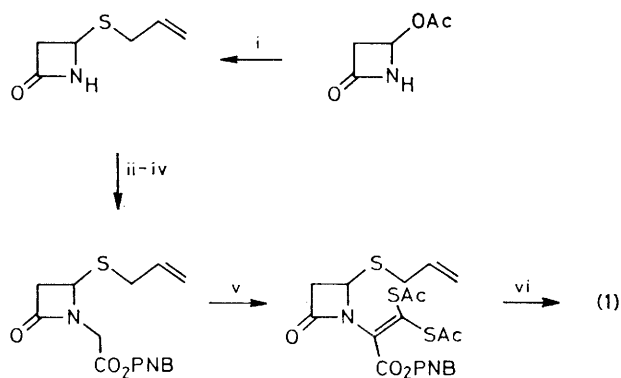
Scheme 1

Accordingly, thermolytic treatment of (1) (dioxan reflux) in the presence of either a proton acid (benzenesulphonic acid) or a Lewis acid (boron trifluoride) gave 17–40% of the desired 2-thiacephem (2) [ν_{\max} (CDCl₃) 1793 and 1739 cm⁻¹; ¹H n.m.r. δ (CDCl₃) 2.37 (s, COMe), 3.17 (dd, *J* 3 and 16 Hz, H-7), 3.88 (dd, *J* 5 and 16 Hz, H-7), 4.88 (dd, *J* 3 and 5 Hz, H-6), 5.38 (s, OCH₂-), and 7.50–8.28 (m, C₆H₄)]. The identification of allyl acetate as a major by-product suggested that attack of allyl alcohol on the thioacetyl group was playing a part in the reaction sequence. Anticipating that incorpor-



PNB = *p*-nitrobenzyl

[†] All new compounds gave satisfactory combustion analyses and/or high resolution mass spectral measurements.



Scheme 2. PNB = *p*-nitrobenzyl. *Reagents and conditions:* i, NaSCH₂CH=CH₂, tetrahydrofuran (THF), room temp.; ii, K₂CO₃, BrCH₂CO₂Me, dimethylformamide; iii, KOH, EtOH, then H₃O⁺; iv, BrCH₂PhNO₂, Na₂CO₃, dimethylacetamide, room temp.; v, LiN(SiMe₃)₂, THF, -78 °C then CS₂, -78 °C then Ac₂O, -78 °C to room temp.; vi, *m*-chloroperbenzoic acid, ethyl acetate, -20 °C.

ation of an external nucleophile might usefully assist in releasing the thiol group more readily, thermolysis of (1) (dioxan, toluene-*p*-sulphonic acid, or BF₃·Et₂O, 1–2 equiv.) in the presence of ethanol or water (5–7 equiv.) was shown to afford a marked improvement in the isolated yield of (2) (50–70%).

Treatment of (2) with triphenylphosphine in acetonitrile or dichloromethane, followed by chromatography gave smoothly and in excellent yield (90%) the 2-acetylthiopenem (3) as a pale yellow crystalline solid m.p. 145 °C [ν_{\max} (CDCl₃) 1800 and 1714 cm⁻¹, ¹H n.m.r. δ (CDCl₃) 2.45 (s, COMe), 3.55 (dd, *J* 2 and 17 Hz, H-6), 3.93 (dd, *J* 4 and 17 Hz, H-6), 5.20 (d, *J* 14 Hz, OCH₂), 5.48 (d, *J* 14 Hz, OCH₂), 5.73 (dd, *J* 2 and 4 Hz, H-5), and 7.55–8.32 (m, C₆H₄)]. Subsequent deacetylation of

(3) (dioxan–water, imidazole, room temp.) gave the corresponding 2-thioxopenam (4)† in quantitative yield [ν_{\max} (CDCl₃) 1800 and 1754 cm⁻¹, ¹H n.m.r. δ (CDCl₃) 3.50 (dd, *J* 2 and 16 Hz, H-6), 4.14 (dd, *J* 4 and 16 Hz, H-6), 5.40 (s, OCH₂), 5.50 (s, H-3), 5.98 (dd, *J* 2 and 4 Hz, H-5), and 7.50–8.50 (m, C₆H₄)].

Compound (4) has been shown^{5,6} to be a valuable intermediate in the preparation of a wide range of broad spectrum antibacterial 2-substituted penems.

We have extended the synthetic sequence described above to prepare 6-substituted 2-acetylthiopenems and the related thioxopenams. These preparations will be described elsewhere.

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References

- 1 D. R. Hogg, 'Comprehensive Organic Chemistry,' Vol. 3, ed. D. N. Jones, Pergamon Press, Oxford, 1979, p. 274.
- 2 D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, 1974, 7, 147.
- 3 For a related synthetic sequence see: T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura, and T. Miyadera, *Tetrahedron Lett.*, 1982, 23, 1075.
- 4 R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, 1963, 85, 1896; R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Acc. Chem. Res.*, 1973, 6, 32; R. D. G. Cooper and D. O. Spry in 'Cephalosporins and Penicillins—Chemistry and Biology,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 183.
- 5 G. Johnson, B. C. Ross, and M. A. Yeomans, unpublished results.
- 6 T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura, and T. Miyadera, *J. Chem. Soc., Chem. Commun.*, 1982, 713.

† Compound (4) exists in the thioxo form as judged by ¹H n.m.r. spectroscopy. The C(3) proton is, however, acidic and in the presence of base, e.g. triethylamine, the C(2) sulphur may be alkylated to give a 2-alkylthiopenem.