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

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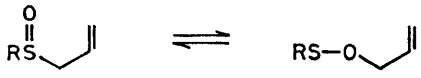
A 2-thioxopenam is synthesised from an acetylthio substituted penem and 2-thiacephem; the latter compound was prepared through the intramolecular nucleophilic capture of an allylic sulphenate ester, generated thermally from the corresponding sulphoxide (**1**).

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**).

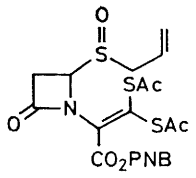
The bis(acetylthio) compound (**1**),† which was synthesised as shown in Scheme 2,[3] possesses both a latent sulphenate ester and a masked thiol. The transformation of (**1**) into the 2-thiacephem would require the controlled release of both groups in such a way that cyclisation could take place.

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 rearrangement[4] of penicillin sulphoxides to cephems led us to incorporate an acid in the thermolysis.

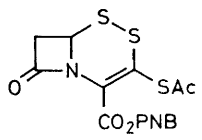


Scheme 1

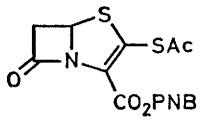
Accordingly, thermolytic treatment of (**1**) (dioxan reflux) in the presence of either a proton acid (benzenesulphonic acid) or a Lewis acid (boron trifluoride) gave 17—40% of the desired 2-thiacephem (**2**) [ν_{max} ($CDCl_3$) 1793 and 1739 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 2.37 (s, COMe), 3.17 (dd, *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, OCH_2–), and 7.50—8.28 (m, C_6H_4)]. 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-



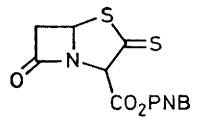
(**1**)



(**2**)



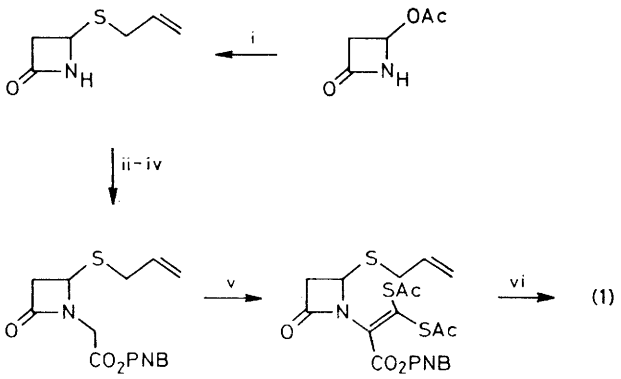
(**3**)



(**4**)

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, $NaSCH_2CH:CH_2$, tetrahydrofuran (THF), room temp.; ii, K_2CO_3, $BrCH_2CO_2Me$, dimethylformamide; iii, KOH, EtOH, then H_3O^+; iv, $BrCH_2PhNO_2$, Na_2CO_3, dimethylacetamide, room temp.; v, $LiN(SiMe_3)_2$, THF, −78 °C then CS_2, −78 °C then Ac_2O, −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 $BF_3.Et_2O$, 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} ($CDCl_3$) 1800 and 1714 cm^{-1}, ^1H n.m.r. δ ($CDCl_3$) 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, OCH_2), 5.48 (d, *J* 14 Hz, OCH_2), 5.73 (dd, *J* 2 and 4 Hz, H-5), and 7.55—8.32 (m, C_6H_4)]. Subsequent deacetylation of (**3**) (dioxan–water, imidazole, room temp.) gave the corresponding 2-thioxopenam (**4**)‡ in quantitative yield [ν_{max} ($CDCl_3$) 1800 and 1754 cm^{-1}, ^1H n.m.r. δ ($CDCl_3$) 3.50 (dd, *J* 2 and 16 Hz, H-6), 4.14 (dd, *J* 4 and 16 Hz, H-6), 5.40 (s, OCH_2), 5.50 (s, H-3), 5.98 (dd, *J* 2 and 4 Hz, H-5), and 7.50—8.50 (m, C_6H_4)].

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

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‡ 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.