A NOVEL SYNTHESIS OF A 2-THIOXOPENAM

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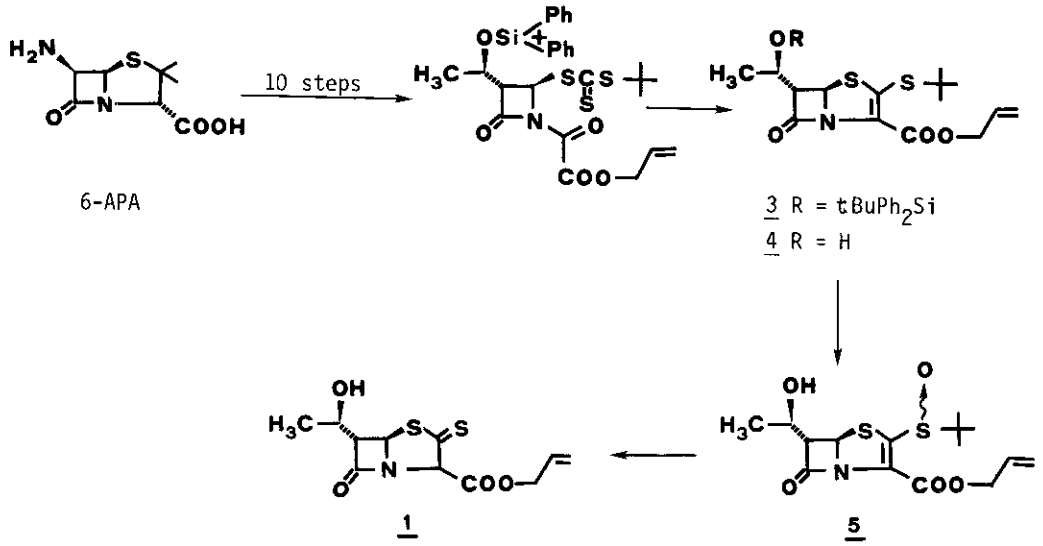
Abstract - The synthesis of an optically active 2-thioxopenam through thermal rearrangement of a 2-t-butylsulfinylpenem to a penemsulfenic acid intermediate and its in situ deoxygenation is described.

Penems are very potent ß-lactam antibiotics with a broad antibacterial spectrum [1]. Biological activity and bioavailability can be influenced by variation of the side chain at C-2 of the penem skeleton. 2-Thioxopenams are convenient synthetic intermediates [2,3] in the multistep syntheses of penems: The C-2 sidechain can be easily introduced at this stage by alkylation [2] or by condensation with alcohols using triphenylphosphine-diethyl azodicarboxylate [4] (scheme 1).

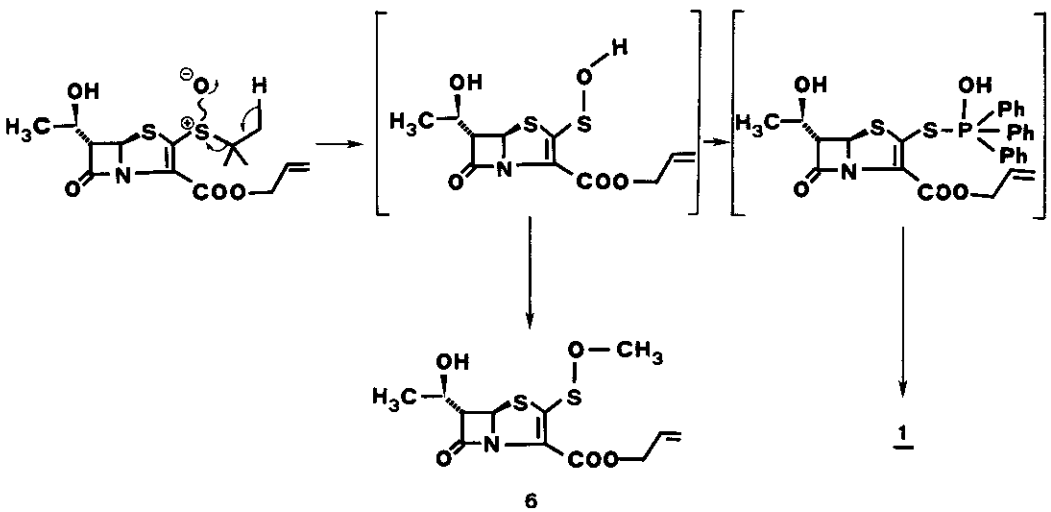
1 2

Scheme 1

There are only few syntheses of 2-thioxopenams [2,3,5,6] reported in the literature and most of these lead to the undesired cis product (5S,6S isomer) [7]. Our method which we present in this paper gives an enantiomerically pure trans-2-thioxopenam with 5R,6S configuration under very mild conditions. Our approach (see scheme 2) is based on the thermal rearrangement of tertiary sulfoxides to sulfenic acids [8] which can be deoxygenated by triphenylphosphine.



Scheme 2



Scheme 3

The 2-t-butylthiopenem 4 which we needed as starting material was prepared from 6-aminopenicillanic acid (6-APA) in analogy to already established methods [9]. The ring closure to the 2-t-butylthiopenem 3 was performed via the corresponding trithiocarbonate using the oxalimide cyclisation reaction [10]. Desylilation gave starting material 4 (3 equiv. n-Bu_4NF, 6 equiv. CH_3COOH, THF, 48 h, 75 % after chromatography)[11].

The exocyclic sulfur atom of 4 could be selectively oxidized to an 8:3 mixture of the epimeric sulfoxides 5 [12] (1 equiv. MCPBA, CH_2Cl_2, -30°C, 40 % after chromatography, plus 30 % unreacted 4 recovered). Rearrangement and deoxygenation were performed by refluxing 5 with 1 equiv. triphenylphosphine in CH_2Cl_2 for 4 h. The isolated 2-thioxopenam 1 [13] (85 % after chromatography) was the pure trans isomer (5R,6S) and existed in $CDCl_3$ solution exclusively in the thioxo form. This is in good agreement with the literature [2,3]. For further structure proof we alkylated 1 to 2 (R = C_2H_5) (10 equiv. C_2H_5Br, 1 equiv. $(iPr)_2EtN$, -20°C, 16 h, 60 % after chromatography). 2 (R = C_2H_5) was in all spectroscopical data identical with a sample prepared by a different way [10].

The existence of an azetidinonesulfenic acid intermediate during the rearrangement of penicillin sulfoxides[14] is well documented in the literature[15] but to our knowledge a penemsulfenic acid which we postulate as intermediate (scheme 3) has never been reported. Therefore we did further investigation to prove the intermediacy of a penemsulfenic acid during the thermal rearrangement of 5. When we kept a freshly prepared sample of 5 in a $CDCl_3$ solution at 50° C for 0.5 h in an NMR test tube the formation of a new compound (40 % of total material) was observed in the NMR spectrum[16]. These new signals could be attributed to the mixture of the postulated penemsulfenic acid and 2-methylpropene. For further structure proof we prepared the more stable methyl ester of the sulfenic acid by treating a solution of 5 in CH_2Cl_2 with diazomethane (room temperature, 16 h, 27 % after chromatography). All spectroscopic data [17] were in good agreement with the proposed structure of 6. These results show that the penemsulfenic acid is generated under very mild conditions during the t-butylsulfoxide rearrangement.

REFERENCES AND NOTES

1. Ivan Ernest, in "Chemistry and Biology of β-Lactam Antibiotics" Volume 2, edited by R.B. Morin and M. Gorman, Academic Press 1982.
2. a) T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura and T. Miyadera, J. Chem. Soc., Chem. Commun., 1982, 713.
   b) T. Miyadera, K. Yokohama, Y. Sugimura, T. Tanaka, T. Hashimoto, S. Toda, K. Iino and S. Sugawara (Sankyo), Offenlegungsschrift DE 31 09 086 A1 (1981).
3. a) V.M. Girijavallabhan, A.K. Ganguly, P. Pinto, and R. Versace, Tetrahedron Lett., 1983, 3179.
   b) V.M. Girijavallabhan, A.K. Ganguly, P. Pinto and R. Versace, J. Chem. Soc., Chem. Commun., 1983, 908.
4. O. Mitsunobu, Synthesis, 1981, 1 and references cited therein.
5. a) N.J. Daniels, G. Johnson, B.C. Ross and M.A. Yeomans, J. Chem. Soc., Chem. Commun., 1982, 1119.

b) B.C. Ross, G. Johnson and M.A. Yeomans (Hoechst), European Patent Application EP 0051813 (1982).

c) N. Daniels, G. Johnson and B.C. Ross, J. Chem. Soc., Chem. Commun., 1983, 1006.

6. M. Cossement, J. Marchand-Brynaert, S. Bogdan and L. Ghosez, Tetrahedron Lett., 1983, 2563.

7. Thermal equilibration leads to a separable mixture of 5S,6R and 5S,6S isomers.

8. J.R. Shelton and K.E. Davis, J. Am. Chem. Soc., 1967, 89, 718.

9. a) V.M. Girijavallabhan, A.K. Ganguly, S.W. McCombie, P. Pinto, and R. Rizvi, Tetrahedron Lett., 1981, 3485 and references cited therein.

b) K. Hirai, Y. Iwano and K. Fujimoto, Heterocycles, 1982, 17, 201.

10. a) A. Afonso, F. Hon, J. Weinstein and A.K. Ganguly, J. Am. Chem. Soc., 1982, 104, 6138.

b) A. Afonso and F. Hon (Schering), European Patent Application EP 0058 317 (1982).

c) A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, Chem. Pharm. Bull., 1983, 31, 768.

11. Spectroscopical data identical with those given in lit. cit. 10b.

12. IR (CH_2Cl_2, cm^{-1}): 1788 (β-lactam), 1708 (ester).
^{1}H-NMR ($CDCl_3$, 250 MHz, δ) a) 5.71 (d, J = 1.5 Hz, H-C_5), 4.20 (m, H-C_8), 3.92 (dd, J_1 = 7 Hz, J_2 = 1.5 Hz, H-C_6), b) 5.86 (d, J = 1.5 Hz, H-C_5), 4.20 (m, H-C_8), 3.87 (dd, J_1 = 7 Hz, J_2 = 1.5 Hz, H-C_6).

13. IR (CH_2Cl_2, cm^{-1}): 1790 (β-lactam), 1742 (ester).
^{1}H-NMR ($CDCl_3$, 90 MHz, δ) 5.90 (d, J = 1.5 Hz, H-C_5), 5.38 (s, H-C_3), 4.38 (quintet, J = 7 Hz, H-C_8), 3.69 (dd, J_1 = 7 Hz, J_2 = 1.5 Hz, H-C_6), 1.41 (d, J = 6.5 Hz, CH_3).

14. 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.

15. for a review: R.D.G. Cooper and G.A. Koppel, in "Chemistry and Biology of β-Lactam Antibiotics", Volume 1, edited by R.B. Morin and M. Gorman, Academic Press 1982.

16. ^{1}H-NMR ($CDCl_3$, 250 MHz, δ) 5.71 (d, J = 1.5 Hz, H-C_5), 4.20 (m, H-C_8), 3.79 (dd, J_1 = 7 Hz, J_2 = 1.5 Hz, H-C_6).

17. IR (CH_2Cl_2, cm^{-1}): 1787 (β-lactam).
^{1}H-NMR ($CDCl_3$, 250 MHz, δ) 5.81 (d, J = 1.5 Hz, H-C_5), 4.26 (quintet, J = 7 Hz, H-C_8), 3.81 (s, OCH_3), 3.78 (dd, J_1 = 1.5 Hz, J_2 = 7 Hz, H-C_6), 1.38 (d, J = 7 Hz, CH_3).
MS (m/z) 317 (M^+), 231 (M^+ - CH_3CHOH-CH=C=O), 200 (231-OCH_3).

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