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A NEW REDUCTIVE ACYLATION OF AZETIDINONE DISULPHIDE IN THE ROUTE TO PENEMS

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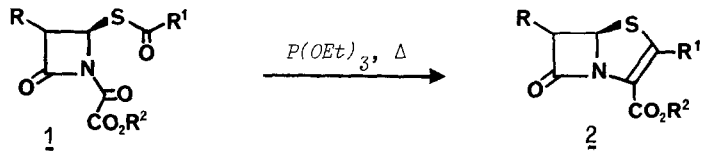
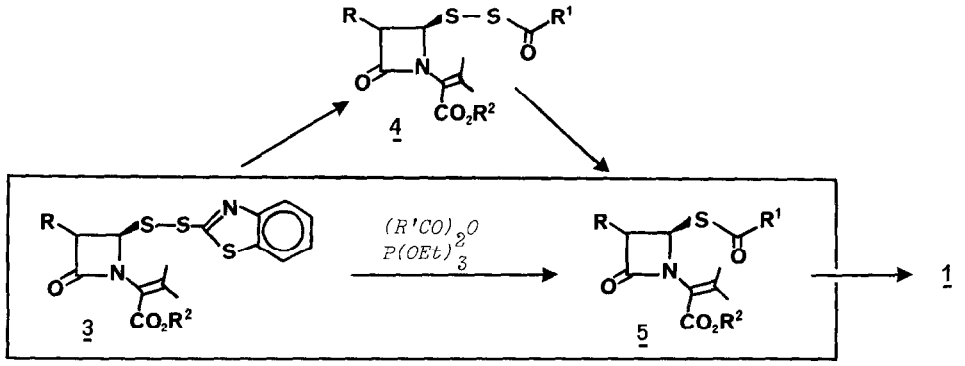
Abstract. *The use of triethyl phosphite and the appropriate carboxylic anhydride was found to constitute an efficient method for the conversion of azetidinyl benzthiazolyl disulphides into acylthio-azetidinones, allowing a short synthesis of penem FCE 22891 from its penam-1-oxide precursor.*

The most direct approach to 2-alkyl substituted penems 2 involves the recently discovered phosphite-mediated cyclization of oxalimido-thiolesters 1[1].



1 2

When penicillins are used as starting material, intermediates 1 can be quantitatively obtained by ozonolysis of the butenoate-thiolesters 5; hence our renewed interest[2,3] in these compounds. In the last approach, a benzthiazolyl disulphide 3 undergoes a sulphur exchange to an acyldisulphide 4 followed by a desulphurative process to give a butenoate-thiolester 5[4].

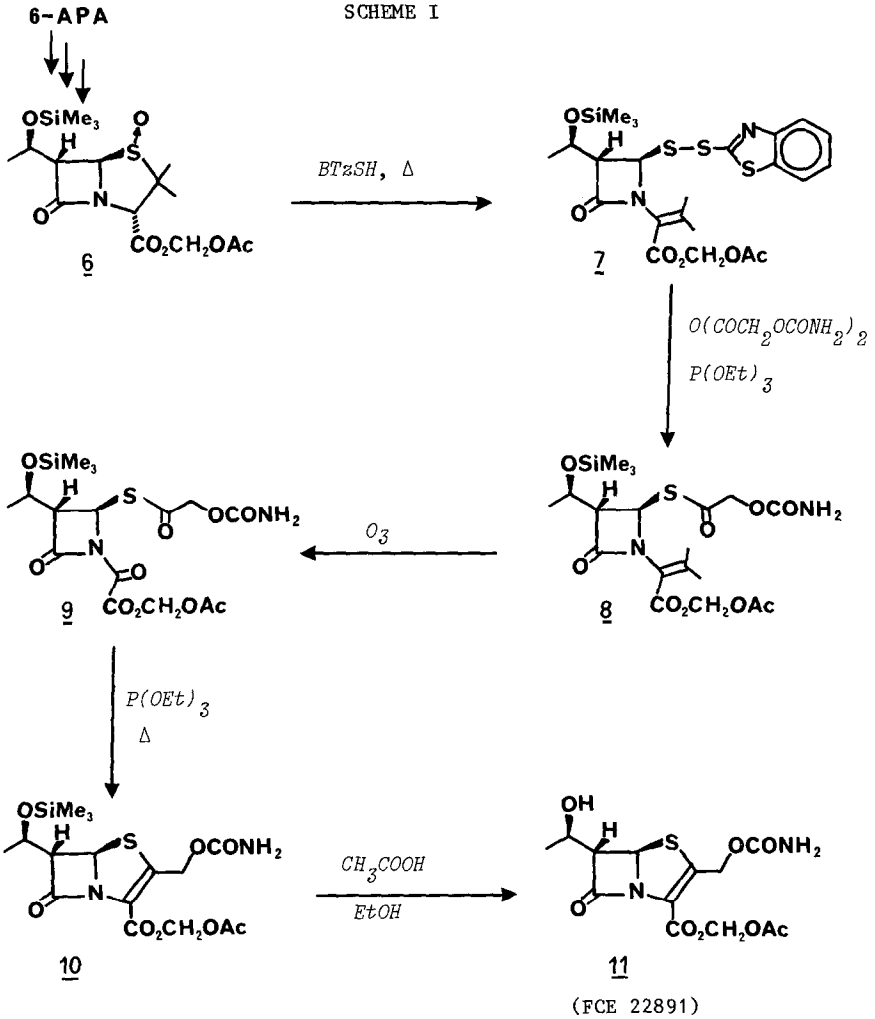


In the present paper we wish to report a direct conversion of the Kamiya disulphide derivative 3[5] into the thiolester 5 by using triethylphosphite and a proper anhydride, thus avoiding the tedious preparation of the corresponding thioacid.

A synthetic utilization of the reaction is shown in our route to the penem FCE 22891 (11)[6] from 6-APA (Scheme I)[7].

In a typical procedure to a diluted solution of the benzthiazole-disulphide 7 (4 mmol) and carbamoyloxyacetic anhydride[8] (15 mmol) in dichloromethane (240 ml) was added dropwise a diluted solution of triethylphosphite in the same solvent (0.75 ml in 120 ml). The reaction mixture was kept under stirring for two hours at room temperature. Filtration and purification by flash chromatography afforded the thiolester 8 (1.5 g) in 76% yield. The crucial requirement is operating with diluted solutions.

SCHEME I



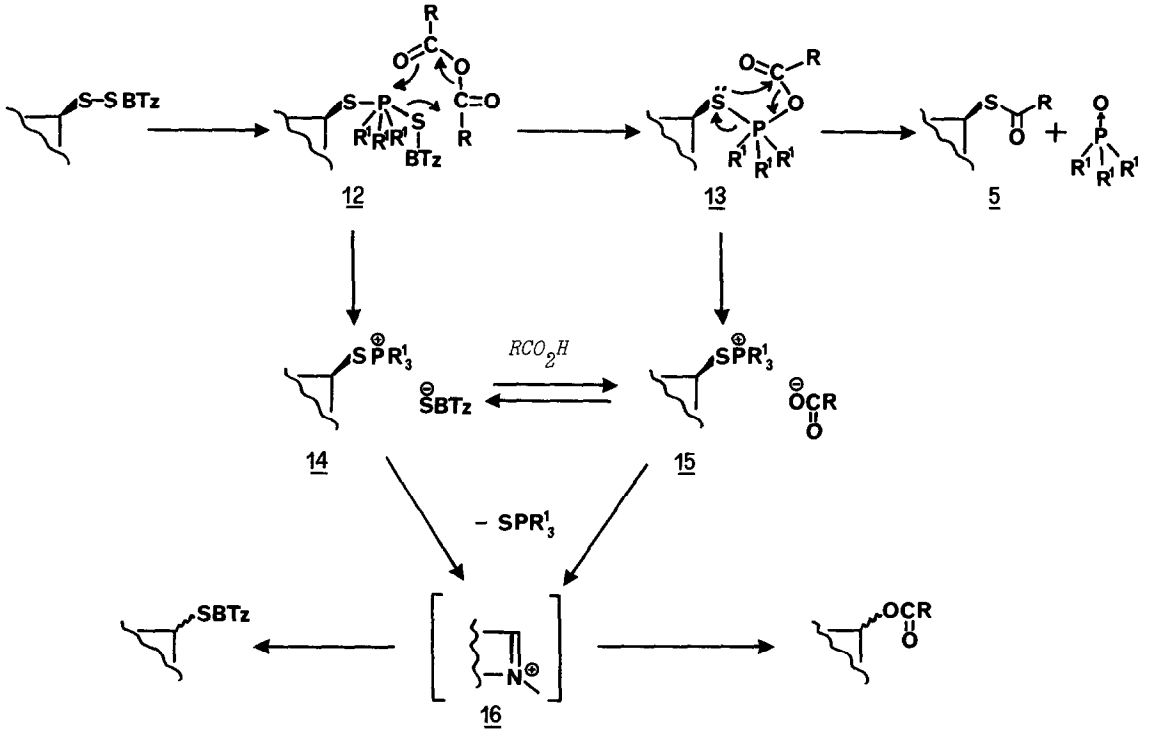
BTzSH= mercaptobenzthiazole

A similar reductive acylation has been previously reported by the Woodward group. They performed the reaction by using triphenylphosphine and a mixture of acetic anhydride and acetic acid in the preparation of 3-acylaminoazetidinones[9] but reported the failure of the same reaction for 3-unsubstituted analogues[10]. We tried the same reagents in the case of 3-hydroxyethylazetidinones without success; however avoiding the presence of the acid gave us encouraging results. In fact the use of triphenylphosphine and carbamoyloxyacetic anhydride led to the target thiolester derivative 8 in 40% yield from 7 (Scheme I). Moreover the replacement of triphenylphosphine with triethylphosphite gratifyingly increased the yield up to 76%.

The beneficial effects of the new conditions are even more apparent in the case of particular substitution at the azetidinone C3: substrates possessing a trichloroethoxycarbonyl protecting group for the hydroxyl function failed to afford any of the desired thiolester when PPh_3 was employed as the phosphorous reagent[11] but the use of $P(OEt)_3$ sufficed in restoring the yields up to an acceptable level (50%).

A speculative suggestion regarding the mechanism of the reaction involves a non-ionic pathway, outlined in Scheme II. The key intermediates might be the pentacovalent phosphorous species 12 and 13 leading to the sulphur acylation through an intramolecular rearrangement.

SCHEME II



Although Mukaiyama[12] reported the collapse of a thiophosphonium carboxylate as a convenient route to thiolesters, it might be questioned whether the ionic azetidinone species 15 could effectively yield the desired acylthio derivative 5 owing to an alternative breakdown mode whereby a phosphine sulphide and a stabilized azetidinium ion 16 is generated instead, being responsible for side-products formation. Since a triphenylphosphonium ion is more stable than its trialkoxy counterpart[13], the use of triphenylphosphine causes a greater extent of deviation to the ionic pathway and hence to the side-product formation. As a matter of fact phosphite shows to be a better reagent for the route to the thiolester. Beside an anhydride represents a suitable acylating agent in the non-ionic pathway,[14] since it allows the direct conversion of 12 into 13 with simultaneous scavenging of the benzthiazolyl mercaptide. Finally the intramolecular nature of the sulphur acylation step hypothesized in the scheme is in accord with the favourable effect of dilution.

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7) We thank G.P. Borsotti and M. Altamura (Istituto Ricerche Donegani, Novara, Italy) for the preparation of the penam sulphoxide 6.
8) Carbamoyloxyacetic anhydride was obtained in situ from carbamoyloxyacetic acid and DCC in dichloromethane (-20°C). Acknowledgments are due to Franco Giudici of our laboratories for synthesizing the acid (from glycolic acid and chlorosulfonyl isocyanate, followed by aq. Na_2SO_3 work up).
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