

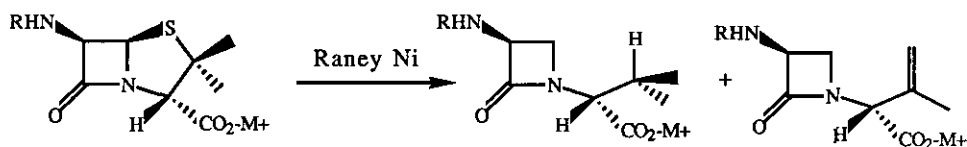
DESULPHURISATION OF PENICILLINS WITH TRIPHENYLSTANNANE

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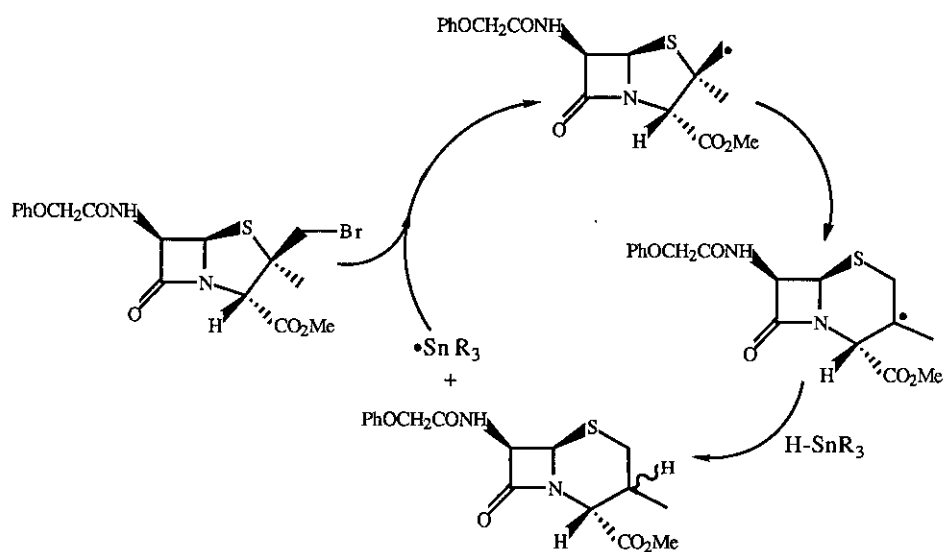
Abstract- Reaction of penicillins (and a cephalosporin) with triphenylstannane provides a novel and efficient route to dethioazetidinones. A study on the mechanism of this process is described.

The discovery of Nocardicin¹ and Sulfazecin² has rekindled interest in the preparation of monocyclic β -lactams.³⁻⁵ Traditionally such compounds can be accessed from commercially available penicillins via Raney Nickel desulphurisation,⁶ however, not only is this process low yielding (typically 30-45%)³⁻⁵ but it also provides mixtures of saturated and olefinic products³ and is normally performed under essentially aqueous conditions (Scheme 1).

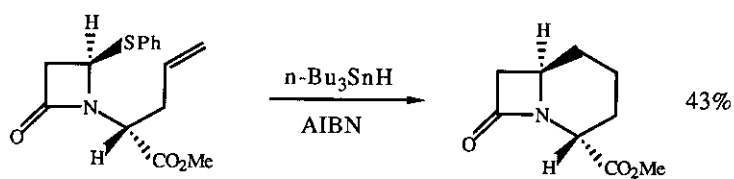


Scheme 1

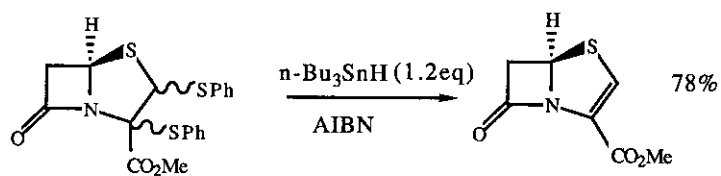
Although applications of trialkylstannanes for the reductive desulphurisation of divalent sulphur compounds are legion,⁷ the potential of triphenylstannane to desulphurise penicillins has, to our knowledge, been overlooked. Literature precedent demonstrates that the reaction of functionalised penicillins with trialkylstannanes occurs primarily at sites other than sulphur,⁸⁻¹¹ e.g. at halogen⁹ (Scheme 2). Desulphurisation can be achieved from 4-phenylthioazetidinones with trialkylstannane to provide a free radical intermediate capable of direct reduction¹² or intramolecular cyclisation followed by reduction,¹³ e.g. Scheme 3. Interestingly, Kametani et al.¹⁴ have reported a penem synthesis via trialkylstannane treatment (1.2 equivs) of a 1,2-bis-sulphide penam for which the ring sulphur remains intact (Scheme 4).



Scheme 2

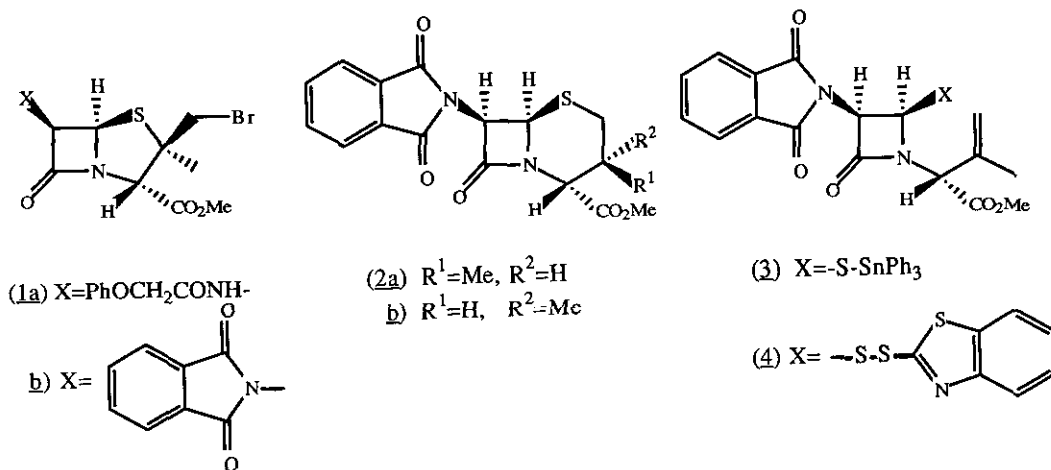


Scheme 3



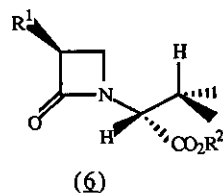
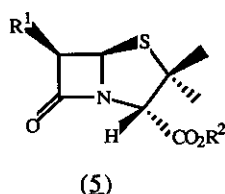
Scheme 4

During the course of our continuing investigation into the mechanisms of penicillin and cephalosporin biosynthesis¹⁵ we developed a radically mediated biomimetic ring expansion reaction⁹ derived from homolytic reductive debromination of phenoxyacetyl-2 β -bromomethyl penam 1a by triphenylstannane. In a subsequent study we examined reaction of the phthalimido-2 β -bromomethylpenam 1b with triphenylstannane [stannane (2 equivs.), AIBN (10 mol %), benzene, reflux, 1h]. In addition to the expected mixture of ring expanded cephams 2a,2b (65%) a third minor β -lactam product 3 was produced. 3 was found to be unstable to normal chromatographic purification and its structure followed from spectroscopic analysis of the crude reaction mixture; for 3 δ_H (500 MHz, CDCl₃) 2.00 (3H, s, vinyl CH₃), 3.67 (3H, s, CO₂Me), 4.72 (1H, s), 4.90 (1H, s), 4.98 (1H, s), 5.31 and 5.49 (2H, ABq, J 5 Hz, β -lactam-H), m/z (positive argon fast atom bombardment) MH⁺ 716 (7), 715 (17), 714 (7), 713 (27), 712 (32), 711 (100), 710 (52), 709 (76), 708 (28), 707 (33), calculated for C₂₅H₂₁N₂O₅SSn 716 (6), 715 (16), 714 (8), 713 (24), 712 (39), 711 (100), 710 (51), 709 (74), 708 (35), 707 (38). Thiostannane 3 was also obtained as a minor product from the reaction of the Kamiya's disulphide 4 with triphenylstannane.⁹ From these observations we concluded that the formation of 3 could result from initial attack of a triphenylstannyl radical on sulphur, which could in principle lead to reductive desulphurisation.



In order to test this postulate penicillin V benzyl ester 5a was reacted with triphenylstannane [2-4 equivs., AIBN (10 mol %), benzene, reflux, 2h]; complete conversion to the dethioazetidinone 6a (95 %) was observed. With 1 equivs. of triphenylstannane a 2:1 ratio of thiostannane 7 : 6a was produced; for 7 δ_H (200 MHz, CDCl₃) 0.87 (3H, d, J 8 Hz, CHMe₂), 1.06 (3H, d, J 8 Hz, CHMe₂), 2.55 - 2.75 (1H, m, CHMe₂), 3.85 (1H, d, J 9 Hz, CHCHMe₂), m/z (+ Ar FAB) MH⁺ 798 (7), 797 (12), 796 (8), 795 (22), 794 (39), 793 (100), 792 (57), 791 (80).

790 (39), 789 (41), $C_{11}H_{11}N_2O_3SSn$ requires 798 (7), 797 (16), 796 (9), 795 (26), 794 (45), 793 (100), 792 (54), 791 (74), 790 (36), 789 (36). Crude thiostannane 7 with further triphenylstannane gave 6a. Secondly the reaction of 5a with tributyltin deuteride (5 equivs.) was performed which provided the dideuteroazetidinone 8 (72 %) in which deuterium label at C4 was stereorandom; for 8 δ_H (200 MHz, $CDCl_3$) 1.00 (3H, br.s, CDMe), 1.02 (3H, br.s, CDMe), 3.53 (ca. 0.5H, br.d, J 2.5 Hz, 4-H), 3.94 (ca. 0.5H, br.d, J 5.5 Hz, 4-H), 4.32 (1H, s, $CHCO_2$), 4.51 (2H, s, $PhOCH_2$), 4.81 - 4.90 (1H, m, 3-H), 5.17 (2H, s, CO_2CH_2), 6.90 - 7.37 (10H, m, aryl-H); δ_D (38 MHz, $CHCl_3$), 2.25 (1D, m, $CDMe_2$), 3.55 and 3.95 (ca. 0.5 D each, m, 4-D); m/z (ammonia desorption chemical ionisation) 430 (MNH_4^+ , 93%), 413 (MH^+ , 100%).

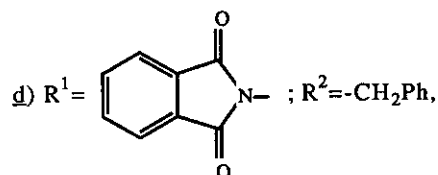


For (5) and (6)

a) $R^1 = PhOCH_2CONH-$; $R^2 = -CH_2Ph$,

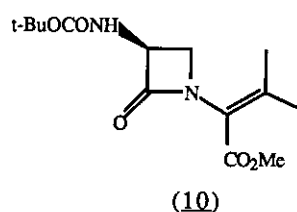
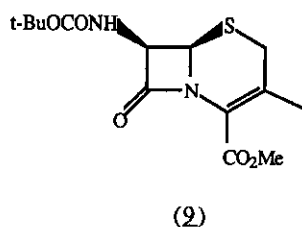
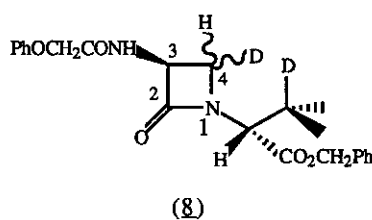
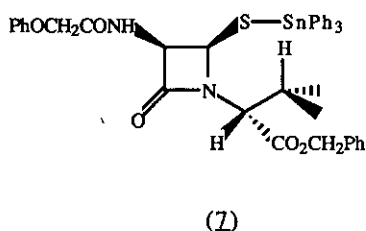
b) $R^1 = PhOCH_2CONH-$; $R^2 = -Me$,

c) $R^1 = PhOCH_2CONH-$; $R^2 = -CHPh_2$,



e) $R^1 = PhCH_2CONH-$; $R^2 = -CH_2Ph$,

f) $R^1 = t-BuOCONH-$; $R^2 = -CH_2Ph$,

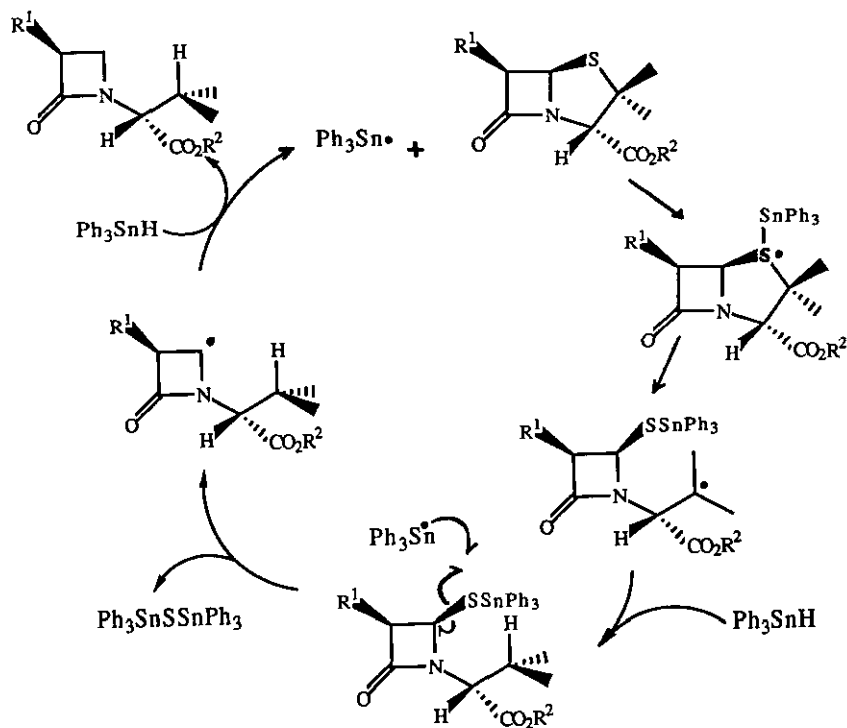


The generality of the desulphurisation process was demonstrated as exemplified in Table 1;
facile desulphurisation of a cephem was also observed (entry 7, Table 1).

Entry	Substrate	Ph ₃ SnH (equiva.)	Time (h.)	Product ^a	(%)
1	<u>5a</u>	2	2	<u>6a</u>	(95)
2	<u>5b</u>	4	2	<u>6b</u> ^e	(93)
3	<u>5c</u>	4	14	<u>6c</u>	(88)
4	<u>5d</u>	4	14	<u>6d</u>	(96)
5	<u>5e</u>	2	2	<u>6e</u>	(91)
6	<u>5f</u>	2	3	<u>6f</u>	(73)
7	<u>9</u>	3	5	<u>10</u>	(88)

a) Products were characterised by microanalysis and/or spectral data, and by comparison to literature data.

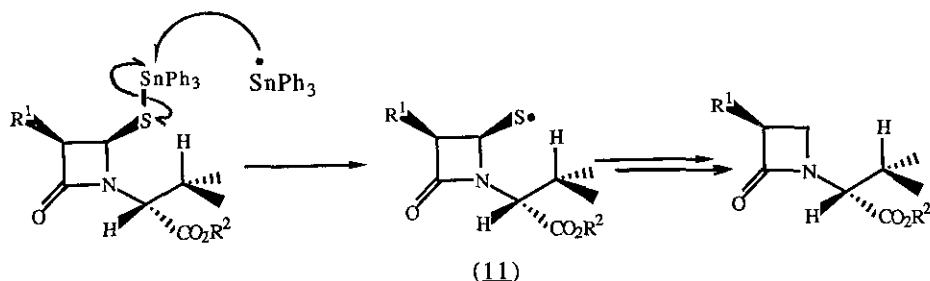
TABLE 1



Scheme 5

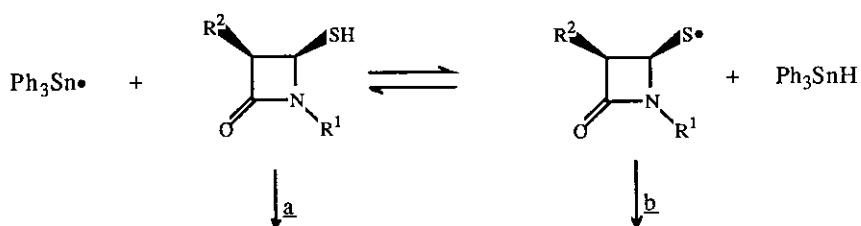
A mechanism for the desulphurisation process is postulated in Scheme 5. In this scheme initial attack of triphenylstannyl radical on sulphur is followed by cleavage to the favoured 3° carbon radical. Reduction of this radical provides the intermediate thiostannanes which we have detected at low stannane concentrations. Homolytic cleavage of the carbon-sulphur bond, promoted by a second triphenylstannane radical attack on sulphur, provides an azetidinone centred radical whose reduction by triphenylstannane would be largely stereorandom. Such a mechanism requires the formation of di-(triphenylstannyl)sulphide which we have isolated from crude reaction products, mp 145-7°C, [lit.,¹⁶ 145.5-147°C], m/z (+ Ar FAB) MH^+ 740 (8), 739 (20), 738 (15), 737 (32), 736 (32), 735 (80), 734 (56), 733 (100), 732 (70), 731 (90), 730 (42), 729 (40), 728 (16), 727 (13), 726 (3), [Calc. for $C_{36}H_{31}SSn_2$ 740 (8), 739 (21), 738 (17), 737 (35), 736 (37), 735 (81), 734 (64), 733 (100), 732 (72), 731 (86), 730 (43), 729 (41), 728 (17), 727 (14), 726 (3)].

An alternative mechanism for thiostannane decomposition, in which the thiostannane is cleaved by attack of triphenylstannyl radical on tin (Scheme 6) generating a thiyl radical, was considered less likely on the basis of further studies.

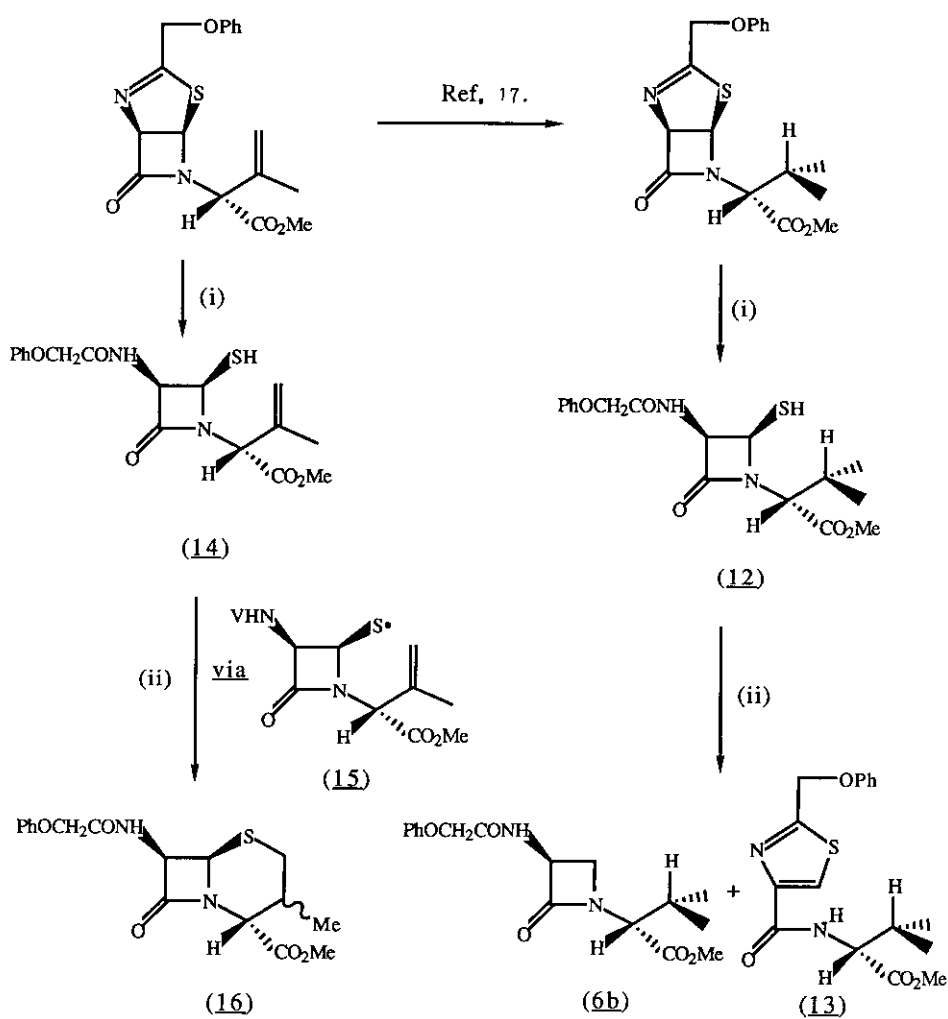


Scheme 6

Such a process would provide the thiyl radical 11 in the presence of triphenylstannane from which it could reasonably be expected that a thiyl-thiol azetidinone equilibrium be established from which product formation could occur from either form, routes a, b, (Scheme 7). Consistent with this view, the thiol azetidinone 12 (Scheme 8) gave, under standard conditions [Ph_3SnH (4 equivs.), AIBN (10 mol %), benzene, reflux, 4 h], in addition to an inefficient desulphurisation yield of 6b (50 %), the enethiazolidine¹⁸ 13 (14 %). This is in contrast to the desulphurisation of 5b under identical conditions which gave 6b (93 %) and no enethiazolidine 13. Access to the thiyl radical 11 from 12 was demonstrated by reaction of the dehydrothiol azetidinone 14 with triphenylstannane under standard conditions, which provided the cepham 16 (84 %) via the analogous thiyl radical⁹ 15. From these studies it appears likely that only with cases where capture of a thiyl radical is favoured, e.g. by an intramolecular alkene, can access to the thiyl radical be productively exploited.



Scheme 7



Scheme 8; Reagents (i) acetone, 2N-HCl(5 equivs., 0°C, 1.5h (ca quant.);

(ii) Ph_3SnH (4 equivs.), AIBN (10 mol %), benzene, reflux, 3h

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cephalosporin precursors.

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Investigation into the mechanism and scope of these types of reactions are current objectives. desulphurisation process consistent with a homolytic chain process has been proposed; further offers an attractive alternative to existing methodology. A mechanism for the provides an efficient and convenient route to synthetically useful dethiazetidiones and thus In summary we have demonstrated that the triphenylstannane reduction of penicillin esters