Triorganotin Hydride Reduction of 6β-Isothiocyanatopenicillanates: A Radical-induced Sulphur–C(2) Bond Cleavage

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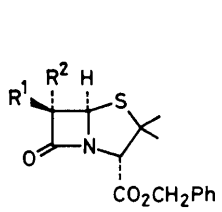
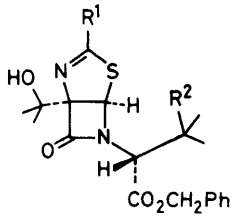
Summary Triorganotin hydride reduction of methyl 6β-isothiocyanatopenicillanate is accompanied by intramolecular radical capture and cleavage of the sulphur–C(2) bond to give thiazolines (**9**) and (**10**); a similar mechanism is proposed for the formation of thiazoline (**3**), a minor product of tri-n-butyltin hydride reduction of benzyl 6α-(1-hydroxy-1-methylethyl)-6β-isocyanopenicillanate (**1**; $R^2 = Me_2COH$).

RECENTLY the tri-n-butyltin hydride reduction of 6α-alkyl-6β-isocyanopenicillanates (**1**) was shown to be a useful stereoselective synthesis of 6β-alkylpenicillanates (**2**).[1] A minor side-product was formed in some of these reductions, and was isolated in 15% yield from the reduction of benzyl 6α-(1-hydroxy-1-methylethyl)-6β-isocyanopenicillanate (**1**; $R^2 = Me_2COH$), being identified as thiazoline (**3**). We here report that reduction of methyl 6β-isothiocyanatopenicillanate (**8**) with tin hydride reagents proceeds with predominant sulphur–C(2) bond cleavage to give rearranged thiazolines as the only isolable products.[2]

Thus, treatment of methyl 6β-isothiocyanatopenicillanate (**8**)[3] with either tri-n-butyl- or triphenyl-tin hydride in refluxing benzene, in the presence of a trace of azobisisobutyronitrile, led to the formation of thiazolines (**9**) and (**10**). These products were difficult to purify, repeated chromatography on silica causing loss of the tin moiety giving dithiourethane (**11**)† which was isolated in 30% overall yield. A more efficient cleavage of the tin moiety was achieved by treatment with tetra-n-butylammonium



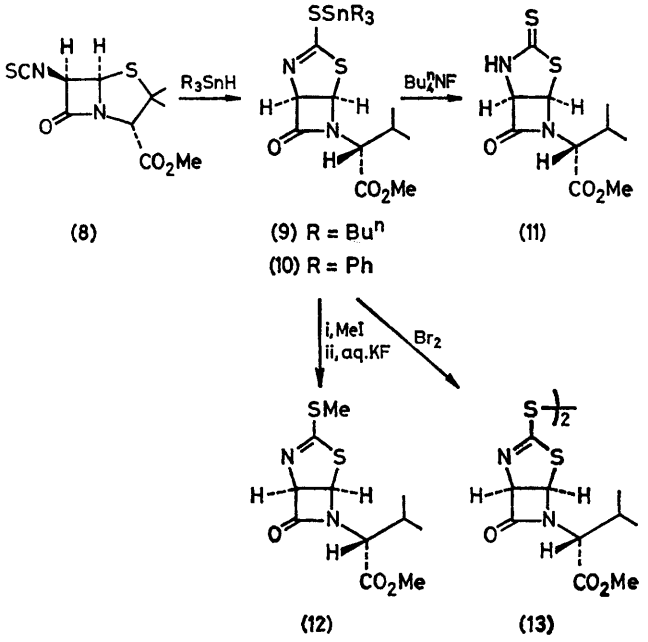
(1) R^1 = CN–, R^2 = alkyl
(2) R^1 = alkyl, R^2 = H



(3) $R^1 = R^2 = H$
(4) R^1 = H, R^2 = D
(5) $R^1 = SnBu^n_3$, R^2 = H
(6) R^1 = D, R^2 = H
(7) $R^1 = R^2$ = D

† Satisfactory spectroscopic data were obtained for all new compounds. In addition thiazolines (**11**), (**12**), and (**13**) were characterized using accurate mass data.

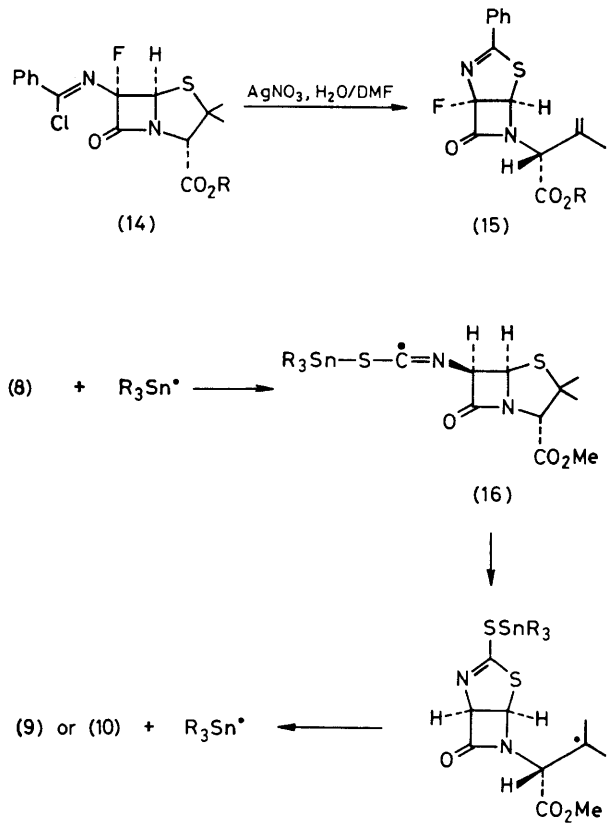
fluoride[4] in dioxan (25 °C, 12 h). Use of this procedure, for example, in the case of the triphenylstannylthiothiazoline (**10**), led to the isolation of the dithiourethane (**11**) in 68% yield after silica chromatography. Alternatively, treatment of the triphenylstannylthiothiazoline (**10**) with methyl



iodide[5] in benzene (25 °C, 5 days), followed by aqueous potassium fluoride (to remove tin residues), led to the isolation of the crystalline methylthiothiazoline (**12**), m.p. 84—86 °C, $[\alpha]_D$ −229° ($CHCl_3$), in 48% yield after silica chromatography. The structure of (**12**) was established by spectroscopic methods, *e.g.* ν_{max} 1760, 1730, and 1560 cm^{-1}, δ ($CDCl_3$) 0·95 and 1·3 (each 3H, d, *J* 6·5 Hz, $CHMe_2$), 2·1—2·4 (1H, m, $CHMe_2$), 2·60 (3H, s, SCH_3), 3·75 (3H, s, CO_2CH_3), 4·15 (1H, d, *J* 8·8 Hz, $CHCO_2Me$), and 5·9 and 6·04 (each 1H, d, *J* 4·1 Hz, NC*H* and C*H*S). Finally, treatment of thiazoline (**9**) with bromine (1 mol)[5] led to the formation of disulphide (**13**), 59% isolated after silica chromatography.

The formation of thiazolines (**9**) and (**10**) is reminiscent of the formation of thiazolines (**15**) on attempted $AgNO_3$-catalysed hydrolysis of the 6α-fluoro-6β-iminochlorides (**14**).[6] However a radical process must be involved in our case. Perhaps addition of the trialkyltin radical to the isothiocyanato-group to give adduct (**16**) is followed by intramolecular capture and cleavage of the sulphur–C(2) bond to give the tertiary radical (**17**). Transfer of a hydrogen atom to this radical from the tin hydride reagent would then complete the cycle. This radical-induced sulphur–C(2) cleavage is analogous to the reverse of a proposed mechanism for the formation of the thiazolidine ring in penicillin biosynthesis.[7]

A similar mechanism seems to be involved in the formation of the thiazoline side products observed in the 6β-



isocyanopenicillanate reductions.[1] Use of Bu^n_3SnD to reduce the 6α-(1-hydroxy-1-methylethyl)-6β-isocyanopenicillanate (**1**; R^2 = Me_2COH) gave the thiazoline (**4**) labelled at the valine β-position only, consistent with this proposal. Moreover, examination of the reduction of isonitrile (**1**; R^2 = Me_2COH) by Bu^n_3SnH suggests that the immediate rearrangement product is the unstable tri-n-butyltin thiazoline intermediate (**5**) since the imino-proton (R^1) is not observable by ^1H n.m.r. spectroscopy. This intermediate thiazoline (**5**) rapidly loses the tin moiety on silica chromatography (or more slowly over a period of weeks in chloroform solution) to provide thiazoline (**3**). If the intermediate (**5**) is decomposed by treatment with D_2O–acetone in the presence of silica, deuteriated thiazoline (**6**) is obtained together with a small amount of the non-deuteriated product, (**6**) : (**3**) = 4 : 1. Moreover reduction of isonitrile (**1**; R^2 = Me_2COH) with Bu^n_3SnD, followed by decomposition of the intermediate tri-n-alkylstannylthiazoline in D_2O–acetone–silica, led to an analogous mixture comprising the dideuteriothiazoline (**7**), and the monodeuteriothiazoline (**4**), again in a ratio of 4 : 1, respectively.

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