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CHEMO- AND STEREOSELECTIVE REDUCTION OF (PIVALOYLOXY)METHYL 6,6-DIHALOPENICILLANATES BY TRINEOPHYLTIN HYDRIDE: SELECTIVE SYNTHESIS OF 6β-HALOPENICILLANATES

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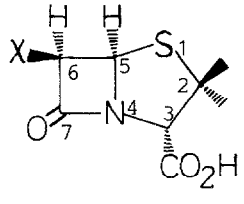
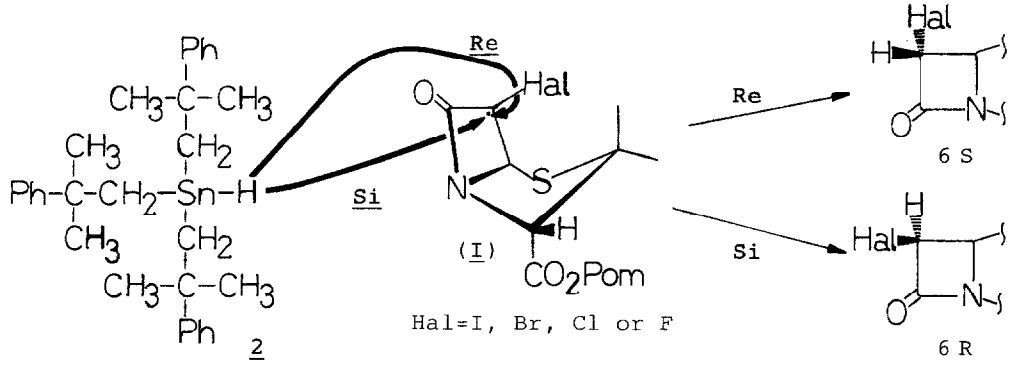
Summary: A new Triorganotin hydride, Trineophyltin hydride was prepared and its chemo- and stereoselectivity towards reduction of Pom 6,6-homo- and hetero- dihalopenicillanates was examined. The trineophyltin hydride reveals higher stereoselectivity compared to that by tributyltin hydride at 25°C.

Since the discovery that 6β-bromo-[1,2] (1a) and 6β-iodo- penicillanic acid[2,3] (1b) are inhibitors of β-lactamase enzymes,[4] the synthesis of 6β-halopenicillanates has become an area of considerable interest and we, as well as several research groups, have developed the tributyl hydride reduction of 6,6-dihalopenams as useful route to these compounds.[5,6] The stereoselectivity in these radical reactions has been atributed to steric factors.[5,6a-c]



1a X=Br
1b X=I

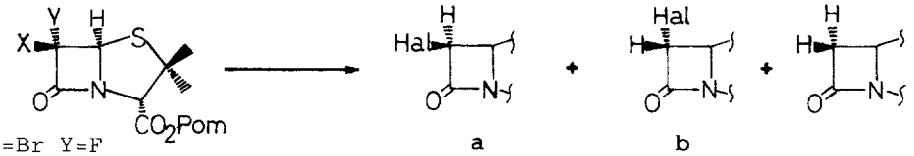
Up to now, the most widely employed triorganotin hydrides for the reduction of alkyl halides are tributyl- and triphenyl- tin hydrides.[7] These organotin hydrides possess unique reducing characteristics, especially showing a high degree of chemo- and stereoselectivity towards gem homo- and hetero-dihalides.[5,8] Our idea of find higher selectivities were based upon the assumption that the highly hindered (2-methyl-2-phenylpropyl) (neophyl) groups would exert a pronounced steric influence on delivering a hydrogen atom to the hindered Re-face of intermediate penicillanate radical (I) leading exclusively or predominantly to (6R)-halopenicillanates. Here we assume that the conformation in solution of (I) is similar to that of Pom 6,6-dibromopenicillanate (9) in solution,[9] that is, the β-lactam ring of the penam nucleous is planar or very nearly so, and the conformation of the thiazolidine ring has the 2β, 3α substituents both "axial" with respect to the five-membered ring.



Trineophyltin hydride (2) was succesfully prepared in 88% yield by reduction of bis(trineophyltin) oxide with borane in THF.[10]

We now report here the use of (2) as an effective chemo- and stereoselective reagent towards the reduction of Pom 6,6-homo- and hetero- dihalopenicillanates. These results and comparable data for tributyltin hydride (3) are summarized in Table 1.

Table 1. Stereoselective reduction of (Pivaloyloxy)methyl (Pom) 6,6-dihalopenicillanates to the corresponding 6β-haloderivatives with (2) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN).



4	X=Br Y=F	a	
6	X=Cl Y=F	5 Hal=F	16
7	X=I Y=Br		
9	X=Br Y=Br	8 Hal=Br	
10	X=I Y=Cl		
12	X=Br Y=Cl	11 Hal=Cl	
13	X=Cl Y=Cl		
14	X=I Y=I	15 Hal=I	

Entry	Substrate	Product(s)[a]	rel. ratio[b] (2)	rel. ratio[b] (3) (α:β:16)	Solvent	Conditions (2) (equiv.)	Conditions Temp. (°C)	Conditions Time (h)	Yield[c] (%)
1	4[5b]	5a[5b] + 5b[12]	20:1	(2.3:1:0)[5b]	Et_2O	1.2	25	5	68
2	6[5b]				THF	1.6	67	8	--[d]
3	7[13]	8a[14]		(c.m.)[e]	Et_2O	1.1	25	6.5	60
4	9[9]	8a + 16	9:1	(4:1:0)[5a]	Et_2O	1.3	25	4	75
5	10[13]	11a[14]		(6:1:0)[5a]	Et_2O	1.4	25	2	68
6	12[13]	11a		(6:1:1)[5a]	Et_2O	1.4	25	2	89
7	13[5b]	11a + 11b[5a]	18:1	(n.d.)[f]	THF	1.2	67	2	71
8	14[9]	15a + 16	3:1	(g)	Et_2O	1.3	25	8	47

(a) Characterized via comparisson with authentic samples (IR, ^{1}H NMR and TLC). Unequivocal proof of the configuration at carbon-6 was secured by ^{1}H NMR spectroscopy on the basis of the H(5)-H(6) coupling constants.[11] (b) Determined by ^{1}H NMR. (c) Isolated yields of 6β-halopenicillanate. (d) At 25°C did not reacts. However, after 8 h at 67°C, total decomposition was observed. (e) c.m.: complex mixture, see ref. 5a. (f) n.d.: not determined. (g) The principal product detected by ^{1}H NMR was the dihydro (16), whereas 6β-halo- (15a) was not present.

The following is a typical procedure for the preparation of Pom 6β-fluoropenicillanate (5a): Pom 6β-bromo,6α-fluoropenicillanate (4) (69 mg, 0.17 mmol) and AIBN (1 mg) were dissolved in dry ether (5 ml). Trineophyltin hydride (104 mg, 0.2 mmol), dissolved in dry ether (2 ml), was added. The mixture was stirred at 25°C for 5 h. The progress of the reaction was monitored by TLC (silica gel, chloroform). After completion, the solution was evaporated in vacuo to dryness and purification of the residue by column chromatography on silica gel (dichloromethane-hexane, 6:4) gave the pure products in the stated yields.

As may be seen from these results the reduction of substrates (7), (10) and (12) (entries 3, 5 and 6) furnishes with complete stereoselectivity their corresponding 6β-bromo- and 6β-chloro- penicillanate (8a) and (11a). Very high diastereoselectivity also was observed in the reduction of substrate (4) (entry 1). In the case of substrates (9) and (14) (entries 4 and 8) a minor amount of over-reduction product (16) was present. In the case of substrate (13) (entry 7) the reaction did not proceed to completion in ether or THF at 25°C and refluxing in THF (67°C) was necessary.

The results in Table 1 demonstrate the excelent chemoselectivity, that is, (2) reacts with different halogen groups at very different rates, e.g. the iodide is reduced faster than bromide or chloride (entries 3 and 5), and in turn the bromide reacts faster than chloride or fluoride (entries 6 and 1). These results are in agreement with our proposed single-electron transfer (SET) mechanism.[5]

The better diastereoselectivity achieved with (2), compared to tributyltin hydride reductions, indicates a better diastereofacial selectivity on the approaching of (2) to donate a hydrogen atom ($H^{\bullet}$) to the encumbered diastereotopic Si face of carbon-6 in intermediate radical (I).

In conclusion, we have therefore succeeded in reaching a very high diastereofacial selectivity and a more selective synthesis of 6β-halopenicillanates.

The trineophyltin hydride (2) is a crystalline solid, melting point 50-51°C. It can be handled in the air and kept at room temperature (~30°C) without appreciable decomposition for some weeks. It is soluble in most organic solvents such as ether, THF, benzene, etc. and its thermal stability was very good.[10]

The present trineophyltin hydride reduction has the following advantages over the existing methodologies: a) the reduction of Pom 6,6-dihalopenicillanates examined occurred with higher stereoselectivity; b) the reagent is quite stable under various conditions and c) the reaction is rapid, clean and the reduced penicillanates are not contaminated with organotin residues.[15]

Synthetic application of (2) in the reduction of acyl halides and unsaturated carbon-carbon bonds are in progress and will be reported in due course. Besides that, this new reagent might also be useful for the reduction of aldehydes, ketones, esters, nitros, dithioketals, dithiacetals, selenoacetals, selenides, tellurides, isocyanos and other functional groups.[16] It should also be noted that this procedure is useful for the stereoselective synthesis

of 6β-deutero,6α-halopenicillanates by using $[PhC(CH_3)_2CH_2]_3SnD$.[17]

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