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Preliminary communication

REGIOSPECIFIC AND STEREOSELECTIVE SYNTHESES OF HYDROXYCYCLOHEXYLTRIPHENYLTIN COMPOUNDS*

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Summary

The syntheses of the *cis*- and *trans*-isomers of 2-, 3- and 4-hydroxycyclohexyltriphenyltin compounds was accomplished using regio- and stereo-selective reactions such as an epoxide—$LiAlH_4$ ring opening, hydroboration—oxidation and other selective methods.

Surprisingly, few carbon-substituted cyclohexyltin compounds have been synthesized [1a—d] or studied spectroscopically [2]. Recently, we have been interested in the synthesis of hydroxycyclohexyltin compounds because of our present work on the biological oxidation of organotin compounds [3a—c]. A survey of the literature showed that several reports have appeared on the regio- and stereo-selectivity of metal hydride ring openings of alkyl-substituted cyclohexene epoxides [4a—d] as well as on the hydroboration—oxidation of alkyl-substituted cyclohexenyl compounds [5a, b], however, no such similar studies with the corresponding organotin-substituted compounds have, to our knowledge, been attempted.

In this communication we wish to describe our initial results toward the goal of synthesizing various hydroxycyclohexyltriphenyltin compounds utilizing these and other selective reactions, while also ascertaining the conformational preference of the triphenyltin group in these reaction schemes.

Thus, the reaction of cyclohex-3-enyltriphenyltin (I)** with *m*-chloroperbenzoic acid gave a 90% yield of two epoxides (1 : 1), II and III***, which we

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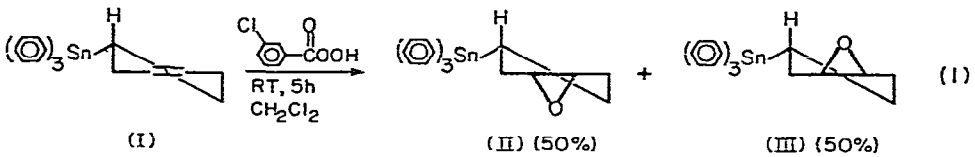
**Prepared by reaction of cyclohex-3-enylmagnesium bromide with triphenyltin chloride in 30% yield (m.p. 161—163°C). NMR, CIMS and elemental analysis were consistent with its structure and composition.

***Prepared by reaction of I with *m*-chloroperbenzoic acid in methylene chloride to give a 1 : 1 mixture of II and III. Separation and quantitation was achieved on 0.25 mm silica-gel 60 plates using 70% hexane and 30% diisopropyl ether as solvents. Appropriate elemental analysis confirmed their composition, while NMR, CIMS and IR confirmed their structures.

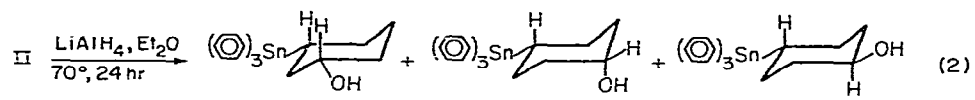
were able to separate and quantify by preparative thin-layer chromatography (eq. 1).



(I) (II) (50%) (III) (50%) (1)

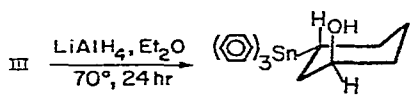
It is interesting to note that the triphenyltin group does not appear to sterically influence the epoxidation transition state and is consistent with it being predominantly in the quasi-equatorial position in compound I [4c, d]. A further confirmation of this point was established (360 MHz ^1H and 90 MHz ^{13}C NMR at low temperature)* by the finding that the triphenyltin group prefers the equatorial position (*A* value > 1.3) on a cyclohexyl ring as also recently shown for the trimethyltin group [2].

The assignment of the stereochemistry as *cis*- and *trans*-3,4-epoxycyclohexyltriphenyltin, II and III respectively, followed from a study of their reactions with lithium aluminum hydride in refluxing ether (sealed tube). Compound II underwent a highly regiospecific ring opening with lithium aluminum hydride to provide in a stereoselective manner, *cis*-3-hydroxycyclohexyltriphenyltin (IV) (> 99%), while a trace amount (< 1%) of a mixture of *cis*- and *trans*-4-hydroxycyclohexyltriphenyltin (V and VI ~40% and 60%) was also formed (eq. 2). The *trans*-



(IV) (>99%) (V) (<1%) (VI) (<1%) (2)

epoxide III, under the same conditions, gave exclusively *trans*-3-hydroxycyclohexyltriphenyltin (VII) (eq. 3).



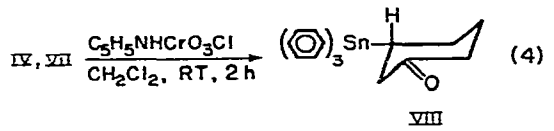
(VII) (100%) (3)

The stereochemical assignments for compounds IV—VII were based on their 360 MHz ^1H NMR spectrum and comparison of these spectra to those of compounds of established stereochemistry**. Additonally, compounds IV and VII

*The conformational analysis of cyclohexyltriphenyltin and compounds IV—VII will be reported separately [9].

**IV (360 MHz ^1H, TMS, $CDCl_3$) had multiplets (m) at 3.93 ppm (H—C—OH) and at 1.1 ppm (H—C—Sn) with coupling patterns consistent with axial hydrogens (see [6]); V, 3.72 ppm (m) (H—C—OH) (equatorial H) and 1.24 ppm (m) (H—C—Sn) (axial H); VI, 3.53 ppm (m) (H—C—OH) (axial H) and 1.24 ppm (m) (H—C—Sn) (axial H); VII, 3.91 ppm (m) (H—C—OH) (equatorial H) and 1.1 ppm (m) (H—C—Sn) (axial H). IV—VII gave satisfactory IR, CIMS and elemental analyses.

were oxidized to a common ketone, VIII* (eq. 4).

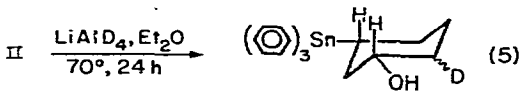


IV, VII

(4)

VIII

The reduction of VIII with lithium aluminum hydride gave predominantly compound IV (> 95%) as expected [4a]. More importantly, in order to preclude VIII as a precursor to IV, we treated II with lithium aluminum deuteride which provided, as analyzed by chemical ionization mass spectrometry (CIMS), incorporation of only one deuterium [4a] (eq. 5). This result eliminates VIII as an inter-



II

(5)

mediate in the reduction of II to IV. Furthermore, in order to insure the correct position of the hydroxyl group for the major compounds, IV and VII, in the ring opening reactions (eq. 2 and 3), compounds V and VI were together (they are not separable by thin-layer chromatography, but are readily analyzed by 360 MHz ^{1}H NMR spectroscopy) oxidized similary as; an eq. 4 to a common ketone, IX. The ketone, IX, cyclohex-4-onyltriphenyltin was then prepared by an unequivocal synthetic route** to fully substantiate the assigned position of the hydroxyl groups in compounds IV—VII.

The above results allowed assignments to be made for epoxides II and III*** i.e., *cis*-epoxide II, gave *cis*-3-alcohol IV and *trans*-epoxide III gave *trans*-3-alcohol VII.

It is of interest to compare the regiospecificity of these ring openings with two alkyl-substituted cyclohexene epoxides, *cis*- and *trans*-t-butylcyclohex-3-ene epoxides (X and XI). The *trans*-epoxide, XI, gave predominantly *trans*-3-alcohol, XII (90%), while *cis*-epoxide X gave *cis*-4-alcohol XIII; which in this latter case, X, is dramatically different than compound II. These regiospecific differences between II and X possibly reflect the unusual electronic, steric and conformational requirements of the triphenyltin group in II.

The alternative synthetic route to compounds IV—VII is via the hydroboration—oxidation procedure [5a,b]. When Compound I reacted with diborane in tetrahydrofuran, followed by alkaline oxidation (H_2O_2/OH^-), alcohols IV—VII were formed (Table 1).

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*Prepared (~50% yield) by reaction of a 1:1 mixture of IV and VII with pyridinium chlorochromate and sodium acetate in methylene chloride [7]. The IR, $\nu_{max}(CHCl_3)$ 1710 cm^{-1} (strong), NMR, and CIMS were consistent with structure VIII.

**Prepared by reaction of the ethylene glycol ketal of 4-bromocyclohexanone with magnesium metal and triphenyltin chloride, then followed by deblocking with acetone in the presence of toluenesulfonic acid.

***The CIMS (isobutane) also confirms the assigned stereochemistry, i.e., *cis*-II does not form a $M + 1$ ion, possibly due to tin—epoxide oxygen interaction, while *trans*-III forms the $M + 1$ ion in 80% relative abundance based on the ^{120}Sn isotope.

TABLE 1

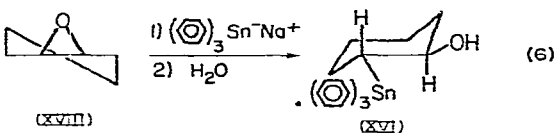
HYDROBORATION—OXIDATION OF I [a,b]

Compound	~%	~*cis/trans* C(3)	~*cis/trans* C(4)
IV	42(32)	1(1.6)	
VII	42(20)		
V	4(23)		0.3(0.9)
VI	12(25)		

[a] The value in parentheses represents that formed with t-butylcyclohex-3-ene (XIV) [5a]. [b] Diborane in THF at 25°C for 24 h followed by oxidation with alkaline hydrogen peroxide.

The predominate site of boron atom attack in I is at C(3) (84%), while attack at C(4) amounts to 16%. In comparison (Table 1) t-butylcyclohex-3-ene (XIV), gives values of 52% at C(3) and 48% at C(4), which indicates that I has a higher regiospecificity for boron at C(3), while XIV shows a higher stereoselectivity (*cis/trans* 1.6). The reverse of the latter results occurs at C(4) with I showing a higher stereoselectivity (*cis/trans* 0.3) than XIV (*cis/trans* 0.9).

In further attempts to synthesize two other isomers, the *cis*- and *trans*-2-hydroxycyclohexyltriphenyltin compounds, (XV and XVI), we studied the hydroboration—oxidation of cyclohex-2-enyltriphenyltin, (XVII)*. Unfortunately, this allyltin compound undergoes elimination and isomerization reactions, under the reaction conditions, and no 2-hydroxyl compounds were isolated. However, we were able to use the stereospecific ring opening of *cis*-cyclohexene epoxide XVIII with triphenylstannylsodium** to prepare, with inversion of configuration, *trans*-2-hydroxycyclohexyltriphenyltin (XVI)*** (eq. 6).



(XVIII) (XVI) (6)

We are presently continuing our studies on the epoxidation-ring opening and hydroboration—oxidation on the vinyl analogue of I, cyclohex-1-enyltriphenyltin (XIX).

Acknowledgments

The 360 MHz NMR spectra were recorded on the HXS 360 spectrometer located at the Stanford Magnetic Resonance Laboratory and supported by grants NSF GR 23633 and NIH RR00711. We thank Dr. W. Conover for recording these spectra. The work reported herein is supported by the National Institute of Environmental Health Sciences (NIH Grant 2 P01 ES00049). We also wish to thank Dr. J.E. Casida for encouraging this study and Dr. R. Holmstead for the CIMS data.

*Prepared by reaction of triphenylstannylsodium with cyclohex-2-enyl bromide (~20% yield), m.p. 81.5—83°C. Elemental analysis, NMR and CIMS confirmed both composition and structure.

**See ref. 8 for similar reactions with ethylene, propylene and *cis*- and *trans*-2,3-butylene oxides.

***Compound XVI has (360 MHz, ^{1}H, $CDCl_3$, TMS) multiplets at 3.68 ppm (H—C—OH) and 1.1 ppm (H—C—Sn) (axial H's). Elemental analysis and CIMS confirms its composition.

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