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THE SYNTHESIS OF β-HYDROXY-(E)-VINYLSTANNANES USING AN "IN-SITU" GENERATED CUPRATE REAGENT DERIVED FROM (E)-BIS-(TRIBUTYLSTANNYL)ETHYLENE

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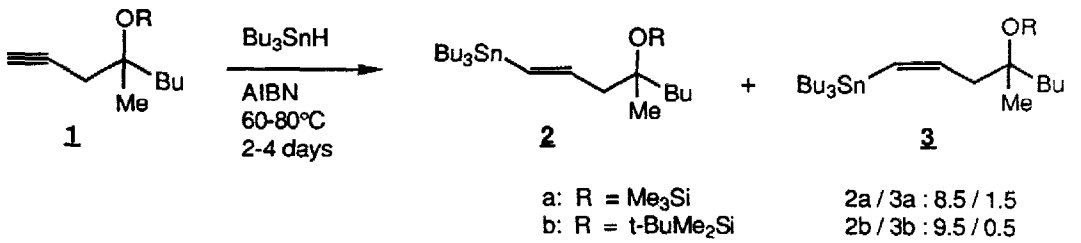
Summary: β-Hydroxy-(E)-vinylstannanes were obtained in good yield by reacting variously substituted terminal epoxides with a higher order cuprate reagent generated "in-situ" by mixing dilithio methyl(thienyl)cyanocuprate (6) with (E)-bis(tributylstannyl)ethylene (5).

In our continuing development of prostaglandin analogs, we were in need of a practical synthesis of vinylstannanes $2_{a,b}$ in which the olefin geometry was exclusively trans. The most popular method for synthesizing vinylstannanes involves the hydrostannylation of alkynes[1]. This approach has been reported to be highly stereospecific in certain cases[2]. However, numerous attempts to hydrostannylate the precursor alkynes $1_{a,b}$ were unsuccessful (see Fig. 1). In all cases, the kinetic (Z)-isomer $3_{a,b}$, was present in varying amounts (5-15%) even after long reaction times (48-72 h) under thermodynamic conditions (excess tributyltin hydride and AIBN as a free radical initiator).

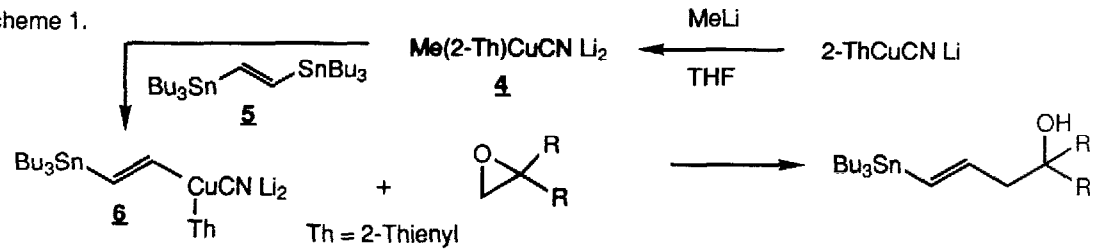
A number of other methods have been reported for the generation of (E)-vinylstannanes[1] but none of them were applicable for the preparation of β-hydroxy-(E)-vinylstannanes. Therefore, we developed a practical method for

Figure 1.



the synthesis of exclusively trans β-hydroxyvinylstannanes which centers around the regiospecific opening of terminal epoxides with dilithio 2-thienyl(2-(E)-tributylstannylethenyl)cyanocuprate (6). This novel cuprate reagent (6) is easily prepared using the recently reported "in-situ" cuprate generation methodology (see Scheme 1)[3]. For example, to a solution of dilithio methyl(2-thienyl)cyanocuprate (4), prepared by the addition of methyllithium (2.4 M in ether) to a solution of lithium 2-thienylcyanocuprate (0.5 M in THF)[4], is added (E)-bis(tributylstannyl)ethylene[5]. Formation of the desired cuprate (6) and methyltributyltin is rapid (15-30 min) and is easily monitored by gas chromatographic analysis of a quenched aliquot[6].

Scheme 1.

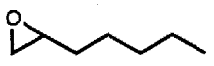
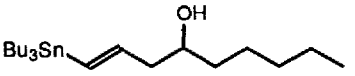
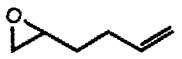
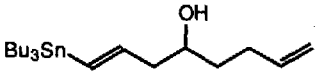
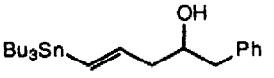
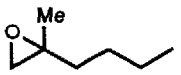
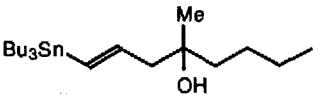
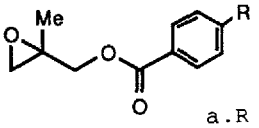
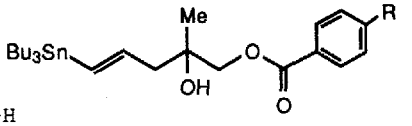
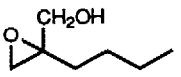
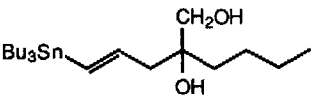
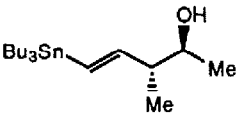
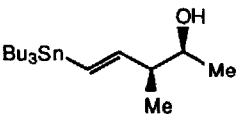


Reaction of cuprate (6) with mono and disubstituted terminal epoxides resulted in excellent regiochemical control. The desired β-hydroxy-(E)-vinylstannanes resulting from cuprate addition to the terminal carbon were isolated in good yields (Table 1, Entry 1-6). Terminal epoxides containing benzoate esters and unprotected hydroxyl groups (Table 1, Entry 5_{a-c} and 6 respectively) also provided regiochemically pure (E)-vinylstannanes in good yields. The isolated yields were typically 5-10% lower than the yields determined by gas chromatography due to silica gel assisted destannylation[7].

Internal epoxides (1,2-disubstituted epoxides), when reacted with cuprate (6) in the presence or absence of BF_3/etherate, did not provide useful yields of vinylstannanes (Table 1, Entry 7 and 8).

The following is a typical procedure for the generation of β-hydroxy-(E)-vinylstannanes via epoxide opening with dilithio 2-thienyl(2-(E)-tributylstannylethenyl)cyanocuprate (6): To a cooled (-10°C) solution of lithium 2-thienylcyanocuprate (2.0 mL, 0.5 M in THF, 1.0 mmol) was added methyllithium (0.76 mL, 1.45 M in ether, 1.10 mmol). The cooling bath was removed and to the homogeneous dilithio methyl(2-thienyl)cyanocuprate (4) solution was added, via syringe, (E)-bis(tributylstannyl)ethylene (5) (0.53 mL, 606 mg, 1.0 mmol). The solution was allowed to warm to room temperature over 30 min. An aliquot (0.01 mL) was withdrawn via syringe and added to 0.5 mL of a 1/1 mixture of hexane/saturated ammonium chloride/ammonium hydroxide (9/1). After vigorously shaking for 5 min the hexane layer was withdrawn, dried over K_2CO_3, and analyzed by gas chromatography[6] for disappearance of (5) (R_t = 9.78 min) and the formation of methyltributylstannane (R^t = 1.38 min) and tributylvinylstannane (R_t = 1.76 min). The dark red solution of cuprate (6) was then

Table I.

Entry	Substrate	Product[a]	Yield(%)[b]
1.			69
2.			58
3.			68
4.			74[c]
5.			
	a.R = -H		59
	b. -OMe		61
	c. -Cl		66
6.			50
7.			30(35)[d]
8.			13(18)[d]

a. All products were characterized by NMR, IR, TLC, MS and CH&N or HRMS.
b. All yields are isolated yields after chromatography and are unoptimized.
c. The reaction temperature was held at -10°C for 6 h following addition of the epoxide. Also, the product was purified by high vacuum distillation (bp 91°C, 3.0 x 10^{-3} mmHg) using a Leybold-Heraeus short path distillation apparatus (Model KDL-4).
d. Yield obtained using one equivalent of BF_3/etherate.

cooled (-78°C) and an epoxide (0.88 mmol) was added via syringe. The reaction mixture was stirred at -78°C for 1 h, warmed to 0°C for 1 h and then quenched by pouring into a vigorously stirred solution of saturated ammonium chloride/ammonium hydroxide:9/1 (10 mL). After stirring for 30 min the dark blue aqueous mixture was extracted with ethyl acetate (25 mL), the layers separated and the aqueous layer re-extracted with ethyl acetate (2 x 25 mL). The organic extracts were combined, washed with saturated sodium chloride (25 mL), dried (Na_2SO_4), concentrated, in vacuo, to an oil which was purified by medium pressure chromatography on silica gel (pretreated with triethylamine) using hexane/ethyl acetate:95/5 as the eluent to provide the desired β-hydroxy-(E)-vinylstannanes in which the olefin geometry was pure trans (determined by ^1H NMR and GC analysis).

This methodology has been used to produce kilogram quantities of 2 (R = H) in 74% isolated yield. In this case the product was purified by vacuum distillation (see Table I) thus, avoiding the destannylation observed using silica gel chromatography.

In summary, dilithio 2-thienyl(2-(E)-tributylstannylethenyl)cyanocuprate (6) is a useful reagent for the synthesis of geometrically pure β-hydroxy-(E)-vinylstannanes via epoxide opening.

References:

1. Pereyre, M.; Quintard, J-P; Rahm, A. In Tin in Organic Synthesis; Butterworths: London, 1987, p. 23.
2. (a) Leusink, A. J.; Budding, H. A.; Drenth, W. J. J. Organometallic Chem. 1968, 11, 541; (b) Corey, E. J. and Williams, D. R. Tetrahedron Letters 1977, 3847.
3. Behling, J. B.; Babiak, K. A.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. J. Amer. Chem. Soc. 1988, 110, 2641.
4. Lithium 2-thienylcyanocuprate can be purchased from Aldrich Chemical Company (0.25 M in THF, catalog no. 32,417-5) or alternatively can be prepared as a 0.5 M THF solution as follows: To triply distilled thiophene (5.25 g, 62.5 mmol.) in cold (-78°C) anhydrous THF (24.7 mL, distilled from benzophenone ketyl) was added via syringe a solution of butyllithium (25.6 mL, 62.5 mmol, 2.4 M in hexane) at such a rate that the internal temperature did not exceed -20°C. The resulting solution was stirred for 30 min, cooled to -60°C and added to a cold (-60°C) slurry of CuCN (5.59 g, 62.5 mmol, flame dried under argon) in anhydrous THF (64.7 mL). The resulting solution was allowed to warm to ambient temperature and then transferred to a dry Aldrich Sure Seal bottle and stored in the refrigerator at 5°C.
5. (E)-Bis(tributylstannyl)ethylene 5 is easily prepared according to the method of Mesmeyanov, A. N. and Borisov, A. E. Dokl. Akad. Nauk. SSSR 1967 174, 96; by hydrostannylation of ethynyltributylstannane which is commercially available from Aldrich Chemical Company (catalog no. 27,506-9) or it can be readily prepared according to the method of Bataro, J. C.; Hanson, R. N.; Seitz, D. E. J. Org. Chem. 1967 46, 5221.
6. Gas chromatography conditions (HP5890 GC, HP methylsilicon megabore column (5 M), temp. initial 40°C for 2 min then programmed to 280°C at 50°C/min, helium flow 10 mL/min).
7. Silica gel has been reported to efficiently destannylate vinyltins; Mook, R. Jr. and Sher, P. M. Organic Syntheses 1987 66, 75 and references cited therein. However, when the silica gel was pretreated with triethylamine and the chromatography done rapidly destannylation was significantly reduced but never completely eliminated.

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