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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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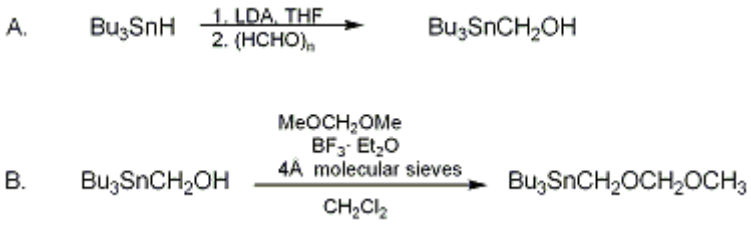
A HYDROXYMETHYL ANION EQUIVALENT: TRIBUTYL [(METHOXYMETHOXY)METHYL]STANNANE

[Stannane, tributyl[(methoxymethoxy)methyl]-]



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1. Procedure

A. *(Tributylstannyl)methanol*. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an argon inlet adapter, and a 150-mL, pressure-equalizing, dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 13.7 mL (0.098 mol) of diisopropylamine (Note 2) and 120 mL of dry tetrahydrofuran (Note 3), and then cooled with an ice-water bath while 58.4 mL (0.093 mol) of a 1.60 M solution of butyllithium in hexane (Note 4) is added dropwise via syringe over 15 min. After 30 min, a solution of 24.75 g (0.0850 mol) of tributyltin hydride (Note 5) in 50 mL of tetrahydrofuran is added dropwise via the addition funnel over 50 min. After 30 min, 3.57 g (0.119 mol) of paraformaldehdye (Note 6) is added in one portion, the ice bath is removed, and the heterogeneous yellow reaction mixture is stirred for 3 hr at room temperature. The resulting clear, colorless solution is diluted with 500 mL of petroleum ether and washed with 300 mL of water. The aqueous phase is separated and extracted with 150 mL of petroleum ether, and the combined organic layers are washed with 200 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford approximately 30 g of (tributylstannyl)methanol as a colorless oil, which was used in the next step without further purification (Note 7).

B. *Tributyl[(methoxymethoxy)methyl]stannane*. A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, an argon inlet adapter, and a rubber septum (Note 1). The flask is charged with the (tributylstannyl)methanol prepared in the previous reaction, 190 mL of dichloromethane (Note 8), 280 mL (3.16 mol) of dimethoxymethane (Note 9), and 50 g of powdered 4 Å molecular sieves (Note 10). Boron trifluoride etherate (13.0 mL, 0.106 mol) (Note 11) is added dropwise over 2 min via syringe to the vigorously stirred reaction mixture, and the resulting orange suspension is stirred at room temperature for 13 hr, and then filtered through a 2-cm pad of Celite in a sintered-glass funnel. The filter cake is washed with 250 mL of dichloromethane, and the combined filtrates are washed with two 250-mL portions of saturated sodium bicarbonate solution. The combined aqueous layers are extracted with 250 mL of dichloromethane, and the combined organic phases are then washed with 250 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The residual pale yellow oil (30 g) is dissolved in 20 mL of hexane and applied to 150 g of alumina (Note 12) packed in a 4.5-cm diameter column. The column is eluted with 1.3 L of 1% ethyl acetate-hexane (Note 13). The total eluant is concentrated at reduced pressure using a rotary evaporator, and the residual colorless oil is transferred to a 100-mL, round-bottomed flask and distilled through a 10-cm Vigreux column to furnish 23 g (74% overall yield based on tributyltin hydride) of tributyl[(methoxymethoxy)methyl]stannane as a colorless liquid, bp 117°C (0.34 mm) ((Note 14) and (Note 15)).

2. Notes

1. The glass components of the apparatus are immersed in a solution of 19.8 g of potassium hydroxide in 20 mL of water and 88 mL of ethanol for 20 min, dried overnight in a 150°C oven, and then assembled and maintained under an atmosphere of argon during the course of the reaction. This procedure removes traces of materials that otherwise can catalyze decomposition of the organotin reagents employed in the reaction.
2. Diisopropylamine was purchased from Aldrich Chemical Company, Inc. and distilled from calcium hydride before use.
3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
4. Butyllithium was purchased from Aldrich Chemical Company, Inc. and titrated using the method of Watson and Eastham.[3]
5. Tributyltin hydride was freshly prepared by the method of Hayashi et al.[4] Commercial tributyltin hydride (Aldrich Chemical Company, Inc.) can also be used, but in this case the yield of product is 5–7% lower.
6. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc. and dried overnight in a desiccator over phosphorus pentoxide at 0.3 mm.
7. If desired, the product can be purified by column chromatograpy on 230–400 mesh silica gel (50 times by weight, elution with 5–10% ethyl acetate-hexane). (Tributylstannyl)methanol exhibits the following spectral properties: IR (film) cm^{-1}: 3320, 2970, 2940, 2880, 2860, 1465, 1440, 1380, 1360, 1345, 1295, 1255, 1185, 1155, 1075, 1045, 1025, 985, 875; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.8–1.1 (m, 15 H), 1.2–1.7 (m, 13 H), 4.02 (d, 2 H, J = 4.5).
8. Dichloromethane was distilled from calcium hydride immediately before use.
9. Dimethoxymethane was obtained from Aldrich Chemical Company, Inc. and distilled from sodium before use.
10. Linde type 4 Å molecular sieve pellets were crushed using a mortar and pestle and then dried under vacuum (0.3 mm) at 300°C[5] for 15 hr prior to use.
11. Boron trifluoride etherate ($BF_3{\cdot}Et_2O$) was purchased from Aldrich Chemical Company, Inc. and distilled at 20 mm from calcium hydride. The overall yield for the reaction is reduced by ca. 10% if less $BF_3{\cdot}Et_2O$ (1.1 equiv) or less dimethoxymethane (20 equiv) is employed.
12. EM Science 80-325 mesh alumina was used for this filtration.
13. Filtration of the crude product through alumina prior to distillation is necessary to obtain pure material. If the filtration step is omitted, product of only 85–90% purity is obtained.
14. The purity of this material was determined to be >99% by gas chromatographic analysis (0.25 mm × 30 m DB-1701 fused silica capillary column, 12 psi column pressure, 120°C for 2 min, 120–250°C at 10°C/min, then 250°C; retention time 13.1 min).
15. The product has the following spectral properties: IR (film) cm^{-1}: 2970, 2930, 2880, 2770, 1465, 1420, 1395, 1380, 1345, 1295, 1245, 1205, 1150, 1100, 1040, 965, 930, 875, 730; ^1H NMR (250 MHz, $CDCl_3$) δ: 0.8–1.1 (m, 15 H), 1.2–1.7 (m, 12 H), 3.33 (s, 3 H), 3.74 (s, 2 H), 4.52 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 8.9, 13.6, 27.3, 29.1, 54.9, 57.6, 99.4. Anal. Calcd for $C_{15}H_{34}O_2Sn$: C, 49.34; H, 9.39. Found: C, 49.68, H, 9.56.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Hydroxymethyl anion equivalents play an important role as building blocks in the synthesis of complex organic compounds.[6] Still[7] has previously demonstrated the utility of $Bu_3SnCH_2OCH(OEt)CH_3$ as a hydroxymethyl anion equivalent. The preparation of this reagent involves the addition of tributylstannyllithium to paraformaldehyde followed by the protection of the resultant alcohol with α-chloroethyl ethyl ether. Transmetalation of the organostannane with one equivalent of butyllithium then furnishes an α-alkoxymethyllithium reagent which adds to carbonyl compounds in good yield. Hydrolysis of the ethoxyethyl protective group provides the desired primary alcohols.

Like Still's reagent, tributyl[(methoxymethoxy)methyl]stannane incorporates an alcohol protective group that can be conveniently unmasked under mild acidic conditions. However, an advantageous feature of this MOM ether derivative is that, in contrast to Still's reagent, it is achiral. In many applications the introduction of an additional chiral center into synthetic intermediates is undesirable because of the complications associated with the manipulation, analysis, and purification of diastereomeric mixtures.

Methoxymethylation of alcohols is generally achieved through alkylation with chloromethyl methyl ether. The procedure described here for the preparation of $Bu_3SnCH_2OCH_2OCH_3$ avoids the use of the highly toxic chloromethyl ether by employing an acid-catalyzed acetal exchange reaction with dimethoxymethane for the key protection step. Two related procedures have been developed for the methoxymethylation of (tributylstannyl)methanol based on this strategy.[8,9,10] The protocol described here employs BF_3-etherate and molecular sieves[8,11] to promote the acetal exchange and results in a higher yield of product compared to the alternative Fujita procedure[12] that uses phosphorus pentoxide. In this fashion the title compound is obtained in excellent purity in 74% overall yield from tributyltin hydride. An application of this organotin compound which illustrates its use as a hydroxymethyl anion equivalent may be found on p. 493.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 493

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

sodium benzophenone ketyl

paraformaldehdye

ethanol (64-17-5)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Dimethoxymethane (109-87-5)

dichloromethane (75-09-2)

chloromethyl ether (542-88-1)

chloromethyl methyl ether (107-30-2)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

tributyltin hydride (688-73-3)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

α-chloroethyl ethyl ether (51202-81-4)

p-toluenesulfonic acid (104-15-4)

diisopropylamine (108-18-9)

ethyl acetate-hexane (2639-63-6)

phosphorus pentoxide (1314-56-3)

Tributyl[(methoxymethoxy)methyl]stannane,
Stannane, tributyl[(methoxymethoxy)methyl]- (100045-83-8)

(Tributylstannyl)methanol (27490-33-1)

tributylstannyllithium

paraformaldehyde (30525-89-4)