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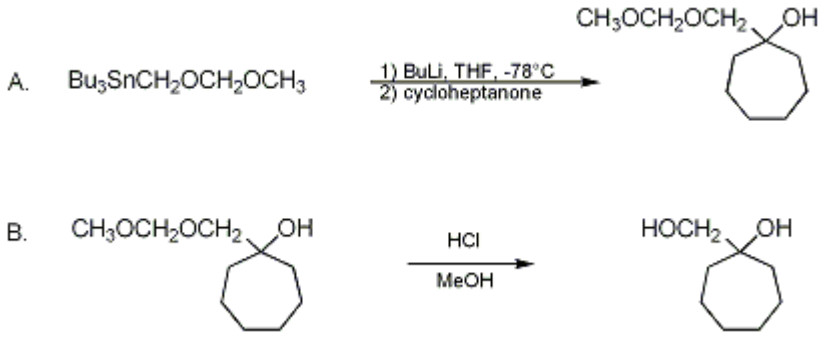
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.071.0140

Organic Syntheses, Coll. Vol. 9, p.493 (1998); Vol. 71, p.140 (1993).

PREPARATION AND USE OF (METHOXYMETHOXY) METHYLLITHIUM: 1-(HYDROXYMETHYL)CYCLOHEPTANOL

[Cycloheptanemethanol, 1-hydroxy-]



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1. Procedure

A. *1-[(Methoxymethoxy)methyl]cycloheptanol.* A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an argon inlet adapter, and a thermometer port. The apparatus is flame dried under reduced pressure and evacuated; the vacuum is broken with argon. The flask is charged with tributyl[(methoxymethoxy)methyl]stannane[4] (10.5 g, 28.7 mmol) and evacuated for 15 min; the vacuum is broken with argon. The flask is charged with 40 mL of dry tetrahydrofuran (Note 1), a low temperature thermometer is set into the flask and the solution is cooled to −78°C using a dry ice-acetone bath. A solution of butyllithium (2.5 M in hexanes, 11.2 mL, 28.0 mmol) (Note 2) is added via a syringe over a period of ~5 min while maintaining a reaction temperature below −60°C. Stirring is continued for no more than 5 min (Note 3), at which time cycloheptanone (2.70 g, 24.0 mmol) (Note 4) is added neat via a syringe. After the solution is stirred for 30 min at −78° C, the dry ice-acetone bath is removed and the reaction mixture is diluted with 40 mL of saturated aqueous ammonium chloride. The resulting mixture is stirred for 30 min and then extracted with three 40-mL portions of ethyl acetate. The combined organic layers are washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to provide 12.8 g of crude product. The crude product is purified by flash chromatography on a 70-mm diameter column packed with 130 g of silica gel (Note 5) using 5% ethyl acetate/hexane to elute the tin by-products and 30% ethyl acetate/hexane to elute the title compound. The product fractions are combined and concentrated at reduced pressure using a rotary evaporator to provide 1-[(methoxymethoxy)methyl]cycloheptanol (4.1–4.3 g, 91–95% based on cycloheptanone) as a colorless liquid (Note 6).

B. *1-(Hydroxymethyl)cycloheptanol*. To a 100-mL round-bottomed flask equipped with a stirring bar and a reflux condenser are added 1-[(methoxymethoxy)methyl]cycloheptanol (3.90 g, 20.7 mmol), methanol (50 mL), and hydrochloric acid (12.1 N, 0.75 mL). The reaction mixture is heated to 55°C for 1.5–2 hr (Note 7). After completion of the reaction, as indicated by TLC (Note 7), the reaction mixture is cooled to ambient temperature and carefully diluted with 35 mL of saturated aqueous sodium bicarbonate and stirred for 30 min. The methanol is removed under reduced pressure using a rotary evaporator and the remaining aqueous mixture is extracted with three 40-mL portions of ethyl acetate. The combined organic layers are washed once with 15 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford 2.9 g of crude product as a pale yellow oil. The crude product is purified by flash chromatography on a 40-mm diameter column packed with 70 g of silica gel (Note 5), using 40% ethyl

acetate-hexane to elute the product. The desired fractions are combined and concentrated under reduced pressure using a rotary evaporator to provide 1-[hydroxymethyl)cycloheptanol (2.3–2.4 g, 76–80% yield) as a white solid (mp 52–53°C) (Note 8).

2. Notes

1. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.
2. Butyllithium was purchased from Aldrich Chemical Company, Inc. and titrated using a solution of 2-butanol (1.0 M in p-xylene) with 1,10-phenanthroline as the end-point indicator.
3. In some cases the submitters have noticed that when the transmetalation mixture was allowed to stir for 15 min or more prior to addition of the carbonyl compound, the expected addition product was contaminated with material resulting from addition of butyllithium.
4. Cycloheptanone was purchased from Aldrich Chemical Company, Inc. and distilled under aspirator vacuum through a 6-in. Vigreux column prior to use.
5. Merck 230–400 mesh silica gel 60 was used for the column chromatography.
6. 1-[(Methoxymethoxy)methyl]cycloheptanol has the following spectral properties: IR (neat) cm^{-1}: 3460, 2930, 2860, 1460, 1445, 1405, 1212, 1198, 1150, 1112, 1042, 965, 920; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35–1.69 (m, 12 H), 2.40 (s, 1 H), 3.35 (s, 2 H), 3.35 (s, 3 H), 4.63 (s, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.3, 30.0, 37.6, 55.2, 74.6, 76.1, 97.0. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.73; H, 10.82.
7. Progress of the reaction should be monitored periodically during the 2 hr to determine when the starting material is consumed in order to avoid unnecessary heating, which leads to the formation of by-products. TLC can be used: 50% ethyl acetate/hexane, silica gel stained with phosphomolybdic acid.
8. 1-(Hydroxymethyl)cycloheptanol has the following spectral properties: IR (KBr) cm^{-1}: 3370, 2920, 2858, 1465, 1445, 1375, 1341, 1230, 1190, 1075, 1029, 991, 961, 935, 920, 890, 850, 800, 710; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.3–1.8 (m, 12 H); 2.98 (s, 1 H), 3.38 (d, 2 H), 3.52 (t, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.4, 30.2, 37.2, 69.6, 76.0. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.35; H, 11.39.

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

The utility of α-alkoxyorganostannanes as precursors to α-alkoxyorganolithiums has been demonstrated by several groups.[5,6,7,8,9,10,11] Primary α-alkoxyorganostannanes[8,9,10,11] have been used as hydroxymethyl anion equivalents.[12,13,14,15] Direct hydroxymethylation of carbonyl compounds was achieved by Seebach and Meyers,[16] who treated tributylstannylmethanol with two equivalents of butyllithium (BuLi) to produce the dianion of methanol. The dianion added to carbonyl compounds to give diols directly. The usefulness of this method, however, is limited because of the instability of the reagent and the moderate yields of addition products. Still prepared tributyl[(ethoxy)(methyl)methoxy] stannnane and (benzyloxymethyl)tributylstannane.[9] These compounds, upon treatment with one equivalent of BuLi, gave α-alkoxyorganolithiums, which added in high yields to carbonyl compounds to provide monoprotected diols. The former reagent results in the introduction of a new chiral center and the latter results in a protected diol that must be unmasked by hydrogenolysis. The related "MOM" reagent described here was foreseen as fulfilling a need for an acid-sensitive protecting group that would not introduce new diastereomers.

Tributyl[(methoxymethoxy)methyl]stannane in tetrahydrofuran readily transmetalates with BuLi and the resulting (methoxymethoxy)methyllithium adds in high yield to carbonyl compounds, providing monoprotected diols.[11] The reagent can also be added in a conjugate fashion to enones, albeit in moderate yield,[11] using the copper methodology of Fuchs and Hutchinson.[17] Deprotection of the alcohol can be achieved in high yield by simple acid hydrolysis.[18]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 704

References and Notes

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

sodium benzophenone ketyl

1-[hydroxymethyl)cycloheptanol

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

tin (7440-31-5)

p-xylene (106-42-3)

butyllithium,
BuLi (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Cycloheptanone (502-42-1)

argon (7440-37-1)

2-Butanol (78-92-2)

phosphomolybdic acid (51429-74-4)

1,10-phenanthroline (66-71-7)

(Methoxymethoxy)methyllithium (115384-62-8)

1-(Hydroxymethyl)cycloheptanol,
Cycloheptanemethanol, 1-hydroxy- (74397-19-6)

1-[(Methoxymethoxy)methyl]cycloheptanol (115384-52-6)

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

tributylstannylmethanol (27490-33-1)

(benzyloxymethyl)tributylstannane