A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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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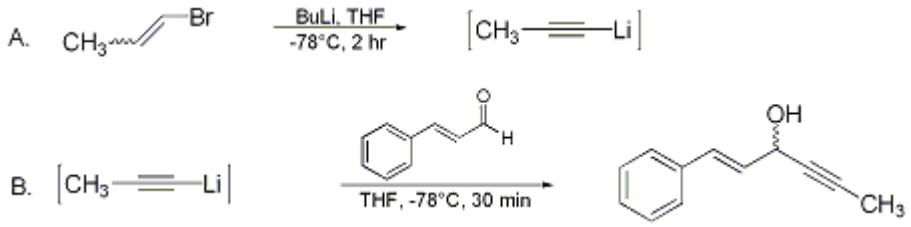
GENERATION OF 1-PROPYNYLLITHIUM FROM (Z/E)-1-BROMO-1-PROPENE: 6-PHENYLHEX-2-YN-5-EN-4-OL

[1-Hexen-4-yn-3-ol, 1-phenyl-, (E)-]



Submitted by Dominique Toussaint and Jean Suffert[1] .
Checked by Robin R. Frey and Stephen F. Martin.

1. Procedure

A. and B. In a dry, 500-mL, two-necked flask flushed with argon, fitted with a magnetic stirring bar and a 250-mL pressure-equalizing addition funnel is placed 18.65 g of (Z/E)-1-bromo-1-propene (0.15 mol) (Note 1) in 100 mL of tetrahydrofuran (THF, (Note 2)). The flask is cooled to −78°C with a dry ice-acetone bath, and 140 mL of butyllithium (BuLi, 1.57 M in hexane, 0.22 mol) (Note 3) is added dropwise over 30 min. The funnel is rinsed with an additional 10-mL portion of THF. The milky white suspension (Note 4) is stirred at −78°C for another 2 hr. Freshly distilled trans-cinnamaldehyde (13.21 g, 0.1 mol) in 50 mL of THF is added dropwise over 10 min, and the funnel is rinsed with 10 mL of THF. The solution is stirred for 30 min at −78°C (Note 5), quenched by the addition of 50 mL of aqueous saturated ammonium chloride (NH_4Cl), allowed to warm to room temperature and poured into a 1-L separatory funnel containing 100 mL of water and 100 mL of ether . The layers are separated, and the aqueous phase is extracted with three 100-mL portions of ether . The combined organic layers are washed with two 100-mL portions of brine , dried over anhydrous sodium sulfate and filtered. The solvent is removed by rotary evaporation leaving 17.17 g of a yellow oil that is almost pure based upon ^{1}H NMR and GC (crude yield: >99%) (Note 6) and (Note 7). Extensive purification can be achieved by flash chromatography on silica gel eluting with 20% ether in hexane (Note 8) to leave a yellow oil that solidifies in the freezer to yield 15.88 g of a pale yellow solid (mp 40-42°C, yield, 92%) (Note 9).

2. Notes

1. 1-Bromo-1-propene was purchased from Lancaster Synthesis Inc. (mixture of isomers, technical grade) and distilled prior to use (bp 58-62°C, 760 mm).
2. THF was distilled from sodium/benzophenone ketyl under nitrogen prior to use.
3. Butyllithium was purchased from Aldrich Chemical Company, Inc. , and titrated with N-pivaloyl-o-toluidine.[2] The checkers observed that use of less concentrated solutions of BuLi resulted in longer reaction times.
4. In some cases no suspension was observed (only a yellowish solution was obtained), but the reactions worked equally well.
5. The progress of the reaction can be monitored by TLC by quenching an aliquot with a mixture of aqueous saturated NH_4Cl/ether and eluting with Et_2O/hexane 20/80 (R_f trans-cinnamaldehyde = 0.40, R_f product = 0.25). Visualization can be achieved with vanillin (25 g/L of ethanol containing 1 mL of concd sulfuric acid) and heating on a hot plate.
6. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ solution on a Varian Unity Plus 300 MHz spectrometer.
7. The purity of the crude solid was determined to be 97% by GC (column conditions: SE-30 column, 25 m × 0.32 mm, He 0.8 kg/cm^2 carrier gas). The recovered oil solidified upon standing in the freezer. Attempts to recrystallize the resulting off-white material (in cyclohexane or pentane/ethyl acetate) only

met with oiling.
8. An 8-cm diameter column packed with 15 cm of silica was used. Some decomposition is observed during purification.
9. This material was >99% pure as determined by GC (column conditions: SE-30 column, 25 m × 0.32 mm, He 0.8 kg/cm^2 carrier gas) and showed the following spectroscopic characteristics: IR ($CHCl_3$) cm^{-1}: 3597, 2242, 1632 ; MS (CI) m/z 173.0958 [$C_{12}H_{12}O$+H (M+1) requires 173.0966], 172, 155, 133 . ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.89 (d, 3 H, J = 2.1), 2.24 (d, 1 H, J = 5.9), 5.00-5.03 (br m, 1 H), 6.28 (dd, 1 H, J = 15.7, 5.9), 6.73 (d, 1 H, J = 15.7), 7.21-7.42 (comp, 5 H) ; ^{13}C NMR (75 MHz) δ: 3.6, 63.1, 65.2, 82.8, 126.7, 127.9, 128.5, 128.7, 131.4, 136.1. Anal. Calcd for $C_{12}H_{12}O$: C, 83.64; H, 7.02. Found: C, 83.56; H, 6.96 .

Waste Disposal Information

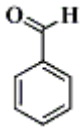
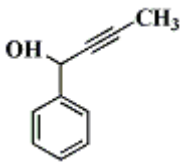
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

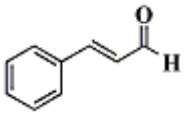
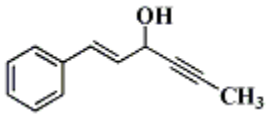
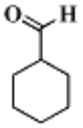
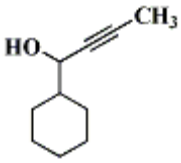
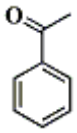
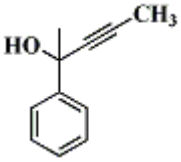
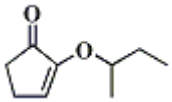
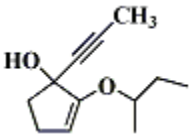
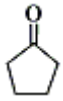
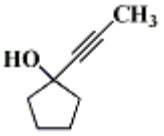
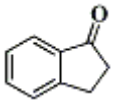
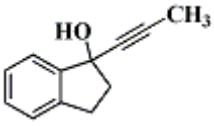
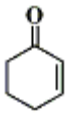
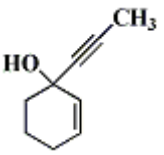
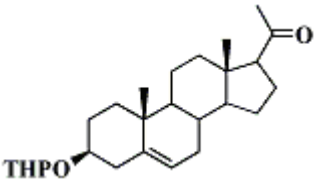
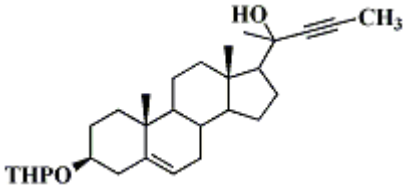
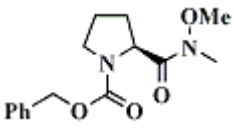
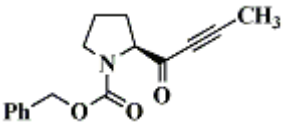
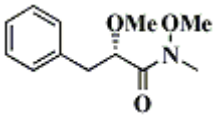
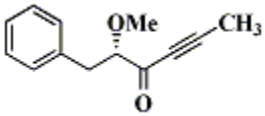
3. Discussion

The use of 1-propynyllithium in the synthesis of natural and unnatural compounds has been extensive, and a number of procedures have been reported for its generation. The most common method uses propyne gas, which may be metallated with lithium in liquid ammonia and other solvents,[3] or butyllithium [4] or lithium hydride in dimethyl sulfoxide (DMSO).[5] However, propyne is expensive, and it is important to have a more economical source of 1-propynyllithium. In some cases, propyne has been replaced by the inexpensive welding gas mixture MAPP (Methyl Acetylene, Propadiene, Propene), which contains up to 13.5% of propyne.[6] The anion can also be prepared by direct metallation of allene with BuLi at −78°C.[7] 1-Propynyllithium has also been generated by the reaction of 1-chloro-1-propene with BuLi or sec-BuLi, but the subsequent reaction with methyl iodide gave at best a 50% yield of product.[8] Moreover, 1-chloro-1-propene is expensive, and, because of its low boiling point (37°C), it is somewhat inconvenient to use. For example, the conditions required for generating propynyllithium from 1-chloro-1-propene involve use of a liquid nitrogen – ethanol cooling bath (−110°C). This technical difficulty somewhat limits the scale and utility of this procedure. The method of Gribble, et al. for generating 1-propynyllithium uses 1,2-dibromopropane and 3 equiv of lithium diisopropylamide (LDA).[9] The presence of such a large excess of base does not allow the addition of 1-propynyllithium to highly functionalized electrophiles. Recently a new procedure for generating 1-propynyllithium was reported that involved the reaction of an allenic telluride with BuLi at −70°C, followed by heating the mixture at 66°C and quenching the anion with an electrophile such as benzaldehyde or cyclohexenone.[10]

The present procedure provides a method for the easy generation of 1-propynyllithium from an inexpensive, commercially available starting material. The anion is prepared in anhydrous THF in high yield by reaction of the commercially available mixture of (Z/E)-1-bromopropene with BuLi at −78°C. Its reaction with various electrophiles such as aldehydes or Weinreb amides[11] is clean and efficient to afford secondary alcohols and ketones respectively (Method a, Table). The 1-propynyllithium generated in this way can be transmetallated with $CeCl_3$ [12] (Method b, Table) or $ZnCl_2$ [in the presence of $Pd(PPh_3)_4$]), Method c, Table][13] to add to enolizable ketones and acid chlorides, respectively. In all cases yields were high (see Table).[14]

ADDITION OF 1-PROPYNLLITHIUM TO VARIOUS ELECTROPHILES

Entry	Starting Compound	Method	Product	Yield (%)
1		a	**3a** 	94

2		a	**3b**		94
3		a	**3c**		95
4		b	**4a**		92
5		b	**4b**		89
6		b	**4c**		90
7		b	**4d**		95
8		b	**4e**		88
9		b	**4f**		86
10		a	**5a**		86
11		a	**5b**		89
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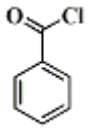
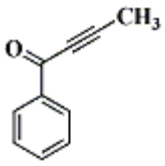
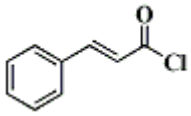
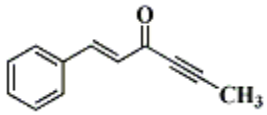
					
13		c	**5d**		78

References and Notes

1. Laboratoire de Pharmacochimie Moléculaire – UPR 421 du CNRS, Centre de Neurochimie, 5, rue Blaise Pascal 67084 Strasbourg Cedex, France. Present address: Laboratoire de Pharmacochimie de la Communication Cellulaire (ERS 655 du CNRS) 74, Route du Rhin B.P. 2467401 Illkirch Cedex, France.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Propynyllithium:

Lithium, 1-propynyl- (8,9); 4529-04-8)

(Z/E)-1-Bromo-1-propene:
1-Propene, 1-bromo- (8,9); (590-14-7)

6-Phenylhex-2-yn-5-en-4-ol:
1-Hexen-4-yn-3-ol, 1-phenyl-, (E)- (10); (63124-68-5)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

trans-Cinnamaldehyde:
Cinnamaldehyde, (E)- (8);
2-Propenal, 3-phenyl-, (E)- (9); (14371-10-9)

N-Pivaloyl-o-toluidine:
Propanamide, 2,2-dimethyl-N-(2-methylphenyl)- (10); (61495-04-3)