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of Reliable Methods
for the Preparation
of Organic Compounds

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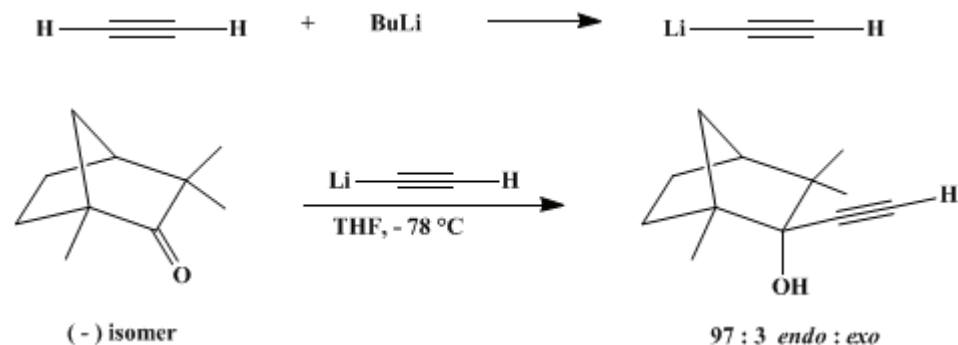
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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PREPARATION AND USE OF LITHIUM ACETYLIDE: 1-METHYL-2-ETHYNYL-*endo*-3,3-DIMETHYL-2-NORBORNANOL

[Bicyclo[2.2.1]heptan-2-ol, 2-ethynyl-1,3,3-trimethyl-, (1*R*-*endo*)]



Submitted by M. Mark Midland, Jim I. McLoughlin, and Ralph T. Werley Jr¹.
Checked by Matthew J. Sharp and Larry E. Overman.

1. Procedure

An oven-dried (Note 1), 500-mL, septum-capped, round-bottomed flask is flushed with nitrogen, charged with 70 mL of tetrahydrofuran (THF) (Note 2), and cooled to -78°C . After the apparatus has cooled, 157 mL of a 2.1 M solution of butyllithium (0.330 mol) (Note 3) is added using a 50-mL syringe. The contents are mixed by swirling the flask and kept at -78°C until needed. An oven-dried, 2-L, round-bottomed flask, equipped with a magnetic stir bar and capped with a septum, is cooled under a nitrogen purge (Note 4). The flask is charged with 500 mL of THF and cooled to -78°C . A 100-mL graduated cylinder (Note 5) is fitted with a septum in which an 8-mm hole has been bored (Note 6). A 9-mm glass tube that can be connected to either a nitrogen or acetylene line through a three-way valve (Note 6) and (Note 7) is inserted through the septum of the graduated cylinder. A double-ended needle is used to connect the cylinder to the 2-L reaction flask. After the cylinder and reaction flask have been thoroughly purged with nitrogen, 70 mL of THF is introduced into the cylinder, and the cylinder is cooled to -78°C (Note 8). Acetylene (Note 7) and (Note 9) is introduced through the 9-mm tube into the bottom of the graduated cylinder at such a rate that 30 mL (Note 10) has been added in 20 min; excess acetylene that does not dissolve in the THF is allowed to flow through the double-ended needle to the 2-L reaction flask. The cold acetylene solution is transferred via the double-ended needle to the 2-L reaction flask. While the solution is cooling in the -78°C bath, nitrogen is blown over the surface to purge the system completely of acetylene (Note 11). The precooled butyllithium/THF solution is then slowly added by a double-ended needle over a 1-hr period (Note 12). The clear solution of lithium acetylide is stirred for an additional 15 min at -78°C before 48.4 mL of (-)-fenchone (0.300 mol, (Note 13)) is slowly added via syringe. The solution immediately becomes yellow. After the addition is complete, the cold bath is removed and the mixture is stirred for 3 hr while it warms to room temperature. The flask is opened to the atmosphere and 400 mL of 1.0 M hydrochloric acid is added (Note 14). The quenched reaction is stirred for 20 min and then transferred to a 2-L separatory funnel. The aqueous material is separated and 200 mL of pentane is added. The organic layer is then sequentially washed with 100 mL of 1.0 M hydrochloric acid, 300 mL of water, and finally 100 mL of saturated brine. The combined aqueous material is extracted with 200 mL of ether. The organic extracts are combined, dried with magnesium sulfate, and filtered. Concentration (rotary evaporation, 40°C under aspirator pressure) provides a thick, yellow oil that is distilled to obtain 48.2 g (90%) of the alcohol as a pale-yellow oil (bp $51\text{--}55^\circ\text{C}$ at 0.05 mm) (Note 15).

2. Notes

1. All glassware was oven-dried for at least 24 hr at 130°C , assembled hot, and cooled under a stream of

nitrogen.^{2,3}

2. Tetrahydrofuran, THF, was obtained from Mallinckrodt Inc. and distilled from sodium/benzophenone ketyl immediately prior to use.

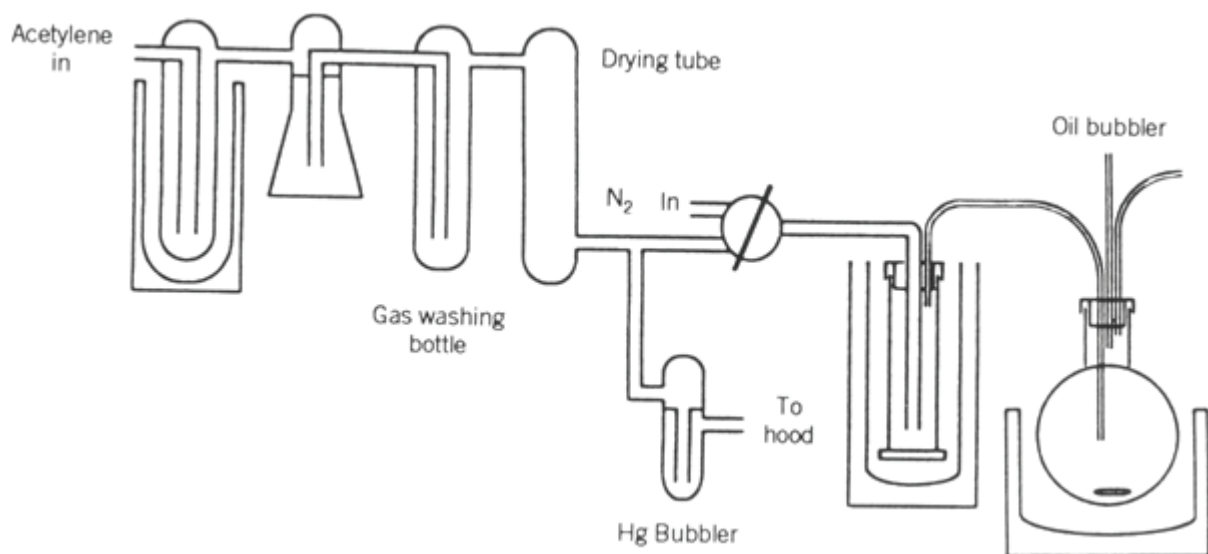
3. The checkers used butyllithium, purchased from Lithium Alkyls, which was standardized by titration with 2,5-dimethoxybenzyl alcohol. The submitters used butyllithium obtained from Aldrich Chemical Company, Inc. as a 1.55 M solution in hexanes that was measured by transfer to a septum-capped 250-mL graduated cylinder with a 15-gauge cannula and nitrogen back pressure.² This solution was then transferred to the flask containing THF in the same manner. The THF must be cooled prior to addition of the butyllithium. Stainless-steel double-ended needles of the type used by the submitters are available from Aldrich Chemical Company, Inc. and Ace Glass, Inc.

4. A slight positive pressure of nitrogen was maintained in the reaction vessel throughout the procedure until the reaction was quenched.

5. Graduated cylinders of various sizes with 24/40 standard taper joints are available from Ace Glass, Inc.; appropriate septa were obtained from Aldrich Chemical Company, Inc.

6. Both nitrogen and acetylene are introduced into the graduated cylinder through a 9-mm glass tube approximately 30 cm in length. An 8-mm hole bored through the septum allows for a good seal and for movement of the glass tube in order to adjust the height of the tube from the bottom of the graduated cylinder. A drawing of the apparatus employed is provided in Figure 1.

Figure 1



7. Acetylene is obtained from Liquid Carbonics and is purified by passage through a -78°C cold trap, a liquid trap (to prevent aspiration of sulfuric acid), a gas washing bottle containing 100 mL of concentrated sulfuric acid, and a calcium chloride drying tube before introduction into the graduated cylinder.⁴ A bubbler and a three-way valve, in that order, are placed before the graduated cylinder. The bubbler with a head of 30 mm of mercury is connected to the system with a T-shaped connecting tube and serves as a relief valve to prevent overpressurization of the acetylene line. The three-way valve allows nitrogen to be flushed through the graduated cylinder and reaction flask for purging the apparatus and to provide back pressure for the transfer of the acetylene solution. (See Fig. 1 for drawing of the reaction apparatus.) *Caution: Reactions with acetylene should be carried out in the hood and all lines carrying exhaust from the bubblers must be vented to a fume hood!*

8. The graduated cylinder and its contents are cooled in a wide-mouth Dewar containing a dry ice-acetone slurry.

9. Acetylene is an explosive compound and reacts with metals (e.g., Cu, Ag).⁵

10. The amount of acetylene is approximated by assuming a density of 0.7 g/mL. Approximately 2.5–3.0 equiv of acetylene is used. THF is added to the graduated cylinder so that the final volume of the acetylene solution will be 100 mL. In this case, 30 mL of acetylene is measured to provide approximately 0.85 mol.

11. Acetylene gas must be removed from above the solution to prevent reaction with the concentrated butyllithium solution entering the flask. Such a reaction in the presence of excess butyllithium will

result in the formation of **dilithium acetylide** on the needle tip. The formation of even small amounts of **dilithium acetylide** must be avoided; **lithium acetylide** readily disproportionates to **dilithium acetylide** and **acetylene** on warming or in the presence of excess **butyllithium**. The formation of a small amount of **dilithium acetylide** accelerates the rate of disproportionation (see (Note 12)).⁶

12. **Butyllithium** must be added slowly to an excess of the efficiently stirred **acetylene** solution at -78°C . Localized warming of the solution or rapid introduction of **butyllithium** to produce a local excess of base must be avoided in order to prevent the formation of the unreactive and insoluble **dilithium acetylide**, which will be observed as a cloudy suspension. Reaction of ketones or aldehydes with a cloudy suspension of **dilithium acetylide** results in substantially lowered yields of the carbinol products.⁶

13. (–)-Fenchone was obtained from Fluka Chemical Corporation and was used without additional purification.

14. After the solution is warmed to room temperature, substantial amounts of **acetylene** and **butane** may remain in solution. The reaction must be quenched in an efficient fume hood, and the first 10–20 mL of **hydrochloric acid** solution should be added slowly.

15. The product displays the following physical and spectral data: $[\alpha]_{\text{D}}^{25} +20.4^{\circ}$ (CHCl_3 , c 9); IR (neat film/NaCl plates) cm^{-1} : 3490, 2110, 1460, 1060; ^1H NMR (200 MHz, CDCl_3) δ : 0.93 (s, 3 H), 1.0–1.15 (m, 2 H), 1.11 (s, 3 H), 1.17 (s, 3 H), 1.20–1.95 (m, 5 H), 1.99 (OH), 2.53 (s, 1 H); ^{13}C NMR (50 MHz, CDCl_3) δ : 17.84, 21.54, 25.77, 27.08, 29.81, 40.95, 42.90, 48.40, 53.06, 74.86, 80.45, 85.61; MS (EI, -70 eV): m/z calcd. for $\text{C}_{12}\text{H}_{18}\text{O}$: 178.1357, m/z found: 178.1355. The product is a 97:3 mixture of endo : exo addition products based on capillary GC analysis. (A Hewlett-Packard 5880 Capillary Gas Chromatograph equipped with Supelcowax-10 30-m capillary column, available from Supelco, Inc., was used.)

3. Discussion

A general procedure for the preparation and use of **monolithium acetylide** is described. **Monolithium acetylide** is a useful reagent for the preparation of a variety of propargyl alcohols and terminal acetylenes.⁷ The formation of **monolithium acetylide** is often complicated by the production of **dilithium acetylide**.^{8–9} The reagent may be formed in liquid **ammonia**, which serves to stabilize the monoanion. Other amines, such as **ethylenediamine**, may be similarly added as a complexing agent.¹⁰ However, it is often desirable to prepare the more reactive amine-free **acetylide** species.^{6,9} **Dilithium acetylide** is an insoluble salt in **tetrahydrofuran** and is generally unreactive toward ketones, aldehydes, and other electrophiles. The slow addition of a dilute, cooled solution of **butyllithium** is critical for the reproducible preparation of a cleaner **lithium acetylide** solution. Solutions of **monolithium acetylide** must be kept colder, near -78°C , to prevent disproportionation to **dilithium acetylide** and **acetylene**. If the solution is warmed to 0°C , irreversible formation of **dilithium acetylide** as the white insoluble precipitate occurs.

Lithium acetylide adds in high yield to a variety of ketones and aldehydes. (Table I). Typically 1.1–1.2 equiv of **lithium acetylide** is employed. Sterically hindered ketones react in higher yield when 2.0 equiv of **lithium acetylide** is used. Optimum yields are obtained with a concentration of **monolithium acetylide** of approximately 0.5 *M*; higher concentrations approaching 1.0 *M*, usually result in slightly lowered yields.⁶ In all cases the reactions are essentially complete upon warming to room temperature. This method allows for a rapid and convenient preparation of propargyl alcohols. The procedure seems to be generally applicable to a wide variety of ketones and aldehydes.

TABLE I
ADDITION OF MONOLITHIUM ACETYLIDE TO ALDEHYDES AND KETONES

R	Ketone RCOR'	R'	Yield (%) ^a
CH_3		CH_3	94
$\text{CH}_3(\text{CH}_2)_4$		H	98
CH_3		$(\text{CH}_2)_3\text{CH}_3$	92
$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2$		$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2$	75,86 ^b
$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)$		$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)$	89

(CH ₃) ₃ C	(CH ₃) ₃ C	66,98 ^b
PhCH ₂	CH ₃	94
Ph	CH ₃	75
Ph	H	93
Ph	Ph	(85)
PhCH=CH	H	96
(CH ₃) ₂ C=CH	CH ₃	86(77)
	β -Ionone	93
	cyclo-(CH ₂) ₄	94
	cyclo-(CH ₂) ₅	95
	cyclo-(CH ₂) ₆	90(83)
	cyclo-(CH ₂) ₇	86
	Norcamphor	97(92) ^c
	Cyclohexanecarboxaldehyde	98

^aBy VPC based on RCOR'. Isolated yields are given in parentheses.

^b100% excess monolithium acetylide was used.

^cThe product was >99% 2-ethynyl-endo-2-norbornanol by VPC and ¹³C NMR examination.

References and Notes

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Appendix

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

brine

sodium/benzophenone ketyl

Tetrahydrofuran, THF

(-)-Fenchone

sulfuric acid (7664-93-9)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

nitrogen (7727-37-9)

mercury (7439-97-6)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

butane (106-97-8)

butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

ethylenediamine (107-15-3)

Cyclohexanecarboxaldehyde (2043-61-0)

Norcamphor (497-38-1)

acetylide

β -Ionone

2,5-dimethoxybenzyl alcohol (33524-31-1)

Lithium acetylide,
dilithium acetylide (6867-30-7)

monolithium acetylide

1-Methyl-2-ethynyl-endo-3,3-dimethyl-2-norbornanol (131062-94-7)

Bicyclo[2.2.1]heptan-2-ol, 2-ethynyl-1,3,3-trimethyl-, (1R-endo)

2-ethynyl-endo-2-norbornanol