Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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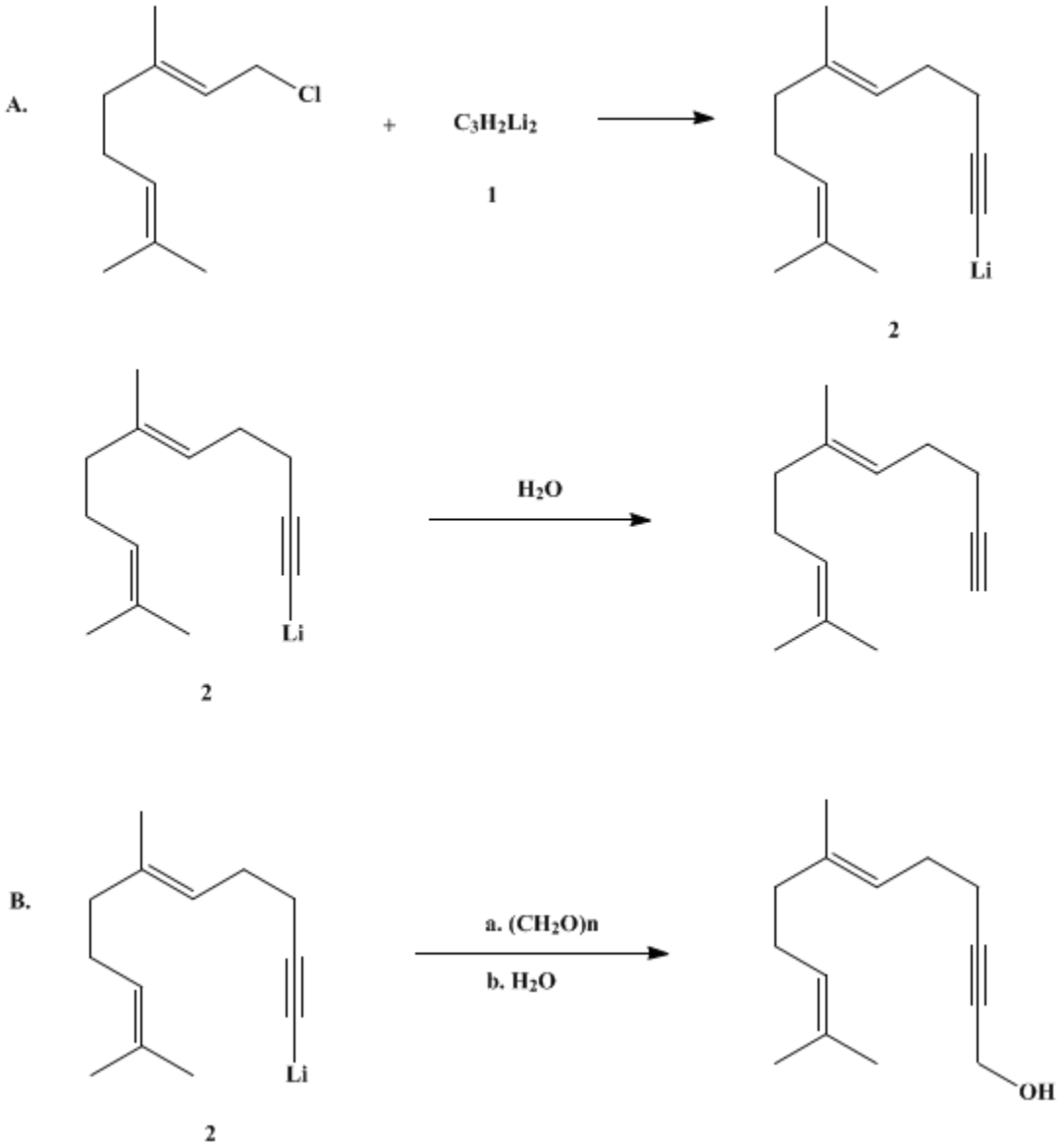
PROPARGYLATION OF ALKYL HALIDES: (*E*)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE AND (*E*)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL

[5,9-Undecadien-1-yne, 6,10-dimethyl-, (*E*)- and 6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (*E*)-]



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1. Procedure

Caution! Allene and ethyl ether are highly volatile and flammable. Paraformaldehyde is a noxious material. The entire operation should be conducted in an efficient fume hood.

A. *(E)-6,10-Dimethyl-5,9-undecadien-1-yne.* An oven-dried (Note 1), 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar (Note 2), a 250-mL pressure-equalizing addition funnel capped by a rubber septum (Note 3), a dry-ice condenser capped by a rubber septum, and a rubber septum (capping the central neck) bearing a stainless-steel cannula that serves as an argon inlet. The flask is charged with 190 mL of anhydrous ethyl ether (Note 4) and cooled to ca. −78°C using a dry ice–acetone bath. On a separate assembly (Note 5), allene gas (*d* at −40°C = 0.67 g/mL) from a compressed-gas cylinder (Note 6) is condensed into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry-ice condenser (containing a slurry of dry ice–acetone) and cooled to −78°C with a bath of dry ice–acetone (Note 7). After 22.5 mL (375 mmol) of liquid allene has been collected, the adapter and the condenser are removed and the graduated cylinder is capped with a rubber septum through which is inserted a cannula. The other end of this cannula is inserted through the rubber septum on the central neck to reach just below the surface of the cooled solvent. The allene is then transferred to the reaction vessel by removing the cylinder from the cooling bath. The temperature of the reaction vessel is maintained at −78°C, and a solution of 190 mL of 1.37 *M* butyllithium (260 mmol) in hexane (Note 8) is added dropwise over 1 hr through the addition funnel, which is then rinsed with 5 mL of dry ether. The reaction mixture is allowed to warm gradually (over ca. 30 min) to −15°C and the white precipitate that forms is stirred an additional 15 min under an argon atmosphere. A solution of 12.9 g (75 mmol) of geranyl chloride (Note 9) in 40 mL of dry ether is added dropwise over 303 min through the addition funnel while maintaining the temperature at −15°C. Then the stirred mixture is allowed to warm to room temperature over 1 hr (Note 10). The resulting white suspension containing the lithium acetylide **2** is carefully poured into 450 mL of ice-water slurry, the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined extracts are dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is distilled at atmospheric pressure using a 25-cm Vigreux column. The residue is distilled through a short-path distillation apparatus to afford 10.5–11.2 g (79–89% yield) of (*E*)-6,10-dimethyl-5,9-undecadien-1-yne, bp 103–107°C (10 mm) (Note 11).

B. *(E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol.* To the suspension containing the acetylide intermediate **2**, as prepared in Part A, is added 14 g (460 mmol) of paraformaldehyde (Note 12) in portions (Note 13) over 10 min (Note 14). After stirring the mixture for 24 hr, the resulting suspension is poured into 450 mL of ice-cold water (Note 15), the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined organic extracts are dried over magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed at room temperature on a rotary evaporator. The residue is distilled through a short-path distillation apparatus to provide a forerun of 2-butyn-1-ol (bp 42–46°C, 6 mm), followed by 10.5 g (68% yield) of (*E*)-7,11-dimethyl-6,10-dodecadien-2-yn-1-ol as a colorless liquid, bp 120–124°C (0.5 mm) (Note 16).

2. Notes

1. All glassware is dried in an oven at 125°C and assembled while warm.
2. Although the reaction mixture will become heterogeneous, mechanical stirring is unnecessary on this scale.
3. A stainless-steel cannula inserted through this septum is connected by means of tygon tubing to a mercury bubbler.
4. Ethyl ether is freshly distilled from the sodium ketyl of benzophenone.
5. This is an adaptation of the method used to condense methyl chloride, illustrated in Figure 1 of an *Organic Syntheses* procedure (Lusch, M. J.; Phillips, W. V.; Sieloff, R. F.; Normura, G. S.; House, H. O. *Org. Synth., Coll. Vol. VII* **1990**, 347).
6. The submitters used allene purchased from Matheson Gas Products, Inc. The checkers found that an old lecture bottle of allene from this source gave unsatisfactory results, affording a crude product that contained up to 20% of unchanged geranyl chloride. Other lecture bottles of allene from Matheson or Pfaltz and Bauer were satisfactory.
7. All temperatures recorded are external bath temperatures.
8. A solution of butyllithium in hexane was purchased from Foote Mineral Company. Before use the concentration is determined by titration according to the procedure of Watson and Eastham.[3]
9. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, Inc., with carbon tetrachloride and triphenylphosphine according to an *Organic Syntheses* procedure.[4]

10. If dienyne product containing less than 1% of geranyl chloride is required, the checkers suggest the following treatment at this point to destroy any remaining geranyl chloride. The addition funnel is removed and a gentle stream of argon is bubbled through the stirred reaction mixture for 15 min to remove excess allene. Additional butyllithium (40 mmol in hexane) is added and the resulting mixture is stirred for 3 hr at room temperature prior to hydrolytic workup. If this modification is employed, the subsequent hydrolysis step should be done slowly. The Erlenmeyer flask (1 L) containing the ice–water mixture is best cooled externally with an ice bath during the hydrolysis. The checkers also report that (*E*)-6,10-dimethyl-5,9-undecadien-1-yne containing <1% geranyl chloride is produced in 78–90% yield when 2.0 mmol of butyllithium per millimole of allene is employed.
11. Capillary GC analysis of the product using a 25-m fused-silica DB-5 column shows the presence of 5% geranyl chloride, which is eluted at a slightly shorter retention time than the enyne product. Similar analysis of the product produced (in 89% yield) by the modification reported in Note 10 showed that the product was >96% pure and contained <1% of geranyl chloride. Spectral properties for (*E*)-6,10-dimethyl-5,9-undecadien-1-yne are as follows: IR (thin film) cm^{-1}: 3312, 2119, 1665; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 3 H), 1.60 (s, 3 H), 1.66 (s, 3 H), 1.97–2.14 (m, 4 H), 2.22 (narrow m, 4 H), 5.11 (m, 2 H), 5.19 (m, 1 H).
12. Paraformaldehyde is dried over P_2O_5 in a vacuum desiccator for 24 hr prior to use.
13. The dropping funnel is removed and replaced by a 250-mL Erlenmeyer flask containing the paraformaldehyde. This is connected to the reaction vessel by rubber tubing. The cannula previously attached to the mercury bubbler is inserted through the septum of the dry-ice condenser.
14. The reaction with paraformaldehyde has an induction period of approximately 7–10 min, when the solvent suddenly begins to boil. The dry-ice condenser should be kept charged with dry ice–acetone to avoid loss of solvent.
15. In some runs the checkers found that the slurry became too thick to stir. In these cases, the ice-cold water (450 mL) was added to the reaction flask while stirring the solid mass with a large spatula. The final yield of the alcohol product was similar in these runs. Alternatively the reaction flask can be stirred mechanically.
16. The purity of the product was determined to be 92–94% by capillary GLC analysis using a fused-silica 25-m × DB-5 column, 70–280°C (10°C/min). The spectral properties of the product are as follows: IR (thin film) cm^{-1}: 3334, 2287, 2224, 1670, 1020; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.50 (t, 1 H, J = 10.8), 1.60 (s, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.99 (m, 2 H), 2.07 (m, 2 H), 2.22 (narrow m, 4 H), 4.25 (d, 2 H, J = 10.8), 5.09 (m, 1 H), 5.16 (m, 1 H). Vinylic signals for minor impurities are apparent at δ 4.7–4.9.

3. Discussion

The highly useful three-carbon homologation, RX → $RCH_2C{\equiv}CH$, often employed in isoprenoid-related syntheses (e.g., sirenin,[5] C_{18}-Cecropia juvenile hormone,[6] 16,17-dehydroprogesterone[7]) is frequently difficult to accomplish cleanly because of the tendency of ambident propargylic nucleophiles, $R\text{-}C{\equiv}C\text{-}CH_2M$, **3**, to produce troublesome mixtures of both the allenic and acetylenic products.[8,9,10] Propargyl alanates **3** [M = $Al(i\text{-}C_4H_9)_3$], for example, couple with allyl bromide to produce mainly the corresponding allene (<4% acetylene), whereas the analogous borate complex **3** [M = $B(sec\text{-}C_4H_9)_3$] produces an 83 : 17 mixture of the corresponding allene : acetylene.[11] The "propargyl" Grignard reagent[12] also couples with allylic halides[7,13,14] to produce acetylenic–allenic mixtures, for which a separation procedure has been developed based on trimethylsilylation of the crude product mixture.[13] An indirect procedure employing lithio-1-trimethylsilylpropyne initially produces the trimethylsilyl-protected acetylene (50–55%), from which the required homologated alkyne is liberated by reaction with ethanolic silver nitrate followed by sodium cyanide.[15] 1,3-Dilithiopropyne in either tetramethylethylenediamine or 1,4-diazabicyclo[2.2.2]octane is reported to couple with simple halides[16] to form acetylenes in moderate yield, although it fails to couple cleanly with allylic halides.[17]

The present procedure, based on the controlled lithiation of allene, produces the operational equivalent of a propargyl dianion **1** ($C_3H_2Li_2$), and provides a convenient single-step route to propargylated derivatives. Lithiation of allene is deceptively complex, and the extent of metalation (i.e., mono-, di-, tri-, tetra-) and the regiochemical outcome of subsequent alkylation (allenic vs. acetylenic) is highly dependent on reaction conditions. Metalation by butyllithium (1 equiv, THF, −70°C) followed

by alkylation with octyl iodide produced an 87 : 13 mixture of the corresponding allene and acetylene,[18] whereas an allene : C_4H_9Li ratio of 1 : 2 (THF, −50°C) followed by trimethylsilylation, produced a mixture comprised of mono-, di-, tri-, and tetra-silylated products.[19] In the current procedure, the solvent ratio (v/v) of ether : hexane of 1 : 1, as well as the stoichiometry and temperature, were empirically determined, and under these conditions there was no detectable evidence (NMR, GLPC) of isomeric allene formation in any of the alkylations examined, for either simple or allylic halides.[20] An additional advantage is that the initially formed lithium acetylide intermediate (e.g., **2**) may be further transformed to other useful functional derivatives in situ, as illustrated by the hydroxymethylation procedure.

References and Notes

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

P_2O_5

C_4H_9Li

sodium ketyl of benzophenone

trimethylsilyl-protected acetylene

acetylene (74-86-2)

ether,
ethyl ether (60-29-7)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

silver nitrate (7761-88-8)

Allyl bromide (106-95-6)

carbon tetrachloride (56-23-5)

methyl chloride (74-87-3)

magnesium sulfate (7487-88-9)

Allene (463-49-0)

octyl iodide (629-27-6)

butyllithium (109-72-8)

hexane (110-54-3)

geraniol (106-24-1)

2-Butyn-1-ol (764-01-2)

argon (7440-37-1)

triphenylphosphine (603-35-0)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

tetramethylethylenediamine (20485-44-3)

Geranyl chloride (5389-87-7)

Lithium acetylide (6867-30-7)

lithio-1-trimethylsilylpropyne

1,3-Dilithiopropyne

(E)-6,10-Dimethyl-5,9-undecadien-1-yne,
5,9-Undecadien-1-yne, 6,10-dimethyl-, (E)- (22850-55-1)

(E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol,
6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (E)- (16933-56-5)

paraformaldehyde (30525-89-4)