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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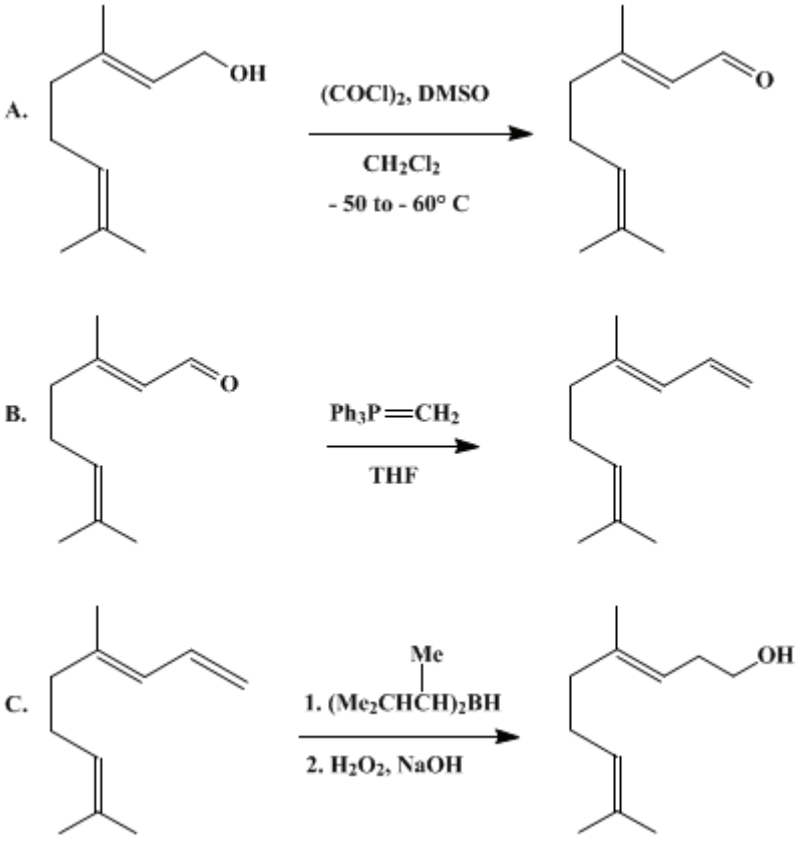
SELECTIVE HYDROBORATION OF A 1,3,7-TRIENE: HOMOGERANIOL

[3,7-Nonadien-1-ol, 4,8-dimethyl-, (*E*)-]



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1. Procedure

A. *Geranial*. A 2-L, three-necked, round-bottomed flask is dried in an oven and equipped with a mechanical stirrer, a thermometer, a Claisen adapter, and two pressure-equalizing dropping funnels. The flask is charged with 500 mL of dichloromethane (Note 1) and 20 mL (29.2 g, 0.23 mol) of oxalyl chloride (Note 2). The solution is stirred and cooled at −50 to −60°C as 34 mL (37.5 g, 0.48 mol) of dimethyl sulfoxide (Note 3) in 100 mL of dichloromethane is added dropwise at a rapid rate. After 5 min 30.8 g (0.2 mol) of geraniol (Note 4) is added dropwise over 10 min maintaining the temperature at −50 to −60°C. After another 15 min, 140 mL of triethylamine is added dropwise while keeping the temperature at or below −50°C. Stirring is continued for 5 min, after which time the mixture if allowed to warm to room temperature and 700 mL of water is added. The aqueous layer is separated and extracted with two 300-mL portions of dichloromethane. The organic layers are combined, washed with two 100-mL portions of saturated sodium chloride, and dried over anhydrous magnesium sulfate. The filtered solution is concentrated to 500 mL by rotary evaporation and washed successively with 1% hydrochloric acid until it is no longer basic. The dichloromethane solution is washed with water, 5% sodium carbonate, water, and saturated sodium chloride before drying over anhydrous magnesium sulfate. Rotary evaporation of the solvent gives ca. 30 g of crude product. Distillation in a Kugelrohr apparatus (Note 5) with an oven temperature of 80–85°C (1 mm) affords 27.3–28.5 g (90–94%) of geranial, n_D^{24} 1.4870 (Note 6).

B. *(E)-4,8-Dimethyl-1,3,7-nonatriene*. A 1-L, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirring bar, and serum caps (Note 7) is charged with 50 g (0.12 mol) of methyltriphenylphosphonium iodide (Note 8) and 320 mL of tetrahydrofuran (Note 9) and is flushed with argon. The flask is cooled in an ice bath and the suspension is stirred under a positive pressure of argon, while about 0.2–0.6 mL of 2.05 *M* phenyllithium in 30 : 70 ether: cyclohexane (Note 10) and (Note 11) is added dropwise until the suspension develops a permanent yellow color (Note 12). Then 56 mL (0.115 mol) of 2.05 *M* phenyllithium is added dropwise over 10 min. The ice bath is removed, and the orange suspension containing excess phosphonium salt is stirred at room temperature for 30 min. The reaction mixture is stirred and cooled at 0–5°C, and 17.2 g (0.11 mol) of geranial in 50 mL of tetrahydrofuran is added dropwise over 10 min. The dropping funnel is rinsed with a small amount of tetrahydrofuran. The mixture is stirred at room temperature for 2 hr. The light-orange mixture is hydrolyzed by adding 2 mL of methanol, and most of the solvent is removed on a rotary evaporator until a slurry results (Note 13). The slurry is diluted with 200 mL of petroleum ether (bp 60–68°C), and the supernatant solution is decanted and filtered through 150 g of Celite on a Büchner funnel. The solids remaining in the flask are heated with three 100-mL portions of hot petroleum ether, and the supernatant solutions are also filtered through Celite. The filtrate is concentrated by rotary evaporation to a yellowish liquid that is filtered through 150 g of Florisil on a Büchner funnel, and the Florisil is washed with 300 mL of petroleum ether. Rotary evaporation of the eluate provides ca. 15 g of clear liquid, which on distillation in a Kugelrohr apparatus with an oven temperature of 60–70°C (2 mm) gives 13.1–13.5 g (77–80%) of the triene, n_D^{22} 1.4871 (Note 14) and (Note 15).

C. *Homogeraniol*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to maintain a positive argon pressure within the apparatus (Note 7). The flask is charged with 102 mL (94.8 mmol) of 0.93 *M* diborane in tetrahydrofuran (Note 16), and the contents are cooled to −30°C. The diborane solution is stirred as 22.1 mL (0.21 mol) of 2-methyl-2-butene (Note 17) is added rapidly. Stirring is continued for 2 hr while maintaining the temperature at 0–2°C. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, pressure-equalizing dropping funnel, and a gas inlet tube to keep a positive pressure of argon (Note 7) is charged with 13.0 g (86.7 mmol) of (*E*)-4,8-dimethyl-1,3,7-nonatriene and 35 mL of tetrahydrofuran (Note 9). The contents are stirred and cooled at 0°C as the solution of disiamylborane in the first flask is transferred via a cannula to the pressure-equalizing dropping funnel attached to the second flask. After approximately 20 mL of disiamylborane is transferred to the dropping funnel via a cannula, the dropwise addition of the disiamylborane is started while the transfer continues. The remainder of the disiamylborane solution in the first flask is kept at 0°C. After the 1-hr addition is completed, stirring is continued for 1 hr at 0°C and overnight at room temperature (15 hr). Excess disiamylborane is destroyed by adding 2 mL of ethanol, the mixture is cooled to 0°C, and 33 mL of 3 *M* sodium hydroxide is added rapidly. Stirring and cooling at −10°C are continued as 33 mL of chilled 30% hydrogen peroxide is slowly added (Note 18). The reaction mixture is stirred at room temperature for 3 hr, the layers are separated, and the aqueous layer is extracted with two 75-mL portions of ether (Note 19). The combined organic layers are washed with two 25-mL portions of saturated sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent gives ca. 21 g of crude product that is purified by chromatography on 400 g of silica gel packed in a 7.5-cm × 20-cm column. The column is eluted with dichloromethane and 100-mL fractions are collected, the first two of which are discarded. Elution is continued by collecting the 100-mL fractions in a weighed flask and evaporating the solvent under reduced pressure until a constant weight of product is obtained (nine 100-mL fractions). Distillation of the residue in a Kugelrohr apparatus with an oven temperature of 150°C (0.02 mm) gives 12.6–13.2 g (88–91%) of homogeraniol, n_D^{21} 1.4740 (Note 20).

2. Notes

1. Dichloromethane was distilled from calcium hydride and stored over Linde 4A molecular sieves.
2. Oxalyl chloride was distilled immediately before use.
3. Dimethyl sulfoxide was distilled from calcium hydride and stored over Linde 3A molecular sieves.
4. Geraniol was obtained from Aldrich Chemical Company, Inc. (Gold Label) and used without purification.

5. Kugelrohr ovens are available from Rinco Instrument Co., Inc., 5035 Prairie St., P.O. Box 167, Greenville, IL 62246.
6. Thin-layer chromatographic analysis of the product by the submitter on silica gel with 20% ethyl acetate in hexane as developing solvent showed one spot, R_f 0.5. Gas chromatographic analysis showed the presence of 1.5% of the cis isomer by coinjection with 40 : 60 cis: trans citral mixture available from Aldrich Chemical Company, Inc. The ^{1}H NMR spectral data for the product are as follows δ: 1.61 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.19–2.23 (m, 4 H, CH_2CH_2), 5.06 (br s, 1 H, vinyl H at C-6), 5.88 (d, 1 H, J = 8, vinyl H at C-2), 9.99 (d, J = 8, CHO).
7. The glassware was dried in an oven at 150°C, assembled while still hot, and alternately evacuated and flushed with argon.
8. Methyltriphenylphosphonium iodide was prepared by the following procedure. Triphenylphosphine was recrystallized from ethanol and dried over phosphorus pentoxide under reduced pressure for 12 hr. A solution of 39 g (0.15 mol) of triphenylphosphine and 10.0 mL (22.8 g, 0.16 mol) of iodomethane in 105 mL of benzene was allowed to stir at room temperature for 12 hr. The precipitate was filtered, washed with benzene, and dried over phosphorus pentoxide under reduced pressure for 12 hr. The yield was 57 g (94%), mp 189°C (lit.[2] mp 182°C). The reagent is also available from Aldrich Chemical Company, Inc.
9. Tetrahydrofuran was distilled from sodium–benzophenone ketyl.
10. The phenyllithium solution was purchased from Aldrich Chemical Company, Inc. The checkers used 64 mL (0.115 mol) of 1.8 *M* phenyllithium in 75 : 25 benzene : ether, which was purchased from Alfa Products, Morton Thiokol, Inc.
11. The submitter states that the slight excesses of phenyllithium (5%) and methyltriphenylphosphonium iodide (10%) specified ensure complete conversion of the aldehyde and simplify the purification of the product since the excess phosphonium salt is readily removed during filtration through Florosil.
12. The addition of 0.2–0.6 mL of the phenyllithium solution presumably destroys small amounts of moisture or other impurities.
13. The submitter cautions against evaporating all the solvent; the triphenylphosphine oxide will tenaciously occlude the product, and the yield will be reduced.
14. A gas chromatographic analysis of the product by the submitter on a 15 M capillary column coated with silicone oil SE-54 at 70°C exhibited one peak (98%).
15. An index of refraction of 1.4826 at 20°C is reported[3] for the product. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3080, 1645, 1600, 1345, 990, 900; ^{1}H NMR ($CDCl_3$) δ: 1.61 (3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3 at C-4), 1.95–2.12 (broad, 4 H, CH_2CH_2), 4.80–5.15 (broad, 3 H, vinyl H), 5.85 (d, 1 H, J = 10, vinyl H at C-3), 6.55 (3 d, J = 10, 10, 17, vinyl H at C-2).
16. The diborane solution was obtained from Aldrich Chemical Company, Inc. It was titrated[4] before use, although the submitter states that this is not necessary. The solution was transferred from the stock solution to the reaction flask via a cannula. The checkers first transferred the diborane solution via a cannula into a graduated cylinder that was capped with a rubber septum and purged with nitrogen. The specified volume was then transferred into the reaction vessel.
17. 2-Methyl-2-butene was obtained from Aldrich Chemical Company, Inc. and was distilled from calcium hydride.
18. The oxidation of organoboranes is exothermic, and efficient cooling and slow addition are necessary to keep the temperature near 0°C.[5].
19. The checkers observed the separation of a heavy, white precipitate presumed to be a borate salt during the addition of hydrogen peroxide. After the three-phase mixture had been stirred at room temperature for 3 hr, the liquid layers were decanted into a separatory funnel. The solid remaining in the flask was washed with two 75-mL portions of ether and these washings were used to extract the aqueous layer.
20. Indices of refraction of 1.4722 at 22°C and 1.4718 at 26°C are reported for homogeraniol.[6,7] The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3330, 2960 (sh), 2920, 1448, 1435 (sh, m), 1374 (m), 1108 (w), 1045 (s), 875 (w); ^{1}H NMR ($CDCl_3$) δ: 1.60 (s, 3 H, CH_3 at C-4), 1.64 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3 at C-4), 1.95–2.15 (s, 4 H, CH_2CH_2), 2.30 (m, 2 H, CH_2CH_2OH), 3.60 (t, 2 H, J = 7, CH_2OH), 4.95–5.25 (m, 2 H, vinyl H).

3. Discussion

Homogeraniol is an important intermediate in syntheses of squalene,[6] aplysistatin[8] dendrolasin,[9] and juvenile hormone analogs.[10] [11] The present procedure affords an efficient, stereoselective method for preparing (*E*)-homogeraniol, contaminated by at most 1–2% of the *Z* isomer.

In Step A geraniol is oxidized to geranial (citral) by Swern's modification of the Moffat oxidation.[12] The stereoisomeric purity of the product is at least 98%. This procedure is readily conducted on a large-scale and requires only a 4-hr time period, including distillation of oxalyl chloride. The oxidation of geraniol to pure (*E*)-geranial may also be accomplished by Collin's oxidation with chromium trioxide–dipyridine complex,[13] or by use of activated manganese dioxide.[14] However, these methods require large amounts of reagents and solvents for 0.2-mol-scale preparations.

The Wittig methylenation of geranial to (*E*)-4,8-dimethyl-1,3,7-nonatriene is best carried out with phenyllithium in tetrahydrofuran as described in Section B. The use of butyllithium in tetrahydrofuran or ether–hexane[3] affords the triene in only 50–60% yield. When the ylide was generated with sodium hydride or potassium *tert*-butoxide in dimethyl sulfoxide by the submitter, the Wittig reaction gave triene containing 10–20% of the *Z* isomer. Step C illustrates the selective hydroboration of a diene with disiamylborane.[15] [16] The reaction is best carried out by adding preformed disiamylborane to the triene. Lower yields of homogeraniol were obtained by the submitter when the triene was added to the borane reagent.

Homogeraniol has been prepared by reduction of homogeranic acid with lithium aluminum hydride,[6] by cyclopropylcarbinol rearrangement to homogeranyl bromide and subsequent displacement of the bromide,[17] by zirconium-catalyzed syn addition of trimethylaluminum to an acetylene precursor followed by reaction with ethylene oxide,[7] and by hydroxymethylation of geranyl chloride with diisopropoxymethylsilylmethyl Grignard reagent.[18] Homogeranic acid has been prepared by base-catalyzed hydrolysis of the nitrile,[6,9,19] [20] [21] copper-catalyzed S_N2-type alkylation of β-isopropenyl-β-propiolactone with dimethylallyl Grignard reagent,[22] alkylation of methoxy(phenylthio)methyllithium with geranyl chloride and subsequent chromic acid oxidation,[23] and carboxylation of geranyl phenyl sulfone followed by reductive desulfonation.[24] Although homogeranic acid prepared by nitrile hydrolysis and by β-isopropenyl-β-propiolactone alkylation[22] is a 70 : 30 mixture of *E* and *Z* isomers,[9,25] the *E* form may be isolated by crystallization at −10°C[6] or by preparative gas chromatography of their *tert*-butyl esters.[26] Homogeraniol prepared by acid-catalyzed cyclopropylcarbinyl to homoallyl rearrangement[17] is also a mixture of *E* and *Z* isomers.[27]

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

petroleum ether

benzophenone ketyl

diborane

disiamylborane

Homogeraniol

aplysistatin

dendrolasin

(E)-homogeraniol

homogeranic acid

homogeranyl bromide

dipyridine

ethanol (64-17-5)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

sodium (13966-32-0)

chromic acid (7738-94-5)

Ethylene oxide (75-21-8)

hydrogen peroxide (7722-84-1)

manganese dioxide (1313-13-9)

iodomethane (74-88-4)

dichloromethane (75-09-2)

Phenyllithium (591-51-5)

magnesium sulfate (7487-88-9)

chromium trioxide (1333-82-0)

borane (7440-42-8)

2-methyl-2-butene (513-35-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

citral (5392-40-5)

geraniol (106-24-1)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

triphenylphosphine (603-35-0)

tert-BUTYL (1605-73-8)

triphenylphosphine oxide (791-28-6)

trimethylaluminum (75-24-1)

squalene

Geranyl chloride (5389-87-7)

Geranial,
(E)-geranial (141-27-5)

methyltriphenylphosphonium iodide (2065-66-9)

diisopropoxymethylsilylmethyl

β-isopropenyl-β-propiolactone

dimethylallyl (29791-12-6)

methoxy(phenylthio)methyllithium

geranyl phenyl sulfone

cyclopropylcarbinyl

homoallyl (2154-62-3)

phosphorus pentoxide (1314-56-3)

potassium tert-butoxide (865-47-4)

3,7-Nonadien-1-ol, 4,8-dimethyl-, (E)- (459-88-1)

(E)-4,8-Dimethyl-1,3,7-nonatriene (19945-61-0)