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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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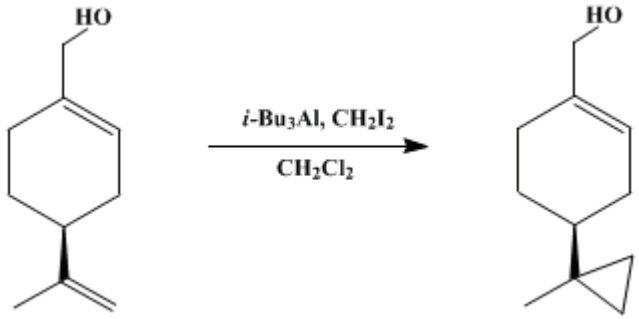
SELECTIVE CYCLOPROPANATION OF (*S*)-(−)-PERILLYL ALCOHOL: 1-HYDROXYMETHYL-4-(1-METHYLCYCLOPROPYL)-1-CYCLOHEXENE

[1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)-]



Submitted by Keiji Maruoka, Soichi Sakane, and Hisashi Yamamoto[1].
Checked by Hisatoyo Kato and Ryoji Noyori.

1. Procedure

A dry, 1-L, three-necked, round-bottomed flask is equipped with a gas inlet, a 50-mL pressure-equalizing dropping funnel, a rubber septum, and a Teflon-coated magnetic stirring bar. The flask is flushed with argon, after which 10.65 g (0.07 mol) of (*S*)-(−)-perillyl alcohol (Note 1) followed by 350 mL of dichloromethane (Note 2) is injected through the septum into the flask. The solution is stirred and 37.3 mL (0.147 mol) of triisobutylaluminum (Note 3) is added from the dropping funnel over a 20-min period at room temperature (Note 4). After the mixture is stirred at room temperature for 20 min, 7.3 mL (0.091 mol) of diiodomethane (Note 5) is added dropwise with a syringe over a 10-min period. The mixture is stirred at room temperature for 4 hr, and poured into 400 mL of ice-cold 8% aqueous sodium hydroxide. The organic layer is separated, and the aqueous layer is extracted twice with 100-mL portions of dichloromethane. The combined extracts are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator at ca. 20 mm. The residual oil is distilled under reduced pressure to give 10.64–11.13 g (92–96%) of 1-hydroxymethyl-4-(1-methylcyclopropyl)-1-cyclohexene as a colorless liquid, bp 132–134°C (24 mm) (Note 6) and (Note 7).

2. Notes

1. (*S*)-(−)-Perillyl alcohol is available from Aldrich Chemical Company, Inc.
2. Reagent-grade dichloromethane was dried and stored over Linde type 4A molecular sieves.
3. Neat triisobutylaluminum of 97.6% purity was supplied in a metal cylinder from Toso-Akzo Chemical Company, Ltd. (Japan). This reagent is also available from Aldrich Chemical Company, Inc. Since neat triisobutylaluminum is pyrophoric and reacts violently with oxygen and water, the used syringe should be immediately washed with hexane.
4. During this operation an exothermic reaction took place.
5. Diiodomethane, available from Tokyo Kasei Kogyo Company, Ltd. (Japan), was used without any purification.
6. The spectral properties of the product are as follows: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.22 and 0.26 (m, 4 H, cyclopropyl C-H), 0.80–0.92, 1.24–1.30, and 1.36–1.47 (m, 3 H, cyclohexenyl C-H), 0.93 (s, 3 H, CH_3), 1.77–1.83 (m, 1 H, cyclohexenyl =C-C-H), 1.91–2.16 (m, 4 H, OH, and cyclohexenyl =C-C-H), 3.99 (brt, 2 H, CH_2-O), 5.69 (br s, 1 H, =C-C-H); IR (liquid film) cm^{-1}: 3330, 2830–2960, 1423–1460, 1390, 1010, 1000.
7. Gas-chromatographic analysis of the trimethylsilyl ether using a 25-m PEG-HT capillary column at 100°C indicated a purity of 93% (retention time: 11.2 min). Under the present conditions, neither the

starting perillyl alcohol nor the isomeric monocyclopropanation product (1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]-heptane) were detected. Dicyclopropanation products amounted to less than 5%.

3. Discussion

This procedure illustrates a new method for selective cyclopropanation of unsaturated alcohols not obtainable with ordinary cyclopropanation reactions.[2] The selectivity in this trialkylaluminum-promoted cyclopropanation is complementary to that obtained in the Simmons–Smith reaction and its modifications,[3] which give facile hydroxyl-assisted cyclopropanations with perillyl alcohol to afford 1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]heptane predominantly. A similar tendency was observed in the case of geraniol. Thus, cyclopropanation with the *i*-Bu_3Al/CH_2I_2 system takes place almost exclusively at the C(6)–C(7) olefinic site far from the hydroxyl group of geraniol, and the C(2)–C(3) olefinic bond is left intact.[2]

The present cyclopropanation using trialkylaluminum-methylene iodide may proceed via dialkyl(iodomethyl)aluminum as an active intermediate,[4] which also can be generated by the reaction of dialkylaluminum iodide with diazomethane.[5] In addition, reaction of diiodomethane with triisobutylaluminum (each 1 equiv) afforded nearly 1 equiv of isobutyl iodide as a product, suggesting the formation of diisobutyl(iodomethyl)aluminum in the solution.[2]

The combined use of a wide variety of trialkylaluminum compounds and alkylidene iodide serves as a highly convenient and versatile method for cyclopropanation of simple olefins under mild conditions.[2] For example, treatment of 1-dodecene with CH_2I_2/R_3Al (R = Me, Et, *i*-Bu) in dichloromethane at room temperature for 3–8 hr gave decylcyclopropane in 96–98% yields.

References and Notes

1. Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan.
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3. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(−)-PERILLYL ALCOHOL

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

diiodomethane (75-11-6)

dichloromethane (75-09-2)

Diazomethane (334-88-3)

hexane (110-54-3)

geraniol (106-24-1)

argon (7440-37-1)

triisobutylaluminum (100-99-2)

trimethylsilyl ether (107-46-0)

1-Hydroxymethyl-4-(1-methylcyclopropyl)-1-cyclohexene,
1-Cyclohexene-1-methanol, 4-(1-methylcyclopropyl)- (98678-72-9)

perillyl alcohol

1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]-heptane,
1-hydroxymethyl-4-isopropenylbicyclo[4.1.0]heptane

Isobutyl iodide (513-38-2)

diisobutyl(iodomethyl)aluminum

1-dodecene (112-41-4)

decylcyclopropane