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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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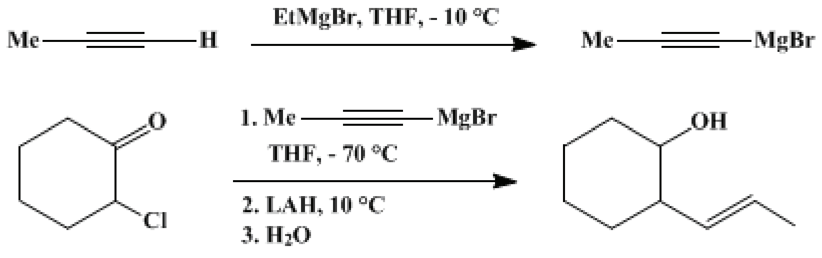
Organic Syntheses, Coll. Vol. 7, p.456 (1990); Vol. 64, p.10 (1986).

2-ALKENYL CARBINOLS FROM 2-HALO KETONES: 2-*E*-PROPENYLCYCLOHEXANOL

[Cyclohexanol, 2-(1-propenyl)-, (*E*)-]



Submitted by P. A. Wender, D. A. Holt, and S. Mc N. Sieburth[1].
Checked by Peggy A. Radel and Clayton H. Heathcock.

1. Procedure

A dry, 5-L, four-necked, round-bottomed flask is equipped with an air-driven stirrer (Note 1), 250-mL pressure-equalizing dropping funnel, thermometer, rubber septum, and a nitrogen-inlet tube that, by means of a T-tube, is also connected to a gas bubbler. After being charged with 1200 mL of anhydrous tetrahydrofuran (Note 2), the flask is swept with dry nitrogen and maintained under an atmosphere of nitrogen throughout the remainder of the reaction. A solution of ethylmagnesium bromide in diethyl ether (1.1 mol, 380 mL, 2.9 *M*) is transferred to the flask and the flask is then cooled to below 10°C by means of an ice–water bath (Note 3). Propyne is bubbled through the cooled, stirred solution (Note 4) at such a rate that a small amount escapes through the nitrogen inlet–gas bubbler. Propyne addition is continued for 2.5 hr, at which time approximately 100 g (2.5 mol) of propyne has been used (Note 5) and the internal temperature has risen 5–10°C. The ice–water bath is then replaced with a dry ice–acetone bath and the mixture is cooled to ca. −70°C. A solution of 2-chlorocyclohexanone (1 mol, 132.6 g) (Note 6) in 50 mL of tetrahydrofuran is added dropwise from the addition funnel over 1.5 hr so as to maintain the temperature below −65°C (Note 7). After stirring for an additional 1.5 hr at −70°C (Note 8), the dry ice–acetone bath is replaced with an ambient-temperature water bath and the reaction mixture is allowed to warm slowly. When the temperature reaches 10°C, a solution of lithium aluminum hydride in tetrahydrofuran (1 mol, 1000 mL, 1 *M*) is added by cannula (Note 9). After addition of the lithium aluminum hydride, the mixture is stirred at ambient temperature for 3–5 hr, at which time the solids have dissolved and reaction is complete (Note 10) and (Note 11). The solution is then cooled to 5°C by means of an ice–water bath. The reaction is quenched by careful, dropwise addition of 38 mL of water over 2 hr to maintain the temperature below 20°C. The solution becomes somewhat cloudy at this point and 2000 mL of hexanes is added. The addition of 38 mL of aqueous 15% sodium hydroxide solution over 15 min is followed by the addition of 100 mL of water over 5 min. Some frothing occurs during the last addition of water and a large amount of white aluminum salts precipitates. After 5 min of stirring, 100 g of anhydrous sodium sulfate is added and stirring is continued for another 5 min. The thick mixture is then filtered by suction through Celite using a 200-mm-diameter Büchner funnel. The solids are removed from the funnel, thoroughly washed with 1500 mL of hot tetrahydrofuran (Note 12), and refiltered. This wash is repeated twice and the combined organic solutions are concentrated with a rotary evaporator (15 mm). The residual yellow liquid is distilled under reduced pressure to yield 118.8 g (85%) of 2-*E*-propenylcyclohexanol as a clear colorless liquid, bp 49–54°C (1 mm) (Note 13).

2. Notes

1. The use of a magnetic stirrer is more convenient than a mechanical stirrer for reactions conducted on small scale (<0.2 mol) or at low concentrations (<0.5 *M*). However, because of the difficulty encountered in stirring the sometimes thick suspensions associated with concentrated (e.g., 1 *M*)

reaction mixtures, and because of the potentially disastrous results if a stir bar should fracture the flask wall during a large-scale preparation, the submitters strongly recommend the use of an air-driven overhead mechanical stirrer for such large-scale reactions. At a later stage in the reaction, when the propynylmagnesium bromide is cooled to −70°C, the THF solution becomes viscous and rather difficult to stir. The checkers recommend the use of a heavy-duty, air-driven stirrer such as the Fisher Scientific Model 14-508.5. An electrically driven overhead stirrer should not be used, as the hydrogen released during the quench represents a considerable explosion hazard.

2. The submitters used "Baker Analyzed" tetrahydrofuran (0.005% H_2O) without further purification or drying.

3. The submitters used ethylmagnesium bromide solution purchased from Aldrich Chemical Company, Inc. and found it most convenient to measure the required amount by transferring the solution by cannula to a nitrogen-flushed graduated cylinder fitted with a rubber septum. This measured amount of solution is then transferred to the flask by cannula. (See [2] for general techniques for handling air-sensitive reagents in this manner.) Some of the Grignard reagent precipitates at this temperature and concentration. There is a tendency for the ethylmagnesium bromide to clog the cannula. The checkers found it convenient to use a cannula made from 2-mm stainless-steel tubing.

4. Propyne of 99.96% purity, purchased from Liquid Carbonic Company in a lecture bottle, was used without purification and was introduced to the flask by means of a Tygon tube that was attached to a 9-in., 18-gauge hypodermic needle.

5. The amount of propyne used is conveniently determined by weighing the lecture bottle before and after addition. In this case the submitters used an excess of alkyne to ensure complete consumption of the Grignard reagent. In cases where nongaseous, nonvolatile alkynes are to be used, stoichiometric amounts suffice.

6. The submitters used 2-chlorocyclohexanone purchased from Aldrich Chemical Company, Inc. without further purification. Alternatively, this compound can be easily prepared by chlorination of cyclohexanone.[3]

7. A flask should be used that is constructed in such a manner that the chloro ketone solution drips directly from the addition funnel into the reaction mixture. Any portion that flows along the sides of the flask will freeze.

8. Chloro alkoxide formation is essentially complete at this time and can be conveniently monitored by quenching a small aliquot and subjecting it to GLC analysis. Using a 50-m × 0.2-mm OV-1 capillary column at 110°C and a flow rate of 0.87 mL/min (H_2 carrier), the submitters found retention times of 3.2 min for 2-chlorocyclohexanone and 6.7 min and 7.2 for *trans*- and *cis*-1-propynyl-2-chlorocyclohexanols, respectively.

9. Lithium aluminum hydride in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc. and was handled in the fashion described above for the Grignard solution (see (Note 3)). While solid lithium aluminum hydride can be used (with appropriate changes in the amount of solvent initially used), the hazards of handling this flammable and even explosive reagent (see [4] and [5]) can be reduced by using the preprepared solution. An excess of hydride reagent is necessary to facilitate complete reaction in a reasonable time. When only the stoichiomeric amounts of hydride reagent are used, the reaction is not complete even after several days at room temperature.

10. In reactions run at high concentration the reaction has a tendency to become slightly exothermic at some point, with the temperature increasing by as much as 30°C. Although the reaction is usually complete in less time, and with no reduction in yield of product, this exothermic reaction can be prevented by keeping the flask in a large ambient-temperature water bath, thus buffering temperature changes that apparently initiate the exothermic reaction. The progress of the reaction can be conveniently monitored by TLC or GLC analysis of a quenched aliquot. Using the same GLC conditions as described in Note 8, the retention times for *cis*- and *trans*-2-*E*-propenylcyclohexanols are 4.1 min and 3.9 min, respectively.

11. The checkers noted that a homogeneous solution occurs after about 2 hr. However, TLC and GLC analysis showed that reaction was not complete until 3.5–5 hr.

12. The tetrahydrofuran used for washing the filtercake should be tested for peroxides before use, since the final distillation is carried out almost to dryness.

13. GLC analysis indicated a purity greater than 98% and a cis : trans ratio of 1 : 2. These isomers can be separated by column chromatography and give the following ^1H NMR spectra: ($CDCl_3$) δ: cis: 1.1–2.0 (m, 12 H, CH_2, CH_3, OH), 2.2 (m, 1 H, allylic CH), 3.75 (m, 1 H, carbinol CH), 5.4–5.6 (m, 2 H,

CH=CH); trans: 1.0–2.2 (m, 10 H, CH_2, OH, allylic CH), 1.70 (d, 3 H, J = 4.9, CH_3), 3.1 (m, 1 H, carbinol CH), 5.0–5.8 (m, 2 H, CH-CH).

3. Discussion

A variety of approaches have been employed to effect the preparation of α-alkenyl ketones and carbinols, including reactions of metallo alkenes with epoxides,[6,7] α-halo ketones,[8,9,10,11] or enolonium ion equivalents[12,13] and the reactions of ketone enolates with vinyl cation equivalents.[14,15,16,17,18,19,20,21,22,23,24,25,26,27] The procedure described here offers several advantages over existing methodology. Starting materials and reagents are all commercially available at low cost. Manipulations are simple, and the procedure can be carried out in a single operation, in a single flask, on a small or large (1-mol) scale and in high yield. In addition, as described in more detail elsewhere,[28] this method permits the use of cyclic as well as acyclic halo ketones, bromo ketones instead of chloro ketones, a variety of alkynes including acetylene, conjugated alkynes, 3-silyloxy functionalized alkynes, and other aluminum hydride reagents such as diisobutylaluminum hydride and lithium trimethoxyaluminum hydride. Furthermore, the method provides for complete control over alkene geometry and easy access to trisubstituted alkenes of defined stereochemistry.

Mechanistically, the reaction proceeds through an alkynyl chloro alkoxide, which, when treated with the reducing agent, is hydroaluminated to yield the vinyl alanate, which subsequently undergoes a facile pinacol-like 1,2-rearrangement. Excess hydride reagent reduces the intermediate alkenyl ketone and the resulting 2-alkenyl carbinol is isolated on aqueous workup (Scheme 1). Table I contains representative examples.

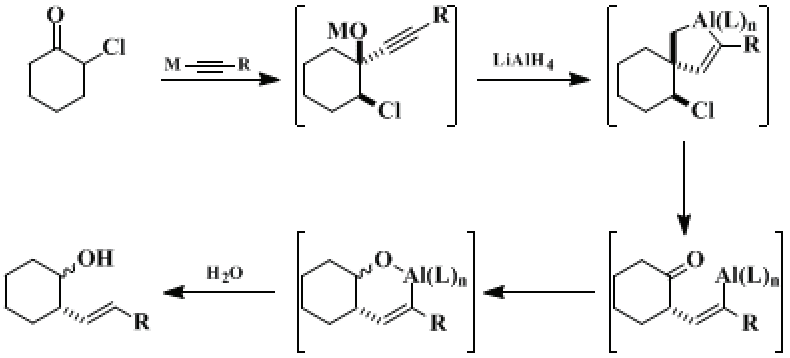
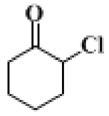
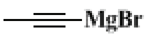
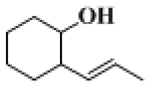
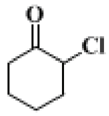
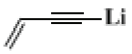
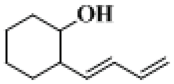
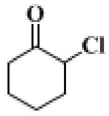
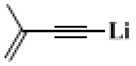
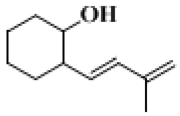
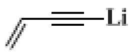
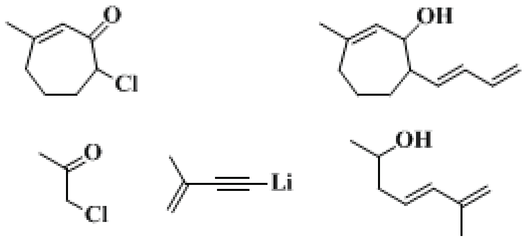


TABLE I

PREPARATION OF ALKENYL CARBINOLS

Carbonyl	Alkynylide	Alkenyl Carbinol	Yield(%)
			85
			71
			76
			91



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

H_2O

trans- and cis-1-propynyl-2-chlorocyclohexanols

cis- and trans-2-E-propenylcyclohexanols

acetylene (74-86-2)

diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

hydride

ethylmagnesium bromide (925-90-6)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2-Chlorocyclohexanone (822-87-7)

propynylmagnesium bromide

diisobutylaluminum hydride (1191-15-7)

propyne (74-99-7)

aluminum hydride

vinyl cation

lithium trimethoxyaluminum hydride

vinyl alanate

2-E-PROPENYLCYCLOHEXANOL

Cyclohexanol, 2-(1-propenyl)-, (E)-