



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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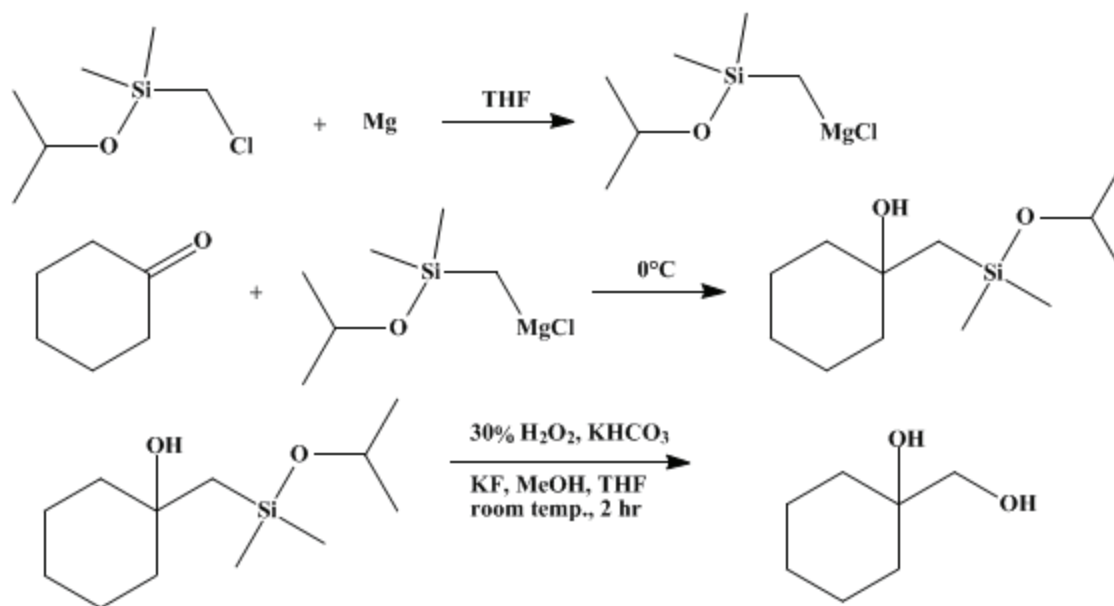
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 8, p.315 (1993); Vol. 69, p.96 (1990).

NUCLEOPHILIC HYDROXYMETHYLATION BY THE (ISOPROPOXYDIMETHYLSILYL)METHYL GRIGNARD REAGENT: 1-(HYDROXYMETHYL)CYCLOHEXANOL FROM CYCLOHEXANONE

[Cyclohexanemethanol, 1-hydroxy-]



Submitted by Kohei Tamao, Neyoshi Ishida, Yoshihiko Ito, and Makoto Kumada¹.
Checked by Vinh D. Tran and Larry E. Overman.

1. Procedure

A. *1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol*. A 500-mL, three-necked flask is equipped with a pressure-equalizing dropping funnel, a magnetic stirrer, a three-way stopcock, and a reflux condenser connected with a nitrogen bubbler. The flask is charged with magnesium turnings (2.43 g, 100 mg-atm) that are dried under a rapid stream of nitrogen with a heat gun. After the flask is cooled to room temperature, the rate of nitrogen flow is reduced. Several milliliters of a solution of (isopropoxydimethylsilyl)methyl chloride (16.67 g, 100 mmol) (Note 1) in dry tetrahydrofuran (THF) (120 mL) (Note 2) and about 50 μL of 1,2-dibromoethane are added. The mixture is stirred at room temperature and within a few minutes an exothermic reaction starts. The remaining solution is added dropwise at room temperature over ca. 45 min at such a rate as to maintain a gently exothermic reaction. After the addition is complete, the tan-gray mixture is refluxed for 0.5 hr and then cooled to 0°C with an ice bath. A solution of freshly distilled cyclohexanone (7.36 g, 75 mmol) in dry THF (30 mL) is added dropwise with stirring over 30 min. The resultant mixture is stirred at 0°C for another 30 min (Note 3) and then hydrolyzed by dropwise addition of an aqueous 10% solution of ammonium chloride (100 mL) at 0°C over 10 min. The organic layer is separated. The aqueous layer is extracted with four 40-mL portions of diethyl ether. The combined organic layer and extracts are washed once with aqueous saturated sodium chloride, dried over magnesium sulfate, filtered into a 500-mL round-bottomed flask and concentrated with a rotary evaporator below room temperature (Note 4) at water aspirator pressure. A colorless oil remains (Note 5).

B. *1-(Hydroxymethyl)cyclohexanol*. The 500-mL, round-bottomed flask containing the crude 1-[(isopropoxydimethylsilyl)methyl]cyclohexanol is equipped with a magnetic stirrer and a thermometer, and is kept open to air throughout the reaction. The flask is charged with tetrahydrofuran (75 mL),

methanol (75 mL) (Note 6), potassium hydrogen carbonate (7.5 g 75 mmol), and potassium fluoride (8.7 g, 150 mmol) (Note 7). To the stirred mixture is added 30% hydrogen peroxide (28.0 mL, 247.5 mmol) in one portion at room temperature. A somewhat cloudy organic layer and a milky-white, heavy inorganic layer result. After several minutes an exothermic reaction begins which is controlled by intermittent, brief cooling with a water bath to maintain the temperature at 40–50°C (Note 8). After about 30 min the exothermic reaction ceases. The mixture is then stirred at room temperature for 2 hr (Note 9). The remaining hydrogen peroxide is decomposed by careful dropwise addition (Note 10) of an aqueous 50% solution of sodium thiosulfate pentahydrate (ca. 30 mL) with stirring over 30 min, during which time the temperature is maintained near 30°C by intermittent cooling with an ice bath (Note 11). A negative starch-iodide test is observed (Note 12). A white precipitate forms and diethyl ether (ca. 100 mL) is added to ensure further precipitation. The mixture is filtered with suction and the filter cake is washed with three 20-mL portions of diethyl ether. The combined filtrate and washes are concentrated with a rotary evaporator at 50°C at water aspirator pressure until much of the water has been removed. The remaining oil is diluted with diethyl ether (ca. 200 mL), transferred to a separatory funnel, and washed with saturated aqueous sodium chloride solution to remove the remaining water. The organic layer is separated, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give a colorless solid. The solid is dissolved in a 10 : 1 mixture of hexane–ethyl acetate (75 mL) at reflux, and the hot solution is filtered. The filtrate is allowed to cool to room temperature and finally is kept at 0°C for 2 hr. The crystals are separated with suction, washed with cold hexane/ethyl acetate (10 : 1, 10 mL), and dried under high vacuum at room temperature. There is obtained 7.54 g (77%) of 1-(hydroxymethyl)cyclohexanol as white crystals, mp 76.0–76.2°C (Note 13) and (Note 14).

2. Notes

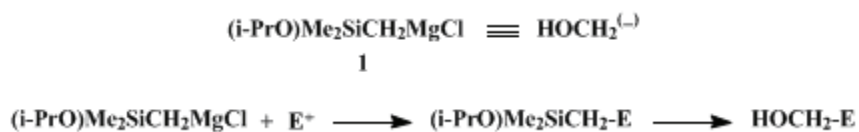
1. (Isopropoxydimethylsilyl)methyl chloride² is readily prepared from (chlorodimethylsilyl)methyl chloride by treatment with isopropyl alcohol (1.1 equiv) and triethylamine (1.1 equiv) in diethyl ether at room temperature (0.5 hr) and then at reflux temperature (0.5 hr). After filtration of the white salt, the filtrate is washed successively once with water, twice with 0.1 N hydrochloric acid, once with an aqueous 10% solution of sodium hydrogen carbonate and once with water, and then dried over sodium sulfate. Filtration and distillation give the product in 80% yield, bp 65–67°C at 50 mm, as an air-stable, colorless liquid. The checkers used commercially available material purchased from Aldrich Chemical Company, Inc.
2. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen (*Caution: See Org. Synth., Coll. Vol. V, 1973, 976 for a warning regarding the purification of tetrahydrofuran. The checkers employed THF that had been purified by distillation from sodium and benzophenone.*).
3. The color of the mixture lightened slightly.
4. Care must be taken not to raise the temperature since β -elimination of the β -hydroxysilane can result.
5. The remaining oil appeared as one spot on silica gel TLC, $R_f = 0.8$ (hexane/ethyl acetate 1 : 1), and showed the following ¹H NMR spectrum (CDCl₃, 300 MHz) δ : 0.19 (s, 6 H, Si(CH₃)₂), 1.01 (s, 2 H, CH₂Si), 1.20 (d, 6 H, $J = 6$, CH(CH₃)₂), 1.38–1.75 (m, 10 H, (CH₂)₅), 3.5 (s, OH), 4.04 (septet, 1 H, $J = 6$, OCH(CH₃)₂).
6. Commercial reagent-grade THF and methanol are used without further purification.
7. Potassium fluoride of anhydrous grade was purchased from Nakarai Chemicals, Ltd. This must be weighed quickly because it is highly hygroscopic. The checkers used material purchased from Allied Chemical Company.
8. The oxidation is so exothermic that the temperature reaches 60–65°C in 10 min if no external cooling is applied.
9. Completion of the oxidation was confirmed by TLC on silica gel: R_f of the product diol is 0.4 (hexane/ethyl acetate 1 : 1).
10. Care must be taken not to add the thiosulfate solution in one portion; otherwise a violent, uncontrollable reaction might suddenly occur.
11. The reaction temperature should be monitored carefully. If it falls below 10°C, the cooling bath should be removed to allow the mixture to warm to ca. 30°C.
12. If the test is still positive, thiosulfate solution should be added until a negative test is attained. The checkers found EM Quant Peroxide Test Strips obtained from EM Science to be more sensitive than conventional KI-Starch test paper.
13. The reported melting point is 75–76°C.³

14. **1-(Hydroxymethyl)cyclohexanol** exhibits the following spectral properties: ^1H NMR (300 MHz, CDCl_3) δ : 1.25–1.70 (broad m, 10 H, $(\text{CH}_2)_5$), 2.12 (s, 1 H, OH), 2.37 (t, 1 H, $J = 6$, OH), 3.45 (d, 2 H, $J = 6$, CH_2OH); IR (KBr) cm^{-1} : 3700–3020 (strong), 2920 (strong), 2845 (strong). Mass spectrum (24 eV): m/z (relative intensity) 130 (M^+ , 0.3), 99 (100), 81 (67). High-resolution mass spectrum: calcd. for $\text{C}_7\text{H}_{14}\text{O}_2$, 130.0992; found, 130.0969.

3. Discussion

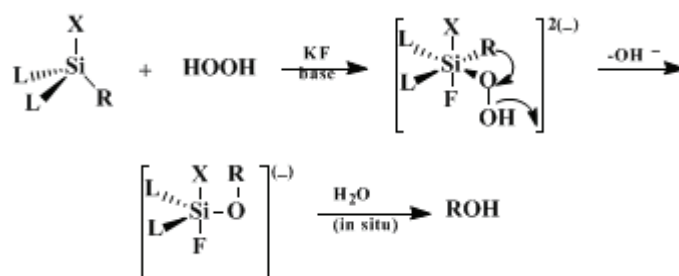
This procedure for the preparation of **1-(hydroxymethyl)cyclohexanol** is a modification of that reported by the submitters.⁴ While **1-(hydroxymethyl)cyclohexanol** has been conventionally prepared from **methylenecyclohexane** by dihydroxylation^{5a} or from **cyclohexanone** in three steps through the cyanohydrin,^{5b} the present method consists of an alternative route from **cyclohexanone** via nucleophilic hydroxymethylation.

Although nucleophilic hydroxymethylating agents (hydroxymethyl anion synthons) or alkoxyethyl anions could be of great use in synthetic organic chemistry,⁶ only a few agents of this type have been developed so far. They include $\text{MeOH}/\text{TiCl}_4/h\nu$,⁷ $\text{Bu}_3\text{SnCH}_2\text{OH}/\text{BuLi}$,⁸ *tert*- BuOCH_2Li ,⁹ $\text{HSiR}_3/\text{CO}/\text{Co}_2(\text{CO})_8$,¹⁰ $\text{PhCH}_2\text{OCH}_2\text{Cl}/\text{SmI}_2$,¹¹ $\text{ArCO}_2\text{CH}_2\text{Li}/\text{LiAlH}_4$,¹² $\text{R}_2\text{BCH}_2\text{Li}/[\text{O}]$,^{13 14} and $(\text{Me}_3\text{SiO})\text{CH}=\text{C}(\text{OSiMe}_3)_2$.¹⁵ These methods are not as convenient or widely applicable as the method reported here. Two points deserve comment.



In addition to the (isopropoxydimethylsilyl)methyl Grignard reagent, $(\text{isoPrO})\text{Me}_2\text{SiCH}_2\text{MgCl}$ (**1**), the (diisopropoxymethylsilyl)methyl counterpart, $(\text{isoPro})_2\text{MeSiCH}_2\text{MgCl}$ (**2**), has also been used as a nucleophilic hydroxymethylating agent.¹⁶ Despite labile alkoxy group(s) on silicon, the Grignard reagents are readily prepared in a normal manner in greater than 90% yields, and are sufficiently stable to be stored at room temperature for at least 2 days with little decrease in activity. The monoisopropoxy Grignard reagent (**1**) is recommended as the reagent of first choice. Its precursor, (isopropoxydimethylsilyl)methyl chloride, is readily available at lower cost, and the reaction products, $(\text{iso-PrO})\text{Me}_2\text{SiCH}_2\text{E}$, are more stable not only to aqueous workup under weakly basic and acidic conditions but also to silica gel chromatography.

The present method is based on the oxidative cleavage reaction of the silicon–carbon bond by hydrogen peroxide.¹⁷ The presence of at least one heteroatom on silicon is essential for the oxidative cleavage. Thus, the silicon-carbon bonds in hydro-, fluoro-, chloro-, alkoxy-, or aminosilanes are cleaved oxidatively to give the corresponding hydroxylated products. Although the oxidation may be performed in several ways, the following conditions (involving weak base and fluoride ion) may be the most efficient and most widely applicable: 30% H_2O_2 (1.2 equiv/Si-C bond), KHCO_3 (1 molar equiv), KF (2 molar equiv), MeOH/THF (1 : 1), room temperature. Under these conditions, the reaction usually occurs exothermically and is typically complete in several hours. Functional groups such as olefin, aldehyde, ketone, ester, amine, ether, ketal and *tert*-butyldimethylsiloxy groups, and furan, thiophene, and pyridine rings are stable under the oxidation conditions. The oxidation proceeds with complete retention of configuration at an sp^3 carbon. The oxidation has been considered to proceed through intramolecular migration of an organic group from silicon to the adjacent oxygen atom in penta- or hexacoordinate hydroperoxysilicon intermediates, as shown in Scheme 1, where X stands for a functional group. The oxidation has found a variety of synthetic applications.¹⁸

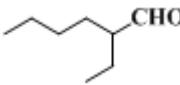
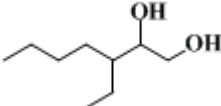
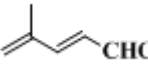
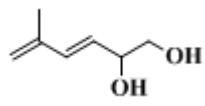
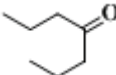
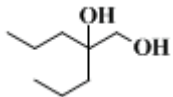

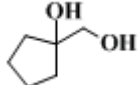
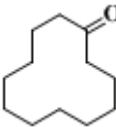
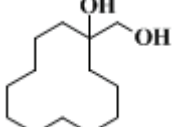
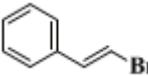
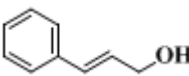


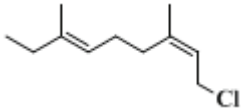
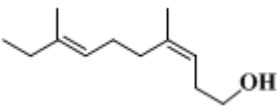
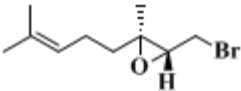
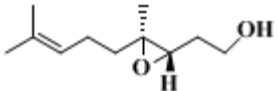
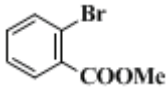
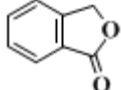

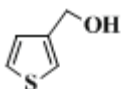
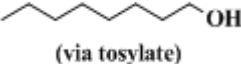
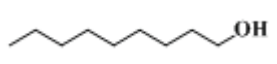


Several representative examples of nucleophilic hydroxymethylation of aldehydes, ketones, organic halides, tosylates, and epoxides are summarized in Table 1. The oxidation conditions given in the original literature are not necessarily optimum, and results may be improved by use of the oxidation method employed here. These results, summarized in Table I, demonstrate the general applicability of the silicon-based nucleophilic hydroxymethylation.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 493](#)
- [Org. Syn. Coll. Vol. 9, 539](#)

TABLE I
NUCLEOPHILIC HYDROXYMETHYLATION OF ALDEHYDES, KETONES, ORGANIC HALIDES, ALCOHOLS, AND EPOXIDES^a

Starting Material	Product	Overall isolated yield (%)	Ref.
		67	4
		75	19
		86	4
		65	4
		63	4
		79	16
		87	16

			
		52	20
		86	16
		65	16
 (via tosylate)		67	21
		74	21

^aIntroduction of the silylmethyl group into organic halides, tosylates, and epoxides is achieved by nickel-, palladium-, or copper-catalyzed cross-coupling reactions.

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

silica gel

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol,
MeOH (67-56-1)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

1,2-dibromoethane (106-93-4)

hydrogen peroxide (7722-84-1)

magnesium sulfate (7487-88-9)

Tetrahydrofuran,
THF (109-99-9)

potassium fluoride (7789-23-3)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

triethylamine (121-44-8)

potassium hydrogen carbonate (298-14-6)

Methylenecyclohexane (1192-37-6)

sodium thiosulfate pentahydrate

1-(Hydroxymethyl)cyclohexanol,
Cyclohexanemethanol, 1-hydroxy- (15753-47-6)

1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol (138080-23-6)

(Isopropoxydimethylsilyl)methyl chloride (18171-11-4)

(chlorodimethylsilyl)methyl chloride (1719-57-9)