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of Reliable Methods
for the Preparation
of Organic Compounds

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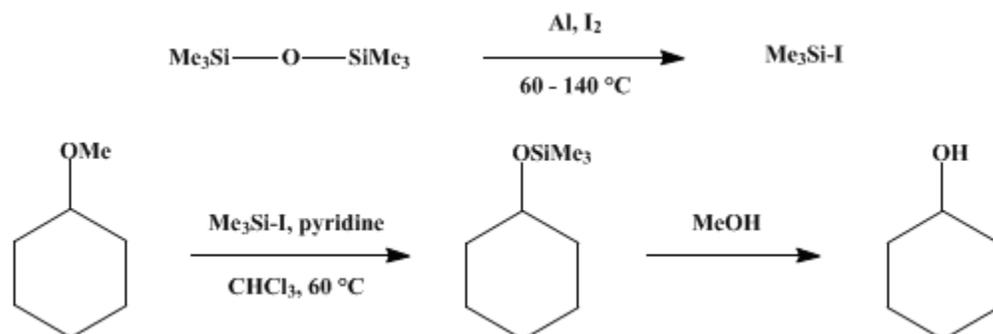
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CLEAVAGE OF METHYL ETHERS WITH IODOTRIMETHYLSILANE: CYCLOHEXANOL FROM CYCLOHEXYL METHYL ETHER



Submitted by Michael E. Jung¹ and Mark A. Lyster¹².

Checked by Joan Huguet, H. Shibuya, and S. Masamune.

1. Procedure

A. *Iodotrimethylsilane*. A 250-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar, an addition funnel for solids (Note 1), and a reflux condenser bearing a nitrogen inlet is charged with 5.6 g. (0.21 mole) of aluminum powder (Note 2) and 16.2 g. (0.100 mole) of hexamethyldisiloxane (Note 3) and purged with nitrogen. The mixture is stirred and heated with an oil bath at 60° as 50.8 g. (0.200 mole) of iodine is added slowly through the addition funnel over 55 minutes (Note 4). The bath temperature is raised to *ca.* 140°, and the mixture is heated under reflux for 1.5 hours. The reflux condenser is removed, and the flask is equipped for distillation at atmospheric pressure. The bath temperature is gradually raised from 140° to 210°, and the clear, colorless distillate is collected, yielding 32.6–35.3 g. (82–88%) of iodotrimethylsilane, b.p. 106–109° (Note 5) and (Note 6).

B. *Cyclohexanol*. A 25-ml., oven-dried, round-bottomed flask is charged with 1.722 g. (0.01524 mole) of cyclohexyl methyl ether (Note 7). The flask is purged with nitrogen and sealed with a rubber septum. With oven-dried syringes, 4 ml. of chloroform (Note 8), 0.5 g. (0.5 ml., 0.006 mole) of pyridine (Note 8) and (Note 9), and 4.8 g. (3.5 ml., 0.024 mole) of freshly prepared iodotrimethylsilane are injected into the flask in the order specified. When the iodotrimethylsilane is added, the solution becomes slightly yellow and a precipitate appears. The mixture is heated without stirring at 60° for 64 hours, after which the reaction is normally complete (Note 10). Anhydrous methanol (2 ml.) is added, the mixture is cooled to room temperature, and the volatile components (Note 11) are removed on a rotary evaporator. Approximately 10 ml. of anhydrous diethyl ether (Note 12) is added, and the resulting suspension is filtered, removing pyridinium hydroiodide. The flask and the filter cake are washed thoroughly with *ca.* 50 ml. of anhydrous ether. The ether is evaporated, and the residual oil is purified by chromatography on 70 g. of silica gel packed with anhydrous ether in a 3 × 50 cm. glass column. The column is eluted with anhydrous ether, and 5–7 ml. fractions are collected and analyzed by TLC (Note 13). Fractions containing product are combined and evaporated, affording 1.26–1.35 g. (83–89%) of cyclohexanol (Note 14).

2. Notes

- The submitters have used both an addition funnel with a worm gear delivery similar to those manufactured by Normag, and an Erlenmeyer flask attached to the neck of the reaction vessel with a piece of Gooch rubber tubing. Normag addition funnels are available from Lab Glass, Inc., P. O. Box 610, Vineland, New Jersey 08360.
- The submitters purchased aluminum powder from MC and B Manufacturing Chemists. The metal used by the checkers was supplied by J. T. Baker Chemical Company.

3. [Hexamethyldisiloxane](#) is available from Aldrich Chemical Company, Inc. The reagent may also be prepared by the procedure described in the following paragraph. The submitters have used [chlorotrimethylsilane](#) purchased from Aldrich Chemical Company, Inc., and Silar Laboratories, Inc. (10 Alplaus Road, Scotia, New York 12302) either as supplied or after distillation from [calcium hydride](#). No appreciable difference in yield was noted between preparations using undistilled and distilled reagent.

A 250-ml., three-necked, round-bottomed flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser bearing a nitrogen inlet is charged with a solution of 7 g. (0.4 mole) of water in 72.7 g. (76.0 ml., 0.601 mole) of [N,N-dimethylaniline](#) and flushed with [nitrogen](#). Stirring is begun, and 62.49 g. (73.00 ml., 0.5754 mole) of [chlorotrimethylsilane](#) is added dropwise over 50 minutes. The mixture is heated under reflux in an oil bath at 125–130° for 1 hour. The reflux condenser is replaced by a distilling head, and the product is distilled at atmospheric pressure. The fraction boiling at 98–101° is collected, dried over anhydrous [magnesium sulfate](#), and filtered, affording 43–44 g. (92–94%) of [hexamethyldisiloxane](#) as a clear colorless liquid.

4. In a similar procedure for the preparation of [iodotrimethylsilane](#), [aluminum](#), [iodine](#), and [hexamethyldisiloxane](#) are combined, and the mixture is heated to reflux.³ When this procedure was attempted by the submitters, violent exothermic reactions occurred at *ca.* 50–60°. The slow addition of [iodine](#) to the warm mixture described in the present procedure leads to a controlled, reproducible reaction.

5. The product is sometimes contaminated with a small amount of [hexamethyldisiloxane](#). The amount of this contaminant is minimized by using longer reaction times and by careful handling to avoid contact with atmospheric moisture. The product may become discolored during storage, in which case it may be purified by distillation from [copper powder](#). The ¹H NMR spectrum of [iodotrimethylsilane](#) (CDCl₃) exhibits a singlet at δ 0.71 in the presence of [benzene](#) as internal standard.

6. The submitters obtained 69.4 g. (87%) of product when the scale was doubled.

7. [Cyclohexyl methyl ether](#) was prepared by the method of Stoochnoff and Benoiton.⁴ A 250-ml., two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser mounted with a nitrogen inlet. The flask is purged with [nitrogen](#) and charged with 8 g. (0.2 mole) of a 60% dispersion of [sodium hydride](#) in mineral oil. The [sodium hydride](#) is washed free of mineral oil with [pentane](#) and suspended in 75 ml. of [tetrahydrofuran](#). After 10 g. (0.10 mole) of [cyclohexanol](#) is added by syringe, the mixture is heated under reflux for 22 hours. A 28.4-g. (12.5 ml., 0.200 mole) portion of [methyl iodide](#) is injected into the flask, and the resulting mixture is heated under reflux for 18 hours. Water and [chloroform](#) are added to the cooled mixture. The aqueous layer is extracted with three 50-ml. portions of [chloroform](#), the combined [chloroform](#) extracts are dried over anhydrous [magnesium sulfate](#), and the solvents are evaporated. Distillation of the remaining liquid affords 7.1 g. (62%) of [cyclohexyl methyl ether](#), b.p. 133–134°.

8. [Chloroform](#) and [pyridine](#) were dried over Linde type 4A molecular sieves.

9. [Pyridine](#) is added to neutralize small amounts of [hydrogen iodide](#), often present in [iodotrimethylsilane](#) as a result of hydrolysis by contact with moisture. The amount of by-products, including [cyclohexyl iodide](#), is reduced by the presence of [pyridine](#). Hindered [pyridine](#) bases such as [2,6-di-tert-butyl-4-methylpyridine](#)⁵ have also been used for this purpose, by the submitters. The [pyridine](#) bases do not appear to react with [iodotrimethylsilane](#).

10. The progress of the reaction may be conveniently monitored by ¹H NMR spectroscopy. After 64 hours the signal at δ 3.25 for the [methoxyl](#) group of [cyclohexyl methyl ether](#) had usually decreased to less than 1% of its original intensity, and peaks for [cyclohexyl iodide](#) could not be discerned. Although the submitters found that the reaction time was decreased by using larger amounts of [iodotrimethylsilane](#), 5–10% of [cyclohexyl iodide](#) was also produced.

11. The volatile components are [chloroform](#), [methanol](#), [methyl iodide](#), [methyl trimethylsilyl ether](#), and [hexamethyldisiloxane](#).

12. When the submitters used technical grade [ether](#), the amount of iodine-containing by-products isolated from the chromatography was increased, and the yield of [cyclohexanol](#) was somewhat lower.

13. When an insufficient amount of [iodotrimethylsilane](#) was used by the submitters, [cyclohexyl methyl ether](#) remained at the end of the reaction and was eluted from the silica gel column before [cyclohexanol](#). When present in the crude product, [cyclohexyl iodide](#) was also eluted from the column before [cyclohexanol](#).

14. The identity and purity of the product were determined by GC, IR spectroscopy, and ¹H NMR spectroscopy by both the submitters and the checkers.

3. Discussion

This procedure describes a convenient method for the preparation of iodotrimethylsilane and illustrates the use of this reagent for ether cleavage, as in the regeneration of cyclohexanol from cyclohexyl methyl ether.⁶ Iodotrimethylsilane was first prepared by Whitmore by the reaction of trimethylphenylsilane with iodine.⁷ The reagent has also been generated *in situ* by halide exchange between magnesium iodide and chlorotrimethylsilane.⁸ The present procedure is essentially that of Voronkov and Khudobin,³ modified by slowly adding iodine to a mixture of aluminum and hexamethyldisiloxane heated at 60° (see (Note 4)).

The use of methyl ethers as protecting groups for aliphatic alcohols has been hampered by the difficulty of liberating the alcohol from this inert derivative.^{9,10} The cleavage of methyl ethers has been previously accomplished with boron reagents such as boron trichloride,^{11,12,13,14,15} boron trifluoride in acetic anhydride,^{16,17} and diborane or sodium borohydride in the presence of iodine.^{18,19} Two recent modifications of early methods for cleavage of aliphatic methyl ethers utilize hydrogen iodide generated *in situ*¹⁰ and magnesium bromide in acetic anhydride.²⁰ Recently described methods for the hydrolysis of methyl ethers include the use of sodium cyanide in dimethyl sulfoxide,²¹ anhydrous hydrogen bromide,²² and thiotrimethylsilanes.²³

The use of iodotrimethylsilane for this purpose provides an effective alternative to known methods. Thus, the reaction of primary and secondary methyl ethers with iodotrimethylsilane in chloroform or acetonitrile at 25–60° for 2–64 hours affords the corresponding trimethylsilyl ethers in high yield.⁶ The alcohols may be liberated from the trimethylsilyl ethers by methanolysis. The mechanism of the ether cleavage is presumed to involve initial formation of a trimethylsilyl oxonium ion which is converted to the silyl ether by nucleophilic attack of iodide at the methyl group. *tert*-Butyl, trityl, and benzyl ethers of primary and secondary alcohols are rapidly converted to trimethylsilyl ethers by the action of iodotrimethylsilane, probably *via* heterolysis of silyl oxonium ion intermediates. The cleavage of aryl methyl ethers to aryl trimethylsilyl ethers may also be effected more slowly by reaction with iodotrimethylsilane at 25–50° in chloroform or sulfolane for 12–125 hours,⁶ with iodotrimethylsilane at 100–110° in the absence of solvent,^{24,25} and with iodotrimethylsilane generated *in situ* from iodine and trimethylphenylsilane at 100°.^{25,26}

Alkyl esters are efficiently dealkylated to trimethylsilyl esters with high concentrations of iodotrimethylsilane either in chloroform or sulfolane at 25–80°²⁷ or without solvent at 100–110°.^{24,26} Hydrolysis of the trimethylsilyl esters serves to release the carboxylic acid. Amines may be recovered from *O*-methyl, *O*-ethyl, and *O*-benzyl carbamates after reaction with iodotrimethylsilane in chloroform or sulfolane at 50–60° and subsequent methanolysis.²⁸ The conversion of dimethyl, diethyl, and ethylene acetals and ketals to the parent aldehydes and ketones under aprotic conditions has been accomplished with this reagent.²⁹ The reactions of alcohols (or the corresponding trimethylsilyl ethers) and aldehydes with iodotrimethylsilane give alkyl iodides³⁰ and α -iodosilyl ethers,³¹ respectively. Iodomethyl methyl ether is obtained from cleavage of dimethoxymethane with iodotrimethylsilane.³² A review by Schmidt³³ covers the applications of iodotrimethylsilane listed above along with many more recently published examples.

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

diborane

trimethylphenylsilane

thiotrimethylsilanes

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)
chloroform (67-66-3)
Cyclohexanol (108-93-0)
sodium cyanide (143-33-9)
hydrogen bromide (10035-10-6)
nitrogen (7727-37-9)
aluminum,
aluminum powder (7429-90-5)
copper powder (7440-50-8)
iodine (7553-56-2)
pyridine (110-86-1)
hydrogen iodide (10034-85-2)
magnesium bromide (7789-48-2)
N,N-dimethylaniline (121-69-7)
Methyl iodide (74-88-4)
Pentane (109-66-0)
Dimethoxymethane (109-87-5)
magnesium sulfate (7487-88-9)
magnesium iodide
iodide (20461-54-5)
boron trifluoride (7637-07-2)
Tetrahydrofuran (109-99-9)
sodium hydride (7646-69-7)
methoxyl (2143-68-2)
boron trichloride (10294-34-5)
dimethyl sulfoxide (67-68-5)

calcium hydride (7789-78-8)

cyclohexyl iodide (626-62-0)

sodium borohydride (16940-66-2)

sulfolane (126-33-0)

CHLOROTRIMETHYLSILANE (75-77-4)

methyl trimethylsilyl ether (1825-61-2)

hexamethyldisiloxane (107-46-0)

Iodotrimethylsilane (16029-98-4)

CYCLOHEXYL METHYL ETHER (931-56-6)

pyridinium hydroiodide

silyl ether (13597-73-4)

trimethylphenylsilane (768-32-1)

Iodomethyl methyl ether (13057-19-7)

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)