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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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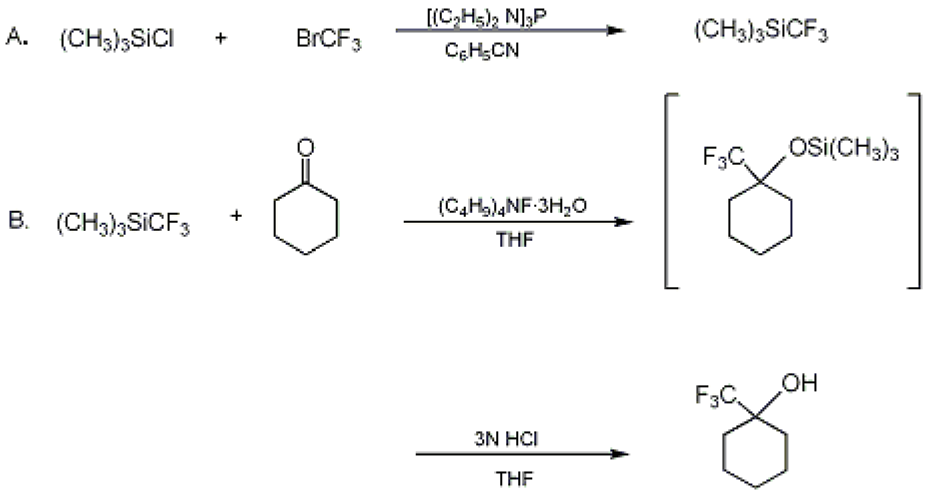
1-TRIFLUOROMETHYL-1-CYCLOHEXANOL

[Cyclohexanol, 1-(trifluoromethyl)-]



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1. Procedure

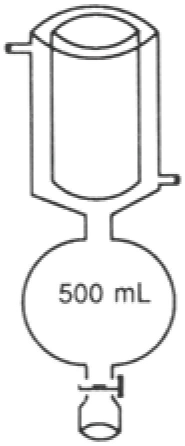
CAUTION! All operations should be performed in a well ventilated hood. Hexaethylphosphorous triamide is potentially toxic and should be handled with protective gear.

A. *(Trifluoromethyl)trimethylsilane*. A 2-L, three-necked flask is fitted with an efficient, overhead, sealed mechanical stirrer, a cold-finger condenser (30-cm in length and 8-cm in diameter) and a rubber septum (Note 1). The top outlet of the condenser is attached to an oil bubbler. The flask is flushed with dry nitrogen and charged with 118.8 g (1.09 mol) of chlorotrimethylsilane (Note 2) in 100 mL of anhydrous benzonitrile (Note 3). The septum is replaced quickly under dry nitrogen with a 500-mL Ace dry ice gas condenser trap (15-cm in length and 8-cm in diameter) (Note 4). The outlet of the trap is protected from moisture by a tube packed with potassium hydroxide and the inlet is connected by tygon tubing to a cylinder of bromotrifluoromethane (Note 5). The 2-L flask is immersed in a dry ice-acetone bath maintained at −30°C (Note 6) and the condensers are filled with dry ice-acetone mixture (−78°C). The cylinder is opened and 250 mL (d = 1.94 g/mL,[2] 485 g, 3.25 mol) of bromotrifluoromethane is condensed into the 500-mL Ace reservoir (Note 7). Stirring is started, and the condensed liquid bromotrifluoromethane is gradually added to the vessel at −30°C by slowly warming the reservoir to −45°C to −50°C. The resulting white slurry is further cooled to −60°C (Note 6) and (Note 8). The Ace dry ice gas condenser trap is disconnected under dry nitrogen and replaced with a 600-mL, pressure-equalizing dropping funnel containing a solution of 325.0 g (1.31 mol) of hexaethylphosphorous triamide (Note 9) in 250 mL of dry benzonitrile. This solution is added with stirring at −60°C to the white slurry mixture over a period of 2.5 hr. After the addition is complete, the reaction mixture is stirred for an additional hour at −60°C (Note 10), and then allowed to warm gradually to room temperature (25°C) over a period of 14 hr, during which time it turns clear yellow (Note 11). The condenser and dropping funnel are removed and replaced by a glass stopper and joint adapter with its glass tube connected to two, 250-mL, dry ice/acetone-cooled traps; then aspirator vacuum (ca. 20 mm) is applied. The reaction flask is gently warmed to 50°C during which time (3 hr) all the volatile material collects in the cooled traps (Note 12). The cooling baths are removed and the material in the traps is brought to 0°C. The colorless liquid is transferred quickly to a 250-mL separatory funnel, washed rapidly with ice cold water (3 × 100 mL), and the top organic product layer is separated (Note 13). The product is dried over 5 g of anhydrous magnesium sulfate, and the dry liquid is decanted into a 250-mL flask. The product is fractionally distilled through a 15-cm column packed with glass helices. Three fractions are collected. The first minor fraction (bp 45–54°C) and the second major fraction (bp 54–55°C) contain the main quantity of (trifluoromethyl)trimethylsilane. The third minor fraction (bp 55–65°C) consists mainly of hexamethyldisiloxane with a small quantity of product (trifluoromethyl)trimethylsilane (Note 14). The first and second fractions are combined to yield 116.9 g (75%) of clear liquid product (Note 15) and (Note 16), bp 54–55°C (Note 17).

B. *1-Trifluoromethyl-1-cyclohexanol*. A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a reflux condenser is attached to a nitrogen source to maintain a positive pressure and the other neck is closed with a glass stopper. Tetrahydrofuran (70 mL) (Note 18) and 19.2 g (0.13 mol) of (trifluoromethyl)trimethylsilane are introduced into the flask through the septum using dry syringes (Note 19). The flask is immersed in an ice-water bath (0°C), and a solution of 10.2 g (0.104 mol) of cyclohexanone (Note 20) in 50 mL of tetrahydrofuran is added to the stirred solution of (trifluoromethyl)trimethylsilane using a syringe. Tetrabutylammonium fluoride trihydrate (33 mg) catalyst (Note 21),(Note 22) is transferred into the reaction vessel. As the exothermic reaction proceeds, a yellowish brown color develops with the initial evolution of fluorotrimethylsilane (Note 23). The reaction mixture is stirred at 0°C for 30 min and then the cooling bath is removed. The reaction mixture is brought to room temperature and stirred for an additional hour. The reaction mixture is periodically analyzed by GC-MS and the reaction is complete within 1 hr at 25°C (Note 24). To the reaction mixture that contains crude 1-trifluoromethyl-1-O-(trimethylsilyl)cyclohexane are added 25 mL of tetrahydrofuran and 40 mL of 3 N hydrochloric acid. The mixture is stirred at room temperature for 8 hr and then transferred to a 500-mL separatory funnel containing 50 mL of water. The product is extracted with 50 mL of ether. The organic layer is separated and the aqueous layer is reextracted with 30 mL of ether. The combined organic layers are washed with 50 mL of water, dried over 10 g of anhydrous magnesium sulfate, and filtered. The residue is repeatedly washed with dry ether (3 × 20 mL). The solvent is removed on a rotary evaporator and the residue is dried to give a semi-solid that is purified by sublimation under vacuum (Note 25) to furnish 13.9–14.3 g (79–82%) of 1-trifluoromethyl-1-cyclohexanol as a white waxy solid, mp 60.8°C (Note 26).

2. Notes

1. All glass apparatus is dried in an oven at 100°C and assembled while still hot under dry nitrogen flow. All ground glass joints are tightly sealed with a Teflon tape and then wrapped with parafilm.
2. Chlorotrimethylsilane (98%) was obtained from the Aldrich Chemical Company, Inc. and was distilled over calcium hydride under a static atmosphere of dry nitrogen just prior to use.
3. Anhydrous benzonitrile (99+%) was purchased from the Aldrich Chemical Company, Inc. and used without further purification.
4. The trap was built in house. A 1000-mL Ace trap is available from the Aldrich Chemical Company, Inc.



Ace dry ice gas condenser trap

5. Bromotrifluoromethane, bp −57°C, was supplied by E.I. du Pont de Nemours & Co., Inc.
6. A temperature of −30°C to −60°C was maintained by adding dry ice to excess acetone.
7. The rate of bromotrifluoromethane transfer was monitored by a Nujol bubbler. A mark is made on the Ace reservoir trap to indicate the 250-mL volume.
8. If the temperature falls below −60°C, the reaction mixture solidifies but returns to a liquid upon warming. The inverse addition, i.e., addition of chlorotrimethylsilane to bromotrifluoromethane, causes formation of a solid block that impedes stirring.
9. Hexaethylphosphorous triamide (97%) was obtained from the Aldrich Chemical Company, Inc., and used as received. It can be prepared from diethylamine and phosphorus trichloride following the literature procedure.[3] [4]
10. An exothermic reaction usually begins after all the hexaethylphosphorous triamide is introduced, and some of the bromotrifluoromethane escapes through the bubbler.
11. To recover excess unreacted bromotrifluoromethane, a dry ice-acetone cooled trap is connected to the condenser outlet before the reaction mixture is warmed to room temperature.
12. The proton NMR of the distillate shows the two methyl group absorptions of (trifluoromethyl) trimethylsilane and chlorotrimethylsilane in a ratio of about 85:15. The material solidifies in a dry ice-acetone cooled trap.
13. The distillate is shaken well with water to convert chlorotrimethylsilane to hexamethyldisiloxane.
14. The product from the third fraction could not be isolated pure by redistillation.
15. The yield is based on chlorotrimethylsilane. A comparable yield of 77% was obtained when the reaction was repeated on one-third the scale. GC and NMR analyses show the product to be 98–99% pure.
16. (Trifluoromethyl)trimethylsilane has the following spectroscopic properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.25 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ: 131.7 (q, $^1J^{13}C\text{-}^{19}F$ = 321.9), −5.2 (CH_3-Si); ^{19}F NMR (188.0 MHz, $CDCl_3$, $CFCl_3$ external) d: −66.1; ^{29}Si NMR (39.7 MHz, $CDCl_3$) δ: +4.7 (q, $^2J(^{29}Si\text{-}^{19}F)$ = 37.9). MS (m/z) 123 (M^+-19).
17. The boiling point for (trifluoromethyl)trimethylsilane is reported as 45°C.[5] The submitters report a boiling point of 55.5°C.
18. Reagent grade tetrahydrofuran was purchased from the Fisher Scientific Company and freshly distilled from sodium benzophenone ketyl under dry nitrogen atmosphere.
19. Prior to use, the hypodermic syringes and needles were dried for several hours in an oven at 100°C and allowed to cool to ambient temperature in a desiccator.
20. Cyclohexanone (99%) was purchased from the Aldrich Chemical Company, Inc., and used as such.
21. Tetrabutylammonium fluoride (TBAF) trihydrate (99%) was purchased from the Aldrich Chemical Company, Inc.
22. TBAF trihydrate acts as an initiator and the water of hydration in TBAF does not pose any problem.
23. Bubbles of fluorotrimethylsilane are seen escaping during the initial stages of the reaction.
24. Progress of the reaction can be monitored by GC-MS using a Finnigan Model Incos-50 GC-MS spectrometer: Column: DB-5; temperature program: 50°C (4.5 min), 30°C/min, 250°C (30 min). Retention time: Cyclohexanone, 7.44 min. and 1-trifluoromethyl-O-(trimethylsilyl)cyclohexane, 11.20 min.
25. The product was sublimed at 2 mm at a bath temperature of 100°C. The receiver is cooled to 0°C, using an ice-bath.
26. The submitters report a melting point of 61.6°C. The product is pure (GC-MS) and has the following spectroscopic and analytical data : IR (KBr) cm^{-1}: 3364(s), 1255(s), 1146(s); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.00–1.90 (m,10 H), 1.93 (br, 1 H, OH); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ: 20.2, 25.0, 29.8, 72.6 (q, $^2J_{C\text{-}F}$ = 28.2), 126.4 (q, $^1J_{C\text{-}F}$ = 284.5 Hz, CF_3); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$, external) δ: −85.0; MS (m/z): 149 (M^+ -19, 0.57), 125 (1.25), 112 (1.23), 99 (100), 92 (1.50), 81 (66.79), 69 (10.49), 55 (26.01), 41 (37.26). Anal. Calcd for $C_7H_{11}F_3O$: C, 50.00; H, 6.59. Found: C, 49.69; H, 6.51.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(Trifluoromethyl)trimethylsilane has been prepared by a modification[6] [7] of the procedure originally published by Ruppert.[5] The optimized yield is 75%. Other less convenient methods are also available for its preparation.[8] [9] (Trifluoromethyl)trimethylsilane acts as an in situ trifluoromethide equivalent under nucleophilic initiation and reacts with a variety of electrophilic functional groups. Carbonyl compounds such as aldehydes, ketones and lactones react rather readily[6,7,10] with (trifluoromethyl) trimethylsilane under fluoride initiation. The reagent also reacts with oxalic esters,[11] sulfonyl fluorides,[12] α-keto esters,[13] fluorinated ketones,[14] and sulfoxides.[15] Homologous trifluoromethyltrialkylsilanes have also been used as nucleophilic trifluoromethylating agents.[16] In the presence of copper(I) iodide (CuI), homologous (trifluoromethyl)triethylsilane reacts with aromatic, allylic and benzylic halides to provide the corresponding trifluoromethyl derivatives.[17] The synthetic applications of trifluoromethyltrimethylsilane have been reviewed.[18] [19]

References and Notes

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

sodium benzophenone ketyl

1-Trifluoromethyl-1-O-(trimethylsilyl)cyclohexane

Tetrabutylammonium fluoride (TBAF) trihydrate

1-trifluoromethyl-O-(trimethylsilyl)cyclohexane

trifluoromethide

hydrochloric acid (7647-01-0)

ether (60-29-7)

benzonitrile (100-47-0)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

phosphorus trichloride (7719-12-2)

diethylamine (109-89-7)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

calcium hydride (7789-78-8)

Hexaethylphosphorous triamide (2283-11-6)

CHLOROTRIMETHYLSILANE (75-77-4)

hexamethyldisiloxane (107-46-0)

Tetrabutylammonium fluoride trihydrate (87749-50-6)

fluorotrimethylsilane (420-56-4)

1-Trifluoromethyl-1-cyclohexanol,
Cyclohexanol, 1-(trifluoromethyl)- (80768-55-4)

bromotrifluoromethane (75-63-8)

(Trifluoromethyl)trimethylsilane,
trifluoromethyltrimethylsilane (81290-20-2)

(trifluoromethyl)triethylsilane (120120-26-5)