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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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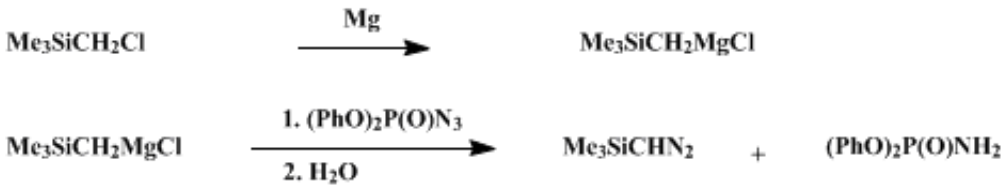
TRIMETHYLSILYLDIAZOMETHANE

[Silane, (diazomethyl)trimethyl-]



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1. Procedure

Caution! Trimethylsilyldiazomethane should be regarded as extremely toxic and should only be handled by individuals trained in its proper and safe use. All operations must be carried out in a well-ventilated fume hood and all skin contact should be avoided.

A. *Trimethylsilylmethylmagnesium chloride*. Magnesium turnings (10.7 g, 0.44 g-atom) are placed in a dry, 300-mL, four-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a 200-mL pressure-equalizing dropping funnel capped with a rubber septum, a thermometer, another rubber septum, and a reflux condenser connected to an argon flow line. The apparatus is flushed with argon, and an argon atmosphere is maintained throughout the reaction. Anhydrous diethyl ether (40 mL) (Note 1) and 0.1 mL of 1,2-dibromoethane are placed in the reaction flask with a syringe, and the mixture is stirred at room temperature for 15 min. The dropping funnel is charged with a solution of 45.4 g (0.37 mol) of chloromethyltrimethylsilane (Note 2) in 100 mL of anhydrous diethyl ether with a syringe. With stirring, about 10 mL of this solution is added at once. When the reaction has started (Note 3), the remaining solution is added dropwise at such a rate that a gentle reflux is maintained throughout the addition (addition time ca. 2 hr). After the exothermic reaction subsides, the resulting solution is stirred at reflux by heating for an additional 1 hr. The reaction mixture is cooled to room temperature, and is used in step B.

B. *Trimethylsilyldiazomethane*. (See (Note 4).) A dry, 1-L, four-necked, round-bottomed flask is equipped with a liquid paraffin-sealed mechanical stirrer (Note 5), a rubber septum, 200-mL pressure-equalizing dropping funnel capped with another rubber septum, and a reflux condenser connected to an argon flow line. The apparatus is flushed with argon, and an argon atmosphere is maintained throughout the reaction. A solution of 91.2 g (0.33 mol) of diphenyl phosphorazidate (Note 6) in 350 mL of anhydrous diethyl ether is placed in the flask with a syringe. The rubber septum is quickly replaced by a low-temperature thermometer. The Grignard reagent prepared in Step A is transferred to the dropping funnel with a syringe. The flask is cooled with an ice–sodium chloride bath, and the stirring is started. When the internal temperature reaches −10°C, the Grignard reagent is added dropwise at such a rate that the internal temperature is maintained below 0°C (addition time ca. 1.5 hr) (Note 7). After the addition is complete, the ice–salt bath is replaced with an ice bath and the mixture is stirred for 2 hr, then allowed to stand in the ice bath for 14–16 hr. The reaction mixture is cooled again to −15°C with an ice–sodium chloride bath. With vigorous stirring, 35 mL of cold water is carefully added dropwise at such a rate that the internal temperature is maintained below 0°C (addition time about 1 hr), and the stirring is continued for 0.5 hr (Note 8). The reaction mixture is then filtered by suction using a glass filter. The white solid is thoroughly washed with three 100-mL portions of diethyl ether. The combined filtrate is washed with two 100-mL portions of cold water and dried over anhydrous sodium sulfate. After the sodium sulfate is removed by filtration, the filtrate is placed in a 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 30-cm Vigreux column (15-mm diameter). With constant stirring by a

magnetic stirrer, the solution is slowly concentrated to a volume of about 200 mL by distillation at atmospheric pressure with the bath temperature below 45°C. The concentration time requires about 6 hr (Note 9) and (Note 10). The remaining deep-yellow solution is distilled through the same apparatus under reduced pressure between 100 mm at 0°C (bath temperature) and 15 mm at 40°C (bath temperature) until no more volatile material comes over, and the distillate is collected in a receiver cooled in a dry ice–acetone bath. The distillate is dried again over anhydrous sodium sulfate. The drying agent is removed by filtration, and 100 mL of hexane (Note 11) is added to the filtrate. In a manner similar to that described above, this solution is slowly concentrated by distillation at atmospheric pressure through a 30-cm Vigreux column (15-mm diameter). The color of the distillate gradually becomes yellow. Concentration is continued until the temperature of the vapor reaches 68°C (final oil-bath temperature 87°C). The concentration requires about 3 hr (Note 9). Approximately 80–110 mL of the remaining yellow hexane solution contains 220–230 mmol of trimethylsilyldiazomethane (67–70% yield based on diphenyl phosphorazidate) (Note 12) and (Note 13). This hexane solution can be stored without decomposition for periods exceeding 6 months at 0°C with protection from light.

2. Notes

1. Diethyl ether was distilled from lithium aluminum hydride under argon before use.
2. Chloromethyltrimethylsilane, obtained from Petrarch Systems Inc., was purified by distillation at 97°C under atmospheric pressure.
3. If the reaction does not start, the flask is gently heated by a heat gun.
4. *Trimethylsilyldiazomethane is both nonexplosive and nonmutagenic.*[2] *Therefore, the very careful operations*[3] *used for the preparation of diazomethane are not necessary. Note added September, 2009: the previous statement refers to precautions associated with the explosivity of diazomethane. TMS-diazomethane should be regarded as having similar toxicity to diazomethane and must be handled with all precautions appropriate for work with highly toxic substances.*
5. A glass or Teflon stirring rod should be used.
6. Diphenyl phosphorazidate, obtained from either Daiichi Pure Chemicals Co., Ltd. or Aldrich Chemical Company, Inc., was purified by distillation under reduced pressure; bp 134–136°C at 0.2 mm. It can be easily prepared according to *Org. Synth., Coll. Vol. VII* **1990**, 206.
7. After approximately two-thirds of the Grignard reagent is added, a large amount of white precipitate appears.
8. The mixture becomes yellow, which is the color of trimethylsilyldiazomethane.
9. The color of the distillate is pale yellow because of codistillation of trimethylsilyldiazomethane. Therefore, the rate of concentration is very important. If the rate of concentration is more rapid, the yield of trimethylsilyldiazomethane will decrease.
10. The submitters report that when a 30-cm Widmer column is used, the concentration time required is shorter (ca. 4 hr).
11. Hexane was purified by distillation.
12. The infrared spectrum (hexane) has absorptions at 2075, 1260, and 885 cm^{-1}. The ^1H NMR spectrum is as follows (hexane) δ: 0.16 (s, 9 H), 2.58 (s, 1 H) (internal chloroform standard).
13. The ^1H NMR of the hexane solution showed the presence of a trace of diethyl ether. The concentration of trimethylsilyldiazomethane was determined by the ^1H NMR analysis as follows: Ninety-one milligrams of dibenzyl was dissolved in 1 mL of a hexane solution of trimethylsilyldiazomethane, and its ^1H NMR spectrum was determined. The concentration (x mmol/mL) of trimethylsilyldiazomethane was calculated as follows: $x = 2b/a$ (mmol/mL) where a = integral value (mm) of methylene protons (δ: 2.99) of dibenzyl b = integral value (mm) of the methine proton (δ: 2.58) of trimethylsilyldiazomethane

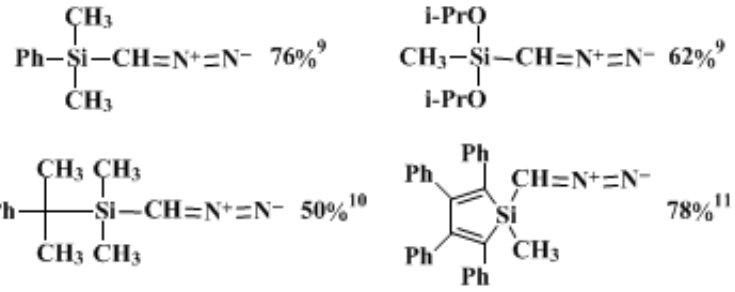
3. Discussion

Trimethylsilyldiazomethane, as a stable and safe substitute for hazardous diazomethane, is useful both as a reagent for introducing a C_1 unit and as a C-N-N synthon for the preparation of azoles.[4] Many methods are described in the literature for the preparation of trimethylsilyldiazomethane, including the

trimethylsilylation of diazomethane (7–74%),[5] the alkaline decomposition of *N*-nitroso-*N*-(trimethylsilylmethyl)amides (25–61%),[2,6] and the diazo group transfer reaction of trimethylsilylmethyllithium with *p*-toluenesulfonyl azide (38%).[7] The present modified diazo group transfer method appears to be the most practical, high-yield, and large-scale procedure for the preparation of trimethylsilyldiazomethane.[8]

Diphenyl phosphorazidate can be replaced with diethyl phosphorazidate in the above procedure. Use of other azides such as *p*-toluenesulfonyl azide, *p*-methoxybenzyloxycarbonyl azide, diphenylphosphinic azide, or diphenylthiophosphinic azide is less satisfactory. No reaction occurs when trimethylsilyl azide, dimethylthiophosphinic azide, or alkaline azides are used, while decomposition of formed trimethylsilyldiazomethane seems to occur when methanesulfonyl azide is used.[9]

The present procedure affords a general method for preparing silyldiazomethanes from the corresponding chloromethylsilyl compounds. Typical examples are as follows:



References and Notes

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

dibenzyl

diethyl ether (60-29-7)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

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

Diazomethane (334-88-3)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

Trimethylsilylmethylmagnesium chloride (13170-43-9)

p-toluenesulfonyl azide (941-55-9)

TRIMETHYLSILYL AZIDE (4648-54-8)

Diphenyl phosphorazidate (26386-88-9)

chloromethyltrimethylsilane (2344-80-1)

Trimethylsilyldiazomethane,
Silane, (diazomethyl)trimethyl- (18107-18-1)

trimethylsilylmethyllithium

diethyl phosphorazidate

diphenylphosphinic azide

diphenylthiophosphinic azide

dimethylthiophosphinic azide

methanesulfonyl azide

p-methoxybenzyloxycarbonyl azide (25474-85-5)