



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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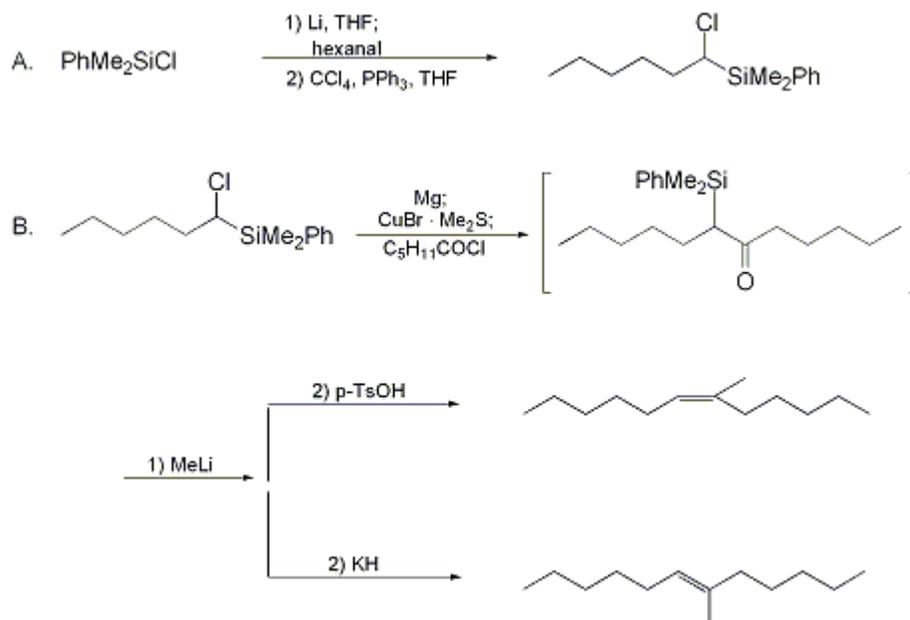
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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STEREOSELECTIVE ALKENE SYNTHESIS via 1-CHLORO-1-[(DIMETHYL)PHENYLSILYL]ALKANES AND α -(DIMETHYL)PHENYLSILYL KETONES: 6-METHYL-6-DODECENE



Submitted by Anthony G. M. Barrett, John A. Flygare, Jason M. Hill, and Eli M. Wallace¹.
Checked by Shuyong Chen and Amos B. Smith, III.

1. Procedure

A. *1-Chloro-1-[(dimethyl)phenylsilyl]hexane*. An oven-dried, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar and a rubber septum, is purged with [argon](#) via an inlet hose equipped with a needle and an outlet hose equipped with a needle leading to an oil bubbler. The flask is charged with 250 mL of dry [tetrahydrofuran](#) (THF) ([Note 1](#)) and 7.37 g of [lithium](#) wire (1.06 mol) cut into small pieces ([Note 2](#)). After cooling the reaction mixture to 0°C in a CryoCool bath ([Note 3](#)), 30 g (29.1 mL, 176 mmol) of [phenyldimethylsilyl chloride](#) is added via syringe and the reaction mixture is stirred at 0°C for 16 hr ([Note 4](#)).² Within 0.5 hr, the reaction mixture turns from clear and colorless to dark red. An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a rubber septum, is purged with [argon](#) via an inlet needle and an outlet needle to an oil bubbler, charged with 16.78 g (20.0 mL, 167.5 mmol) of [hexanal](#) and 400 mL of dry THF ([Note 5](#)), and cooled to -78°C with a dry ice-acetone bath. The solution of [phenyldimethylsilyllithium](#) in THF prepared above is then added via cannula. After addition, the red reaction mixture is warmed to 0°C and stirred for 1 hr. A saturated aqueous [ammonium chloride](#) solution (250 mL) is then added in one portion and the resulting mixture is poured into a 2-L separatory funnel containing 250 mL of [diethyl ether](#). The organic layer is washed with saturated aqueous [ammonium chloride](#) (3 × 250-mL) and brine (250 mL), dried over MgSO_4 , and concentrated under reduced pressure. Purification via flash column chromatography (silica gel 230-400 mesh, 450 g of oil, loaded with hexanes, eluant 10:1 hexanes:[diethyl ether](#)) yields a total of 32.6 g (82%) of *1-[(dimethyl)phenylsilyl]-1-hexanol* as a colorless oil (a second column with 250 g of silica gel may be required for rechromatography of tailing fractions).

An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 500 mL of dry THF and *1-[(dimethyl)phenylsilyl]-1-hexanol* (32.6 g, 138 mmol). [Carbon tetrachloride](#) (53.20 g, 33.4 mL, 345.9 mmol) and [triphenylphosphine](#) (54.30 g, 207 mmol) are added and the flask is equipped with a condenser and a rubber septum and purged with [argon](#) via inlet needle and outlet needle to an oil bubbler.³ The reaction mixture is heated to reflux under [argon](#) for 12 hr. After the reaction

mixture is allowed to cool to room temperature, the volatiles are removed under reduced pressure, and the residue is triturated with hexanes (3 × 300-mL). Concentration of the extracts under reduced pressure and purification via flash column chromatography (silica gel 230-400 mesh, 450 g, eluant hexanes) yields 30.4–31.7 g of 1-chloro-1-[(dimethyl)phenylsilyl]hexane (71–74% from hexanal) as a colorless oil (Note 6)

B. *6-Methyl-6-dodecene*. An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a condenser, a 125-mL, pressure-equalizing addition funnel, a magnetic stirring bar, and a rubber septum. The flask is purged with argon and charged with 96.23 g (373 mmol) of magnesium bromide etherate (MgBr₂·Et₂O) (Note 2) and 250 mL of dry THF. A total of 26.67 g (682 mmol) of potassium metal, freshly rinsed with 60 mL of dry THF, is added piecewise (Note 7). The reaction mixture is heated at reflux with stirring for 3 hr, at which time the activated magnesium has formed as a finely divided black powder (Note 8). The activated magnesium is allowed to cool and settle. The supernatant THF layer is carefully transferred via cannula into a 500-mL Erlenmeyer flask containing 250 mL of isopropyl alcohol. The activated magnesium is rinsed with dry diethyl ether (2 × 200-mL) and diluted with 100 mL of dry diethyl ether all via cannula. The crude 1-chloro-1-[(dimethyl)phenylsilyl]hexane (31.58 g, 124 mmol) is diluted with 100 mL of dry diethyl ether and transferred via cannula to the addition funnel. The ethereal solution of the α-silyl chloride is added to the activated magnesium slurry in diethyl ether slowly in portions causing the reaction mixture to reflux gently (Note 9). Upon completion of the addition, the reaction mixture is stirred for 15 min (Note 10).

An oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and a rubber septum. The flask is charged with 25.61 g of copper bromide-dimethyl sulfide complex (124 mmol) and 250 mL of dry diethyl ether, and the resulting slurry is cooled to –78°C with a dry ice-acetone bath. The Grignard reagent solution prepared above is added to the copper bromide-dimethyl sulfide slurry via cannula (Note 11). The residual activated magnesium is rinsed once with 200 mL of dry diethyl ether, and the supernatant layer is transferred via cannula to the copper bromide-dimethyl sulfide slurry (Note 12). The reaction mixture is slowly warmed to –10°C, and then 16.78 g (17.42 mL, 125 mmol) of hexanoyl chloride is added dropwise via syringe after which the reaction mixture is warmed to room temperature. After stirring for 3 hr, the reaction mixture is filtered through a 75-g layer of Celite 545 (Note 13) and the filter cake rinsed with three 100-mL portions of diethyl ether. Concentration of the filtrate under reduced pressure yields the α-silyl ketone which is utilized without further purification (Note 14).

(1) Acidic Elimination:

An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a 125-mL pressure-equalizing addition funnel, a magnetic stirring bar, and a rubber septum, and the system is purged with argon. The flask is charged with the crude α-silyl ketone prepared above and 500 mL of dry THF. Via cannula, a 125-mL (175 mmol) portion of a 1.4 M solution of methyllithium in hexanes is transferred to the addition funnel. After the α-silyl ketone solution is cooled to –78°C with a dry ice-acetone bath, the methyllithium solution is added dropwise over approximately 1 hr, and the reaction mixture is stirred for 0.5 hr at –78°C. A second, oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and a rubber septum. The second flask is charged with 47.39 g (249 mmol) of p-toluenesulfonic acid monohydrate and 100 mL of dry THF, and purged with argon. The β-alkoxysilane solution prepared above is transferred to the flask containing the solution of p-toluenesulfonic acid monohydrate in THF via cannula and stirred for 2 hr. The reaction mixture is then poured into a separatory funnel containing a biphasic mixture of 500 mL of saturated aqueous sodium bicarbonate and 250 mL of diethyl ether. The resulting organic layer is washed with saturated aqueous sodium bicarbonate (3 × 250-mL) and brine (250 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification of the residue via flash column chromatography (silica gel 230-400 mesh, 450 g, eluant hexanes) yields 11.31–11.75 g of (Z)-6-methyl-6-dodecene (50–52% from the α-silyl chloride) as a 92:8 Z/E ratio of isomers (Note 15) and (Note 16).

(2) Basic Elimination:

An oven-dried, 1-L, three-necked flask is equipped with a 125-mL pressure-equalizing addition funnel, a magnetic stirring bar, and a rubber septum. The flask is purged with argon and is charged with

the crude α -silyl ketone (from 30.00 g, 118 mmol of α -silyl chloride) and dry THF (500 mL). Methyllithium (1.4 M, 118 mL, 165 mmol) is added to the addition funnel via cannula. The α -silyl ketone solution is cooled to -78°C with a dry ice-acetone bath, and methyllithium is added dropwise over approximately 1 hr after which the reaction mixture is stirred for 0.5 hr. A second, oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar and a rubber septum, is charged with 27 g of potassium hydride (35% wt/wt dispersion in oil which is rinsed with three 100-mL portions of dry diethyl ether), and diluted with 100 mL of dry THF, and 0.200 g of 18-crown-6 (0.76 mmol) is added. The β -alkoxysilane solution prepared above is added to the potassium hydride slurry via cannula, and the mixture is stirred for 16 hr. Excess potassium hydride is quenched with isopropyl alcohol (~50 mL) until no further hydrogen gas is evolved (Note 17). Saturated aqueous ammonium chloride (250-mL) is added to the reaction mixture which is then combined with 250 mL of diethyl ether in a separatory funnel. The organic layer is washed successively with three 250-mL portions of saturated aqueous ammonium chloride and 250 mL of brine, dried over MgSO_4 , and concentrated under reduced pressure. Purification of the residue via flash column chromatography (silica gel 230-400 mesh, 450 g, eluant hexanes) provides 11.19–11.62 g (E)-6-methyl-6-dodecene, (52–54% from the α -silyl chloride) as a 95:5 E/Z ratio of isomers (Note 15) and (Note 18).

2. Notes

1. Both THF and diethyl ether were obtained from Mallinckrodt Inc. Before use they were dried by distillation from sodium metal and benzophenone under an atmosphere of nitrogen.
2. Lithium wire (3.2 mm diam.), carbon tetrachloride, triphenylphosphine, $\text{MgBr}\cdot\text{Et}_2\text{O}$, copper bromide-dimethyl sulfide complex, hexanoyl chloride, methyllithium, p-toluenesulfonic acid monohydrate, potassium hydride, and 18-crown-6 were purchased from Aldrich Chemical Company, Inc. and used without further purification.
3. The CryoCool bath may be obtained from CryoCool CC-80II Neslab Instruments, Inc. Portsmouth, N.H. 03801, USA. The reaction may be run in an ice bath under supervision.
4. Phenyldimethylsilyl chloride was purchased from the Petrarch Chemical Company and used without further purification.
5. Hexanal was purchased from the Aldrich Chemical Company Inc. and distilled (bp 131°C) before use.
6. The product exhibits the following properties: IR (film) cm^{-1} : 3016, 2968, 2940, 2866, 1465, 1430, 1253, 1117; ^1H NMR (400 MHz, CDCl_3) δ : 0.40 (s, 3 H), 0.41 (s, 3 H), 0.85 (t, 3 H, $J = 7.1$), 1.17–1.34 (m, 5 H), 1.58–1.68 (m, 3 H), 3.42 (dd, 1 H, $J = 2.9, 11.2$), 7.35–7.39 (m, 3 H), 7.54–7.56 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ : -5.7, -4.6, 14.0, 22.5, 27.4, 31.0, 33.1, 51.2, 127.8, 129.5, 134.1, 136.0; high resolution mass spectrum (CI, NH_3) m/z 272.1615 [$(\text{M}^+\text{NH}_4)^+$; calcd for $\text{C}_{14}\text{H}_{27}\text{NSiCl}$: 272.1602].
7. Potassium metal, purified, was purchased from J.T. Baker Chemical Company. **CAUTION: Potassium metal is pyrophoric and reacts violently with water.**
8. Activated magnesium is prepared as described in *Org. Synth., Coll. Vol. VI* **1988**, 845.
9. **CAUTION: The reaction is exothermic.**
10. The Grignard solution may be stored overnight under argon.
11. Care should be taken not to add excess activated magnesium, although a small amount does not seem to affect cuprate formation.
12. Activated magnesium is quenched by the addition of isopropyl alcohol until hydrogen gas is no longer evolved. **CAUTION: Hydrogen gas is flammable and should be vented into a fume hood.**
13. The Celite used is NOT the acid-washed reagent. Acid-washed Celite will cause some desilylation of the α -silyl ketone intermediate.
14. The α -silyl ketone may be stored overnight either under vacuum or under argon at -20°C .
15. The ratio of isomers was determined by GC/MS (Hewlett Packard 5890 Series II Gas Chromatograph/5870 Series Mass Selective Detector).
16. The product exhibits the following properties: IR (film) cm^{-1} : 2966, 2935, 2867, 1460, 1379; ^1H NMR (500 MHz, CDCl_3) δ : 0.89 (t, 3 H, $J = 7.1$, overlapping 0.88 (t, 3 H, $J = 6.9$)), 1.23–1.39 (m, 12 H), 1.58 (s, 0.26 H, E-methyl), 1.67 (s, 2.74 H, Z-methyl), 1.94–2.01 (m, 4 H), 5.11 (t, 1 H, $J = 7.1$); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.10, 22.63, 22.64, 23.40, 27.75, 27.77, 29.80, 31.60, 31.70, 31.80, 125.30, 135.40; high resolution mass spectrum (CI, NH_3) m/z 182.2029 [(M) $^+$; calcd for $\text{C}_{13}\text{H}_{26}$: 182.2035].
17. **CAUTION: Hydrogen gas is flammable and should be vented into a fume hood.**

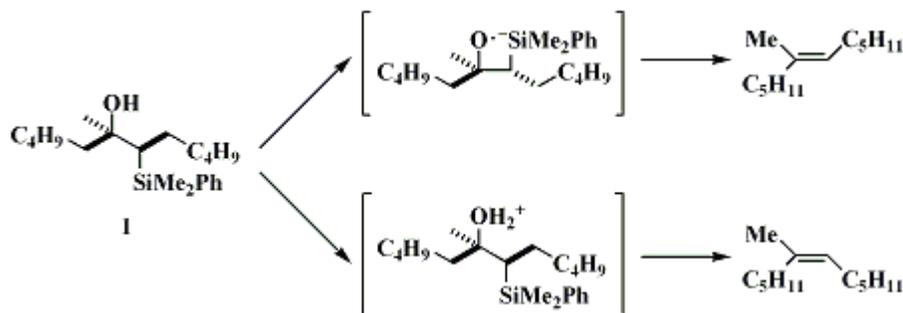
18. The product exhibits the following properties: IR (film) cm^{-1} : 2968, 2936, 2867, 1460, 1380; ^1H NMR (500 MHz, CDCl_3) δ : 0.89 (t, 6 H, $J = 7.0$), 1.21–1.41 (m, 12 H), 1.58 (s, 2.73 H, E-methyl), 1.67 (s, 0.27 H, Z-methyl), 1.94–1.99 (m, 4 H), 5.11 (t, 1 H, $J = 7.1$); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.1, 15.8, 22.6, 27.7, 27.9, 29.6, 29.9, 31.6, 31.7, 31.8, 39.7, 124.6, 135.1; high resolution mass spectrum (CI, NH_3) m/z 182.2026 [(M) $^+$]; calcd for $\text{C}_{13}\text{H}_{26}$: 182.2035].

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

The acid or base elimination of a diastereoisomerically pure β -hydroxysilane, **1**, (the Peterson olefination reaction⁴ For reviews see: ^{5,6,7,8,9}) provides one of the very best methods for the stereoselective formation of alkenes. Either the E- or Z-isomer may be prepared with excellent geometric selectivity from a single precursor (Scheme 1). The widespread use of the Peterson olefination reaction in synthesis has been limited, however, by the fact that there are few experimentally simple methods available for the formation of diastereoisomerically pure β -hydroxysilanes.^{10,11,12,13} Also see: ^{14,15,16,17,18,19} One reliable route is the Cram controlled addition of nucleophiles to α -silyl ketones,^{18,19} but such an approach is complicated by difficulties in the preparation of (α -silylalkyl)lithium species or the corresponding Grignard reagents. These difficulties have been resolved by the development of a simple method for the preparation and reductive acylation of (α -chloroalkyl)silanes.²⁰



The procedure shown here describes the preparation of α -silyl ketones from aldehydes and acyl chlorides. The α -silyl ketones undergo Cram addition of various nucleophiles to produce diastereoselectively β -hydroxysilanes. These compounds are then subjected directly to elimination in situ under basic or acidic conditions to produce the corresponding alkenes.

References and Notes

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

hexanes

brine

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

potassium (7440-09-7)

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

Methyl lithium (917-54-4)

argon (7440-37-1)

hexanoyl chloride (142-61-0)

triphenylphosphine (603-35-0)

magnesium bromide etherate

α -silyl chloride (13465-78-6)

18-Crown-6 (17455-13-9)

potassium hydride (7693-26-7)

Hexanal (66-25-1)

p-toluenesulfonic acid monohydrate (6192-52-5)

α -silyl ketone

6-METHYL-6-DODECENE

phenyldimethylsilyl chloride (768-33-2)

phenyldimethylsilyllithium

1-[(Dimethyl)phenylsilyl]-1-hexanol (125950-71-2)

1-Chloro-1-[(dimethyl)phenylsilyl]hexane (135987-51-8)

(Z)-6-Methyl-6-dodecene (101165-44-0)

(E)-6-methyl-6-dodecene (101146-61-6)

copper bromide-dimethyl sulfide (54678-23-8)