



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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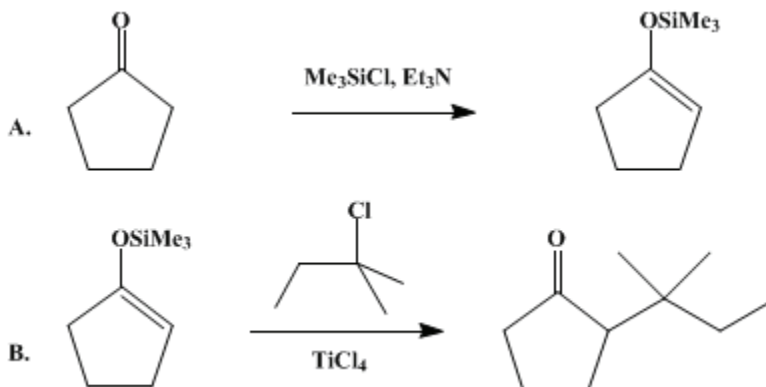
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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***α*-tert-ALKYLATION OF KETONES: 2-*tert*-PENTYLCYCLOPENTANONE**

[Cyclopentanone, 2-*tert*-pentyl-]



Submitted by M. T. Reetz, I. Chatziiosifidis, F. Hübner, and H. Heimbach¹.
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1. Procedure

A. *1-Trimethylsilyloxycyclopentene*.² A 1-L, two-necked, round-bottomed flask is equipped with a mechanical stirrer and a reflux condenser having a drying tube (calcium chloride). The flask is charged with 200 mL of dimethylformamide (Note 1), 45 g (0.54 mol) of cyclopentanone (Note 2), 65.5 g (0.6 mol) of chlorotrimethylsilane (Note 2), and 185 mL (1.33 mol) of triethylamine (Note 1), and the mixture is refluxed for 17 hr (Note 3). The mixture is cooled, diluted with 350 mL of pentane, and washed four times with 200-mL portions of cold saturated aqueous sodium hydrogen carbonate. The aqueous phases are extracted twice with 100-mL portions of pentane and the combined organic phases are washed rapidly with 100 mL of ice-cold aqueous 2 *N* HCl and immediately thereafter with a cold saturated solution of sodium hydrogen carbonate. After the mixture has been dried over anhydrous magnesium sulfate, the pentane is removed by rotary evaporation. Distillation of the oily residue at 60° C (12 mm) using a 20-cm Vigreux column affords 50.1–51.6 g (60–62%) of 1-trimethylsilyloxycyclopentene (1) as a colorless liquid (Note 4).

B. *2-tert-Pentylcyclopentanone*. A dry, 250-mL, three-necked, round-bottomed flask is fitted with a gas inlet, a gas bubbler, rubber septum, and magnetic stirrer. The apparatus is flushed with dry nitrogen or argon and charged with 120 mL of dry dichloromethane (Note 5), 15.6 g (0.10 mol) of 1-trimethylsilyloxycyclopentene and 11.7 g (0.11 mol) of 2-chloro-2-methylbutane (Note 6). The mixture is cooled to –50° C (Note 7) and a cold (–50° C) solution of 11 mL (0.10 mol) of titanium tetrachloride (Note 8) in 20 mL of dichloromethane is added within 2 min through the rubber septum with the aid of a syringe. During this operation rapid stirring and cooling is maintained. Sunlight should be avoided. The reddish-brown mixture is stirred at the given temperature for an additional 2.5 hr and is then rapidly poured into 1 L of ice-water (Note 9). After the addition of 400 mL of dichloromethane, the mixture is vigorously shaken in a separatory funnel; the organic phase is separated and washed twice with 400-mL portions of water. The aqueous phase of the latter two washings is extracted with 200 mL of dichloromethane; the organic phases are combined and dried over anhydrous sodium sulfate. The mixture is concentrated using a rotary evaporator and the residue is distilled at 80° C (12 mm) (Note 10) to yield 9.2–9.5 g (60–62%) (Note 11) of 2-*tert*-pentylcyclopentanone as a colorless oil (Note 12).

2. Notes

1. Dimethylformamide and triethylamine were purchased from Baker (Baker Analyzed Reagent) and

used without further purification.

2. **Cyclopentanone** and **chlorotrimethylsilane** were purchased from Aldrich Chemical Company and used without further purification.

3. According to the original procedure of House,² only 4 hr is needed, affording a 59% yield. However, the submitters found that an increase in reaction time raises the yield.

4. The spectral properties of the compound are as follows: ¹H NMR (CCl₄) δ: 0.2 (s, 9 H), 1.6–2.4 (m, 6 H), 4.4 (m, 1 H); IR (film) 1645 cm⁻¹ (lit.² 1645 cm⁻¹).

5. Reagent-grade **dichloromethane** is dried by passing over a column of aluminum oxide (activity I).

6. The submitters purchased **2-chloro-2-methylbutane** from Eastman Kodak Company. The checkers prepared the halide as follows. A separatory funnel was charged with 21.5 mL (0.2 mol) of **2-methyl-2-butanol** and 100 mL of concentrated **hydrochloric acid**. The mixture was shaken vigorously with periodic venting for 10 min. The layers were separated and the **2-chloro-2-methylbutane** layer (upper) was washed several times with equal volumes of cold water. The product was dried over **calcium chloride** and distilled, bp 85°C.

7. The precise temperature is not critical. The checkers observed that the reaction proceeds in about the same time and yield at -78°C. However, at temperatures above -40°C a drop in yield may occur.

8. The **titanium tetrachloride** should be clean, colorless, and free of **hydrogen chloride**. The checkers used material freshly distilled in an **argon** atmosphere.

9. If **sodium bicarbonate** is used, large amounts of titanium oxide-containing emulsions tend to form that hamper the purification of the product.

10. The by-products consist of volatile **cyclopentanone** and an unknown high-boiling material, so that rapid vacuum transfer at room temperature and 0.02 mm is also possible. Extremely slow distillation at high temperatures should be avoided. The value of 72°C (2.2 mm) cited in the literature³ seems to be in slight error.

11. The submitters ran the reaction on a 0.5 scale and reported yields of 63–68%.

12. The product is >96% pure as checked by gas chromatography (4% UCON LB 550X, Chromasorb G, AW-DMCS 80–100 mesh, 130°C). The spectral properties are as follows: IR (neat) cm⁻¹: 3050–2800, 1735, 1460, 1150; ¹H NMR (CCl₄) δ: 0.80 (*J* = 6 Hz, CH₃ of the ethyl group, which partially overlaps with the signals of the other two diastereotopic methyl groups), 0.82 (s), 0.92 (s), 1.15–2.25 (m); ¹³C NMR (CDCl₃) δ: 7.78, 19.87, 23.72 (slightly broad), 25.57, 32.62, 34.70, 40.02, 55.39, 219.57.

3. Discussion

This procedure solves the long-pending problem of *α-tert*-alkylation of ketones. The generality is shown by the fact that a wide variety of structurally different ketones can be alkylated via the corresponding silyl enol ethers with good yields.⁴ Variation of the alkylating agent is also possible, branched and cyclic tertiary alkyl halides reacting position specifically without signs of rearrangement.⁴ Chemoselectivity studies reveal that esters, aromatic groups, and primary alkyl halide moieties are tolerated.⁴ In the case of a sensitive enol ether such as that derived from **acetone**, **titanium tetrachloride** should be replaced by more mild Lewis acids such as **zinc chloride**, although the yields are lower.⁵ Finally, it should be noted that any S_N1-reactive alkyl halide is likely to be a suitable alkylating agent in Lewis acid-promoted *α*-alkylation of carbonyl compounds. Indeed, aryl-activated secondary alkyl halides and acetates react in the same way.⁶ Heteroatom substituted alkyl halides and acetates also react smoothly with enol silanes in the presence of ZnX₂.^{4,6} Generally, such alkylating agents are unsuitable in classical enolate chemistry because of the ease of hydrogen halide elimination and/or the failure to react regioselectively. The methods are thus complementary.

A related *tert*-butylation procedure in which the silyl enol ether is added to a mixture of **titanium tetrachloride** and **tert-butyl chloride** gives rise to distinctly lower yields.^{7,8} This is also the case if the tertiary halide is added to a mixture of silyl enol ether and **titanium tetrachloride**.⁵

A number of alternative multistep procedures for the synthesis of *α-tert*-alkyl ketones are known, none of which possess wide generality. A previous synthesis of **2-tert-pentylcyclopentanone** involved reaction of ***N*-1-cyclopentenylpyrrolidine** with **3-chloro-3-methyl-1-butyne** and reduction of the resulting **acetylene** (overall yield 46%).³ However, all other enamines tested afford much lower yields.³ Cuprate addition to unsaturated ketones may be useful in certain cases.⁹ Other indirect methods have been briefly reviewed.⁵

References and Notes

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Appendix

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

calcium chloride (10043-52-4)

acetylene (74-86-2)

hydrogen chloride,
hydrochloric acid,
HCl (7647-01-0)

sodium bicarbonate,
sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

zinc chloride (7646-85-7)

tert-Butyl chloride (507-20-0)

Cyclopentanone (120-92-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

2-Methyl-2-butanol (75-85-4)

dimethylformamide (68-12-2)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

argon (7440-37-1)

2-chloro-2-methylbutane (594-36-5)

CHLOROTRIMETHYLSILANE (75-77-4)

1-Trimethylsiloxycyclopentene (19980-43-9)

2-tert-Pentylcyclopentanone,
Cyclopentanone, 2-tert-pentyl- (25184-25-2)

N-1-cyclopentenylpyrrolidine

3-chloro-3-methyl-1-butyne (1111-97-3)