



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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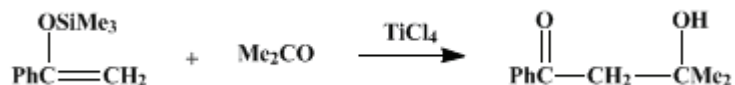
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 8, p.323 (1993); Vol. 65, p.6 (1987).

3-HYDROXY-3-METHYL-1-PHENYL-1-BUTANONE BY CROSSED ALDOL REACTION

[1-Butanone, 3-hydroxy-3-methyl-1-phenyl-]



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Checked by Kathleen Hug and Clayton H. Heathcock.

1. Procedure

A 500-mL, three-necked flask is fitted with a stirring bar, a rubber stopper, a 100-mL pressure-equalizing dropping funnel, and a three-way stopcock that is equipped with a balloon of argon gas (Note 1). The flask is charged with 140 mL of dry methylene chloride (Note 2) and cooled in an ice bath. Titanium tetrachloride (11.0 mL) (Note 3) is added by a syringe with stirring by a magnetic stirrer, and a solution of 6.5 g of acetone in 30 mL of methylene chloride is added dropwise over a 5-min period. On completion of this addition a solution of 19.2 g of acetophenone trimethylsilyl enol ether (Note 4) in 15 mL of methylene chloride (Note 5) is added dropwise over a 10-min period, and the mixture is stirred for 15 min.

The reaction mixture is poured into 200 mL of ice water with vigorous stirring and the organic layer is separated. The aqueous layer is extracted with two 30-mL portions of methylene chloride. The combined methylene chloride extracts are washed with two 60-mL portions of a 1 : 1 mixture of saturated aqueous sodium bicarbonate and water, and then with brine. The methylene chloride solution is dried over sodium sulfate and the methylene chloride is removed using a rotary evaporator.

The residue is dissolved in 30 mL of benzene, and the solution is transferred to a chromatographic column (50-mm diameter) consisting of 600 mL of silica gel. The product is eluted sequentially with (a) 1 L of 4 : 1 (v/v) hexane : ethyl acetate and (b) 1.5 L of 2 : 1 (v/v) hexane : ethyl acetate (flash chromatography) (Note 6).

The initial ca. 900 mL of the eluent is discarded. Concentration of the later fractions (ca. 1.3 L) under reduced pressure yields the pure product as an oil (Note 7). The total yield is 12.2–12.8 g (70–74%).

2. Notes

- All apparatuses should be oven-dried before use.
- Methylene chloride was purified by distillation from phosphorus pentoxide, then from calcium hydride, and was stored over Linde 4A molecular sieves.
- Freshly distilled titanium tetrachloride (bp 152–153°C) was used. The checkers distilled the titanium tetrachloride from calcium hydride.
- The silyl enol ether may be obtained from the Fluka Chemical Corp., 255 Oser Avenue, Hauppauge, NY 11788. Alternatively, it may be prepared by the following modification of the procedure of Walshe and co-workers.² The Walshe procedure is followed exactly with 36 g (0.30 mol) of acetophenone, 41.4 g (0.41 mol) of triethylamine, 43.2 g (0.40 mol) of chlorotrimethylsilane, 60 g (0.40 mol) of sodium iodide, and 350 mL of acetonitrile. After extraction, the organic layer is dried over potassium carbonate and then concentrated with a rotary evaporator under reduced pressure. The crude product is a mixture of 97% of the desired silyl enol ether and 3% of acetophenone, as shown by gas chromatography. The crude product is distilled in a Claisen flask at a pressure of about 40 mm. After a small forerun (ca. 3 g), 52.3 g (91%) of silyl enol ether, bp 124–125.5°C, is obtained. The purity of this material is approximately 98%, as judged by gas chromatography and ¹H NMR spectroscopy.

5. Submitters report using 60 mL of hexane.

6. 3-Hydroxy-3-methyl-1-phenyl-1-butanone is too unstable to be purified by distillation, and decomposes to acetophenone and acetone.

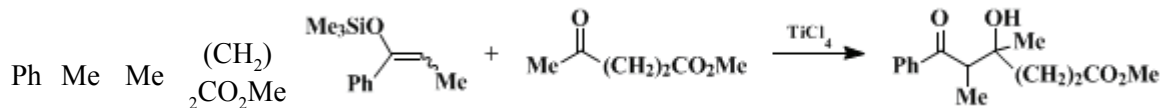
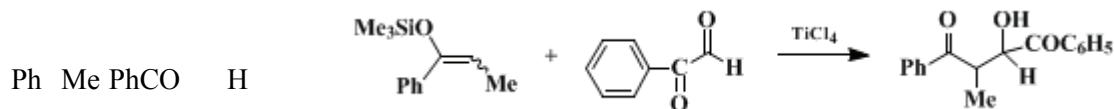
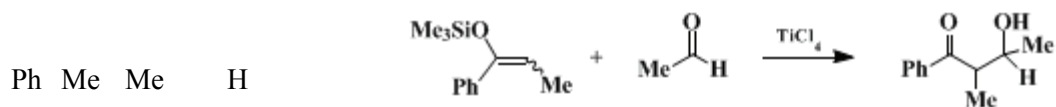
7. The initial fractions are sometimes contaminated with a less polar by-product. These fractions are condensed and purified again by column chromatography using 6 : 1 (v/v) hexane : ethyl acetate and then 2 : 1 (v/v) hexane : ethyl acetate as developing solvents. The NMR spectrum (CDCl₃) shows singlets at δ 1.33 (6 H, CH₃), 3.12 (2 H, CH₂), 4.12 (broad, OH) and complex signals between 7.24–8.01 (5 H).

3. Discussion

This procedure illustrates a general method for the preparation of crossed aldols. The aldol reaction between various silyl enol ethers and carbonyl compounds proceeds smoothly according to the same procedure (see Table 1). Silyl enol ethers react with aldehydes at -78°C, and with ketones near 0°C.³ Note that the aldol reaction of silyl enol ethers with ketones affords good yields of crossed aldols, which are generally difficult to prepare using lithium or boron enolates. Lewis acids such as tin tetrachloride and boron trifluoride etherate also promote the reaction; however, titanium tetrachloride is generally the most effective catalyst.

TABLE I
PREPARATION OF CROSSED ALDOLS

R ¹	R ²	R ³	R ⁴	Substituents	Yield of Aldols (%)
$\text{Me}_3\text{SiO}-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)- + \text{R}^3-\text{C}(=\text{O})-\text{R}^4 \xrightarrow{\text{TiCl}_4} \text{R}^1-\text{C}(=\text{O})-\text{C}(\text{R}^2)-\text{C}(\text{OH})(\text{R}^3)-\text{R}^4$					
-	(CH ₂) ₄	Me ₂ CH	H		92
-	(CH ₂) ₃	PhCH ₂	PhCH ₂		64
-	(CH ₂) ₃	PhCH ₂	H		95
Ph	H	Me ₂ CH	H		94



Ketene alkyl silyl acetals may also be used as nucleophiles for the formation of β -hydroxy esters.⁴ The present reaction can be carried out equally well on large or small (mmole) scales. For small scale applications, it is convenient to prepare a stock solution of titanium tetrachloride in methylene chloride. (A rubber stopper is gradually destroyed by titanium tetrachloride; therefore, a Teflon stopper should be used.) Titanium tetrachloride also promotes the aldol-type reaction between silyl enol ethers and acetals to give β -alkoxy carbonyl compounds.⁵

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 8, 210](#)

References and Notes

1. Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-Ku, Tokyo 113, Japan.
2. Walshe, N. D. A.; Goodwin, G. B. T.; Smith, G. C.; Woodward, F. E. *Org. Synth., Coll. Vol. VIII* **1993**, 1.
3. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
4. Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 989.
5. Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15.

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

silica gel

brine

acetophenone trimethylsilyl enol ether

[potassium carbonate](#) (584-08-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

Acetophenone (98-86-2)

sodium iodide (7681-82-5)

methylene chloride (75-09-2)

tin tetrachloride (7646-78-8)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

argon (7440-37-1)

boron trifluoride etherate (109-63-7)

calcium hydride (7789-78-8)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus pentoxide (1314-56-3)

3-Hydroxy-3-methyl-1-phenyl-1-butanone,
1-Butanone, 3-hydroxy-3-methyl-1-phenyl- (43108-74-3)