



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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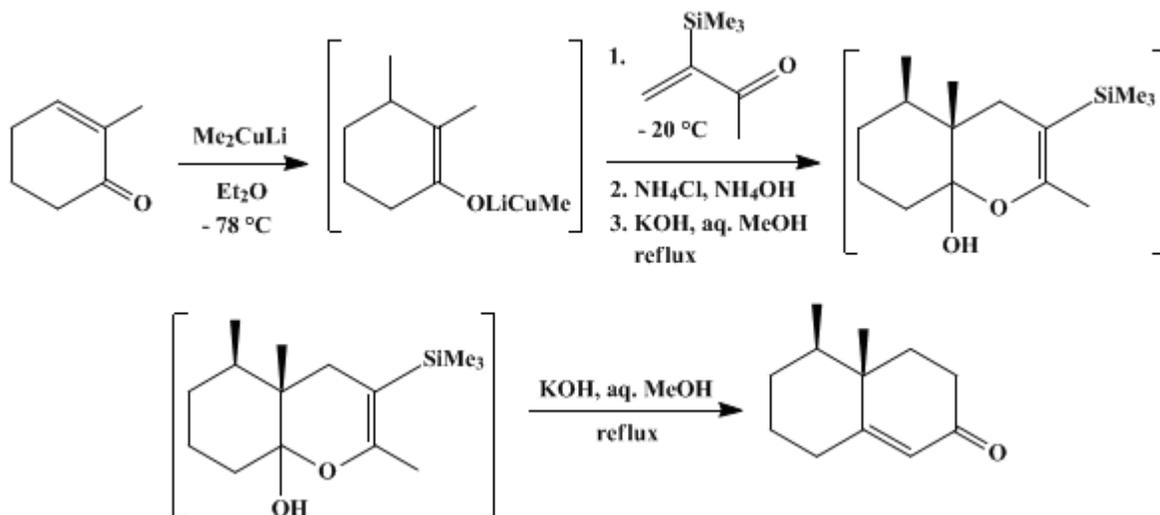
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.666 (1988); Vol. 58, p.158 (1978).

3-TRIMETHYLSILYL-3-BUTEN-2-ONE AS MICHAEL ACCEPTOR FOR CONJUGATE ADDITION-ANNELETION: *cis*-4,4*a*,5,6,7,8-HEXAHYDRO-4*a*,5-DIMETHYL-2(3*H*)-NAPHTHALENONE

[2(3*H*)-Naphthalenone, 4,4*a*,5,6,7,8-hexahydro-, 4*a*,5-dimethyl-, *cis*-, (±)-]



Submitted by Robert K. Boeckman, Jr.¹, David M. Blum, and Bruce Ganem².
Checked by Seiichi Inoue and Robert M. Coates.

1. Procedure

A 100-ml., three-necked flask fitted with an argon inlet, a rubber septum, a magnetic stirrer, and a 25-ml. pressure-equalizing dropping funnel (Note 1) is charged with 1.9 g. (0.010 mole) of copper(I) iodide (Note 2) and 40 ml. of anhydrous diethyl ether. The mixture is stirred and cooled in an ice bath while 10 ml. (0.02 mole) of a 2 *M* solution of methyllithium in ether (Note 3) is injected through the septum into the flask. The resulting straw-yellow solution of lithium dimethylcuprate is cooled to -78° in an acetone-dry ice bath, and a solution of 1.10 g. (0.0100 mole) of 2-methyl-2-cyclohexenone (Note 4) in 10 ml. of ether is injected into the flask, with stirring, over a 2–3 minute period. The cooling bath is allowed to warm slowly to about -20° over *ca.* 1 hour (Note 5) before a solution of 2.13 g. (0.0150 mole) of 3-trimethylsilyl-3-buten-2-one (Note 6) in 10 ml. of ether is added dropwise over 5 minutes. The stirred mixture is cooled between -20° and -30° for another hour by occasional addition of dry ice to the cooling bath. The contents of the flask are poured into 100 ml. of an ammonium chloride–ammonium hydroxide buffer solution (Note 7) that has been cooled to 0° (Note 8). The ether layer is extracted with two or three additional 100-ml. portions of buffer solution (Note 9), and the combined aqueous solutions are extracted with two 75-ml. portions of ether. The combined ether extracts are washed once with saturated sodium chloride, dried with anhydrous magnesium sulfate, and evaporated at reduced pressure.

The residual yellow liquid (2.7–3.4 g.) is dissolved in a mixture of 40 ml. of methanol and 5 ml. of 4% aqueous potassium hydroxide, then heated at reflux under an argon atmosphere for 4 hours. The methanol is evaporated from the cooled solution under reduced pressure, and the residue is dissolved in 50 ml. of ether. The ether solution is washed once with water, dried with anhydrous magnesium sulfate, and evaporated. Distillation of the residual liquid with a Kugelrohr apparatus (Note 10) at 0.5 mm. affords, after separation of a 0.1–0.2 g. forerun collected at an oven temperature of 50° , 0.76–1.02 g. (43–57%) of the octalone at an oven temperature of 85 – 90° (Note 11) and (Note 12).

2. Notes

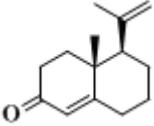
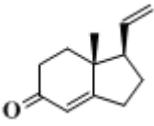
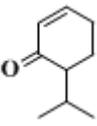
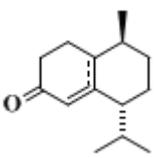
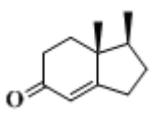
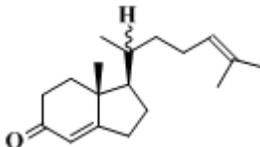
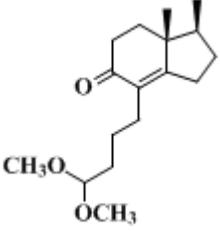
1. The apparatus is flamed dry and maintained under an atmosphere of argon during the reactions.
 2. The submitters purified copper(I) iodide by precipitation from a concentrated aqueous solution of potassium iodide as described by Kauffman and Teter,³ and dried it at 100° over phosphorus pentoxide at high vacuum. Copper(I) iodide from Fisher Scientific Company was used by the checkers after drying at high vacuum.
 3. A solution of methyllithium in ether may be purchased from Ventron Corporation. Directions for the preparation of ethereal methyllithium from methyl bromide are also available [*Org. Synth.*, **Coll. Vol. 6**, 901 (1988)]. The solution should be standardized before use by a titration procedure such as that of Watson and Eastham⁴ [*Org. Synth.*, **Coll. Vol. 6**, 121 (1988)].
 4. 2-Methyl-2-cyclohexenone is prepared by the method in *Org. Synth.*, **Coll. Vol. 4**, 162 (1963).
 5. This warming operation was effected by the checkers by removing the original cooling bath and replacing it with another one that had been cooled to -30°. The bath temperature was then allowed to rise to -20° over *ca.* 1 hour.
 6. 3-Trimethylsilyl-3-buten-2-one was prepared by the method in *Org. Synth.*, **Coll. Vol. 6**, 1033 (1988).
 7. The buffer solution is prepared by adding enough concentrated ammonium hydroxide to 10% ammonium chloride to raise the pH to 8.
 8. The checkers recommend that the mixture be stirred for 30 minutes at 0° to dissolve the pasty precipitate which forms and facilitate the following extractions.
 9. The extractions with buffer solution should be continued until the characteristic blue color of copper (II) is no longer visible in the aqueous layer.
 10. Kugelrohr distillation ovens produced by Büchi Glasapparatefabrik are available from Brinkmann Instruments, Inc.
 11. The checkers collected the 0.1–0.2 g. forerun at an oven temperature of about 70–85° and the main fraction over a 5–10° range between about 105 and 120°. Combination of the main fraction from two runs gave 2.03 g., which, on redistillation with the Kugelrohr apparatus at 0.4 mm., provided a 0.2 g. forerun collected with an oven temperature of 45–53° and a main fraction totalling 1.5 g., collected at 88–93°.
 12. The product has the following spectral properties: IR (thin film) cm^{-1} : 2960 (C-H), 1685 (C=O), 1620 (C=C); ¹H NMR (CCl₄), δ (multiplicity, number of protons, assignment): 0.92 (m, 3H, CH₃), 1.11 (s, 3H, CH₃), 5.64 (broad s, 1H, vinyl-H), minor absorption of an unidentified impurity at 5.75 (m, 0.1–0.2H, vinyl-H).
- A GC analysis of the product by the submitters using a 1.8-m. column packed with 20% Carbowax 20 M suspended on Chromosorb P and operated at 150° with a flow rate of 30 ml. per minute showed a peak for the major component having a retention time of 16 minutes and two minor peaks having retention times of 4 and 7 minutes, with relative areas amounting to 6% and 2% of the major peak, respectively. The stereochemical purity of the product was shown to be >95% *cis* by the submitters by GC analysis using a 50-ft. capillary column coated with Carbowax 20 M and heated to 140°; these conditions give separate peaks for a 3 : 2 mixture of the *cis* and *trans* isomers of the two octalones.^{5,6}

3. Discussion

4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone, an important intermediate in the total syntheses of the sesquiterpenes, aristolone,^{5,6} and fukinone,⁷ has been prepared in 15% yield as a 3 : 2 mixture of *cis* and *trans* isomers by the Robinson annelation reaction between 2,3-dimethylcyclohexanone and methyl vinyl ketone.^{5,6} This *cis*-octalone has also been synthesized stereoselectively *via* the crystalline enol lactone, *cis*-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-2*H*-1-benzopyran-2-one.⁶ In the procedure reported here the *cis*-octalone is prepared from 2-methyl-2-cyclohexen-1-one in a simple, three-step procedure consisting of conjugate addition with lithium dimethylcuprate, Michael addition of the resulting enolate anion to 3-trimethylsilyl-3-buten-2-one, and cyclization of the intermediate diketone.⁸ Reasonable structures for the intermediates are proposed in the lead equation but have not been experimentally established. This procedure also illustrates the general utility of 1-trimethylsilylvinyl ketones in regio- and stereoselective enolate trapping reactions⁹ and the application of the method in the synthesis of polycyclic ketones (Table I).^{8,9,10,11}

This preparation is referenced from:

TABLE I
SYNTHESIS OF POLYCYCLIC
KETONES^{8,9,10,11}

Reactant	Product	Yield (%)
		57
		54
		53
		57
		67
		>60

References and Notes

1. Department of Chemistry, Wayne State University, Detroit, Michigan, 48202 [Present address: Department of Chemistry, University of Rochester, Rochester, New York 14627].
2. Department of Chemistry, Cornell University, Ithaca, New York 14853.
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 10. R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **96**, 6179 (1974).
 11. G. Stork and J. Singh, *J. Am. Chem. Soc.*, **96**, 6181 (1974).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium chloride (7647-14-5)

potassium iodide (7681-11-0)

potassium hydroxide (1310-58-3)

methyl bromide (74-83-9)

ammonium hydroxide (1336-21-6)

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

magnesium sulfate (7487-88-9)

methyl vinyl ketone (78-94-4)

Methylithium (917-54-4)

2-Methyl-2-cyclohexenone,
2-methyl-2-cyclohexen-1-one (1121-18-2)

argon (7440-37-1)

copper(II)

lithium dimethylcuprate

2,3-dimethylcyclohexanone

3-Trimethylsilyl-3-buten-2-one (43209-86-5)

phosphorus pentoxide (1314-56-3)

cis-4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)-naphthalenone,

2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-, 4a,5-dimethyl-, cis-, (±)- (20536-80-5)

4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)-naphthalenone

cis-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-2H-1-benzopyran-2-one

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