



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

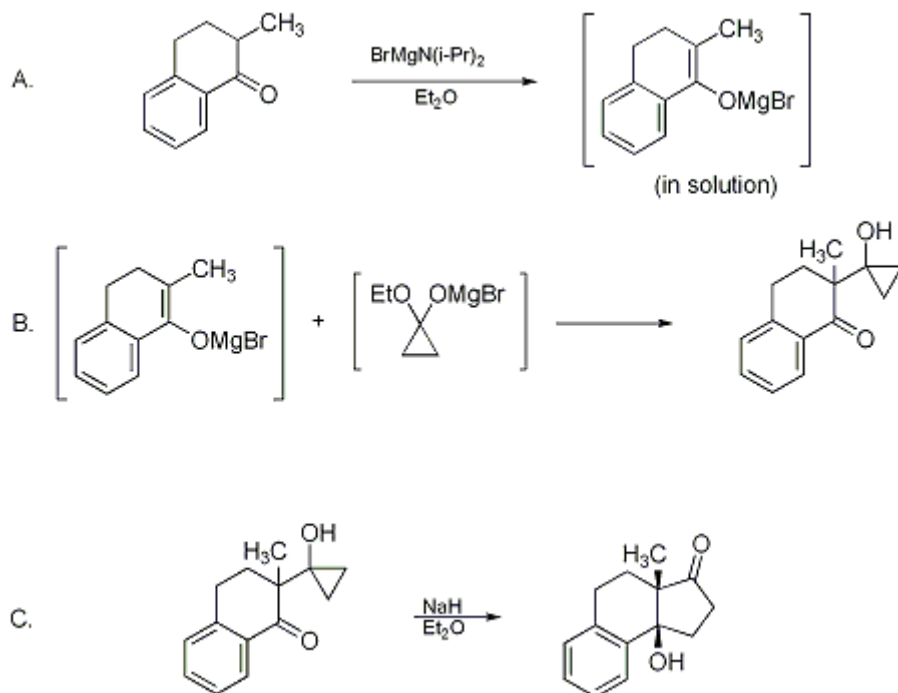
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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CYCLOPENTANONE ANNULATION VIA CYCLOPROPANONE DERIVATIVES: (3a β ,9b β)-1,2,3a,4,5,9b-HEXAHYDRO-9b-HYDROXY-3a-METHYL-3H-BENZ[e]INDEN-3-ONE



Submitted by Michael J. Bradlee and Paul Helquist¹.
Checked by Steve Berberich and Stephen F. Martin.

1. Procedure

A. *Magnesium enolate of 2-methyl-1-tetralone.* Into a 500-mL, round-bottomed flask equipped with a magnetic stirring bar is placed 6.72 g of magnesium bromide diethyl etherate ($\text{MgBr}_2 \cdot \text{Et}_2\text{O}$) (26.0 mmol) under nitrogen (Note 1). Anhydrous ether, 350 mL, (Note 2) is added with a syringe, and the mixture is stirred at 25°C for a few minutes to dissolve the solid. Using an air-tight syringe, 11.2 mL of a 3.0 M solution of methylmagnesium bromide in ether (34 mmol, (Note 3)) is added to the slightly turbid solution at 25°C over a period of a few minutes. *N,N*-Diisopropylamine, 4.46 mL (34 mmol, (Note 4)) is added over 5 min, and the mixture is stirred for 16–18 hr, during which time a fine white precipitate forms (Note 5). The mixture is cooled to 0°C, and a solution of 5.28 g of 2-methyl-1-tetralone (33 mmol, (Note 6)) in 20 mL of anhydrous ether is added with a cannula over a 10-min period. The mixture becomes a bright yellow solution during the addition, and after 45 min of additional stirring, it becomes pale yellow.

B. *2-(1-Hydroxycyclopropyl)-2-methyl-1-tetralone.* Simultaneously with the above operations, a separate 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, reflux condenser, nitrogen inlet, and a septum, and the flask is placed under a nitrogen atmosphere. Anhydrous ether, 600 mL, and 20 mL of a 3.0 M solution of methylmagnesium bromide in ether (60 mmol, (Note 3)) are added to the flask with a cannula and a syringe, respectively, and the solution is cooled to 0°C. A solution of 6.12 g of cyclopropanone ethyl hemiketal² (60.0 mmol, (Note 7)) in 20 mL of anhydrous ether is added with vigorous stirring over several minutes with a cannula. During this addition, gas evolution is observed, and a fine white precipitate forms. After the mixture is stirred for 15 min, the solution of the enolate of 2-methyl-1-tetralone is added using a wide gauge cannula (ca. 1 mm id) over several minutes. The resulting turbid, light yellow solution is heated at reflux for 4 hr. The resulting

clear, yellow solution is cooled to 25°C and diluted with 200 mL of ether. The organic solution is washed with saturated aqueous ammonium chloride (3 × 200 mL) and saturated aqueous sodium chloride (200 mL) and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated by rotary evaporation under reduced pressure to give 7.92 g of crude 2-(1-hydroxycyclopropyl)-2-methyl-1-tetralone (Note 8) as a clear yellow oil that is used in the next step without further purification.

C. (3 α ,9 β)-1,2,3 α ,4,5,9 β -Hexahydro-9 β -hydroxy-3 α -methyl-3H-benz[e]indene-3-one.³ The yellow oil from Part B is dissolved in 100 mL of anhydrous ether in a 100-mL round-bottomed flask at 25°C under nitrogen. Into a separate 250-mL flask containing a magnetic stirring bar are placed 4.0 g of powdered sodium hydride (166 mmol, (Note 9)), and 100 mL of anhydrous ether at 25°C under nitrogen. The solution of the yellow oil is added with stirring over a period of a few minutes using a cannula. The mixture is stirred at 25°C for 3 hr, during which time it becomes yellow-orange. The reaction is quenched by adding 100 mL of ice-cold saturated aqueous ammonium chloride and 100 mL of ether. The organic layer is washed with saturated aqueous ammonium chloride (3 × 100 mL) and saturated aqueous sodium chloride (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation under reduced pressure. The crude product is obtained as 5.8 g of yellow-orange crystals. The solid is dissolved in about 150 mL of warm ether, and 100 mL of hexanes is added. The mixture is concentrated to ca. 100 mL in a heating bath (or on a steam bath), and the resulting cloudy solution is cooled slowly to 0°C. An initial crop of 4.73 g (67%) of pale yellow crystals is obtained and the mother liquor is decanted from the solid and concentrated by rotary evaporation under reduced pressure to ca. 5 mL to give 0.39 g (5%) of pale yellow crystals as a second crop. The mother liquor may then be concentrated and the residue purified by flash chromatography⁴ on silica gel using 1:1 ether/hexane to give 0.29 g (4%) of additional product (R_f = 0.33) as yellow crystals after washing with warm 1:1 ether/hexane. The total combined yield of (3 α ,9 β)-1,2,3 α ,4,5,9 β -hexahydro-9 β -hydroxy-3 α -methyl-3H-benz[e]indene-3-one is 5.41 g (76%) (Note 10).

2. Notes

1. The MgBr₂·Et₂O was obtained from Aldrich Chemical Company, Inc., as a white solid in the form of a powder mixed with lumps. The solid was transferred to the 250-mL, round-bottomed flask in a nitrogen-filled glove box and carefully crushed with a glass stirring rod until the solid was a uniform powder. The flask was then equipped with a septum, taken out of the glove box, and attached to a standard nitrogen/vacuum double manifold system to maintain an inert, dry atmosphere of prepurified nitrogen in the flask throughout the remainder of the reaction sequence.
2. Anhydrous diethyl ether and anhydrous tetrahydrofuran (THF) were obtained from Fisher Scientific Company. They were redistilled under nitrogen from dark blue or purple solutions of sodium benzophenone ketyl immediately prior to use. All transfers of these and other anhydrous materials were performed with syringes or stainless steel cannulas while carefully maintaining a nitrogen atmosphere.
3. Methylmagnesium bromide was purchased from Aldrich Chemical Company, Inc., as a solution in ether, and the solution was used as obtained without titration.
4. N,N-Diisopropylamine was purchased from Aldrich Chemical Company, Inc., and distilled under nitrogen from calcium hydride prior to use.
5. The submitters observed the fine white precipitate after 12 hr of stirring.
6. 2-Methyl-1-tetralone was purchased from Aldrich Chemical Company, Inc., and used without further purification.
7. Cyclopropanone ethyl hemiketal is contaminated with 8–9% of the cyclopropanone methyl hemiketal as a result of exchange with the solvent.² The calculated number of mmoles of total cyclopropanone hemiketal is based upon this composition.
8. ¹H NMR analysis of the crude product indicated greater than 90% conversion of the starting 2-methyl-1-tetralone to 2-(1-hydroxycyclopropyl)-2-methyl-1-tetralone: IR (CHCl₃) cm⁻¹: 3485 (O-H), 3067 (aromatic C-H), 2972 (aliphatic C-H), 1670 (C=O); ¹H NMR (300 MHz, CDCl₃) δ : 0.49–0.72 (m, 4 H, cyclopropyl CH₂CH₂), 1.20 (s, 3 H, CH₃), 1.61–1.71 (dt, 1 H, J = 13.4, 4.5, CHH), 2.03–2.15 (m, 1 H, CHH), 2.88–3.04 (m, 2 H, benzylic CH₂), 3.68 (s, 1 H, OH), 7.15–7.96 (m, 4 H, aromatic CH); ¹³C NMR (75 MHz, CDCl₃) δ : 9.0, 10.4 (cyclopropyl CH₂CH₂), 18.2 (CH₃), 25.5 (CH₂), 31.0 (benzylic CH₂), 48.0 (C=O), 59.3 (cyclopropyl COH), 126.7, 127.8, 128.7, 131.7 (aromatic CH), 133.6, 143.4 (ipso aromatic C), 204.0 (C=O).

9. Sodium hydride was obtained as a powder of 95% purity grade from Aldrich Chemical Company, Inc. A nitrogen-filled glove box was used to weigh the reagent and transfer it into the reaction flask.

10. Yields of the product ranged from 67 to 81% over a series of several runs. For (3a β ,9b β)-1,2,3a,4,5,9b-hexahydro-9b-hydroxy-3a-methyl-3H-benz[e]indene-3-one, mp 117–118°C; IR (CHCl₃) cm⁻¹: 3466 (O-H), 3066, 3070 (aromatic C-H), 2976 (aliphatic C-H), 1736 (C=O); ¹H NMR (300 MHz, CDCl₃) δ : 1.14 (s, 3 H, CH₃), 1.58–1.67 (m, 1 H), 1.80 (s, 1 H, OH), 1.87–1.99 (m, 1 H), 2.20–2.41 (m, 3 H), 2.48–2.61 (m, 1 H), 2.66–2.76 (m, 1 H), 2.84–2.97 (m, 1 H), 7.08–7.68 (m, 4 H, aromatic CH); ¹³C NMR (75 MHz, CDCl₃) δ : 14.5 (CH₃), 25.0 (CH₂), 29.1 (CH₂COH), 34.9 (CH₂C=O), 36.1 (benzylic CH₂), 52.5 (CCH₃), 79.8 (benzylic COH), 126.6, 126.9, 127.5, 128.5 (aromatic CH), 134.6, 140.5 (ipso aromatic C), 204.5 (C=O); CIMS, m/e (rel intensity) 217 (10%, MH⁺), 199 (100%, MH⁺ -18); Anal. Calcd for C₁₄H₁₆O₂: C, 77.75; H, 7.46. Found: C, 78.00; H, 7.60.

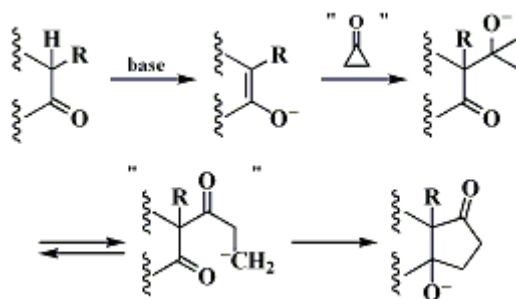
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

A large number of methods have been developed for the construction of five-membered carbocyclic systems. These methods are too numerous to review here, but a number of key references are cited.^{5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21}

The method that is used in the present preparation is based upon the *formal concept* of employing cyclopropanone in an aldol condensation with an enolate of another ketone. The resulting aldolate exhibits characteristics of a "homoenolate" and may undergo a second carbonyl addition reaction to form a five-membered ring as suggested in the following generalized pathway:



The homoenolate is not necessarily an intermediate in this pathway, but rather, it is shown only to illustrate the basic concept.

Cyclopropanone itself is a very unstable compound that has been isolated only at low temperature. Its chemistry has been studied thoroughly during the past several years.^{22,23,24,25,26,27} Various forms of homoenolates have also been investigated, and their applications in synthesis are being actively developed.^{28,29,30,31,32,33,34,35,36,37,38,39,40,41,42} The combination of cyclopropanone and homoenolate chemistry employed here is most closely related to studies of Narasimhan^{43,44} and follows from a series of studies in the laboratory of the submitters.^{3,45,46,47,48,49} Whether free cyclopropanone or the homoenolate form of the aldol adduct are produced as actual species in the above pathway is uncertain, but at least the formal concept of their hypothetical intermediacy and expected reactivity patterns have proven useful in the design of the annulation method employed in the present preparation. The cyclopropanone hemiketal used in this work could conceivably undergo ethoxide elimination to produce cyclopropanone in situ which would then serve as a very reactive acceptor for nucleophilic addition,^{2,22,23,24,25,26,27,50} but other mechanistic pathways may also be consistent with the observed reaction sequence.

An attractive feature of this procedure is the directness with which the annulation of 3-hydroxycyclopentanone systems onto preexisting ketone skeletons can be accomplished to give usefully functionalized products. However, this method does have important limitations in its scope. The most

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

sodium benzophenone ketyl

magnesium bromide diethyl etherate

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Cyclopentanone (120-92-3)

magnesium sulfate (7487-88-9)

methylmagnesium bromide (75-16-1)

Tetrahydrofuran (109-99-9)

sodium hydride (7646-69-7)

hexane (110-54-3)

calcium hydride (7789-78-8)

N,N-Diisopropylamine (108-18-9)

CYCLOPROPANONE (5009-27-8)

cyclopropanone ethyl hemiketal (13837-45-1)

cyclopropanone methyl hemiketal

cyclopropanone hemiketal

2-methyl-1-tetralone (1590-08-5)

2-(1-Hydroxycyclopropyl)-2-methyl-1-tetralone

(3a β ,9b β)-1,2,3a,4,5,9b-hexahydro-9b-hydroxy-3a-methyl-3H-benz[e]inden-3-one