



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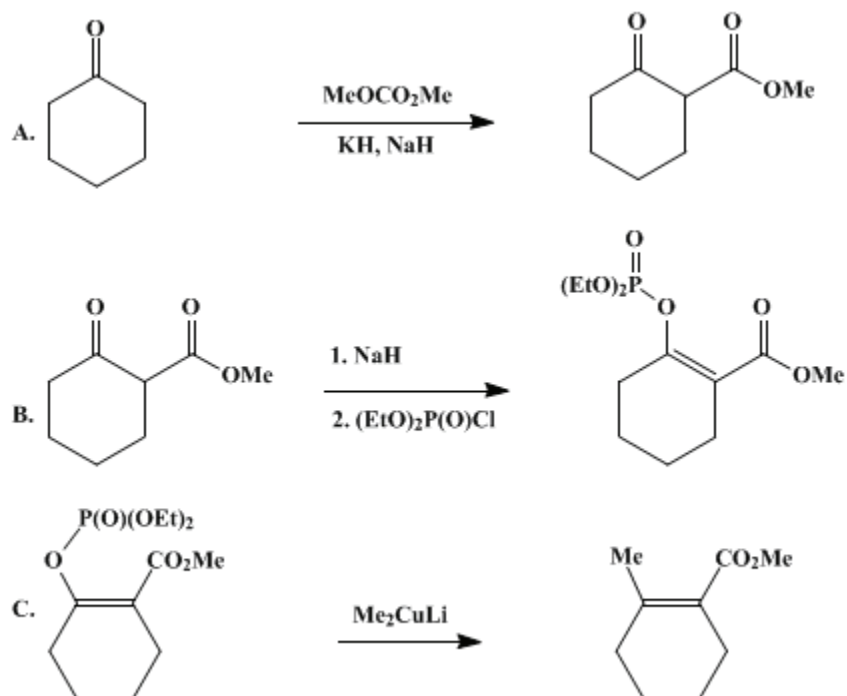
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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**β -ALKYL- α,β -UNSATURATED ESTERS FROM ENOL
PHOSPHATES OF β -KETO ESTERS: METHYL 2-METHYL-1-
CYCLOHEXENE-1-CARBOXYLATE**

[1-Cyclohexene-1-carboxylic acid, 2-methyl, methyl ester]



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1. Procedure

A. *Methyl 2-oxocyclohexanecarboxylate*. A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser, and a pressure-equalizing dropping funnel bearing a nitrogen inlet (Note 1). The flask is flushed with nitrogen and charged with 18.02 g (0.20 mol) of dimethyl carbonate, 50 mL of anhydrous tetrahydrofuran, and 6.12 g (0.25 mol) of sodium hydride (Note 2). The suspension is stirred and heated to reflux temperature, at which time the slow, dropwise addition of 7.80 g (0.080 mol) of cyclohexanone in 20 mL of dry tetrahydrofuran is begun. After 2 min, 0.306 g (0.0076 mol) of powdered potassium hydride (*Caution! Dry potassium hydride is pyrophoric.*) (Note 3) is added to initiate the reaction. The addition of cyclohexanone is continued over a 1-hr period. The mixture is stirred and heated at reflux for another 30 min, cooled in an ice bath for 15–20 min, and hydrolyzed by slowly adding 75 mL of 3 M aqueous acetic acid. The contents of the flask are poured into 100 mL of aqueous sodium chloride, and the aqueous mixture is extracted with four 150-mL portions of chloroform. The organic layers are combined, dried with anhydrous sodium sulfate, and concentrated at room temperature with a rotary evaporator. Distillation of the residual liquid under reduced pressure gives 9.8–10.8 g (79–87%) of methyl 2-oxocyclohexanecarboxylate as a colorless liquid, bp 53–55°C (0.35 mm) (Note 4).

B. *Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate*. A 250-mL, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a gas inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is flushed with nitrogen and charged with 1.58 g (0.0329 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 5). The sodium

hydride is freed from the mineral oil by washing with four 40-mL portions of anhydrous diethyl ether (Note 6) and withdrawing the supernatant solvent with a syringe, after which 120 mL of anhydrous ether is added. The mixture is stirred and cooled in an ice bath as 4.68 g (0.0300 mol) of methyl 2-oxocyclohexanecarboxylate (Note 7) in 10 mL of ether is added at a moderately rapid rate such that vigorous but controlled evolution of hydrogen occurs (Note 8). The resulting creamy suspension is stirred at 0°C for another 30 min, after which time 4.5 mL (5.37 g, 0.031 mol) of diethyl chlorophosphate (Note 9) is injected through the septum with a syringe. The ice bath is removed, the mixture is stirred at room temperature for an additional 3 hr, and 0.6 g of solid ammonium chloride is added. Stirring is continued for 30 min, and the salts are then separated by suction filtration through a medium porosity fritted-glass funnel. Concentration of the filtrate under reduced pressure affords 8.18–8.63 g of the enol phosphate that is used in Step C without purification (Note 10).

C. *Methyl 2-methyl-1-cyclohexene-1-carboxylate*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a pressure-equalizing addition funnel, and an inlet tube connected to a nitrogen source and a mineral oil bubbler (Note 1). The flask is charged with 8.03 g (0.042 mol) of copper(I) iodide (Note 11) and 50 mL of dry diethyl ether (Note 6), flushed with nitrogen, and cooled in an ice bath. The mixture is stirred and cooled as 92.7 mL (0.084 mol) of 1.1 M methyllithium in diethyl ether (Note 12) is added quickly through the septum by means of a syringe. The resulting clear and colorless, or light tan, solution of lithium dimethylcuprate is then cooled in a carbon tetrachloride–dry ice slush bath maintained at –23°C (Note 13). A solution of 8.18–8.63 g (ca. 0.028–0.030 mol) of the enol phosphate in 35 mL of dry ether is added from the addition funnel over 5–10 min. Stirring and cooling are continued for 3 hr, after which time the dark-purple solution is poured into a 1-L Erlenmeyer flask containing 75 mL of ice-cold 5% hydrochloric acid saturated with sodium chloride (Note 14). The mixture is stirred, or shaken vigorously, and cooled in an ice bath for 5–10 min to complete the hydrolysis. A 150-mL portion of 15% aqueous ammonia is added to the gray suspension and the mixture is swirled vigorously for a few minutes until the organic layer becomes clear and the aqueous layer turns bright blue. The mixture is transferred to a separatory funnel, the aqueous layer is withdrawn, and the organic phase is washed with 50 mL of 15% aqueous ammonia. The aqueous layers are combined and extracted with one 100-mL portion of ether. The combined ethereal layers are washed with two 50-mL portions of saturated sodium chloride, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. Distillation of the remaining 4.25–5.47 g of liquid in a short-path distillation apparatus affords 3.99–4.17 g (86–90% based on β -keto ester) of methyl 2-methyl-1-cyclohexene-1-carboxylate, bp 96–97°C (27 mm) (Note 15),(Note 16),(Note 17).

2. Notes

1. The glassware was dried in an oven at 125°C and assembled while warm.
2. Dimethyl carbonate is available from Aldrich Chemical Company, Inc. The checkers dried the tetrahydrofuran immediately before use by distillation from the sodium ketyl of benzophenone under a nitrogen atmosphere. The submitters purchased sodium hydride (50% oil dispersion) from Alfa Products, Morton Thiokol, Inc. The checkers used 12.24 g of a 50% dispersion of sodium hydride in mineral oil obtained from the same supplier. The dispersion was washed with three portions of pentane to remove the mineral oil and the remaining sodium hydride was allowed to dry under nitrogen.
3. The submitters used a 35% dispersion of potassium hydride in mineral oil supplied by Alfa Products, Morton Thiokol, Inc.; the mineral oil was separated by washing the dispersion with five portions of dry hexane. The checkers used a 25% dispersion of potassium hydride in mineral oil obtained from the same source but without removing the mineral oil. The oil remained in the distillation pot when the product was distilled.
4. A boiling point of 68°C (0.8 mm) and a melting point of 25°C have been reported for methyl 2-oxocyclohexanecarboxylate.² The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 1745, 1715, 1615; $^1\text{H NMR}$ (CDCl_3) δ : 1.62 (m, 4 H, 2 CH_2), 2.22 (m, 4 H, 2 CH_2), 3.37 (t, 0.25 H, $J = 7$ Hz, CH at C-2 in keto form), 3.74 (s, 3 H, CH_3), 12.10 (s, 0.75 H, enol OH).
5. The sodium hydride-mineral oil dispersion was purchased from Alfa Products, Morton Thiokol, Inc.
6. Diethyl ether was dried by the submitters by refluxing over lithium aluminum hydride and was distilled immediately before use. The checkers distilled diethyl ether from the sodium ketyl of benzophenone before use.
7. A mixture of methyl and ethyl 2-oxocyclohexanecarboxylate, available from Aldrich Chemical

Company, Inc., may also be used. The product obtained is a mixture of methyl and ethyl 2-methylcyclohexene-1-carboxylates.

8. No gas evolution was observed by the checkers in some runs in which an older lot of sodium hydride was used. In this case, the cooling bath was removed and the mixture was allowed to stir at room temperature until the bubbling ceased.

9. Diethyl chlorophosphate, supplied by Aldrich Chemical Company, Inc., was used by the submitters without purification and was handled in a glove bag under an atmosphere of dry nitrogen in a well-ventilated hood. The reagent was distilled and stored under nitrogen by the checkers. Aliquots were withdrawn with a syringe as needed.

10. The spectral properties of the enol phosphate are as follows: IR (CHCl₃) cm⁻¹: 1715, 1660, 1290, 1030; 90 MHz ¹H NMR (CDCl₃) δ: 1.3–1.9 (m, 4 H, CH₂CH₂), 1.35 (t, 6 H, *J* = 7 Hz, OCH₂CH₃), 2.3 (m, 4 H, allylic CH₂), 3.68 (s, 3 H, OCH₃), 4.15 (quintet, 4 H, *J* = 7 Hz, OCH₂CH₃).

11. Copper(I) iodide, supplied by either MC and B Manufacturing Chemists or Fisher Scientific Company, was purified by recrystallization from water saturated with potassium iodide.^{3,4,5} The wet powder was washed successively with ethanol, acetone, and ether, and dried by heating overnight at 100°C in an evacuated drying pistol containing phosphorus pentoxide.^{4,6} The submitters advise that the compound should not be dried by heating in air.⁶ When oven-dried copper(I) iodide was used in this procedure, the yield of product was somewhat lower (77–88%) and as much as 10–20% of 1-acetyl-2-methylcyclohexene was formed. It is probable that the presence of small amounts of copper(II) impurities is responsible for the increased proportion of this by-product.^{5,7} Purified copper(I) iodide may be stored under nitrogen without change for several months.⁴

12. Ethereal methyllithium (as the lithium bromide complex) was obtained by the submitters from Aldrich Chemical Company, Inc. The checkers used 1.19 M methyllithium–lithium bromide complex in ether supplied by Alfa Products, Morton Thiokol, Inc. The concentration of the methyllithium was determined by titration with 1.0 M *tert*-butyl alcohol in benzene using 1,10-phenanthroline as indicator.⁸ The submitters report that ethereal methyllithium of low halide content purchased from Alfa Products, Morton Thiokol, Inc., gave similar results.

13. The coupling reaction between lithium dimethylcuprate and acyclic enol phosphates must be carried out between –47 and –98°C for stereoselective formation of β-methyl-α,β-unsaturated esters.

14. The submitters have found that the reaction may also be hydrolyzed with a solution of 60 mL of saturated ammonium chloride and 15 mL of concentrated aqueous ammonia. The ethereal layer is then washed with 15% aqueous ammonia until the aqueous layer is no longer blue. When lithium di-*n*-butylcuprate is used, the yields are often improved by adding 1-bromobutane to the reaction mixture before hydrolysis with aqueous ammonium chloride.

15. The product exhibits the following spectral properties: IR (CHCl₃) 1720, 1640, 1080 cm⁻¹; ¹H NMR (CDCl₃) δ: 1.3–1.7 (m, 4 H, CH₂CH₂), 1.8–2.4 (m, 4 H, allylic CH₂), 1.97 (s, 3 H, CH₃), 3.69 (s, 3 H, OCH₃); MS (70 eV) *m* / *e* (assignment, relative intensity): 154 (M⁺, 50%), 95 (-CO₂CH₃, 100%).

16. The purity of the product was determined by the checkers by GLC analysis using the following column and conditions: 3-mm × 1.8-m column, 5% free fatty acid phase (FFAP) on acid-washed Chromasorb W (60–80 mesh) treated with dimethyldichlorosilane, 90°C (1 min) then 90° to 200°C (15° C / min). The chromatogram showed a major peak for methyl 2-methyl-1-cyclohexene-1-carboxylate preceded by two minor peaks for methyl 1-cyclohexene-1-carboxylate and 1-acetyl-2-methylcyclohexene. The areas of the two impurity peaks were 5–6% and 0.5–2% that of the major peak. The purity of the product seems to depend on careful temperature control during the reaction. The total amount of the two impurities was 14–21% in runs conducted at about –15 to –20°C or at temperatures below –23°C.

17. The submitters purified the product by distillation in a Kugelrohr apparatus with an oven temperature of 85–88°C (20 mm) and obtained 3.80–3.85 g (88–89%). The purity of the product was 93–96% according to GLC analysis. The major impurity (2–6%) was 1-acetyl-2-methylcyclohexene. The product may also be purified by flash chromatography⁹ using 19 / 1 (v / v) petroleum ether, (bp 30–60°C) / ethyl acetate as eluant. A column of 2-cm diameter was packed to a height of 25 cm with Kieselgel 60 (230–400 mesh) supplied by BDH Chemicals Ltd. In one run chromatography of 4.19 g of crude product afforded 3.70 g (88%) of the α,β-unsaturated ester that was completely free of the more polar by-product, 1-acetyl-2-methylcyclohexene. However, the checkers found that the other by-product, methyl 1-cyclohexene-1-carboxylate, is not readily separated by flash chromatography.

3. Discussion

This procedure illustrates a new method for the preparation of β -alkyl- α,β -unsaturated esters by coupling lithium dialkylcuprates with enol phosphates of β -keto esters.¹⁰ The procedure for the preparation of methyl 2-oxocyclohexanecarboxylate described in Section A is based on one reported by Ruest, Blouin, and Deslongchamps.² Methyl 2-methyl-1-cyclohexene-1-carboxylate has been prepared by esterification of the corresponding acid with diazomethane¹¹ and by reaction of methyl 2-chloro-1-cyclohexene-1-carboxylate with lithium dimethylcuprate.¹²

The formation of β -alkyl- α,β -unsaturated esters by reaction of lithium dialkylcuprates or Grignard reagents in the presence of copper(I) iodide, with β -phenylthio-,^{13,14 15} β -acetoxy-,^{16 17 18,19} β -chloro-,^{12,20} and β -phosphoryloxy- α,β -unsaturated esters¹⁰ has been reported. The principal advantage of the enol phosphate method is the ease and efficiency with which these compounds may be prepared from β -keto esters. A wide variety of cyclic and acyclic β -alkyl- α,β -unsaturated esters has been synthesized from the corresponding β -keto esters.¹⁰ However, the method is limited to primary dialkylcuprates. Acyclic β -keto esters afford (Z)-enol phosphates that undergo stereoselective substitution with lithium dialkylcuprates with predominant retention of stereochemistry (usually >85–98%). It is essential that the cuprate coupling reaction of the acyclic enol phosphates be carried out at lower temperatures (–47 to –98°C) to achieve high stereo-selectivity. When combined with the γ -alkylation of methyl acetoacetate dianion,²¹ this method provides a facile means of isoprenoid chain extension.^{22 23 24} The procedures have been employed to advantage in syntheses of (E,E)-10-hydroxy-3, 7-dimethyldeca-2, 6-dienoic acid,²² latia luciferin,²³ and mokupalide.²⁴ β -Diketones may be converted to β -alkyl- α,β -unsaturated ketones in a similar manner.¹⁰

References and Notes

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

sodium ketyl of benzophenone

methyl and ethyl 2-oxocyclohexanecarboxylate

methyl and ethyl 2-methylcyclohexene-1-carboxylates

1.0 M tert-butyl alcohol

[ethanol \(64-17-5\)](#)

[hydrochloric acid \(7647-01-0\)](#)

[acetic acid \(64-19-7\)](#)

[ammonia \(7664-41-7\)](#)

[Benzene \(71-43-2\)](#)

[ethyl acetate \(141-78-6\)](#)

[ether,](#)
[diethyl ether \(60-29-7\)](#)

[ammonium chloride \(12125-02-9\)](#)

[hydrogen \(1333-74-0\)](#)

[chloroform \(67-66-3\)](#)

[Cyclohexanone \(108-94-1\)](#)

[sodium chloride \(7647-14-5\)](#)

[1-bromobutane \(109-65-9\)](#)

[sodium sulfate \(7757-82-6\)](#)

[potassium iodide \(7681-11-0\)](#)

[nitrogen \(7727-37-9\)](#)

[acetone \(67-64-1\)](#)

[Pentane \(109-66-0\)](#)

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

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

hexane (110-54-3)

Methylithium (917-54-4)

Methyl 2-oxocyclohexanecarboxylate (41302-34-5)

diethyl chlorophosphate (814-49-3)

copper(II)

lithium dimethylcuprate

1,10-phenanthroline (66-71-7)

dimethyldichlorosilane (75-78-5)

potassium hydride (7693-26-7)

lithium bromide (7550-35-8)

phosphorus pentoxide (1314-56-3)

Methyl 2-methyl-1-cyclohexene-1-carboxylate,
1-Cyclohexene-1-carboxylic acid, 2-methyl, methyl ester (25662-38-8)

dimethyl carbonate (616-38-6)

1-acetyl-2-methylcyclohexene

methyl 1-cyclohexene-1-carboxylate

methyl 2-chloro-1-cyclohexene-1-carboxylate

lithium di-n-butylcuprate

(E,E)-10-hydroxy-3, 7-dimethyldeca-2, 6-dienoic acid

Methyl 2-(diethylphosphoryloxy)-1-cyclohexene-1-carboxylate (71712-64-6)

