



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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

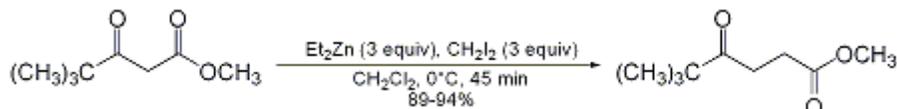
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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FORMATION OF γ -KETO ESTERS FROM β -KETO ESTERS: METHYL 5,5-DIMETHYL-4-OXOHEXOATE

[Hexanoic acid, 5,5-dimethyl-4-oxo-, methyl ester]



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Discussion Addendum *Org. Synth.* **2014**, *91*, 248

1. Procedure

CAUTION! Neat diethylzinc may ignite on exposure to air and reacts violently with water. It must be handled and reacted under nitrogen.² The reaction solvent must be dried and distilled prior to use and all glassware and syringes must be thoroughly dried.

An oven-dried, 3-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 1000 mL of freshly distilled methylene chloride (Note 1). One of the outer two necks of the flask is equipped with a gas inlet adapter attached to a nitrogen source and the other with a septum connected through a needle to a bubbler (Notes 2, 3). A 125-mL pressure-equalizing addition funnel capped with a septum is placed in the center neck of the flask with the stopcock closed. The funnel is charged with 12.1 mL (150 mmol) of methylene iodide (Note 4) dissolved in 75 mL of distilled methylene chloride. The solution is stirred under nitrogen for 1 hr and the flask is cooled in an ice-water bath. Using a syringe, 15.4 mL (150 mmol) of neat diethylzinc (Note 5) is added to the methylene chloride through the septum (Note 6). The stopcock of the addition funnel is opened carefully and the methylene iodide solution is allowed to drip into the diethylzinc solution over the course of 30 min (Note 7). After the reaction is stirred for an additional 10 min, 8.0 mL (50 mmol) of methyl 4,4-dimethyl-3-oxopentanoate is added to the flask over a period of 15 sec through the septum using a syringe (Note 8). The reaction mixture is stirred for 45 min (Note 9), the septum is removed, and the reaction is quenched through the careful addition of 125 mL of saturated aqueous ammonium chloride (Notes 10, 11). Stirring is maintained for an additional 10 min, at which time the reaction mixture is transferred to a 2-L separatory funnel. The lower organic layer is withdrawn and placed in a large, round-bottomed flask. The methylene chloride is removed using a rotary evaporator (Note 12) and the residue is diluted with 500 mL of diethyl ether and placed in the separatory funnel. It is washed successively with 125-mL portions of saturated aqueous sodium bicarbonate, 1 M aqueous sodium thiosulfate solution (Note 13), deionized water and brine. The aqueous washings are extracted with diethyl ether (3 × 150 mL) and the combined organic layers are dried over 50 g of anhydrous sodium sulfate prior to concentration under reduced pressure. The product is purified by vacuum distillation from anhydrous potassium carbonate (58°C, 1 mm) to give methyl 5,5-dimethyl-4-oxo-hexanoate (7.63-8.09 g, 89-94% yield) as a clear liquid (Notes 14, 15).

2. Notes

1. Methylene chloride, reagent grade, was obtained from Pharmco Products, Inc. and was distilled from phosphorus pentoxide prior to use. Benzene can be substituted for methylene chloride in the chain extension reaction with similar results; however the use of benzene in the reaction has not been independently checked.
2. The first step of the chain extension reaction mechanism has been shown to be enolate formation, the by-product of which is ethane gas. The nitrogen line should be attached to a large adapter to provide adequate venting of the gas.
3. The checkers used a sidearm vacuum adapter fitted with a septum and connected to a nitrogen

manifold. The third neck was stoppered.

4. **Methylene iodide** was obtained from Lancaster Synthesis, Inc. , and used without further purification. Distillation of the **methylene iodide** from **copper** prior to use does not lead to increased product yield or purity.

5. Three equivalents of the carbenoid (EtZnCH₂I) are necessary for the clean formation of the product. One of the equivalents serves to facilitate formation of the enolate, while a second equivalent provides the methylene group that is incorporated into the product. However, if the reaction is performed with only two equivalents, significant amounts of starting material and a second product, **methyl 2,4,4-trimethyl-3-oxopentanoate** , are generated in the reaction.

6. **Diethylzinc** was obtained from Aldrich Chemical Company, Inc. , and used without further purification. If the reaction flask has been carefully flushed with **nitrogen**, there should be very little smoke evident when the **zinc** reagent is added. **Diethylzinc** can be added with the syringe tip placed below the surface of the solvent rather than above it.

7. Formation of the zinc carbenoid is exothermic and potentially explosive.³ The ice bath should be present in order to control the reaction temperature, and **methylene iodide** should be added gradually rather than all at once. During the addition of the **methylene iodide** , or shortly thereafter, the reaction mixture should develop a cloudy, white appearance.

8. **Methyl 4,4-dimethyl-3-oxopentanoate** was obtained from Lancaster Synthesis, Inc. , and used without further purification.

9. Disappearance of the starting material may be monitored by thin layer chromatography (R_f = 0.6, 2:1 **hexane:ethyl acetate**). It is important that the reaction time not be extended past the point when all of the β-keto ester is consumed, because long exposure to the zinc carbenoid has been shown to result in substrate decomposition and reduced yields.

10. Addition of the aqueous solution is exothermic and should, therefore, be carried out over the course of a few minutes. The checkers found that the initial internal temperature was 5-6°C which rose to 10°C upon addition of the first few mL of quench solution.

11. The checkers found that addition of 150 mL of 2 N aqueous **hydrochloric acid** rather than 125 mL of saturated aqueous **ammonium chloride** does not alter the yield or purity of the product.

12. **Methylene chloride** is exchanged for **diethyl ether** , since removal of the **zinc** salts formed as reaction by-products is facilitated by use of an extraction solvent that is less dense than water.

13. The checkers found that washing the organic extracts with **sodium thiosulfate** solution was necessary to obtain a colorless product.

14. The NMR spectra were as follows and were consistent with those reported in the literature:⁴ ¹H NMR (500 MHz, CDCl₃) δ: 1.16 (s, 9 H), 2.57 (t, 2 H, J = 6.36), 2.81 (t, 2 H, J = 6.36), 3.67 (s, 3 H) ; ¹³C NMR (125 MHz, CDCl₃) δ: 26.4, 27.8, 31.4, 43.9, 51.7, 173.5, 214.4 ; IR (neat) 2970, 2874, 1741, 1707, 1366, 1204, 1167, 1087 . MS: (EI) 172.1 (0.23), 155.1 (0.43), 141.1 (16), 115.0 (100), 57.1 (64) . Anal. Calcd. for C₉H₁₆O₃: C, 62.75; H, 9.36. Found: C, 62.42; H, 9.38

15. The checkers found that distillation from anhydrous **potassium carbonate** is required in order to obtain a clear, analytically pure sample. Simple distillation yields a slightly yellow liquid which is free from major contamination, but not analytically pure.

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 variety of methods have been reported for the preparation of γ-keto esters. Although strategies in which the ketone and ester functionalities are assembled from different sources are frequently used,⁵ reactions that promote the insertion of a single methylene unit between the carbonyl functionalities of readily accessible β-keto esters are very attractive. The formation and fragmentation of 2-carboxycyclopropyl alcohols have been central to this methodological development.⁶

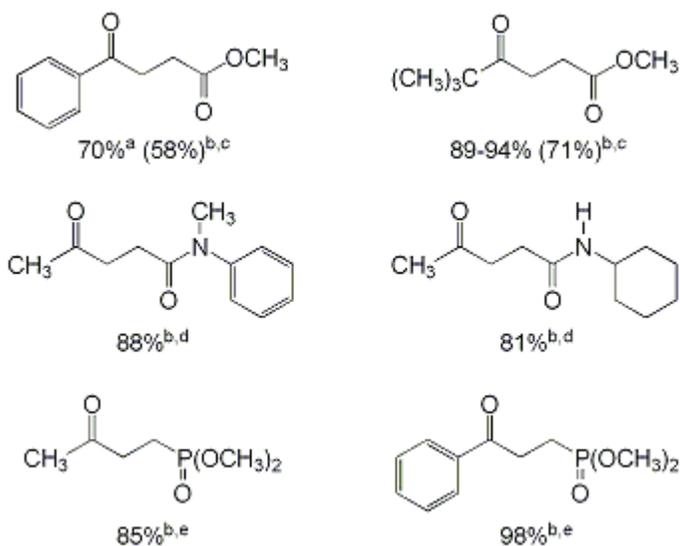
Three complementary strategies have been implemented for the formation of γ-keto esters through these functionalized cyclopropyl alcohols.⁷ While each of the three methods provided access to γ-keto esters, the multiple steps and/or poor yields of the transformations serve to discourage their widespread

applicability. The submitters have developed a simple and efficient one-step method for the formation of γ -keto esters from β -keto esters that appears to proceed through a similar [cyclopropyl alcohol](#) intermediate.⁸ Exposure of an α -unsubstituted β -keto ester to a 1:1 mixture of [diethylzinc](#) and [methylene iodide](#) results in its clean and rapid conversion to the chain-extended keto ester. This zinc-mediated process has two distinct advantages over the previously reported chain-extension methods. The most obvious advantage is that no additional steps are required for the formation of the intermediate enol ether or for the cleavage of the protected [cyclopropyl alcohol](#). Secondly, utilization of [diethylzinc](#) is operationally much simpler than preparation and application of the zinc-copper couple reported by Sagio.^{7h}

The zinc-mediated reaction tolerates a variety of functionality in the β -keto ester. In fact, the method described above has been applied successfully to β -keto amides⁹ and β -keto phosphonates.¹⁰ Unsubstituted β -keto esters, amides and phosphonates have been chain-extended in yields that ranged from 58% to 98% (Table I). The primary limitation to this method is the inefficiency with which α -substituted esters and amides undergo methylene insertion. The zinc carbenoid must be employed in at least a threefold excess in order to fully convert β -keto ester to products and to avoid the formation of α -methylated β -keto esters. Side products that result from an intermolecular reaction are observed on occasion. For example, the preparation of [ethyl 4-oxo-4-phenylbutanoate](#) from [ethyl benzoylacetate](#) on a 50-mmol scale proceeded in only 70% isolated yield because of a competing intermolecular reaction.

TABLE

PRODUCTS OF ZINC CARBENOID-MEDIATED CHAIN EXTENSION REACTIONS



(a) 50-mmol scale with 4 equiv of carbenoid; (b) isolated yield after chromatographic purification of a 1-mmol scale reaction; (c) 5 equiv of carbenoid; (d) 4 equiv of carbenoid; (e) 6 equiv of carbenoid.

References and Notes

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

Methyl 5,5-dimethyl-4-oxohexanoate:
Hexanoic acid, 5,5-dimethyl-4-oxo-, methyl ester (9); (34553-32-7)

Diethylzinc: FLAMMABLE LIQUID:
Zinc, diethyl- (8, 9); (557-20-0)

Methylene iodide:
Methane, diiodo- (8, 9); (75-11-6)

Methyl 4,4-dimethyl-3-oxopentanoate:
Pentanoic acid, 4,4-dimethyl-3-oxo-, methyl ester (9); (55107-14-7)