Organic Syntheses

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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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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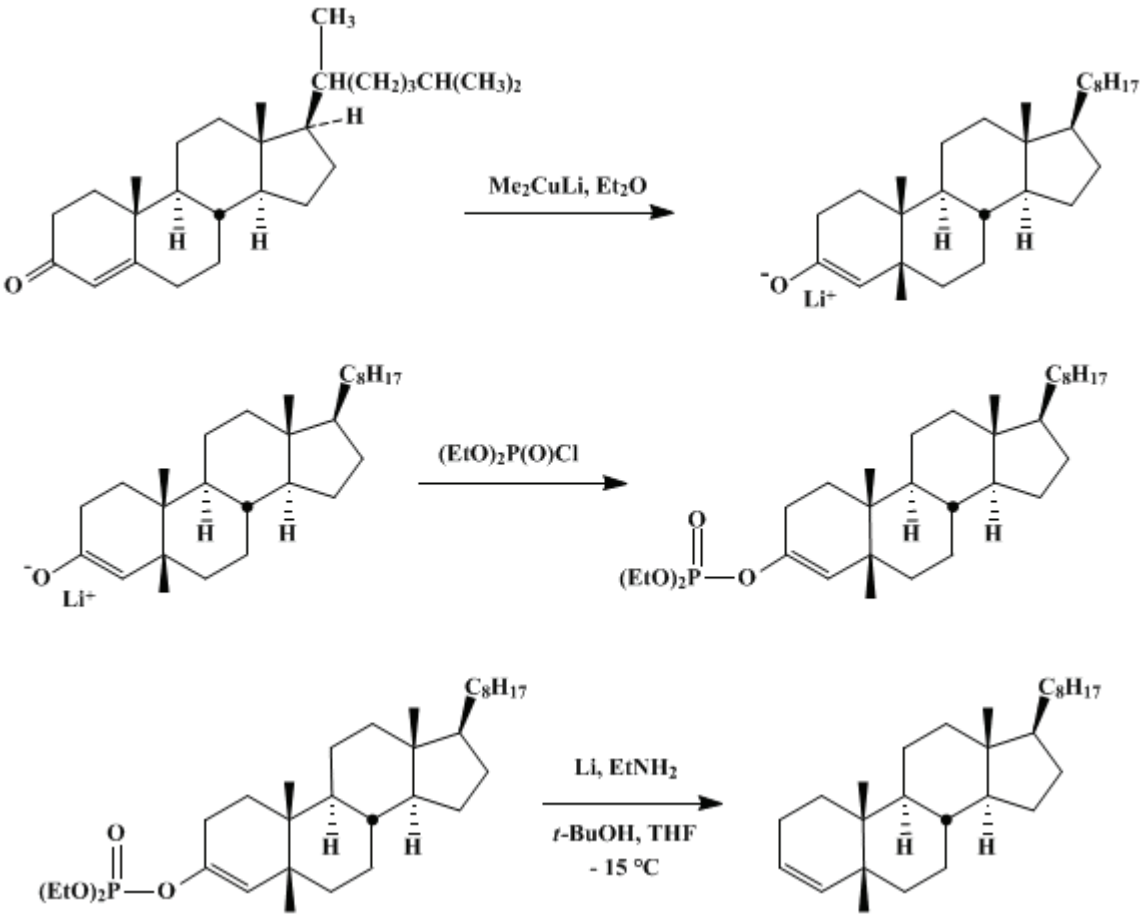
PREPARATION AND REDUCTIVE CLEAVAGE OF ENOL PHOSPHATES: 5-METHYLCOPROST-3-ENE

[Cholest-3-ene, 5-methyl-, (5β)-]



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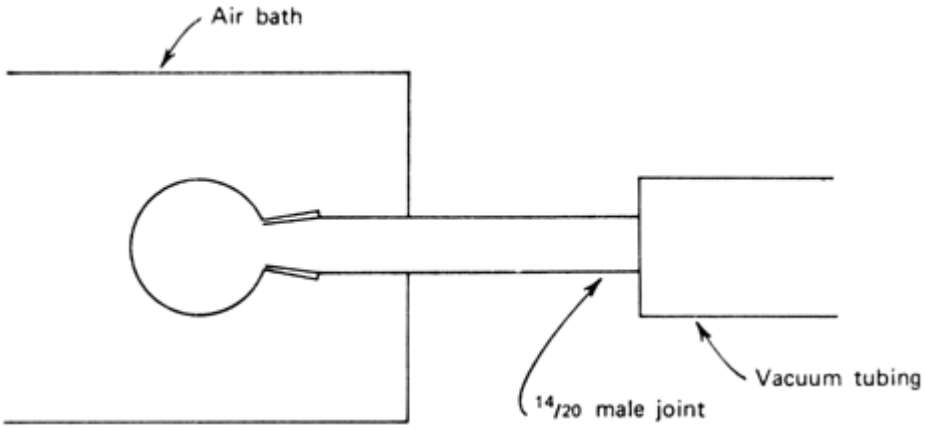
1. Procedure

A. *Diethyl 5-methylcoprost-3-en-3-yl phosphate.* A dry, 100-ml., three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, a nitrogen inlet tube, and a rubber septum is charged with 384 mg. (0.00201 mole) of copper(I) iodide (Note 1) and 20 ml. of anhydrous diethyl ether (Note 2). After the reaction vessel has been flushed with nitrogen, a static oxygen-free nitrogen atmosphere is maintained in the reaction vessel throughout the remainder of the reaction. The reaction mixture is cooled in an ice bath and an ether solution, containing 0.0040 mole of methyllithium (Note 3), is added with a hypodermic syringe, dropwise and with stirring. As the methyllithium is added, the initial yellow precipitate of polymeric methylcopper(I) redissolves, forming a colorless to pale-yellow solution of lithium dimethylcuprate (Note 4). To the resulting cold solution is added, dropwise and with stirring over 20 minutes, a solution of 576 mg. (0.00150 mole) of cholest-4-en-3-one (Note 5) in 20 ml. of ether (Note 2). During the addition of the enone, a yellow precipitate of polymeric methylcopper(I) separates from the reaction solution. After the addition is complete, the cooling bath is removed, and the reaction mixture is stirred for 2 hours at room temperature. The dropping funnel is replaced with a second dry dropping funnel which contains a loose plug of glass wool above the stopcock. The reaction mixture is again cooled in an ice bath and a mixture of 4.0 ml. of triethylamine (Note 6) and 2.00 g.

(0.0115 mole) of diethyl phosphorochloridate (Note 7) is added from the dropping funnel to the reaction mixture, rapidly and with stirring. After this addition, the cooling bath is removed, and stirring is continued for one hour. Saturated aqueous sodium hydrogen carbonate is added to hydrolyze any remaining organometallic reagents before the reaction mixture is transferred to a separatory funnel and washed successively with two 50-ml. portions of cold (0°) 1 *M* ammonium hydroxide and a 50-ml. portion of water. The aqueous washes are extracted in turn with a 30-ml. portion of ether. The combined ether solutions are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. A solution of the residual liquid in 3 ml. of ether is applied to a 2.5 cm. by 15 cm. chromatographic column packed with a slurry of 50 g. of silica gel (Note 8) in ether. The column is eluted with ether. After the first 70 ml. of eluent has been collected and discarded, the next 120 ml. of ether eluent is collected and concentrated with a rotary evaporator, yielding 420–480 mg. of crude phosphate ester (Note 9), a colorless liquid, sufficiently pure for use in the following procedure.

B. 5-*Methylcoprost*-3-*ene.* A dry, 100-ml., three-necked flask equipped with a polyethylene-coated magnetic stirring bar, two gas-inlet tubes, and a pressure-equalizing dropping funnel is immersed in a 2-propanol–dry ice cooling bath maintained at −15° to −20°. The reaction vessel is flushed with either helium or argon, and a static atmosphere of one of these gases is maintained in the reaction vessel throughout the reaction. Ethylamine (Note 10) is distilled through a tower of sodium hydroxide pellets into the cold reaction flask until 50 ml. of the liquid amine has been collected. A 70-mg. (0.010 g.-atom) piece of lithium wire is cleaned by dipping it successively into methanol and pentane and added to the reaction flask. The resulting cold (−15°) mixture is stirred for 10 minutes to dissolve the lithium before a solution of the diethyl 5-methylcoprost-3-en-3-yl phosphate and 0.50 ml. (0.39 g., 0.0053 mole) of *tert*-butyl alcohol (Note 11) in 15 ml. of tetrahydrofuran (Note 2) is added, dropwise and with stirring over 15 minutes, to the cold, blue lithium–amine solution. The blue solution is stirred for an additional 15 minutes before 1 ml. of saturated ammonium chloride is added to consume excess lithium. The resulting colorless mixture is warmed, evaporating ethylamine, and the residue is diluted with 90 ml. of 10% aqueous sodium hydroxide and extracted with two 30-ml. portions of pentane. The combined organic solutions are washed with 50 ml. of aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. The residual, viscous liquid is subjected to evaporative distillation, from a 25-ml. flask into a male 14–20 standard-taper glass joint as shown in Figure 1. The air bath is heated to 150–180° while the pressure in the system is maintained at 0.05 mm. to 0.4 mm. Distillation of 5-methylcoprost-3-ene yields 260–295 mg. (45–51%) of colorless liquid, n_D^{25} 1.5115–1.5123 (Note 12).

Figure 1. Apparatus for evaporative distillation.



2. Notes

1. A purified grade of copper(I) iodide, purchased from Fisher Scientific Company, was used without purification.
2. Reagent grade ether and tetrahydrofuran were distilled from lithium aluminum hydride immediately prior to use.
3. Ethereal solutions of methyllithium are available from either Foote Mineral Company or Alpha

Inorganics, Inc. These solutions should be titrated immediately before use with 2-butanol and 2,2-bipyridyl as an indicator [*Org. Synth.*, **Coll. Vol. 5**, 211 (1973); *Org. Synth.*, **Coll. Vol. 6**, 121 (1988)].[2] In a typical run, 2.44 ml. of ethereal 1.64 *M* methyllithium was employed.
4. The appearance of a brown to black precipitate indicates either oxidative or thermal decomposition of the cuprate. If such decomposition has occurred, it is best to prepare the reagent again with greater care, avoiding molecular oxygen and/or excessive reaction temperatures.
5. A commercial sample of cholest-4-en-3-one from Eastman Organic Chemicals was used without further purification. The preparation of this ketone has also been described in *Org. Synth.*, **Coll. Vol. 4**, 192 (1963).
6. The glass wool filter collects any of the insoluble triethylammonium chloride which might be formed. A reagent grade of triethylamine (b.p. 88°) was distilled from calcium hydride prior to use. *N,N,N′,N′*-Tetramethylethylenediamine has also been found to be a satisfactory Lewis base for less reactive enolates[3,4].
7. Commercial diethyl phosphorochloridate, b.p. 60–62° (1.5 mm.), purchased from Eastman Organic Chemicals, was distilled prior to use in this reaction.
8. A good grade of silica gel, such as that available from E. Merck and Company, Darmstadt, is appropriate for this chromatography.
9. The ^{1}H NMR spectrum ($CDCl_3$) of the crude product has absorption at δ 0.6–2.3 (m, *ca.* 52 H, aliphatic C*H*), 3.9–4.4 (m, 4H, 2CH_2O), and 5.1 (m, 1H, vinyl *H*).
10. Ethylamine (b.p. 17°) is available from Eastman Organic Chemicals.
11. A commercial grade of *tert*-butyl alcohol (b.p. 83°) should be distilled from calcium hydride before use.
12. The product exhibits end absorption in the UV (95% C_2H_5OH) with ε 330 at 210 nm and a series of ^{1}H NMR peaks ($CDCl_3$) at δ 0.67, 0.82, 0.85, 0.88, and 0.92 (18H, 6CH_3) with a multiplet at δ 1.0–2.2 and a partially resolved multiplet attributable to two vinyl protons. This latter absorption corresponds approximately to signals at δ 5.28 (d of t, J = 8 and 1 Hz., 1H) and 5.60 (d of t, J = 8 and 2.8 Hz., 1H). The mass spectrum of the product has the following abundant peaks: *m/e* (rel. int.), 384 (100, M^+), 369 (69), 355 (70), 229 (27), 122 (28), 109 (28), 107 (60), 95 (33), 93 (34), 81 (72), 55 (30), and 43 (31).
The submitters report that ozonolysis of the product at −10° in a mixture of ethyl acetate and acetic acid, followed by reaction with hydrogen peroxide, formed 3,4-*seco*-5-methylcoprostan-3,4-dioic acid as crystals from ethyl acetate, m.p. 168–172° with prior softening at 130°.

3. Discussion

The conjugate addition of lithium dimethylcuprate and other organocopper reagents to α,β-unsaturated ketones is a reaction which has had wide application and has been fairly well studied.[5 6 7] In order that the positional specificity which has been conferred upon the enolate anions generated by such additions might be maintained, these intermediates have been intercepted with acetic anhydride,[5] chlorotrimethylsilane,[8 9] diethyl phosphorochloridate,[4,10] tetramethyldiamidophosphorochloridate,[3,4] alkyl halides,[11 12] aldehydes,[13] ketones,[14] acid chlorides,[15] and Michael acceptors.[16]

The reductive fission of enol phosphates to olefins is a modification of the procedure used by Kenner and Williams[17] to deoxygenate phenols. The enol phosphates, which have been reduced by the action of lithium in ammonia or alkylamines and by the action of titanium metal,[18] have been prepared by treatment of α-bromoketones with triethyl phosphite,[4,19] by interception of enolates generated by the addition of lithium dimethylcuprate to α,β-unsaturated ketones,[4,10] by interception of enolates resulting from treatment of unsaturated ketones with lithium in ammonia,[10] and by phosphorylation of enolates of ketones.[20]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 346

References and Notes

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

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

nitrogen (7727-37-9)

hydrogen peroxide (7722-84-1)

ammonium hydroxide (1336-21-6)

Pentane (109-66-0)

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

lithium (7439-93-2)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

Methyllithium (917-54-4)

Cholest-4-en-3-one (601-57-0)

triethylamine (121-44-8)

argon (7440-37-1)

tert-butyl alcohol (75-65-0)

Triethyl phosphite (122-52-1)

ethylamine (75-04-7)

calcium hydride (7789-78-8)

helium (7440-59-7)

2-Butanol (78-92-2)

2,2-bipyridyl (366-18-7)

diethyl phosphorochloridate (814-49-3)

lithium dimethylcuprate

CHLOROTRIMETHYLSILANE (75-77-4)

methylcopper(I)

5-Methylcoprost-3-ene (23931-38-6)

Cholest-3-ene, 5-methyl-, (5β)-

Diethyl 5-methylcoprost-3-en-3-yl phosphate (23931-37-5)

triethylammonium chloride

tetramethyldiamidophosphorochloridate (1605-65-8)

titanium (7440-32-6)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

3,4-seco-5-methylcoprostan-3,4-dioic acid