



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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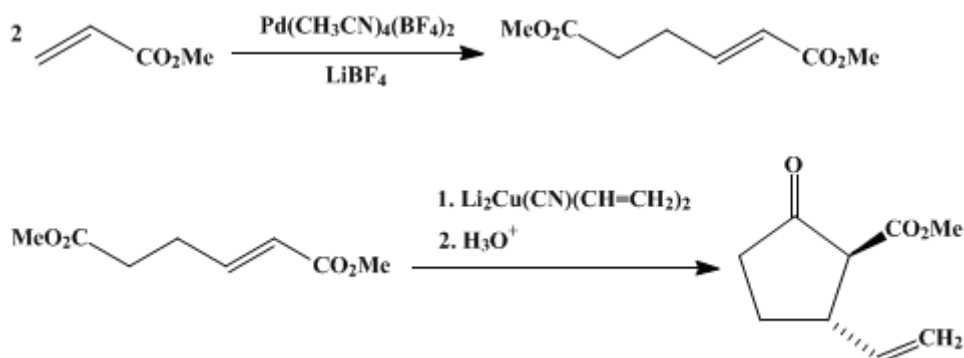
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Organic Syntheses, Coll. Vol. 8, p.112 (1993); Vol. 66, p.52 (1988).

CONJUGATE ADDITION–CYCLIZATION OF A CYANOCUPRATE: 2-CARBOMETHOXY-3- VINYL-CYCLOPENTANONE

[Cyclopentanecarboxylic acid, 2-ethenyl-5-oxo-, methyl ester]



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1. Procedure

A. *Dimethyl (E)-2-hexenedioate*.² A 100-mL, one-necked, round-bottomed flask is capped by a septum, swept with dry nitrogen and flame-dried. The flask is charged with methyl acrylate (50 mL, 0.55 mol, (Note 1)), then anhydrous lithium tetrafluoroborate (9 g, 0.096 mol, (Note 2)), and finally tetrakis(acetonitrile)palladium tetrafluoroborate (1.33 g, 0.003 mmol, (Note 3)). The mixture is stirred briefly until homogeneous. It is warmed under nitrogen in a 40°C oil bath for 72 hr (Note 4) and then allowed to cool to room temperature. The mixture is added to saturated aqueous sodium bicarbonate (100 mL) and extracted with ether (3 × 50 mL). The combined ether extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil with a rotary evaporator. The residue is distilled through a 10-cm Vigreux column to give dimethyl (E)-2-hexenedioate (38.6 g, 81%, (Note 5)) as a colorless liquid, bp 100°C (1.1 mm).

B. *2-Carbomethoxy-3-vinylcyclopentanone*. A 1-L, three-necked, round-bottomed flask is fitted with a 125-mL pressure-equalizing addition funnel capped with a septum, an overhead stirrer, and a septum. The apparatus is flame-dried and purged with dry nitrogen. The flask is charged through the addition funnel with tetravinyltin (12.48 g, 0.055 mol, (Note 6)) and anhydrous ether (250 mL). The solution is cooled to 0°C under nitrogen, and low-halide methyllithium in ether (133 mL, 1.5 M, 0.20 mol, (Note 7)) is slowly added directly by syringe to the stirred solution. After 15 min, the vinyl lithium mixture is cooled in a dry ice–acetone bath to –78°C for 20 min. The septum on one neck is briefly removed, and copper(I) cyanide (9.31 g 0.107 mol, (Note 8)) is added all at once. The septum is replaced by a low-temperature thermometer in an adapter. The bath and reaction are allowed to warm under nitrogen slowly, with stirring, so that the internal temperature is –30°C after 1 hr (Note 9). The addition funnel is charged with dimethyl (E)-2-hexenedioate (6.89 g, 0.040 mol) and anhydrous ether (16 mL). The contents of the addition funnel are added dropwise over 30 min to the cuprate at –30°C, and stirring is continued under the nitrogen atmosphere for an additional 30 min at that temperature. A mixture of saturated aqueous ammonium chloride (80 mL) and water (80 mL) is added dropwise over 20 min through the addition funnel while the temperature of the system is allowed to rise. After the mixture is stirred for an additional 90 min it is filtered through a medium-porosity glass frit. The flask and filter cake are rinsed with water (2 × 30 mL) and ether (2 × 30 mL). The ether layer is separated, and the aqueous layer is further extracted with ether (2 × 75 mL). The combined organic layers are washed with water (25 mL), dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator (Note 10). The residue (Note 11) is distilled through a short-path distillation apparatus to

afford 2-carbomethoxy-3-vinylcyclopentanone (5.39 g, 80%, (Note 12)) as a colorless liquid, bp 65–70°C at 0.4 mm (Note 13).

2. Notes

1. Reagent-grade methyl acrylate from Fisher Scientific Company, containing *p*-methoxyphenol as inhibitor, was used as received.
2. Anhydrous 98% pure lithium tetrafluoroborate (LiBF₄) from Alfa Products, Morton/Thiokol, Inc. was used as received.
3. The palladium complex was purchased from Strem Chemical Company and was used as received. Alternatively, material prepared from palladium sponge and nitrosonium tetrafluoroborate in acetonitrile³ worked equally well.
4. The grayish precipitate which begins to appear after ca. 40 hr is the 1 : 1 adduct of the product with lithium tetrafluoroborate.
5. Submitters find that the product typically contains 95% of 2-hexenedioates as measured by capillary column GLC (30-m DB17 column, 120°C isothermal). Retention times for the isomeric hexenedioates were (*Z*)-2 (2.44 min), (*Z*)-3 (2.75 min), (*E*)-3 (3.08 min), (*E*)-2 (3.44 min). TLC (30 : 70 ethyl acetate/hexane, UV) for some runs shows, in addition to the product at $R_f = 0.36$, a weak spot due to an intensely UV-active impurity at $R_f = 0.41$. The spectra are as follows: ¹H NMR (CDCl₃) δ: 2.45–2.58 (m, 4 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 5.87 (d, 1 H, $J = 16$), 6.96 (dt, 1 H, $J = 16, 6$); IR (CCl₄) cm⁻¹: (C=O) 1743 s, 1730 s, (C=C) 1661 m.
6. The submitters obtained tetravinyltin from Columbia Organic Chemicals Company; it was used as received. The checkers obtained it from K&K Laboratories, ICN Biomedicals Inc., Plainview, NY. It may also be synthesized by literature methods.^{4 5}
7. Low-halide methyllithium in ether from Alfa Products, Morton/Thiokol, Inc. or Aldrich Chemical Company, Inc. was used as received. A single run using methyllithium/lithium bromide complex gave a significantly reduced yield (53%). Use of commercial vinylithium in tetrahydrofuran gave a product contaminated with starting dimer, requiring chromatographic purification.
8. Copper (I) cyanide from Alfa Products, Morton/Thiokol, Inc. was used as received. *Caution! Copper (I) cyanide is severely toxic.* Care should be taken not to expose cyanide-containing wastes to strong acid, thus liberating hydrogen cyanide. Prior to disposal, insoluble wastes should be treated overnight with a strong alkaline solution containing calcium hypochlorite.
9. If the internal temperature is allowed to rise too quickly, rapid exothermic cuprate formation can occur with resultant decomposition of the reagent.
10. Tetramethyltin (bp 78°C) is a potentially hazardous side product of this reaction. This workup should therefore be done with gloves in a well-ventilated hood. Most of the tetramethyltin ends up in the condensate from the rotary evaporator; the condensate should be disposed of by incineration.
11. In two cases submitters have observed that the residue separated into two layers. The upper layer consists of a heavy oil apparently because of incomplete washing of the lithium suspension used in manufacturing methyllithium. When this happens it is necessary to remove the oil with a pipette prior to distillation. Failure to do so gives a product that appears pure by TLC but is substantially impure according to elemental analysis (1 % high in carbon).
12. Submitters find that the product is homogeneous by TLC (30 : 70 ethyl acetate/hexane, I_2 , $R_f = 0.43$). Capillary column GLC analysis (30-m DB17 column, 120°C isothermal) is complicated by some thermal decarboxylation on the column. However, using a clean injection port liner and 180°C injection port, 95% of the product is eluted as a single, somewhat broad peak at 3.0-min retention time. The spectra are as follows: ¹H NMR (CDCl₃) δ: 1.72 (m, 1 H), 2.1–2.6 (m, 3 H), 3.05 (d, 1 H, $J = 11$), 3.1–3.3 (m, 1 H), 3.75 (s, 3 H), 5.09 (d, 1 H, $J = 11$), 5.16 (d, 1 H, $J = 17$), 5.75–5.85 (m, 1 H); IR (CCl₄) cm⁻¹: (C=O) 1762 s, 1735 s, 1662 m, 1618 m; (C=C) 1644 w.
13. The submitters have carried out these steps on twice the scale given here. On that scale their yields for Step A were 91–93%; for step B, 77–85%.
The checkers found that the diastereomeric purity of the product was much greater than 90% based on its 300 MHz ¹H and fully decoupled ¹³C NMR spectra. Based on the proton–proton coupling constant ($J = 11$), *trans* geometry has been assigned.

3. Discussion

This procedure illustrates a general route to the 3-substituted 2-carbomethoxycyclopentanones, which are versatile intermediates for the preparation of a variety of cyclopentanoid products. For example, the product of this procedure, 2-carbomethoxy-3-vinylcyclopentanone, has been utilized in the synthesis of methyl dihydrojasmonate⁶ and 18-hydroxyestrone.⁷ This conjugate addition–cyclization approach (utilizing "Gilman reagents" prepared from copper(I) iodide) has been applied⁸ to the synthesis of the methyl-, butyl-, *sec*-butyl-, neopentyl-, and phenyl-substituted 2-carbomethoxycyclopentanones. The present procedure takes advantage of the greater stability of higher order cyanocuprates⁹ ("Lipshutz reagents") to overcome the moderate yield of the vinyl analog due to cuprate decomposition as reported in earlier studies.⁸ With either the Gilman or Lipshutz reagents, Michael addition to dimethyl (*E*)-2-hexenedioate produces an enolate that undergoes Dieckmann cyclization faster than proton transfer. Therefore, no 4-substituted cyclopentanones are formed. This approach has now been extended to the synthesis of the corresponding cyclopentenones by using dimethyl 2-hexynedioate as the Michael acceptor.¹⁰

Alternatively, 3-substituted 2-carbomethoxycyclopentanones have been prepared by Michael addition to 2-carbomethoxycyclopentenone.^{11,12,13} However, this Michael acceptor is unstable, is difficult to prepare, and polymerizes in the presence of many nucleophiles.¹² A longer synthesis of 2-carbomethoxy-3-vinylcyclopentanone has been reported.⁶ The general route to 2-carbomethoxy-3-vinylcyclopentanones developed by Trost¹⁴ has the advantage of producing these compounds in optically active form.

Several catalyst systems have been described for the tail-to-tail dimerization of methyl acrylate.^{15,16,17,18,19,20} Advantages of the dimerization procedure described here are its mild conditions, efficient use of the catalyst, and high selectivity for the Δ^2 isomer. Tetrakis(acetonitrile)palladium tetrafluoroborate, Pd(NCMe)₄(BF₄)₂, also efficiently catalyzes dimerization of ethyl acrylate and methyl methacrylate. The presence of lithium tetrafluoroborate in the reaction mixture increases the rate of the reaction and prolongs catalyst life. Dimerization of methyl acrylate can be effected without lithium tetrafluoroborate if the reaction is performed in nitromethane.

References and Notes

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

18-hydroxyestrone

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

sodium bicarbonate (144-55-8)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

copper(I) cyanide,
Copper (I) cyanide (544-92-3)

carbon (7782-42-5)

palladium sponge (7440-05-3)

ethyl acrylate (140-88-5)

Nitromethane (75-52-5)

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

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

calcium hypochlorite (7778-54-3)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methylithium (917-54-4)

p-methoxyphenol (150-76-5)

vinylithium (917-57-7)

methyl methacrylate (80-62-6)

nitrosonium tetrafluoroborate (14635-75-7)

cyanocuprate

tetramethyltin (594-27-4)

2-Carbomethoxy-3-vinylcyclopentanone,
Cyclopentanecarboxylic acid, 2-ethenyl-5-oxo-, methyl ester (75351-19-8)

lithium tetrafluoroborate (14283-07-9)

tetrakis(acetonitrile)palladium tetrafluoroborate

tetravinyltin (1112-56-7)

dimethyl 2-hexynedioate

2-carbomethoxycyclopentenone

Dimethyl (E)-2-hexenedioate (113327-79-0)

methyl dihydrojasmonate