A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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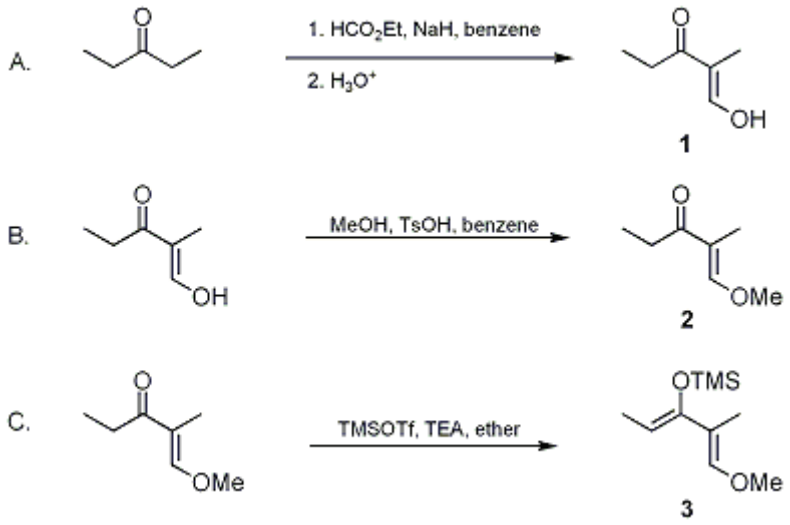
(E,Z)-1-METHOXY-2-METHYL-3-(TRIMETHYLSILOXY)-1,3-PENTADIENE

[Silane, [[1-(2-methoxy-1-methylethenyl)-1-propenyl]oxy]trimethyl-, (Z,E)-]



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Checked by David I. Magee and Robert K. Boeckman, Jr..

1. Procedure

CAUTION! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

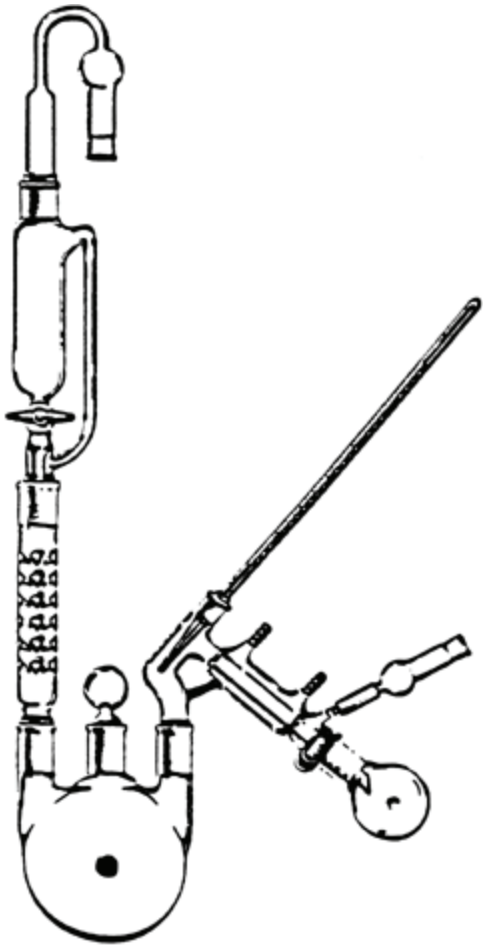
A. A 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, calcium sulfate drying tube, and 500-mL pressure equalizing addition funnel is charged with 2.4 L of dry benzene (Note 1), 81.7 g (2.04 mol) of 60% sodium hydride dispersion in benzene (Note 2), and 1.9 mL (0.05 mol) of methyl alcohol (Note 3). The flask is immersed in an ice bath and the addition funnel is charged with a mixture (Note 4) of 222 mL (172 g, 2 mol) of 95% 3-pentanone and 163 mL (148 g, 2 mol) of 99% ethyl formate (Note 5). This mixture is added dropwise to the cooled, stirred suspension over 1.5 hr. During the addition, there is a visible evolution of gas, the mixture darkens, and a paste-like precipitate forms. At the completion of the addition, the ice bath is removed and the mixture is stirred an additional 1.5 hr, until gas evolution has ceased. The stirred reaction mixture is then diluted with 1.5 L of anhydrous ether (Note 6). The suspension is filtered through an 18.5-cm Büchner funnel fitted with two Whatman 1 filter papers and the solid is washed with two 500-mL portions of anhydrous ethyl ether. The solid is transferred to a 19 × 10-cm evaporating dish and dried under reduced pressure in a vacuum desiccator to afford crude sodium salt of **1** (270–280 g) as a colorless or slightly tan hygroscopic solid. The material is carried on directly in the continuation of this procedure.

A 4-L Erlenmeyer flask equipped with a 2-in Teflon-coated magnetic stirbar is charged with 1.5 L of deionized water and placed in an ice bath. To the stirring water is added in small portions (*CAUTION*, (Note 7)) the crude sodium salt of **1**. When all of the salt has dissolved, the cooled, dark brown solution is acidified to pH 5 (Hydrion paper) by dropwise addition of concd hydrochloric acid. The resultant two-phase mixture is poured into a 3-L separatory funnel and the Erlenmeyer flask is washed with two 100-mL portions of ethyl ether which are added to the separatory funnel. An additional 800 mL of ether is added to the mixture. The upper (organic) and lower (aqueous) phases are separated.

The aqueous phase is extracted six additional times (Note 8) with 400 mL of ether each time. The combined organic phases are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure at 10°C to afford approximately 250 mL of crude **1** as a clear amber oil. This is distilled (Note 9) under reduced pressure (bp 58.5°C, 20 mm) to afford 125–137 g (55–60% yield) of **1** as a slightly yellow oil which solidifies on standing. An analytical sample of **1** was prepared by recrystallization from pentane (mp 42–43°C) (Note 10).

B. A 3-L, three-necked, round-bottomed flask is equipped (see Figure 1) with a 2-in Teflon-coated magnetic stirring bar, a 150-mm Vigreux column topped by a 500-mL pressure-equalizing addition funnel and calcium sulfate drying tube, a short path distillation apparatus, and a ground glass stopper. The flask is charged with 1 L of benzene and 0.5 L of a 60:40 mixture of benzene/methanol (Note 11). To this solution is added 114 g (1.0 mol) of 1-hydroxy-2-methylpent-1-en-3-one **(1)** in a small amount of benzene and 0.95 g (0.005 mol) of p-toluenesulfonic acid monohydrate. The addition funnel is charged with 500 mL of the 60:40 benzene/methanol mixture. The magnetically stirred solution is warmed to a gentle reflux at which time the solution begins to darken to a light brown color. The distillation temperature rises to 59°C (the boiling point of the benzene/methanol azeotrope) and stabilizes. The distillate volume is monitored throughout the course of the reaction. When 250 mL of distillate has collected, the reaction vessel is replenished with 250 mL of fresh benzene/methanol mixture. This cycle is repeated 6 times until starting material is consumed (Note 12). At this time any residual benzene/methanol mixture in the addition funnel is discarded and the funnel is charged with 500 mL of benzene. The reaction volume is maintained by the addition of benzene as the boiling point of the distillate rises to 79°C. In this way, a total of 750 mL of benzene is distilled out of the reaction mixture as the reaction is driven to completion. The reaction mixture is allowed to cool to room temperature and is quenched by the addition of 500 mL of 1.0 M aqueous sodium bicarbonate solution. The two phase mixture is stirred for 5 min and then transferred to a 2-L separatory funnel. The phases are separated and the aqueous (lower) phase is extracted two times with 500 mL of ether each time. The combined organic phases are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give crude **2** as a brown oil. The oil is fractionally distilled under reduced pressure (bp 94–96°C, 22 mm) to afford 90–96 g (70–75%) of **2**. Assay of this material by GLC shows it to be ca. 95% pure (Note 13).

Figure 1



C. A 2-L, round-bottomed flask equipped with a 2-in Teflon-coated magnetic stirring bar is charged with 750 mL of anhydrous ether, 102 g (1.0 mol) of 99% triethylamine (Note 14) and 96 g (0.75 mol) of 1-methoxy-2-methylpent-1-en-3-one **(2)**. The flask is capped with a rubber septum equipped with a 16-gauge needle connected to a dry nitrogen source. The magnetically stirred solution is cooled in an ice bath and 167 g (0.75 mol) of trimethylsilyl trifluoromethanesulfonate (Note 15) is added via an 18-gauge cannula over 10 min. The cooled mixture is stirred for 30 min, during which time a red-brown oily precipitate forms. The reaction mixture is transferred to a 2-L separatory funnel and the red-brown (lower) phase is separated and discarded. The remaining ethereal phase is washed with 500 mL of 1.0 M aqueous sodium bicarbonate solution and separated. The aqueous (lower) phase is extracted with 500 mL of ether, separated and discarded. The combined organic phases are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield crude diene **3** as a yellow oil. This is fractionally distilled through a 150-mm Vigreux column at reduced pressure (bp 83–85°C, 22 mm) to afford 121–131 g (81–87%) of **3** as a colorless or slightly yellow liquid. Assay of this material by GLC shows it to be ca. 95% pure (Note 16).

2. Notes

1. Unless otherwise indicated, the solvents are reagent grade and are used without further purification.
2. Commercially available (Aldrich Chemical Company, Inc.) 60% sodium hydride dispersed in mineral oil is dispersed in benzene in the following manner: 81.7 g of 60% sodium hydride mineral oil dispersion is suspended in 100 mL of benzene in a 500-mL Erlenmeyer flask equipped with a Teflon-coated magnetic stirbar. The suspension is vigorously stirred for 1 hr until all of the lumps are gone. The suspension is then transferred to the reaction vessel with a small amount of benzene.
3. Methyl alcohol functions as a catalytic base in this reaction.
4. The efficiency of the procedure is enhanced by complete premixing of the 3-pentanone and ethyl

formate.
5. 3-Pentanone and ethyl formate were purchased from Aldrich Chemical Company, Inc. and used without further purification.
6. Efficient mixing is essential during the addition of the ether to ensure the formation of a flocculent precipitate. Inadequate agitation results in the formation of large clumps of product.
7. *CAUTION: Small amounts of sodium hydride from the previous step may remain in the solid. The addition should be carried out slowly enough to allow any residual sodium hydride to quench completely before the next portion of solid is added.*
8. TLC analysis (Merck 0.25-mm silica gel plates with 254 nm UV indicator, 1:4 ethyl acetate:hexanes) of the organic phase of each extraction reveals the presence of **1** (R_f = 0.32). Extraction is continued until **1** is no longer seen in the organic extracts.
9. Crude **1** may solidify in the pot as any remaining solvent evaporates, but can be reliquified by gentle heating. Stirring is facilitated by a powerful magnetic stirrer and 2-in Teflon-coated magnetic stirbar. To prevent solidification of the distillate on the condenser, the water temperature through the condenser is maintained at 25°C. To minimize product loss, all fractions were collected in a receptacle cooled with an ice bath.
10. The ^{1}H-NMR spectrum of **1** is as follows: (90 MHz, $CDCl_3$, TMS = 0 ppm) δ: 1.13 (t, 3 H, J = 7), 1.79 (s, 3 H), 2.46 (q, 2 H, J = 7), 7.45 (s, 1 H), 7.57 (s, 1 H).
11. The composition of the binary azeotrope of benzene and methanol is 60.5% benzene, 39.5% methanol.
12. The progress of the reaction is monitored by TLC (R_f of **1** = 0.32, R_f of **2** = 0.25; 1:4 ethyl acetate:hexanes). A non-UV absorbing spot (R_f = 0.29) is seen to form as an intermediate between **1** and **2**. This is presumed to be the 1,1-dimethyl acetal of **1**. When this spot is nearly gone, the reaction is presumed to be complete.
13. The ^{1}H-NMR of **2** is as follows: (90 MHz, $CDCl_3$, TMS) δ: 1.10 (t, 3 H, J – 7.4), 1.71 (s, 3 H), 2.52 (q, 2 H, J = 7.4), 3.86 (s, 3 H), 7.23 (bs, 1 H).
14. Triethylamine was purchased from Aldrich Chemical Company, Inc. and was used without further purification.
15. Trimethylsilyl trifluoromethanesulfonate was purchased from Petrarch Systems and was used without further purification.
16. The ^{1}H-NMR of **3** is as follows: (90 MHz, $CDCl_3$, $CHCl_3$, δ 7.27) δ: 0.23 (s, 9 H), 1.63 (d, 3 H, J = 7), 1.70 (s, 3 H), 3.66 (s, 3 H), 4.75 (q, 1 H, J = 7), 6.35 (s, 1 H).

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

Siloxy dienes have been shown to be highly effective in both the Diels-Alder[3] [4] reaction and the hetero Diels-Alder (diene-aldehyde cyclocondensation)[5] reactions. Diene **3** has been used in the synthesis of several important natural products including zincophorin,[6] rifamycin,[7] and the Prelog-Djerassi lactone.[8] Recently, under the aegis of chiral catalysts, **3** has been shown to participate in the diene-aldehyde cyclocondensation reaction with several aldehydes to afford cycloadducts of very high enantiomeric excess.[9] [10]

The procedure described here allows the convenient preparation of large quantities of diene **3** and has several advantages over previously published sequences. 1-Methoxy-2-methylpenten-3-one **(2)** can be prepared in ca. 90-g lots and can be stored for several months at 0°C under argon. The earlier procedure for the synthesis of **2**[11] relies on dimethyl sulfate as the methylating reagent in the formation of the methyl enol ether moiety. The high toxicity of this reagent renders this strategy unattractive for routine use. The published procedure for the conversion of **2** to 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene **(3)**[3] uses trimethylsilyl chloride, triethylamine and a catalytic amount of zinc chloride in benzene (40°C, ca. 12 hr) for the silylation. This mixture results in the formation of copious quantities of triethylamine hydrochloride, which greatly complicates the work up and purification. This new procedure, using trimethylsilyl trifluoromethanesulfonate and triethylamine,

allows the convenient separation of the amine salt and significantly shortens the reaction time (30 min vs 12 hr). The silylation can be carried out on scales ranging from 0.10 mol to 0.75 mol with consistently good yields. Diene **3** can be stored for several months at 0°C under argon without significant decomposition.

References and Notes

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

hexanes

1,1-dimethyl acetal

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methyl alcohol,
methanol (67-56-1)

ether,
ethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

ethyl (2025-56-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

zinc chloride (7646-85-7)

ethyl formate (109-94-4)

Triethylamine hydrochloride (554-68-7)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

3-pentanone (96-22-0)

sodium hydride (7646-69-7)

triethylamine (121-44-8)

argon (7440-37-1)

trimethylsilyl chloride (75-77-4)

Trimethylsilyl trifluoromethanesulfonate (27607-77-8)

p-toluenesulfonic acid monohydrate (6192-52-5)

(E,Z)-1-Methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene,
Silane, [[1-(2-methoxy-1-methylethenyl)-1-propenyl]oxy]trimethyl-, (Z,E)- (72486-93-2)

1-Hydroxy-2-methylpent-1-en-3-one (50421-81-3)

1-Methoxy-2-methylpent-1-en-3-one,
1-Methoxy-2-methylpenten-3-one

1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene