



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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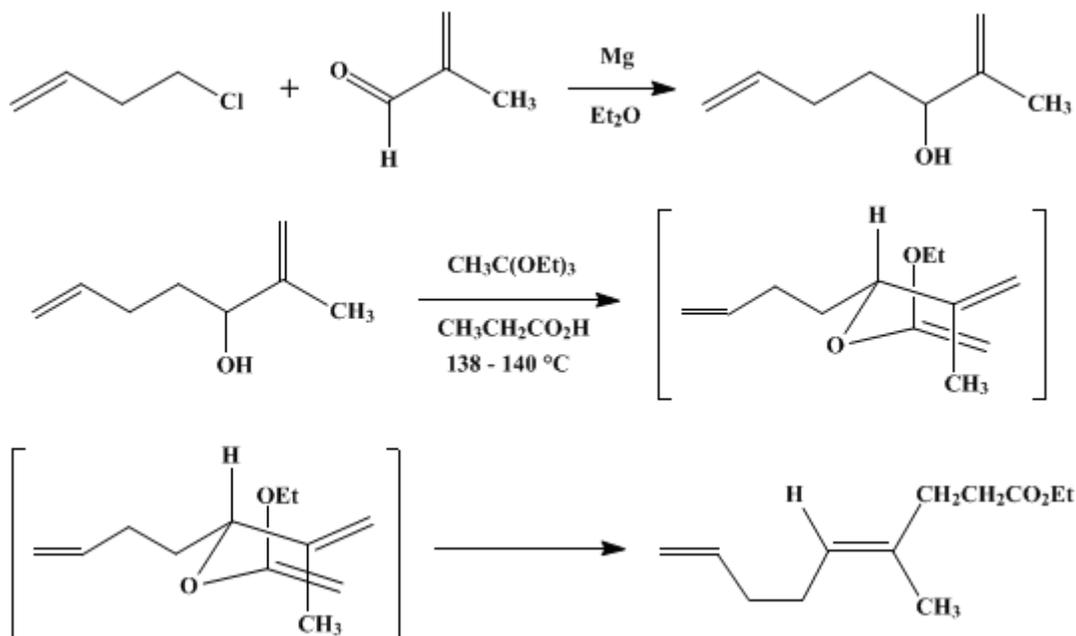
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.606 (1988); Vol. 53, p.116 (1973).

STEREOSELECTIVE SYNTHESIS OF TRISUBSTITUTED OLEFINS: ETHYL 4-METHYL-(*E*)-4,8-NONADIENOATE

[4,8-Nonadienoic acid, 4-methyl, ethyl ester, *trans*-]



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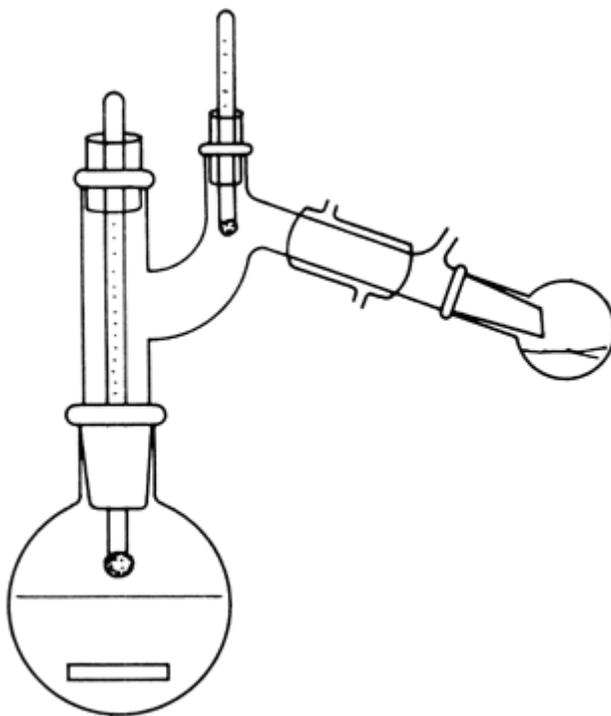
1. Procedure

A. *2-Methyl-1,6-heptadien-3-ol*. A dry, three-necked, 1-l., round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a nitrogen inlet tube, and a 125-ml., pressure-equalizing dropping funnel capped with a rubber septum is charged with 15.7 g. (0.646 g.-atom) of **magnesium turnings**. The flask is dried by heating with a flame while a stream of dry **nitrogen** is passed through the reaction vessel from the condenser and allowed to exit from a hypodermic needle inserted in the rubber septum. After drying, the hypodermic needle is removed and the flask is allowed to cool; a static **nitrogen** atmosphere is maintained in the reaction vessel for the remainder of the reaction. A small crystal of **iodine** and 450 ml. of anhydrous **diethyl ether** are added (**Note 1**). A solution of 49.4 g. (0.546 mole) of **4-chloro-1-butene** (**Note 2**) in 50 ml. of anhydrous **ether** is then added from the dropping funnel, dropwise and with stirring. Sufficient external heat is applied to the reaction flask to keep the temperature of the reaction mixture at about 30°. After approximately 10–50% of the chloride solution has been added, a spontaneous reaction ensues as evidenced by the disappearance of the yellow iodine color, the appearance of a gray color in the reaction solution, and the commencement of gentle refluxing. The external heat is removed, and the remainder of the chloride solution is added at a rate that maintains gentle refluxing. After the addition is complete, the reaction mixture is refluxed for 30 minutes before a solution of 40.1 g. (0.572 mole) of **methacrolein** (**Note 3**) in 50 ml. of anhydrous **ether** is added, dropwise with stirring and refluxing, over 45 minutes. Since the reaction with **methacrolein** is exothermic, the application of external heat may not be necessary to maintain refluxing during this addition. During the addition the reaction mixture usually becomes cloudy. When the addition is complete, the reaction mixture is refluxed with stirring for 1.5 hours before it is cooled in an ice water bath and 250 ml. of 5% **hydrochloric acid** is added slowly and with stirring (**Note 4**). The organic layer is separated and the aqueous layer is extracted with four 200-ml. portions of **ether**. The combined organic solutions are washed successively with 200 ml. of saturated aqueous **sodium hydrogen**

carbonate and 200 ml. of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The resulting ether solution is concentrated, and the residual liquid is distilled under reduced pressure, yielding 37.2–47.3 g. (54–69%) of 2-methyl-1,6-heptadien-3-ol as a colorless liquid, b.p. 85–88° (33 mm.), n_D^{25} 1.4531–1.4535 (Note 5).

B. *Ethyl 4-methyl-(E)-4,8-nonadienoate*. A 500-ml., one-necked, round-bottomed flask containing a magnetic stirring bar is fitted with a Claisen adapter, two thermometers, and a receiving flask as illustrated in Figure 1. To the flask is added 186 g. (1.15 moles) of ethyl orthoacetate (Note 6), 25.2 g. (0.200 mole) of 2-methyl-1,6-heptadien-3-ol, and 0.70 g. (0.0094 mole) of propionic acid (Note 7). The mixture is heated with stirring to keep the temperature above the liquid at 138–142°. Heating is continued until ethanol no longer distils from the reaction flask (approximately one hour is required). The reaction mixture is allowed to cool to room temperature, and the excess ortho ester and propionic acid are removed by distillation under reduced pressure (approximately 50–60° at 20 mm.). The colorless to yellow residual liquid is then distilled under reduced pressure (0.25 mm., (Note 8)), giving 32.6–34.6 g. (83–88%) of ethyl 4-methyl-(E)-4,8-nonadienoate as a colorless liquid, b.p. 54–55° (0.25 mm.), n_D^{25} 1.4504 (Note 9).

Figure 1. Apparatus for the preparation of ethyl 4-methyl-(E)-4,8-nonadienoate.



2. Notes

1. After drying, exposure of the reaction vessel and its contents to the atmosphere should be minimized. The iodine crystal should be added by lifting the dropping funnel, then replacing it quickly. The ether (anhydrous grade from Mallinckrodt Chemical Works) should be distilled from lithium aluminum hydride immediately before use and transferred to the reaction vessel with a stainless-steel cannula or a large hypodermic syringe inserted through the rubber septum.
2. 4-Chloro-1-butene is commercially available from Chemical Samples Company. The checkers employed this material without further purification. The submitters used material prepared from 3-buten-1-ol by a modified procedure of Roberts and Mazur.² Since material prepared according to the literature is invariably contaminated with thionyl chloride, which will interfere with formation of the Grignard reagent, the following modification is recommended. A two-necked, 200-ml., round-bottomed flask is equipped with a magnetic stirring bar, a 60-ml., pressure-equalizing dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube. The flask is charged with 49.8 g. (0.691 mole) of 3-buten-1-ol and 1.57 ml. of anhydrous pyridine (distilled from calcium hydride). With stirring

and external cooling (ice water bath), 82 g. (49 ml., 0.69 mole) of **thionyl chloride** (Matheson, Coleman and Bell commercial grade was used without further purification) is added dropwise over 3.5 hours. On completion of the addition, the mixture is heated under reflux for one hour. The external heating is then momentarily discontinued, and the condenser and dropping funnel are replaced by a stopper and short-path distilling head with receiver. Distillation of the mixture gives an opaque, colorless liquid (b.p. 68°). The crude product is washed with two 20-ml. portions of saturated aqueous **sodium hydrogen carbonate** solution (frothing) and 20 ml. of saturated brine, then dried over **magnesium sulfate** and filtered. The filtrate is distilled, giving 43.4 g. (67–69%) of **4-chloro-1-butene** as a colorless liquid, b.p. 68–70°.

3-Buten-1-ol, although commercially available from Aldrich Chemical Company, Inc., can be prepared economically and in large quantities by the addition of **paraformaldehyde** to **allylmagnesium bromide** [*Org. Synth.*, **Coll. Vol. 4**, 748 (1963)] in ether according to procedures outlined for a similar synthesis [*Org. Synth.*, **Coll. Vol. 1**, 188 (1944)]. In the present case, the submitters found it convenient to add the **paraformaldehyde** (Matheson, Coleman and Bell commercial grade was dried overnight under reduced pressure and in the presence of **phosphorus pentoxide**) directly to the **allylmagnesium bromide** solution. After a reaction period of 6 hours at reflux, the previously described [*Org. Synth.*, **Coll. Vol. 1**, 188 (1944)] isolation procedure gave **3-buten-1-ol** in 56% yield.

3. Technical grade (90%) **methacrolein** (Aldrich Chemical Company, Inc.) was distilled (b.p. 67–69°) immediately before use.

4. Since the **methacrolein** is used in excess, frothing is no problem as there is no Grignard reagent remaining after the reaction is completed. Addition of 5% **hydrochloric acid** causes some coagulation of magnesium salts in the aqueous layer, which can be redissolved by addition of more 5% **hydrochloric acid**.

5. The product has the following spectral characteristics: IR (CCl₄), 3620 (free OH), 3480 (associated OH), 1645 (C=C), and 910 cm⁻¹ (CH=CH₂); UV (95% C₂H₅OH) end absorption 210 nm (ϵ 208); ¹H NMR (CCl₄), δ 1.2–2.3 (m, 4H, 2CH₂), 1.70 (s, 3H, CH₃), 2.93 (broad, 1H, OH), 4.00 (t, $J = 6$ Hz., 1H, OCH), 4.6–5.2 (m, 4H, vinyl CH), and 5.5–6.1 (m, 1H, vinyl CH); *m/e* (rel. int.), 111(28), 84(29), 83(21), 71(51), 71(100), 69(23), 67(28), 57(30), 55(51), 43(71), 41(49), and 39(37).

6. Ethyl orthacetate, available from Aldrich Chemical Company, Inc., was distilled before use. A large forerun was collected, consisting of hydrolysis products of the ortho ester. Material boiling at 135–142° is suitable for use in the reaction. It is convenient to transfer the material to the reaction flask with a stainless-steel cannula to avoid its exposure to atmospheric moisture. A fivefold excess of the ortho ester is needed, since the first step in the reaction is probably the reversible acid-catalyzed exchange of **2-methyl-1,6-heptadien-3-ol** with **ethanol**.³

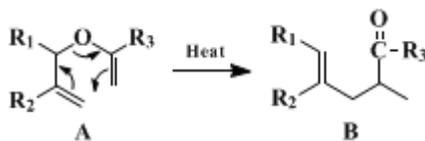
7. Practical grade **propionic acid** (Matheson, Coleman and Bell) was distilled before use (b.p. 141°).

8. On two occasions, the submitters noticed a sublimable solid crystallizing in the distilling head just before the product began to distill. The distilling head was rinsed with **ether**, dried, and replaced, and the distillation was continued. The checkers observed the same phenomenon.

9. The product has the following spectral properties: IR (CCl₄) 1735 (ester C=O), 1645 (C=C), and 920 cm⁻¹ (CH=CH₂); UV (95% C₂H₅OH) end absorption 210 nm (ϵ 1960); ¹H NMR (CDCl₃), δ 1.24 (t, $J = 7$ Hz., 3H, OCH₂CH₃), 1.63 (broad, 3H, C=CCH₃), 1.9–2.2 (m, 4H, 2CH₂), 2.37 (broad, 4H, 2CH₂), 4.14 (q, $J = 7$ Hz., 2H, OCH₂CH₃), 4.8–5.4 (m, 3H, vinyl CH), 5.5–6.2 (m, 1H, vinyl CH); *m/e* (rel. int.), 196 (M⁺, 4), 155(67), 151(30), 113(34), 109(100), 108(33), 85(47), 81(80), 67(74), 55(41), 53(31), 43(32), and 41(30). In C₆D₆ the allylic CH₃ signal of the major component present, the *trans*-isomer, is found at δ 1.50 and is accompanied by a minor peak at δ 1.61 attributable⁴ to 3–4% of the *cis*-olefin in the product.

3. Discussion

The use of the Claisen rearrangement and several other methods for the stereoselective synthesis of trisubstituted olefins has been reviewed.⁴ In allyl vinyl ethers of type A, the stereochemistry of the rearrangement is determined largely by the steric requirements of R₁, which can be either axial or equatorial in the transition state.⁵ When R₃ = H, the *trans/cis* ratio is approximately equal to the equatorial/axial equilibrium ratio of R₁-cyclohexane at the reaction temperature. When R₃ is larger than **hydrogen**, the steric effect is even greater, due to a potential 1,3-interaction which would develop in the transition state if R₁ were axial. No significant effect of R₂ on the *trans/cis* ratio has been observed.



The use of **ethyl orthoacetate** in the formation of vinyl ethers where $R_3 = \text{OC}_2\text{H}_5$ has been described.^{3,6} The method described herein appears to be quite general, in that a variety of esters of type B ($R_3 = \text{OC}_2\text{H}_5$; $R_2 = \text{CH}_3$) may be prepared by merely varying the Grignard reagent used in preparing the starting **allyl alcohol**. The only limitation is the use of alcohols that are unsymmetrically bis-allylic, from which mixtures of structural isomers may be obtained.

Stereoselectivity in the synthesis of trisubstituted olefins is necessary for the study of biosynthetic routes to polyisoprenoids, the nonenzymatic cyclization of polyolefinic substrates, and the study of insect hormones.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 6, 298](#)

References and Notes

1. Department of Chemistry, California Institute of Technology, Pasadena, California 91109.
2. J. D. Roberts R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).
3. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
4. D. J. Faulkner, *Synthesis*, 175 (1971).
5. D. J. Faulkner and M. R. Petersen, *Tetrahedron Lett.*, 3243 (1969).
6. W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).

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

brine

Ethyl orthoacetate

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

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

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

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

[thionyl chloride \(7719-09-7\)](#)

[sodium hydrogen carbonate \(144-55-8\)](#)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

propionic acid (79-09-4)

Allyl alcohol (107-18-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

iodine (7553-56-2)

pyridine (110-86-1)

magnesium sulfate (7487-88-9)

lithium aluminum hydride (16853-85-3)

Allylmagnesium bromide (1730-25-2)

methacrolein (78-85-3)

calcium hydride (7789-78-8)

3-buten-1-ol (627-27-0)

4-chloro-1-butene (927-73-1)

2-Methyl-1,6-heptadien-3-ol (53268-46-5)

ethyl orthoacetate

phosphorus pentoxide (1314-56-3)

Ethyl 4-methyl-(E)-4,8-nonadienoate,
4,8-Nonadienoic acid, 4-methyl, ethyl ester, trans- (53359-96-9)

paraformaldehyde (30525-89-4)