



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.

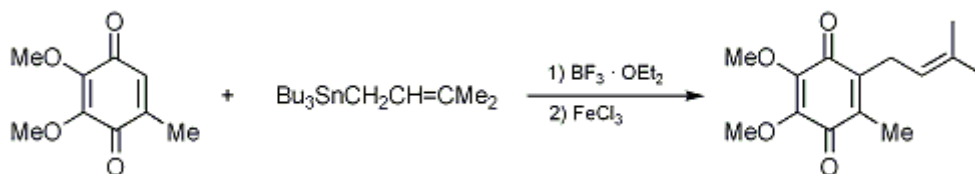
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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.

Organic Syntheses, Coll. Vol. 9, p.741 (1998); Vol. 71, p.125 (1993).

UBIQUINONE-1

[2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-]



Submitted by Yoshinori Naruta and Kazuhiro Maruyama¹.
Checked by Steven W. Elmore and Leo A. Paquette.

1. Procedure

CAUTION! This experiment should be performed with gloves in an efficient hood in order to avoid the contact of toxic tributyltin derivatives with the skin and to avoid their unpleasant odor.

A 500-mL, three-necked, round-bottomed flask fitted with a low-temperature thermometer, 125-mL pressure-equalizing dropping funnel, and nitrogen gas inlet is flame-dried under vacuum, cooled to room temperature, and flushed with nitrogen. The flask is charged with 5.00 g (27.4 mmol) of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (Note 1) as a solid followed by 100 mL of dry dichloromethane (Note 2) via syringe. The addition funnel is charged with 11.8 g (32.9 mmol) of tributyl(3-methyl-2-butenyl)tin (Note 3) in 100 mL of dry dichloromethane. The flask is immersed in an acetone/dry ice bath, the solution cooled to -78°C , and 10.1 mL (82.3 mmol) of boron trifluoride etherate (Note 4) is added dropwise from a syringe. Next, the stannane solution is added dropwise over a 30-min period. Following completion of the addition, the cooling bath is removed and the reaction mixture is allowed to warm to room temperature. At -40°C , the color of the solution turns from deep red to yellow. When the reaction mixture reaches 0°C , it is treated with 100 mL of 10% hydrochloric acid, stirred for 5 min, and allowed to stand. The aqueous phase that separates is washed with dichloromethane (2×20 mL) and the combined organic layers are washed with water (2×20 mL) and brine (2×20 mL), dried over anhydrous magnesium sulfate, and concentrated. The residual yellow oil is dissolved in 200 mL of ether and this solution is added to 37.1 g (137 mmol) of ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$) in 200 mL of water in a 500-mL conical flask. The resulting mixture is stirred for 8 hr at room temperature. The layers are then separated, the aqueous phase is extracted with ether (2×50 mL), and the combined organic solutions are stirred with 100 mL of 10% aqueous potassium fluoride for 2 hr (Note 5). The insoluble tin salts are separated by filtration (Note 6). The organic phase in the filtrate is washed with water (3×20 mL) and brine (3×20 mL), dried over anhydrous magnesium sulfate, and concentrated to give a deep red oil, that is purified by column chromatography (Note 7). The red-orange band is collected (1600–3000 mL) to give 6.15 g (90%) of 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone as a deep red oil (Note 8).

2. Notes

- Commercial 2,3-dimethoxy-5-methyl-1,4-benzoquinone (Aldrich Chemical Company, Inc.) was used without further purification.
- Dichloromethane was distilled from phosphorus pentoxide.
- Tributyl(3-methyl-2-butenyl)tin was prepared by the procedure on p. 707.
- Boron trifluoride etherate was purchased from Nacalai Tesque or Aldrich Chemical Company, Inc. and used without further purification. Since the purity of the BF_3 complex affects the yield of the quinone, reagent stored for a long period should be distilled prior to its use.
- This facile method for removing organotin impurities was developed by Keck.²
- Tin wastes are collected and disposed of in an environmentally safe manner. (See Waste Disposal

Information below.)

7. A gravity column (7 cm × 15 cm) was packed with 60-230 mesh silica gel. Elution was effected with 10% ethyl acetate in petroleum ether.

8. Spectroscopic data are as follows: ¹H NMR (400 MHz, CDCl₃) δ: 1.68 (s, 3 H, cis-CH₃), 1.74 (s, 3 H, trans-CH₃), 2.20 (s, 3 H, ring CH₃), 3.17 (d, 2 H, J = 7.0, CH₂), 3.98 (s, 3 H, CH₃O), 3.99 (s, 3 H, CH₃O), 4.94 (t, 1 H, J = 7.0, C=CH); IR (neat) cm⁻¹: 2790, 1650, 1617, 1455, 1329, 1262, 1555, 1102, 1013.

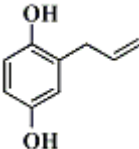
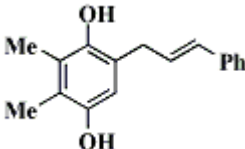
Waste Disposal Information

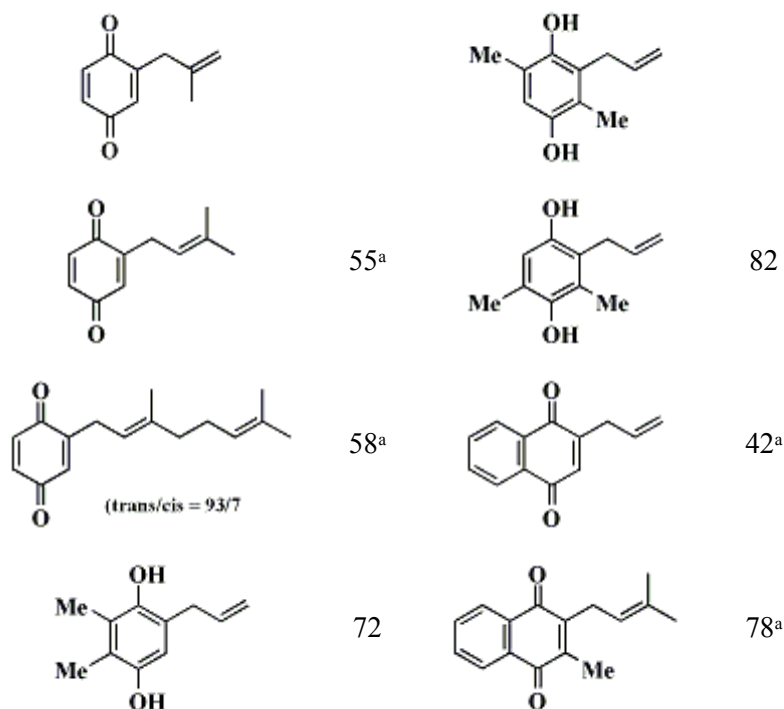
A chloroform solution of toxic tributyltin fluoride was placed in a round-bottomed flask equipped with a reflux condenser, and bromine (3 equiv per Bu₃SnF) was added all at once. After the mixture was stirred for 2–3 days at room temperature, aqueous sodium thiosulfate was added until the brown color of bromine disappeared. The aqueous layer containing inorganic tin compounds was disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Ubiquinones are synthesized by the introduction of an isoprenyl side chain to the corresponding quinone or hydroquinone using several compounds: Lewis acid-isoprenyl alcohols,³ π-allylnickel bromides,^{4,5} isoprenyltrialkyltins,⁶ N-sulfinylamideisoprenyl alcohols,⁷ amalgamated zinc-isoprenyl bromides,⁸ and Claisen rearrangement of isoprenyl aryl ethers.⁹ Among these procedures, the isoprenyltin method is superior to the others with respect to yield, simplicity of manipulation, and purity of product. This method can be also applied to the synthesis of the higher homologues of ubiquinone-n (n = 2–10). In general, synthesis of allylated quinones or hydroquinones can be performed by the reaction with allylborane,¹⁰ π-allylnickel complexes,¹¹ allyltrimethylsilane,¹² or allyltrialkyltins.^{6,13,14} Direct allylation to the quinone is considered to be the best procedure compared with stepwise methods including protection/deprotection of quinone.¹⁵ The present method is applicable to a broad range of quinones and allylated trialkyltins to give the corresponding hydroquinone (or quinone after oxidation) in good to excellent yields. Several other examples are shown in the Table. In this reaction, boron trifluoride plays two roles: activation of the quinones resulting in 1,2-addition and acceleration of dienone-phenol rearrangement of the allylic group.⁸ In addition this method can be applied to the synthesis of many other polyprenylated quinones,^{6,13} including naturally occurring quinones, plastoquinone-n, phyloquinone (vitamin K₁), and menaquinone-n (vitamin K_{2(n)}). The polyprenyl side chain can be stereoselectively introduced into a quinone nucleus without formation of the corresponding chromanol or other side chain-cyclized products. Other methods of polyprenyl group introduction to quinones or their protected forms are known: a Friedel-Crafts alkylation,¹⁶ a free-radical alkylation,¹⁷ and coupling reactions with organometallic reagents including lithium,¹⁸ magnesium,^{19,20} and tin.²¹

TABLE
PREPARATION OF ALLYLATED QUINONES FROM QUINONES
AND ALLYLATED TRIBUTYLTINS

	Yield (%)		Yield (%)
	68		81
	45 ^a		90



^aisolated after oxidation in ether with aqueous FeCl₃ solution

References and Notes

- Department of Chemistry, Faculty of Science, Kyoto University, Sakyo-ku, Kyoto 606, Japan.
- Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.
- Mayer, H.; Isler, O. In "Methods in Enzymology;" McCormick, D. B.; Wright, L. D., Eds.; Academic Press: New York, 1971; Vol. 18C, p. 182.
- Hegedus, L. S.; Evans, B. R.; Korte, D. E.; Waterman, E. L.; Sjöberg, K. *J. Am. Chem. Soc.* **1976**, *98*, 3901.
- Inoue, S.; Yamaguchi, R.; Saito, K.; Sato, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3098.
- Maruyama, K.; Naruta, Y. *J. Org. Chem.* **1978**, *43*, 3796; Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774; Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097.
- Sugihara, H.; Sasaki, M.; Kawamatsu, Y.; Morimoto, H. *Justus Liebig's Ann. Chem.* **1972**, *763*, 121.
- Sugihara, H.; Kawamatsu, Y.; Morimoto, H. *Justus Liebig's Ann. Chem.* **1972**, *763*, 128.
- Yoshizawa, T.; Toyofuku, H.; Tachibana, K.; Kuroda, T. *Chem. Lett.* **1982**, 1131.
- Mikhailov, B. M.; Ter-Sarkisyan, G. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 380; *Chem. Abstr.* **1966**, *64*, 15907h; Mikhailov, B. M.; Ter-Sarkisyan, G. S.; Nikolaeva, N. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 541; *Chem. Abstr.* **1968**, *69*, 67448v.
- Hegedus, L. S.; Waterman, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 6789.
- Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, 4041.
- Naruta, Y.; Maruyama, K. *Chem. Lett.* **1979**, 885.
- Takuwa, A.; Naruta, Y.; Soga, O.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1857.
- Naruta, Y.; Maruyama, K. In "The Chemistry of Quinonoid Compounds;" Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. 2, Part 1, pp. 241–402.
- Hirschmann, R.; Miller, R.; Wendler, N. L. *J. Am. Chem. Soc.* **1954**, *76*, 4592.
- Jacobsen, N.; Torssell, K. *Acta Chem. Scand.* **1973**, *27*, 3211; Jacobsen, N. *Org. Synth. Coll. Vol. VI* **1988**, 890.
- Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1977**, 499.
- Snyder, C. D.; Rappoport, H. *J. Am. Chem. Soc.* **1974**, *96*, 8046; Araki, S.; Sato, T.; Miyagawa,

- H.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3523.
20. Evans, D. A.; Hoffman, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1983.
21. Godschalx, J. P.; Stille, J. K. *Tetrahedron Lett.* **1983**, *24*, 1905.
-

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

H₂O

brine

plastoquinone-n

phyloquinone (vitamin K₁)

menaquinone-n (vitamin K_{2(n)})

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

chloroform (67-66-3)

magnesium (7439-95-4)

bromine (7726-95-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

tin (7440-31-5)

Quinone (106-51-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

boron trifluoride (7637-07-2)

ferric chloride hexahydrate (10025-77-1)

potassium fluoride (7789-23-3)

tributyltin (688-73-3)

boron trifluoride etherate (109-63-7)

phosphorus pentoxide (1314-56-3)

allyltrimethylsilane (762-72-1)

Tributyl(3-methyl-2-butenyl)tin (53911-92-5)

tributyltin fluoride

stannane (7440-31-5)

2,3-dimethoxy-5-methyl-1,4-benzoquinone

2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone,
2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)- (727-81-1)