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.

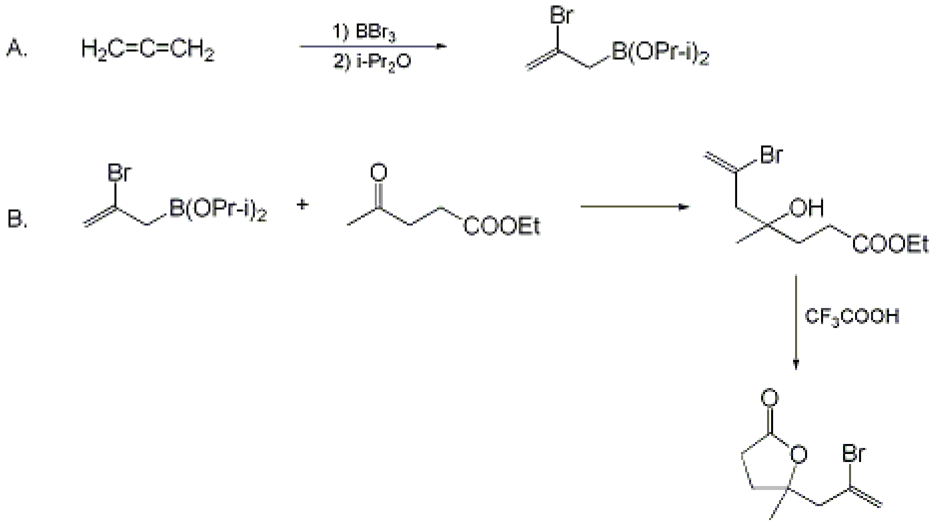
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.075.0129

Organic Syntheses, Coll. Vol. 10, p.135 (2004); Vol. 75, p.129 (1998).

SYNTHESIS OF 4-(2-BROMO-2-PROPENYL)-4-METHYL-γ-BUTYROLACTONE BY THE REACTION OF ETHYL LEVULINATE WITH (2-BROMOALLYL) DIISOPROPOXYBORANE PREPARED BY HALOBORATION OF ALLENE

[2(3H)-Furanone, 5-(2-bromo-2-propenyl)dihydro-5-methyl-]



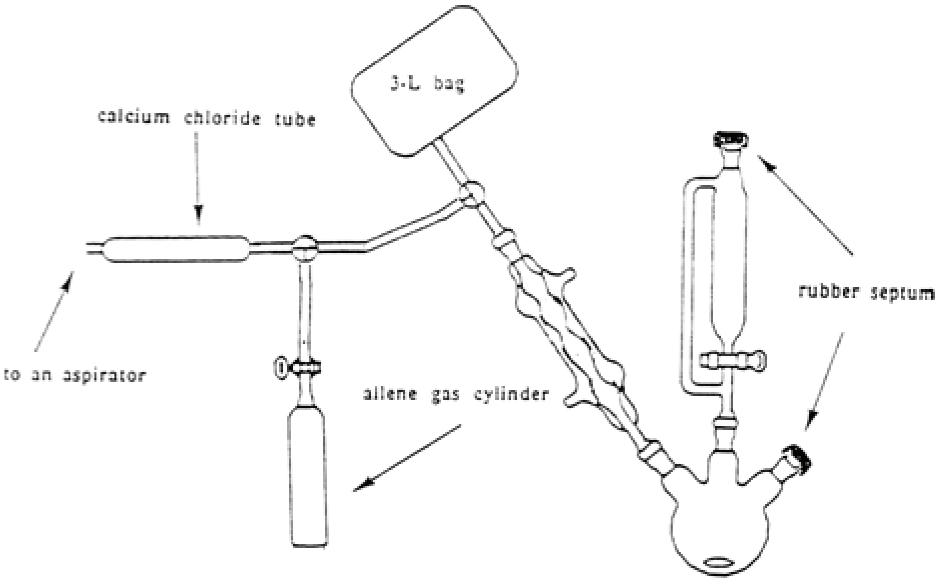
Submitted by Shoji Hara[1] and Akira Suzuki[2] .
Checked by Sherry R. Chemler and William R. Roush.

1. Procedure

Caution! Boron tribromide is moisture sensitive and decomposes in air with the evolution of hydrogen bromide. It should be used in an efficient hood.

A. (2-Bromoallyl)diisopropoxyborane. A flame-dried, 200-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum, 125-mL dropping funnel, and an Allihn-type condenser. To the top of the condenser, a 3-L bag (Note 1), water aspirator through a calcium chloride tube, and allene gas cylinder (Note 2) are connected with two three-way stopcocks as shown in Figure 1. The flask and the bag are evacuated twice using a water aspirator, and filled with allene gas each time (Note 3). The stopcock between the bag and the reaction flask is closed off (Note 4), and the flask is cooled to −20°C in a cooling bath made of dry ice and a 9 : 1 mixture of ethylene glycol and acetone . Boron tribromide, BBr_3 (25 g, 9.4 mL, 100 mmol) is introduced through the rubber septum via cannula (Note 5). The stopcock separating the bag from the reaction vessel is then opened. Gas absorption starts immediately and is complete within 10 min to give a dark red solution. When the allene is completely consumed, the gas cylinder is replaced by a nitrogen inlet tube and nitrogen is introduced into the flask. The mixture is stirred at −20°C for 30 min and then 30 mL of dry dichloromethane (Note 6) is added. Next, 33 mL (0.23 mol) of diisopropyl ether (Note 7) in 50 mL of dry dichloromethane is introduced from the dropping funnel over 1 hr (*exothermic*!). The mixture is stirred at −20°C for 30 min, then at room temperature for 2 hr, and finally under reflux for 1 hr. The mixture is cooled to room temperature and all volatile components are removed under reduced pressure using a water aspirator (Note 8). The vessel is filled with nitrogen, and the residue is transferred to a distillation flask via a cannula using nitrogen. Distillation of the residue under reduced pressure gives 16.4-17.1 g (66-69%) of (2-bromoallyl)diisopropoxyborane as a clear liquid, bp 39-43°C (0.4 mm) (Note 9),(Note 10),(Note 11), (Note 12).

Figure 1



B. 4-(2-Bromo-2-propenyl)-4-methyl-γ-butyrolactone. A flame-dried, 200-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum, nitrogen inlet adapter, and a 100-mL dropping funnel. The flask is purged with nitrogen and charged with (2-bromoallyl) diisopropoxyborane (16.2 g, 0.065 mol), prepared above, in 50 mL of dry tetrahydrofuran (Note 13). The flask is cooled in an ice bath, and ethyl levulinate (9.96 g, 0.069 mol) (Note 7) in 30 mL of dry tetrahydrofuran is added dropwise over 1 hr from the dropping funnel. After the mixture is stirred at 0°C for 1 hr and then at room temperature overnight, it is poured into 50 mL of water and extracted three times with 50-mL portions of ether . The combined organic layers are dried over magnesium sulfate and concentrated using a rotary evaporator. The residue is diluted with 50 mL of dry dichloromethane , and 1 mL of trifluoroacetic acid (Note 7) is added. After the mixture is stirred at room temperature overnight, it is poured into water (50 mL) and the organic layer is separated. The aqueous layer is extracted twice with 100-mL portions of ether . The combined organic extracts are washed with 50 mL of saturated sodium bicarbonate and 50 mL of water, dried over magnesium sulfate, and concentrated using a rotary evaporator. The residue is distilled through a 15-cm Vigreux column under reduced pressure to give 9.22 g (65%) of 4-(2-bromo-2-propenyl)-4-methyl-γ-butyrolactone , bp 88-90°C (0.6 mm) (Note 14), (Note 15), plus 1.9 g of recovered ethyl levulinate, bp 48°C (0.6 mm), and a mixed fraction (0.8 g) containing ethyl levulinate and the product.

2. Notes

1. A Tedlar bag, made of polyvinyl fluoride, was used. These bags were purchased from SKC, Inc. (US).
2. Cylinders of allene were purchased from PCR (Japan) or Matheson Gas Products (US).
3. This step is very important. If all the air is not replaced by allene, the reaction with BBr_3 sometimes does not go to completion.
4. Allene must not be allowed to condense in the reaction vessel prior to the introduction of the BBr_3 . Boron tribromide reacts rapidly and exothermically with liquid allene to give a black mixture that yields very little of the desired product. In one experiment in which the connection between the Tedlar bag and the reaction vessel was not closed while the vessel was cooled to −20°C, the yield of (2-bromoallyl)-diisopropoxyborane was 9%.
5. BBr_3 (≥99.99% purity) was purchased in glass ampoules from Wako Pure Chemical Industries, Ltd., or Aldrich Chemical Company, Inc. The submitters transferred the reagent into a storage vessel equipped with septum inlets before use, as follows. The ampoule stem was scored with a file and broken off in a nitrogen-filled glove bag. A septum was then placed over the opening. While BBr_3 can be

transferred by syringe, it is advisable to use a cannula to avoid problems with the plunger freezing. The beveled point of a 2-mm Teflon tube obtained from Nippon Rikagaku Kikai Co., Ltd. was inserted through the pre-punctured septum on the ampoule leaving the tip above the liquid level. The other end of the tube was inserted through a septum on the storage vessel that was vented through a bubbler. The tube was placed below the liquid level in the ampoule, and the BBr_3 was transferred into the storage vessel by applying a positive nitrogen pressure through a hypodermic needle. When all the liquid had been transferred, the Teflon tube and the bubbler vent were withdrawn from the ampoule and inserted into the measuring vessel. Graduated cylinders or centrifuge tubes with standard taper joints are excellent measuring vessels when fitted with a two-inlet adapter obtained from Aldrich Chemical Company, Inc. In the same way, the required amount of BBr_3 was transferred from the storage vessel to the measuring vessel, and then from the measuring vessel to the reaction flask. The submitters recommend that if the BBr_3 is not from a freshly opened ampoule, it should be distilled under nitrogen before use.[3] The checkers purchased 25-g lots of BBr_3 and used the entire ampoule in each run, thereby avoiding the need to store and redistill any excess, unused reagent. The checkers transferred the BBr_3 in a dry box under an atmosphere of dry nitrogen into a glass vessel, and then into the reaction vessel via cannula as specified by the submitters.

6. Dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves.

7. Ethyl levulinate, diisopropyl ether, and trifluoroacetic acid were purchased from Wako Pure Chemical Industries, Ltd., or Aldrich Chemical Company, Inc. , and distilled before use. The checkers distilled diisopropyl ether from calcium hydride.

8. A −78°C trap to collect all volatile materials should be placed between the aspirator and the reaction vessel during this evaporative distillation.

9. The submitters obtained 18.4 g of product (70%) starting from 26.5 g (10 mL, 106 mmol) of BBr_3 .

10. As (2-bromoallyl)diisopropoxyborane is thermally labile, the distillation should be carried out below 100°C. It is not very sensitive to air but decomposes slowly. It is recommended that it be handled under an inert atmosphere and stored in a refrigerator. The spectral properties are as follows: ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (d, 12 H, J = 6.0), 2.25 (br s, 2 H), 4.42 (septet, 2 H, J = 6.0), 5.31 (d, 1 H, J = 0.6), 5.48 (d, 1 H, J = 1.3) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.4, 28-32 (br), 65.7, 116.3, 131.3 ; ^{11}B NMR ($CDCl_3$, 128 MHz) δ: 28.04 ; HRMS for $C_9H_{19}BBrO_2$ ($M^+ + 1$) calcd 249.0661, found 249.0667.

11. The checkers determined the purity of the reagent to be ca. 94% by manual integration (cut and weigh) of the three ^{11}B resonances observed in the sample: δ 17.42 (4.3 %), δ 28.04 (94.3 %) and δ 47.49 (1.4 %) respectively

12. The checkers found that the ^1H NMR spectrum of (2-bromoallyl)-diisopropoxyborane is concentration dependent. When the NMR spectrum was measured at a concentration of 20 μL of product in ca. 0.5 mL of $CDCl_3$, (2-bromo-allyl)diisopropoxyborane was observed along with a substantial amount of a second material that had ^1H resonances for the vinylic and allylic protons that were very similar in chemical shift to the vinylic and allylic resonances of the desired product. However, when the ^1H NMR spectrum of a much more concentrated solution (ca. 250 μL in 0.250 mL of $CDCl_3$) was measured, the resonances of the contaminant were barely apparent. The origin of this phenomenon has not been conclusively determined.

13. Tetrahydrofuran was distilled from benzophenone ketyl under nitrogen just before use.

14. The submitters obtained 11.6 g (72%) of product starting from 18.4 g of (2-bromoallyl) diisopropoxyborane and 10.7 g of ethyl levulinate . The checkers obtained yields of 65-69% in runs on several different scales.

15. The product contained traces of ethyl levulinate and was redistilled to give an analytical sample: ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 3 H), 2.02-2.07 (m, 1 H), 2.09-2.48 (m, 1 H), 2.61 (d, 1 H, J = 8.5), 2.63 (dd, 1H, J = 7.6, J = 1.6), 2.85 (AB q, 2 H, J_{AB} = 15.0, δν = 16.0), 5.65 (d, 1 H, J = 1.9), 5.74 (t, 1 H, J = 0.9) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.3, 29.1, 32.4, 51.1, 85.1, 122.7, 125.9, 176.1 ; IR (neat) cm^{-1}: 1780 (C=O), 1635 (C=C) ; HRMS for $C_8H_{15}O_2NBr$ ($M + NH_4^+$) calcd 236.0286, found 236.0287. Anal. Calcd. for $C_8H_{11}O_2Br$: C, 43.86; H, 5.06. Found: C, 43.57; H, 4.97.

3. Discussion

The haloboration reaction of 1-alkynes proceeds stereo- and regioselectively to give 2-halo-1-alkenylboranes that can be used for the stereoselective synthesis of haloalkenes and di- or trisubstituted alkenes.[4] Although isolated double bonds do not undergo the haloboration reaction with haloboranes,[5] allene [5] and conjugated dienes[6] give the 1 : 1 adducts. The bromoboration reaction of allene with tribromoborane proceeds very rapidly, but the resulting (2-bromoallyl)dibromoborane is difficult to isolate, because it readily polymerizes during distillation. On the other hand, this intermediate can be converted into dialkoxyborane derivatives by the reaction with ethers such as diisopropyl ether or anisole ; the resulting (2-bromoallyl)dialkoxyboranes are stable and readily isolated by distillation. Alcohols have also been used for the conversion of bromoboranes to the corresponding alkoxyboranes.[7] However, the reaction with ethers is preferred because evolution of hydrogen bromide is avoided. This method is especially effective when the product is sensitive to acids, as in the case reported here. Diisopropoxyborane derivatives have the same reactivity as that of the diphenoxyborane derivatives described in a previous paper;[8] however, diisopropoxyborane derivatives are easier to isolate because of their lower boiling points. As described here, (2-bromoallyl)diisopropoxyborane can be prepared by the bromoboration reaction of allene with tribromoborane, followed by addition of isopropyl ether . Isopropyl bromide thus generated does not cause any problems and can be removed readily.

(2-Bromoallyl)diisopropoxyborane reacts with aldehydes and ketones under mild conditions to give the corresponding 2-bromohomoallylic alcohols in good yields. The resulting 2-bromohomoallylic alcohols are useful intermediates for the synthesis of α-methylene-γ-lactones.[9] 2-Bromohomoallylic alcohols have also been prepared from carbonyl compounds via reaction with 2,3-dibromo-1-propene in the presence of tin ,[10] and the reaction with 2-bromo-3-(trimethylsilyl)propene in the presence of a Lewis acid.[11] However, (2-bromoallyl)diisopropoxyborane reacts with carbonyl compounds under very mild conditions, even at −78°C in some cases, and the reaction proceeds smoothly without the addition of any other reagents such as metals or Lewis acids. The ketone functional group of ethyl levulinate reacts selectively with (2-bromoallyl)diisopropoxyborane to give the hydroxy ester that partially cyclizes to the lactone under the reaction conditions. The hydroxy ester is completely converted into the lactone by treatment with trifluoroacetic acid.

Although (2-bromoallyl)diisopropoxyborane can be stored under nitrogen in a refrigerator for a few months, it is recommended that the reagent be redistilled if stored for a longer time.

References and Notes

1. Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060, Japan.
2. Department of Chemical Technology, Kurashiki University of Science and the Arts, Tsurajima-cho, Kurashiki 712, Japan.
3. Techniques for handling air-sensitive compounds are discussed in Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley: New York, 1975; Gill, G. B.; Whiting, D. A. *Aldrich Chemica Acta* **1986**, *19*, 31.
4. Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 629; Suzuki, A. *Reviews on Heteroatom Chemistry* **1988**, *1*, 291; Suzuki, A.; Hara, S. *Trends in Organic Chemistry* **1990**, 77.
5. Joy, F.; Lappert, M. F.; Prokai, B. *J. Organometal. Chem.* **1966**, *5*, 506.
6. Joy, F.; Lappert, M. F. *Proc. Chem. Soc.* **1960**, 353.
7. Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392.
8. Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6749.
9. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94
10. Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172.
11. Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879.

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

4-(2-Bromo-2-propenyl)-4-methyl-γ-butyrolactone:

2(3H)-Furanone, 5-(2-bromo-2-propenyl)dihydro-5-methyl- (13); (138416-14-5)

Ethyl levulinate:
Levulinic acid, ethyl ester (8);
Pentanoic acid, 4-oxo-, ethyl ester (9); (539-88-8)

Allene (8);
1,2-Propadiene (9); (463-49-0)

Boron tribromide:
Boron bromide (8);
Borane, tribromo- (9); (10294-33-4)

Trifluoroacetic acid:
Acetic acid, trifluoro- (8,9); (76-05-1)