



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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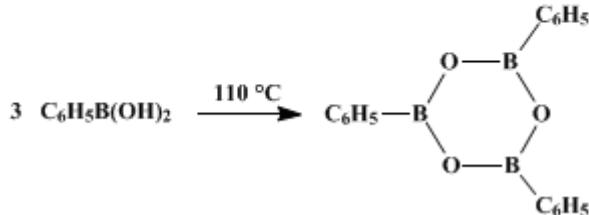
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 4, p.68 (1963); Vol. 39, p.3 (1959).

BENZENEBORONIC ANHYDRIDE

[Boroxin, triphenyl-]



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1. Procedure

Caution! Benzeneboronic acid and its anhydride are toxic substances and may irritate mucous tissues such as those of the eyes. In case of contact, carefully wash exposed parts of the body with soap and water (Note 1).

The apparatus consists of a four-necked 5-l. round-bottomed Morton flask² fitted with a 500-ml. graduated dropping funnel with a pressure-equalizing side arm, a 1-l. graduated dropping funnel of the same type, a thermometer, an efficient mechanical stirrer (Note 2), and an inlet for dry nitrogen. The apparatus is thoroughly swept with dry nitrogen, and the reaction flask is charged with 1.5 l. of anhydrous ether, dry nitrogen (Note 3) being used for pressure transfer.

Three hundred thirty-six milliliters (312 g., 3 moles) of methyl borate is distilled directly into the 500-ml. dropping funnel shortly before starting the reaction (Note 4). One liter (544 g., 3 moles) of a 3*M* ethereal solution of phenylmagnesium bromide is pressure-transferred with dry nitrogen to the 1-l. dropping funnel (Note 5). During subsequent operations until the hydrolysis step, a positive pressure of 10–20 mm. of nitrogen is maintained in the closed system by means of a mercury bubbler to prevent access of atmospheric moisture. The ether is cooled to below –60° by a bath of Dry Ice and acetone and is kept below –60° all during the reaction (Note 6). The reactants are added to the well-stirred reaction mixture alternately in small portions, first 10 ml. of methyl borate and then 30 ml. of phenylmagnesium bromide, the rate of addition being as rapid as is possible without the temperature of the mixture rising above –60° (Note 7). Stirring is continued for an additional 20 minutes below –60° after the addition of the reagents is completed.

The stirred mixture, maintained at or below 0°, is hydrolyzed by the addition of 200 ml. of distilled water during 5 minutes. It is then neutralized by addition of a solution of 84 ml. of concentrated sulfuric acid in 1.7 l. of distilled water during 15 minutes. The mixture is transferred to a 5-l. separatory funnel, the ether layer is separated, and the aqueous layer is extracted with three 250-ml. portions of ether.

The combined ether layer and extracts are transferred to a 5-l. round-bottomed flask equipped with a Hershberg stirrer,³ a dropping funnel, a Claisen head with a water-cooled condenser, an electric heating mantle, and an ice-cooled receiver (Note 8). After approximately one-half of the ether has been removed by distillation from the stirred mixture, 1.5 l. of distilled water is added slowly while the distillation is continued until a head temperature of 100° is reached (Note 9).

While stirring is continued, the aqueous distilland is cooled in an ice bath (Note 10). The benzeneboronic acid, which separates as small white crystals, is collected on a Büchner funnel and washed with petroleum ether. The petroleum ether removes traces of dibenzeneborinic acid, which are seen in the hot mother liquor as globules of brown oil and which may color the product. The acid is dehydrated to benzeneboronic anhydride by heating it in an oven at 110° and atmospheric pressure for 6 hours (Note 11). Benzeneboronic anhydride is obtained as a colorless solid, weight 240–247 g. (77–79%) (Note 12), m.p. 214–216°.

2. Notes

1. A summary of the physiological activity of benzeneboronic acid may be found in reference ⁴.
2. The submitters found that for a preparation of this size a 1-inch Duplex Dispersator (Premier Mill Corp., Geneva, New York) operating at 7500 r.p.m. provided excellent agitation of the heterogeneous reaction mixture. For smaller preparations (1-l. flask) they found that a Stir-O-Vac (Labline, Inc., 217 N. Desplaines St., Chicago 6, Illinois) operating at 5000 r.p.m. was satisfactory. The type of agitation is very important for, whereas the submitters obtained yields of around 91%, the checkers obtained yields of only 77–80% with either a Morton stirrer² (excessive splashing deposited some of the reaction mixture on the warm upper walls of the flask) or a Polytron dispersion mill type of stirrer (there was too much hold-up in the stirrer housing).
3. Tank nitrogen was dried with phosphorus pentoxide.
4. Methyl borate (b.p. 68°) forms a 1:1 azeotrope (b.p. 54.6°) with methanol (b.p. 64°).⁵ Since the presence of even a small amount of methanol reduces the yield considerably more than would be expected from the stoichiometry,^{46,7} methyl borate stocks should be freshly distilled through a good column to remove as fore-run any methyl borate-methanol azeotrope which may have been formed by hydrolysis during storage.
5. Mallinckrodt analytical reagent grade ether, dried over sodium, was used. The methyl borate was the commercial product of American Potash and Chemical Corporation containing 99% ester as received. The phenylmagnesium bromide was purchased as a 3.0M solution in ether from Arapahoe Special Products, Inc., Boulder, Colorado.
6. The yield of benzeneboronic anhydride is highly dependent upon the reaction temperature, as the following data of the submitters show. At a reaction temperature of 15° the yield was 49%; at 0°, 76%; –15°, 86%; –30°, 92%; –45°, 92%; –60°, 99%. The yields are based on the combined first and second crops of benzeneboronic acid.
7. At a given temperature, the maximum yield of benzeneboronic acid and the minimum amount of by-product dibenzeneborinic acid are obtained when neither reagent is present in excess. The addition of small increments of reactants is a convenient approximation imposed by the difficulty of adjusting stopcocks to small rates of flow. Alternatively, the Hershberg dropping funnel⁸ or other metering device may be used to maintain the stoichiometry. Addition times, which depend upon the efficiency of stirring and heat transfer, vary from about 1 hour at –60° to 15 minutes at 0°.
8. Stirring is helpful during the ether distillation to prevent superheating.
9. Small amounts of benzene, phenol, and biphenyl, which may be formed in the reaction, are removed by the steam distillation. Enough water has been added to ensure solution of all of the product.
10. The product crystallizes at 43° with a temperature rise to 45°. The solubility of benzeneboronic acid in water (g./100 g. of water) is approximately 1.1 at 0° and 2.5 at 25°; the solubility-temperature relationship is linear to at least 45°.
11. If benzeneboronic acid rather than its anhydride is desired, it can be obtained by air-drying the moist acid in a slow stream of air nearly saturated with water. The yield of acid is 282–332 g. One can readily convert the anhydride to the acid by recrystallizing it from water. Benzeneboronic acid gradually dehydrates to the anhydride if left open to the atmosphere at room temperature and 30–40% relative humidity. The melting point observed is that of the anhydride because the acid dehydrates before it melts.
12. The submitters report a yield of 91% and state that an additional 27 g. (9%) of acid can be obtained from the aqueous mother liquor.

3. Discussion

The procedure described^{4,6} is a modification of the method of Khotinsky and Melamed,⁹ who first

reported the preparation of boronic acids from Grignard reagents and borate esters. Benzeneboronic acid and the corresponding anhydride also have been prepared by reaction of phenylmagnesium bromide with boron trifluoride;¹⁰ by the reaction of phenyllithium with butyl borate;¹¹ by the reaction of diphenylmercury with boron trichloride;¹² by the reaction of benzene with boron trichloride in the presence of aluminum chloride;¹³ and by the reaction of triphenylborane with boric oxide.¹⁴

The present procedure is also applicable to the synthesis of substituted benzeneboronic acids.⁴ Benzeneboronic acid and its anhydride are of use as starting materials for the synthesis of phenylboron dichloride¹⁵ and of various substituted boronic and borinic acids and esters.^{7,16}

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 613

References and Notes

1. American Potash and Chemical Corporation, Whittier, California.
 2. Morton, *Ind. Eng. Chem., Anal. Ed.*, **11**, 170 (1939); Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).
 3. *Org. Syntheses Coll. Vol. 2*, 117 (1943).
 4. Washburn, Levens, Albright, Billig, and Cernak, *Advances in Chem. Ser.*, **23**, 102 (1959);
 5. Schlesinger, Brown, Mayfield, and Gilbreath, *J. Am. Chem. Soc.*, **75**, 213 (1953).
 6. Washburn, Billig, Bloom, Albright, and Levens, *Advances in Chem. Ser.*, **32**, 208 (1961).
 7. Seaman and Johnson, *J. Am. Chem. Soc.*, **53**, 711 (1931).
 8. *Org. Syntheses Coll. Vol. 2*, 129 (1943).
 9. Khotinsky and Melamed, *Ber.*, **42**, 3090 (1909).
 10. Krause and Nitsche, *Ber.*, **55B**, 1261 (1922); Krause, German pat. 371,467 (1923) [*C. A.*, **18**, 992 (1924)].
 11. Brindley, Gerrard, and Lappert, *J. Chem. Soc.*, **1955**, 2956.
 12. Michaelis and Becker, *Ber.*, **15**, 180 (1882).
 13. Muettterties, *J. Am. Chem. Soc.*, **82**, 4163 (1960).
 14. McCusker, Hennion, Ashby, and Rutowski, *J. Am. Chem. Soc.*, **79**, 5194 (1957).
 15. Dandegaonker, Gerrard, and Lappert, *J. Chem. Soc.*, **1957**, 2893.
 16. Lappert, *Chem. Revs.*, **56**, 987, 1013 (1956).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

boric oxide

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

phenol (108-95-2)
nitrogen (7727-37-9)
aluminum chloride (3495-54-3)
sodium (13966-32-0)
Biphenyl (92-52-4)
Phenylmagnesium bromide (100-58-3)
Diphenylmercury (587-85-9)
Phenyllithium (591-51-5)
boron trifluoride (7637-07-2)
Benzeneboronic anhydride
Boroxin, triphenyl- (3262-89-3)
Benzeneboronic acid (98-80-6)
methyl borate
dibenzeneborinic acid
methyl borate-methanol
Butyl borate (688-74-4)
boron trichloride (10294-34-5)
triphenylborane (960-71-4)
phenylboron dichloride (873-51-8)
phosphorus pentoxide (1314-56-3)