

Chlorination of Methaneboronic Acid Derivatives with *t*-Butyl Hypochlorite

DONALD S. MATTESON¹

Department of Chemistry, Washington State University,
Pullman, Washington

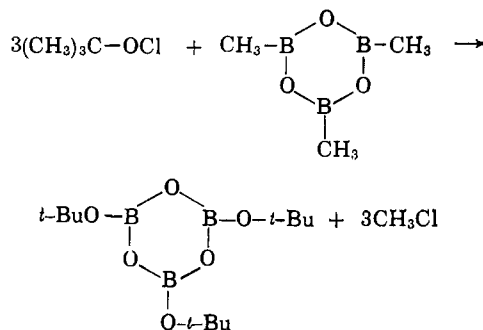
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We undertook a study of the halogenation of methaneboronic acid derivatives in the hope of finding a method of preparing halomethaneboronic esters, $\text{XCH}_2\text{-B(OR)}_2$. Because of their simple structure and high boron content, these are particularly attractive intermediates for making new compounds to be tested for utility in B^{10} neutron capture brain-tumor therapy. The preparation of more complicated α -haloalkaneboronic esters and their promise as synthetic intermediates have been reported.²

Methaneboronic acid and its derivatives have previously been prepared in mediocre yields because of problems with volatility and water solubility.³ We have overcome these problems with a procedure which leads to the methaneboronic anhydride-pyridine complex (see Experimental), from which any desired methaneboronic acid derivative is easily generated.

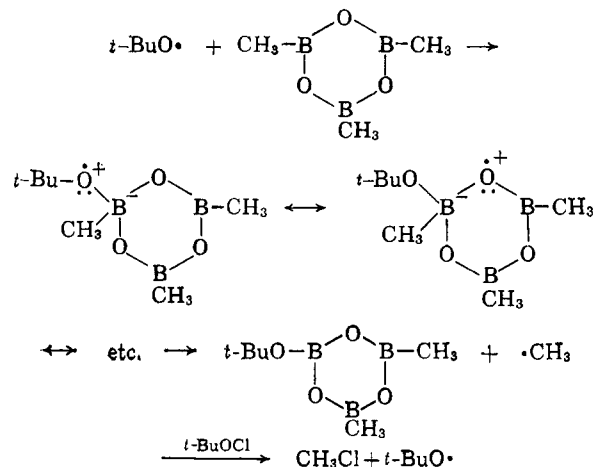
Because boron appears to stabilize an adjacent free radical,⁴ we thought that methaneboronic anhydride might react with *N*-bromosuccinimide. It does not. The usual conditions were tried (refluxing carbon tetrachloride, radical initiators) as well as heating in perchlorobutadiene until the *N*-bromosuccinimide decomposed, after which 65% of the methaneboronic anhydride was recovered.

We then tried the irresistible *t*-butyl hypochlorite with light initiation. The products were methyl chloride and an unstable oil, apparently tri-*t*-butoxyboroxine, which on attempted distillation decomposed to tri-*t*-butyl borate and a solid, presumably boric oxide. Infrared examination indicated that acetone was not a major product.



This reaction proceeded easily in benzene or no solvent at 0–15° under irradiation, but was very slow (30 hr., 25°) in the dark. It appears that the *t*-butoxy radical must displace a methyl radical from boron. Al-

though radical displacements do not ordinarily occur on polyvalent atoms, the vacant orbital of boron would permit an addition-elimination mechanism. The process might be more or less concerted, since an oxygen-boron bond is 30–40 kcal./mole stronger than a carbon-boron bond.⁵



The B-methyl group was chlorinated by resorting to the *t*-butyl ester, which hindered the boron atom sufficiently to suppress most of the cleavage reaction. Unfortunately, the preference of *t*-butoxy radical for attacking B-methyl hydrogens over C-methyl hydrogens was slight (perhaps a factor of 1.1–1.5), and in a 1:1 mixture of reactants the latter outnumbered the former by 9:1. After losses due to trialkyl borate formation by B-methyl cleavage (about 10–15%) and decomposition of *t*-butoxy radicals to acetone (another 10%), the conversion of B-methyl to B-chloromethyl was 10% by n.m.r. analysis, 9% by product isolation.

Because of the rapid equilibration of boronic esters during distillation, all of the chloromethaneboronic ester would be left in the residue as an intractable mixture of chloro-*t*-butyl esters. Accordingly, we recovered the remaining *t*-butyl methaneboronate (40%) by fractionation, then treated the residue of chloro-*t*-butyl esters with *n*-butyl alcohol. The equilibrium lies far in favor of free tertiary alcohols and *n*-butyl boronic esters, which were separable by distillation. Some di-*n*-butyl methaneboronate was recovered, followed by fractions containing a 9% yield of di-*n*-butyl chloromethaneboronate, $\text{ClCH}_2\text{B(Obu)}_2$, contaminated with some of the by-product tributyl borate, which boils slightly higher. The n.m.r. spectrum of pure dibutyl chloromethaneboronate showed a single peak at δ 2.80 downfield from tetramethylsilane plus the characteristic butoxy pattern.

We also tried bis(2-trichloromethyl-2-propyl)methaneboronate, but this solid ester was not very soluble in *t*-butyl hypochlorite and n.m.r. indicated little if any chlorination of the B-methyl group. Dimethyl methaneboronate was not detectably chlorinated on the B-methyl group. Instead, n.m.r. examination of the crude product mixture seemed to confirm the expected chlorination of the methoxy groups, a peak of about the right intensity appearing at δ 6.8, presumably $\text{O-CH}_2\text{-O}$. There were two *t*-butyl peaks, *t*-butoxy at δ 1.3 and a stronger one, presumably *t*-butyl chloride, at 1.1. The

(1) Supported by Public Health Service Research Grants No. CA-05513-03 and -04 from the National Cancer Institute.

(2) (a) D. S. Matteson and R. W. H. Mah, *J. Am. Chem. Soc.*, **85**, 2599 (1963); (b) D. S. Matteson and J. D. Liedtke, *Chem. Ind. (London)*, 1241 (1963).

(3) (a) A. B. Burg, *J. Am. Chem. Soc.*, **62**, 2228 (1940); (b) P. A. McCusker, E. C. Ashby, and H. S. Makowski, *ibid.*, **79**, 5179 (1957).

(4) D. S. Matteson, *ibid.*, **82**, 4228 (1960).

(5) T. Charnley, H. A. Skinner, and N. B. Smith, *J. Chem. Soc.*, 2288 (1952).

B-methyl peak at $\delta -0.15$ remained intact, with its integral ratio to the sum of the *t*-butyl peaks the same as in the starting mixture.

We are exploring other routes to halomethaneboronic esters.

Experimental

Methaneboronic Anhydride-Pyridine Complex.—A solution of 2.4 moles (800 ml., 3 *M*) of methylmagnesium bromide in ether (Arapahoe Chemical Co.) was added under nitrogen to 300 ml. of methyl borate in 1 l. of ether which was stirred and kept below -55° . The mixture was acidified with a slight excess of 3 *M* hydrochloric acid saturated with sodium chloride and then was separated and extracted with three 250-ml. portions of butanol. The organic phase was washed with 150 ml. of saturated sodium chloride, then extracted with 100 g. of sodium hydroxide in 180 ml. of water followed by two portions of 20 g. of sodium hydroxide in 36 ml. of water, and finally with 100 ml. of water. The aqueous solution of sodium methaneboronate was concentrated at 20 mm. until the pot temperature reached $60-80^\circ$ and a frothy semisolid residue remained. To this was added 400 ml. of pyridine and 50 ml. of water. A solution of pyridine bisulfate was prepared by adding 90 ml. of pyridine dropwise to 110 ml. of concentrated sulfuric acid (caution: exothermic). The pyridine bisulfate was added dropwise to the stirred suspension of sodium methaneboronate and the mixture was refluxed for 2 hr. After cooling, the sodium sulfate was filtered and washed with 250 ml. of benzene. The combined organic phase was refluxed under an efficient 30-cm. packed column fitted at the head with a Dean-Stark trap until all the water was removed (~ 140 ml.). Benzene and pyridine were distilled through the column, the methaneboronic anhydride-pyridine complex was distilled, b.p. $139-143^\circ$ (700 mm.), yield 134 g. (82%), solidified on cooling. The analytical sample was sublimed under vacuum, m.p. $91.5-95.5^\circ$.

Anal. Calcd. for $C_5H_{14}B_3NO_2$: C, 46.95; H, 6.90; B, 15.86; N, 6.85. Found: C, 46.74; H, 7.04; B, 15.62; N, 6.91.

Methaneboronic anhydride^{3a} was obtained in 77% yield by adding 1.67 ml. of 96% sulfuric acid to 6.36 g. of the boronic anhydride-pyridine complex cooled in an ice bath, stirring, and distilling at atmospheric pressure under nitrogen.

Chlorination of Methaneboronic Anhydride.—Ultraviolet irradiation of 2.7 g. of methaneboronic anhydride and 6.8 g. of *t*-butyl hypochlorite⁶ in 20 ml. of benzene led to an exothermic reaction. Distillation at 20 mm. led to decomposition. The infrared spectrum of the distillate was that of *t*-butyl borate apparently contaminated with a related substance. The glassy residue crystallized on treatment with water. Attempts to distill the product at lower pressure also led to decomposition. When 0.42 g. of methaneboronic anhydride and 1.20 g. of *t*-butyl hypochlorite in 3 ml. of benzene were irradiated at room temperature, about 70 ml. of gas (30%) was collected over water, in which it was somewhat soluble. The same reactants without the solvent were irradiated and the gas was condensed at -70° . It was shown to be methyl chloride by infrared comparison with an authentic sample. The infrared spectrum of the nonvolatile liquid product showed the presence of only a trace of ketone. The bulk of the material was a compound related to *t*-butyl borate, the chief difference in the infrared spectrum being strong bands at 13.5, 13.7, and $14.0\ \mu$ and the absence of *t*-butyl borate band at $15\ \mu$.

Di-*t*-butyl Methaneboronate.—The method described for the preparation of di-*t*-butyl ethyleneboronate⁷ was used. Methaneboronic anhydride-pyridine complex (31 g.), 250 ml. of *t*-butyl alcohol, and 120 ml. of benzene refluxed for 5 days under a 30-cm. column with removal of the water formed yielded 55 g. (70%) of di-*t*-butyl methaneboronate, b.p. $44-45^\circ$ (21 mm.), m.p. -39 to -37° . When the reaction was run on four times this scale in the same apparatus, the yield was only 63% after 27 days. Water failed to separate when a Dean-Stark trap was used. A still head with a cold-finger condenser and space for about 1 ml. of liquid to collect above the takeoff valve proved satisfactory.

Anal. Calcd. for $C_8H_{18}BO_2$: C, 62.82; H, 12.30; B, 6.29. Found: C, 62.61; H, 12.35; B, 6.19.

Bis(2-trichloromethyl-2-propyl) methaneboronate was prepared in a manner analogous to the *t*-butyl ester from 2-trichloromethyl-

2-propanol and the methaneboronic anhydride-pyridine complex in about 50% yield. The analytical sample was sublimed at $0.1\ \text{mm.}$, m.p. $94-106^\circ$.

Anal. Calcd. for $C_9H_{15}BCl_6O_2$: C, 28.5; H, 3.99; B, 2.85; Cl, 56.2. Found: C, 28.32; H, 3.95; B, 2.80; Cl, 55.84.

Di-*n*-butyl Chloromethaneboronate.—A mixture of 43 g. (0.25 mole) of di-*t*-butyl methaneboronate and 30 mg. of *t*-butyl hypochlorite⁶ in a Pyrex flask surrounded by an ice bath was irradiated with a mercury vapor lamp. The lamp distance was adjusted so that several hours were required for the color to fade. *t*-Butyl alcohol was distilled in a spinning-band column at atmospheric pressure, then di-*t*-butyl methaneboronate (18.4 g.). *n*-Butyl alcohol (50 ml.) was added to the residue and distilled at 20 mm. Di-*n*-butyl methaneboronate recovery was 8.0 g., b.p. 28° (0.1 mm.). Two fractions of dibutyl chloromethaneboronate were collected at $41-42^\circ$ (0.02 mm.), 4.05 g. of 91% and 1.39 g. of 69% material by n.m.r. analysis, the remainder being butyl borate. The yield was 9% or, based on *t*-butyl methaneboronate consumed, 15%. About 4 g. of butyl borate and a similar amount of higher boiling residue remained. Pure dibutyl chloromethaneboronate was obtained by refractionation, b.p. $34-35^\circ$ (0.02 mm.).

Anal. Calcd. for $C_8H_{20}BClO_2$: C, 52.35; H, 9.76; B, 5.24; Cl, 17.16. Found: C, 52.12; H, 9.53; B, 5.29; Cl, 17.35.

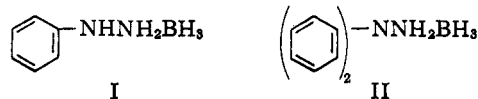
The Structure and Some Properties of Phenylhydrazine Borane and 1,1-Diphenylhydrazine Borane

RONALD J. BAUMGARTEN AND MALCOLM C. HENRY

U. S. Army Natick Laboratories,
Natick, Massachusetts

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The synthesis of phenylhydrazine borane (I) from phenylhydrazine hydrochloride and sodium borohydride has been reported by Lang.¹ Although the elemental analyses and structural proof of borane I were not included in Lang's patent, its melting point and solubility characteristics, as well as its instability to 50% sulfuric acid, and stability to water and acetic acid, were noted. A later patent of Fleming² reported that borane I, hydrazobenzene borane, and hydrazine borane, had a mild reducing action on vat dyes.



We have prepared borane I and the previously unreported 1,1-diphenylhydrazine borane (II) by a procedure similar to the methods previously described.^{1,2} The elemental analyses and molecular weight determinations, and the spectral and chemical properties reported in this paper for boranes I and II, lend support to the assigned structures.³ In particular, the infrared data summarized for various boron compounds in Table I, lend support for the structures as written.

Borane I is a stable, white, crystalline compound. Hydrolysis of borane I with 3 *N* hydrochloric acid gave phenylhydrazine hydrochloride, hydrogen, and boric

(1) K. Lang, German Patent 1,068,231 (1959); *Chem. Abstr.*, **55**, 23950g (1961).

(2) R. A. Fleming, U. S. Patent 2,992,061 (1961); *Chem. Abstr.*, **55**, 24030d (1961).

(3) There is still some doubt in regards to which nitrogen the BH_3 is bonded, but considerations of the relative basicities of the two nitrogens and the method of preparation favor the structures as assigned.

(6) H. M. Teeter and E. W. Bell, *Org. Syn.*, **32**, 20 (1952).

(7) D. S. Matteson, *J. Org. Chem.*, **27**, 3712 (1962).