

THE SYNTHESIS AND REACTIONS OF
DICHLOROMETHANEBORONIC ESTERS

Thesis for the Degree of M. S.
MICHIGAN STATE UNIVERSITY
SHOW-JEN GRACE WU
1971

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ABSTRACT

THE SYNTHESIS AND REACTIONS OF DICHLOROMETHANEBORONIC ESTERS

By

Show-jen Grace Wu

Dichloromethylithium is obtained by slow addition of n-butyllithium-hexane solution to methylene chloride-tetrahydrofuran solution at -100° . The reaction of dichloromethylithium with trimethyl borate, followed by hydrolysis produces dichloromethaneboronic acid. A variety of reaction conditions to synthesize the dichloromethaneboronic acid were studied. Also a number of esters of this acid were synthesized, but only the isopropanol ester was isolated in pure form. The failure to isolate the other boronic esters is due to the presence of the corresponding borate and bis-dichloromethaneborinate.

Since the isopropanol ester is obtained in good yield, its reactions with bases were investigated. It is found that in benzene di-isopropyl dichloromethaneboronate fails to generate carbene via α -elimination. Also, removal of the α -hydrogen from di-isopropyl dichloromethaneboronate by lithium bis-(trimethylsilyl)amide is unsuccessful. However, the isopropanol ester does react with diethanolamine to form

Show-jen Grace Wu

the acid derivative of diethanolamine, $\text{Cl}_2\text{HCB}(\text{OCH}_2\text{CH}_2)_2\text{NH}$, and react with bases such as n-butyllithium, phenylmagnesium bromide or t-butyllithium to form the corresponding α -chloroalkaneboronate or α -chloroareneboronate. Hydrogen peroxide oxidation of the α -chloroalkaneboronates or α -chloroareneboronates provides a convenient route for the synthesis of aldehydes. The yield of the aldehyde is dependent on the solvent used, reaction time and reaction temperature of the reaction of the isopropanol ester with base. However, sodium hydride fails to react with the isopropanol ester as a nucleophile in many common organic solvents.

THE SYNTHESIS AND REACTIONS OF
DICHLOROMETHANEBORONIC ESTERS

By

Show-jen Grace Wu

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

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1971

To

My Grandmother, Dad, Mom and Husband

ACKNOWLEDGMENTS

The author wishes to express her sincere appreciation to Professor Michael W. Rathke for his continuous guidance and inspiration throughout the course of this investigation.

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INTRODUCTION

α -Haloalkaneboronic esters are potentially useful intermediates for the synthesis of a wide variety of new organofunctional boronic esters. The reported reactions of α -haloalkaneboronic esters include dehydrohalogenation and nucleophilic displacement. The reactivity of the halogen as a leaving group in nucleophilic displacements is known to be markedly enhanced by the neighboring boron atom. Therefore, efforts are still being made to find convenient synthetic methods for preparing α -haloalkaneboronic compounds.

Dichloromethaneboronic acid (I) has been synthesized recently.¹ In this thesis, the synthesis of a variety of esters of dichloromethaneboronic acid and an investigation of the synthetic utility of their reactions with nucleophiles is reported. Also, an improved method of synthesis of dichloromethaneboronic acid is presented.

Since dichloromethaneboronic acid is obtainable in good yield, it is hoped that its esters may open new possibilities in synthesis of more complicated α -haloalkaneboronic esters, alkaneboronic esters and alkeneboronic esters. A number of esters of dichloromethaneboronic acid

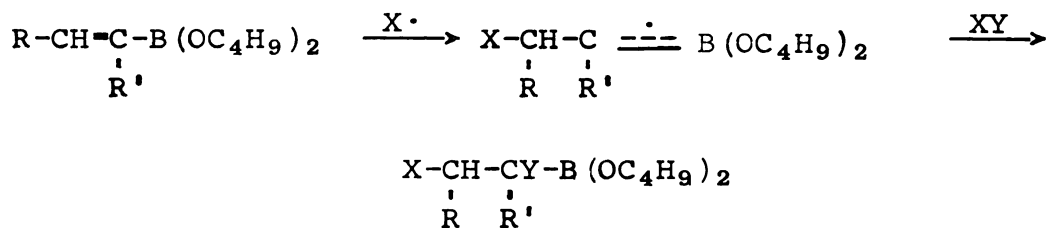
were synthesized, but only the isopropanol ester and 1,3-propandiol ester were isolated in pure form. The reactions of isopropanol ester with some nucleophiles were investigated.

LITERATURE REVIEW

A. The Synthesis of α -Haloorganoboronic Compounds

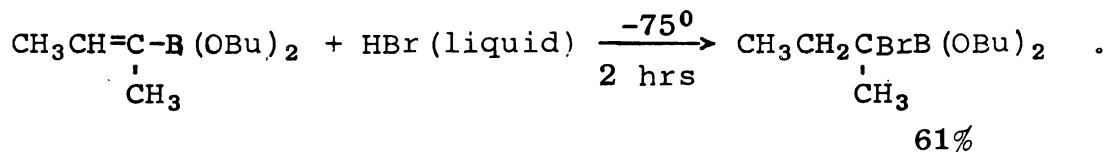
A number of α -haloalkaneboronic compounds have been synthesized during the last ten years, most of the work has been done by D. S. Matteson.

In 1960, D. S. Matteson first obtained the α -haloalkaneboronic compounds by radical-catalyzed addition of polyhalomethanes such as bromotrichloromethane or carbon tetrachloride to α,β -unsaturated boronic esters.² The general reaction equation is expressed as:

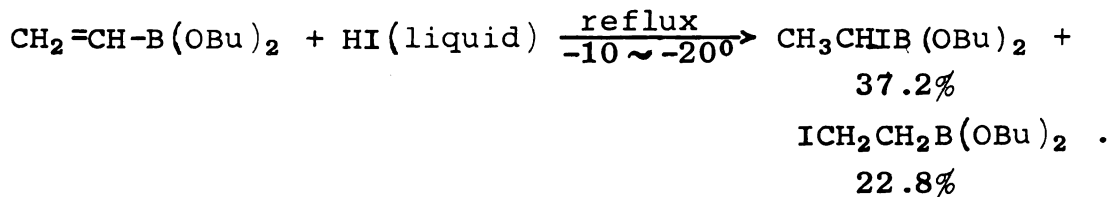


The reactivity of the double bond is decreased by the presence of the alkyl group at the β -position, and the intermediate radical of the reaction is stabilized by electron delocalization. It has been found that both the ester and the α -halo group of the α -haloalkaneboronic esters are hydrolyzed in alkaline solutions, but if treated with cold water only the corresponding α -haloalkaneboronic acid is obtained.²

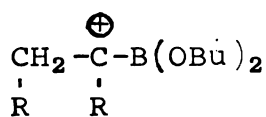
In 1963, Matteson reported that the ionic addition of hydrogen bromide to α,β -unsaturated boronic esters provided another useful route to the α -haloalkaneboronic esters.^{3,4} For example,



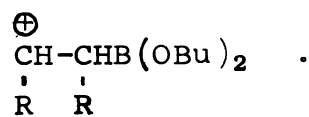
In 1965, the ionic addition of hydrogen iodide to α,β -unsaturated boronic esters was carried out by Matteson.⁵



The addition of the hydrogen halide across the double bond is directed by the electron-donating inductive effect of the dibutoxyboryl group which stabilizes form (A) over form (B)^{3,5}

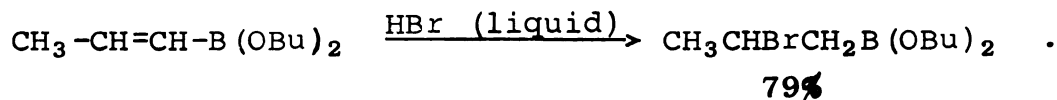


(A)



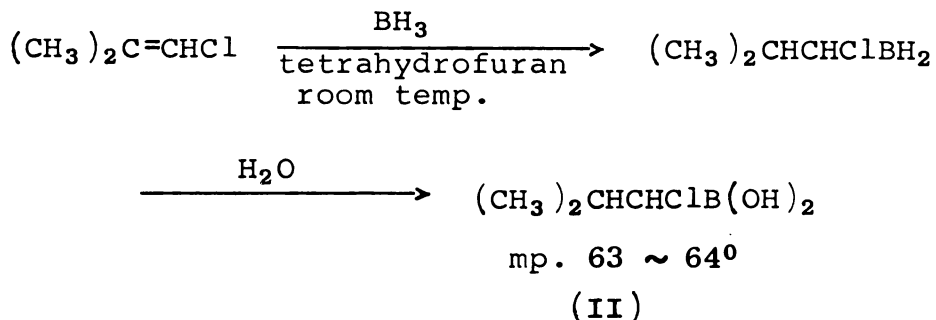
(B)

On the other hand, if only the β -carbon has methyl substituents, the preferential attack of the halide ion on the double bond will be at the β -position.³ Such as:

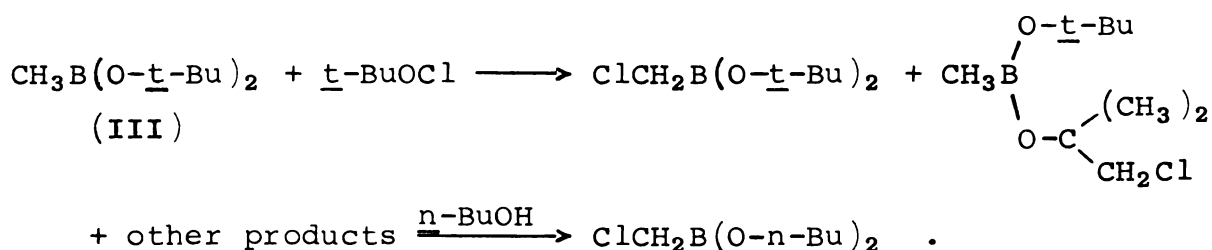


It seems that the directing influence of the dibutoxyboryl group is less than that of a methyl group.

In 1968, D. J. Pasto found that by Hydrolysis of the corresponding borane, 1-chloro-2-methylpropaneboronic acid (II) was formed in excellent yield, $\geq 84\%$.⁶ The reaction is shown as:

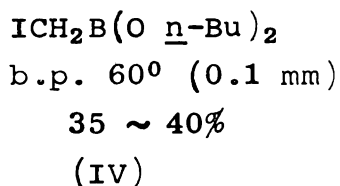
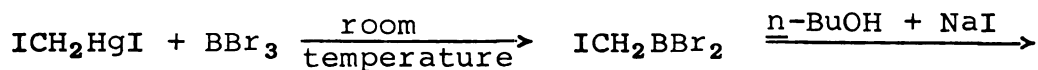


Although there are many useful synthetic routes to α -haloalkaneboronic compounds, the preparation of halomethaneboronic compounds is very difficult. According to D. S. Matteson, the irradiation of t-butyl hypochlorite and di-t-butyl methaneboronate (III) at 0° did produce some chloromethaneboronic ester. The product which was isolated was obtained in only 9% yield as the di-n-butyl chloromethaneboronate.⁷



The problem is that the chlorination of the C-methyl groups is competing with the chlorination of the B-methyl group.

However, in 1966, by starting from boron tribromide and iodomethylmercuric iodide, useful quantities of dibutyl iodomethaneboronate (IV) were prepared.⁸



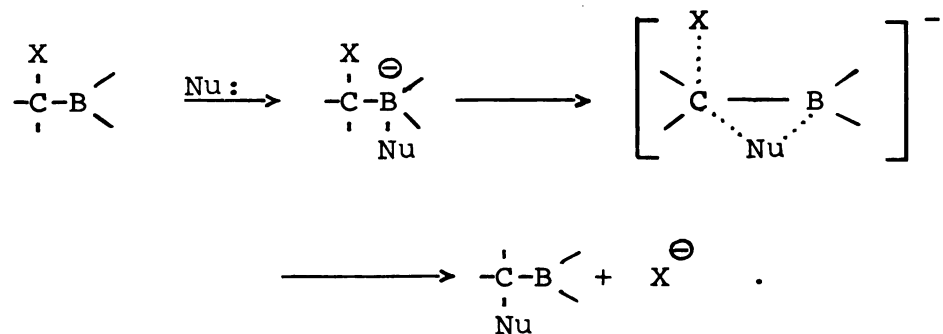
B. Reactions of α -Haloalkaneboronates with Nucleophiles

1. Dehydrohalogenation

Dehydrohalogenation occurs when α -haloalkaneboronic esters are treated with hindered bases such as t-butylamine.⁹ This reaction forms alkeneboronic esters.

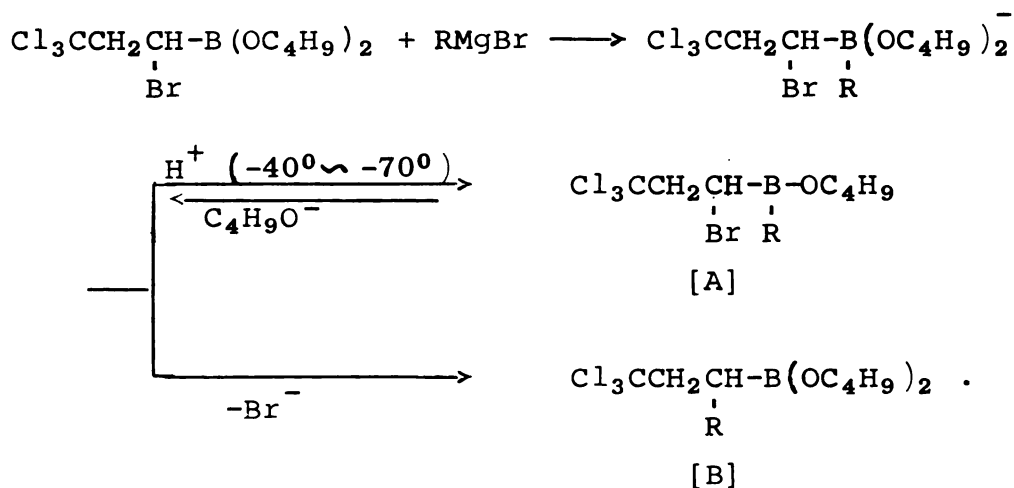
2. Displacement of Halide Ion

Displacement of the halide ion from an α -haloalkaneboronic compound by nucleophiles such as iodide ion, butoxide ion, butyl mercaptide ion, etc. has been studied in considerable detail by Matteson and his coworkers. Attack of the nucleophile is assumed to occur initially on the boron atom, followed by the migration of the nucleophile to the α -carbon atom with expulsion of the α -halide ion^{5,8,10,11,12} The following mechanism is representative:



Strong support for this mechanism was furnished by the behavior of butyl B-aryl- and B-alkyl-B-(α -haloalkane)-borinates, which upon mild base treatment, expel halide ion with migration of the B-aryl or B-alkyl group from boron to carbon.¹⁰

Grignard reagents also displace halide ion from the α -haloalkaneboronic ester to yield the corresponding α -alkyl- or α -aryl-alkaneboronic esters. The reaction mechanism is proposed as above. Indeed, if the Grignard reagent is added to α -haloalkaneboronic ester at -70° and the product is acidified in the cold, the corresponding borinic ester can be isolated.¹⁰ For example,



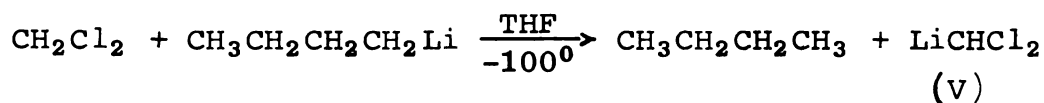
The reaction of α -bromoalkaneboronic compounds with sodium iodide in acetone leading to halide exchange was studied. Comparison with literature values for simple alkyl halide gives the following relative rate constants:⁵

<u>Compound</u>	<u>Relative Rate Constant</u>
isopropyl bromide	1.0
ethyl bromide	4.0
dibutyl 2-bromopropane-2-boronate	1600
allyl bromide	4000
dibutyl 1-bromoethaneboronate	6000

It is concluded that the neighboring boron atom participates in and greatly accelerates nucleophilic displacement of the α -halide ion. These effects are due to the electron donation from boron to carbon and the partial bond formation by nucleophiles with the vacant boron orbital.⁵

RESULTS

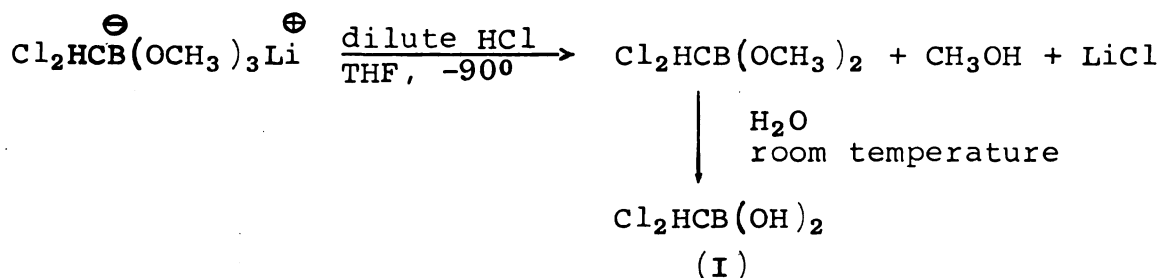
Slow addition of n-butyllithium-hexane solution to excess methylene chloride-tetrahydrofuran solution at -100° under nitrogen forms a white precipitate of dichloromethyl-lithium (V).^{13,14,15,16}



Conversely, the rapid introduction of n-butyllithium to methylene chloride solution causes the thermal decomposition of the dichloromethyl-lithium(V) and formation of a black solution.¹⁷

The reaction between dichloromethyl-lithium (V) and trimethyl borate is very fast even at -100° . At -80° it was observed that the white precipitate of the dichloromethyl-lithium (V) dissolves and another white precipitate reforms again within 10 min. Removal of the solvent affords an oil-like material with a positive flame test for boron. The nmr spectrum shows singlets at δ 5.25 (1 H) and δ 3.3 (9-10 H). Therefore, the product of the reaction of dichloromethyl-lithium (V) and trimethyl borate possibly forms according to the following equation:

Hydrolysis of the lithium salt (VI) solution with dilute hydrochloric acid at -90° , followed by removal of the solvent affords the corresponding boronic acid (I).



The results of a study on the preparation of dichloromethaneboronic acid (I) under various reaction conditions are listed in Table I.

The crude boronic acid is very soluble in polar solvents such as alcohols, acetone, tetrahydrofuran and water but

Table I. The preparation of dichloromethaneboronic acid (I) under various reaction conditions.

Methylene Chloride moles	Trimethyl Borate moles	Reaction Temperature <u>n</u> -BuLi ² and CH ₂ Cl ₂	Reaction Temperature CHCl ₂ Li and B(OCH ₃) ₃	% Yield Isolated as di-isopropyl ester
100	100	- 90°	- 90°	20 ~ 28
100	115	-100°	-100°	36 ~ 40
110	110	-100°	-100°	42 ~ 48
110	110	-100°	Starting From -120° then warmed to -100°	50 ~ 58

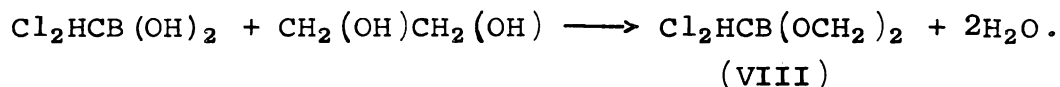
¹The hydrolysis is carried out at low temperature.

²The amount of the n-butyllithium used is one hundred mmoles.

insoluble in methylene chloride, chloroform, benzene and acetonitrile; and can be stored in ethereal extract without autooxidation. Prolonged exposure of the dry boronic acid to air leads to a decrease in the intensity of the H-C-B signal in the nmr spectrum.¹⁹

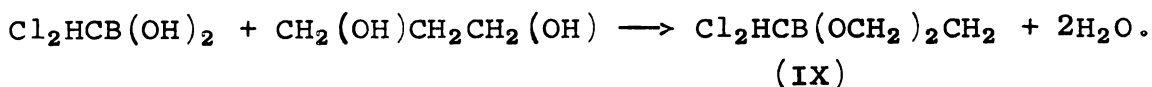
Several dichloromethaneboronic esters are prepared, but only the isopropanol ester (Xb) and 1,3-propandiol ester (IX) can be obtained in pure form. The esterifications are carried out by simply heating a mixture of the corresponding alcohol with crude dichloromethaneboronic acid. Although the desired reactions do occur; for some of the reactions the separation of the reaction product from the corresponding borate and borinate by-products is difficult. For those alcohols whose boiling points are higher than 100° the esterification is performed in acetone and the water formed is removed by anhydrous magnesium sulfate. Otherwise, a solution of the crude boronic acid containing excess alcohol and benzene is distilled under nitrogen at atmospheric pressure to remove the water-alcohol-benzene azeotrope. The desired product is collected by vacuum distillation.

In 1957, Sugihara and Bowman reported that the reaction of benzeneboronic acid with diols formed cyclic boronic esters with ring structures containing 5-, 6-, and 7-members.²⁰ It was hoped that the reaction of ethylene glycol and dichloromethaneboronic acid would produce a 5-membered cyclic boronic ester (VIII) according to the following equation.



In fact, the reaction provides a solid product, which after recrystallization from anhydrous ethyl ether gives a melting range of 98 ~ 100° and nmr spectrum with singlets at δ 5.3 (1 H), δ 4.6 ~ 5.0 (3 ~ 5H), and δ 3.7 (4 ~ 7H) in variable proton ratios. These results indicate that the solid compound is not the desired ester (VIII) (the pure 1,3-propandiol ester (IX) is a viscous liquid). Possibly, polymerization occurs during the esterification to form a mixture of compounds. Other attempts to synthesize the pure ethylene glycol ester (VIII) failed.

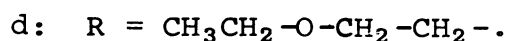
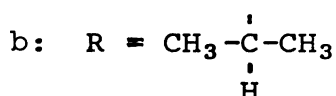
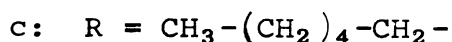
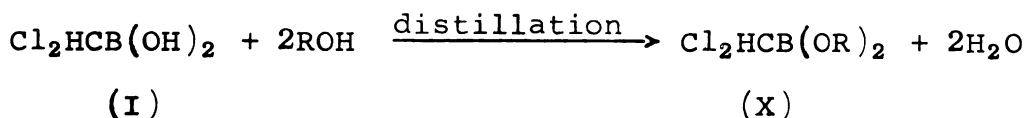
The reaction between dichloromethaneboronic acid (I) and 1,3-propandiol in acetone can be shown as:



After removal of drying agent and acetone, the viscous boronic ester (IX) was collected at 97 ~ 98° (8 ~ 8.5 mm Hg). This was contaminated with unreacted 1,3-propandiol, whose boiling point is slightly lower than that of the ester (IX). Since these two liquids are immiscible, there is no problem of separation. Collection of the bottom layer yields 7 g (52%) of pure ester (IX), n_D^{25} 1.4758. This viscous ester (IX) is very soluble in alcohols, ethers and acetone; and can be stored under nitrogen. The nmr spectrum shows a singlet at δ 5.28 (1 H), a triplet at δ 4.15 (4 H), a quintet at δ 2.05 (2 H). The mass spectrum displays the expected parent peak at m/e 168.

Both of the spectra are consistent with the assigned structure (IX).

The reactions of dichloromethaneboronic acid (I) with mono-hydroxyalcohols can be generalized as follows:



The n-propanol ester (Xa) is collected at 106 ~ 107° (31 mm Hg) in 46% yield based on the nmr spectrum. The nmr spectrum indicates that the ester (Xa) is contaminated with a small amount of the corresponding borate and borinate. Several redistillations failed to separate these by-products and it was found that the ester (Xa) boils between the by-products with the borinate as the highest boiling component. The nmr spectrum shows a H-C-B singlet at δ 5.32.

The reaction of dichloromethaneboronic acid (I) with hexanol or 2-ethoxyethanol seems to go to completion easily in acetone. Although the yield of the boronate (Xc or Xd) is high, the separation of the product from the corresponding borate, which boils slightly higher than the desired ester, is impossible. Both of the reaction products are obtained by distillation; the hexanol ester (Xc) is collected at 127 ~ 128° (0.5 mm Hg) and the 2-ethoxyethanol ester (Xd) is collected at 143~144° (8.5 ~ 9 mm Hg). The nmr spectra

of the hexanol ester (Xc) and 2-ethoxyethanol ester (Xd) show a H-C-B singlet at δ 5.29 and δ 5.54 respectively.

In the preparation of the di-isopropyl boronate (Xb), the acid, isopropanol and benzene were heated to maintain slow distillation of, successively, water-isopropanol-benzene azeotrope at 66.5° , water-benzene azeotrope at 69.3° , isopropanol-benzene azeotrope at 71.9° and finally excess of benzene. The esterification is very slow and takes almost five days to complete. Although the esterification gives the corresponding borate and borinate by-products, the separation is possible. Fractionation yields borate, boronate and finally a mixture of boronate (small amount) and borinate. An attempt to collect the pure borinate, which has the highest boiling point of the three, leads to decomposition.

The pure ester (Xb), $n_D^{23.5} 1.4211$, is collected at 65° (10 mm Hg) in 50 ~ 58% (10.5 g ~ 12.2 g) yields based on the amount of n-butyllithium used in the preparation of the boronic acid (I). The ester (Xb), which is a slightly fuming liquid, has been found to be completely stable in the absence of air and moisture and shows no tendency to disproportionate. The ester (Xb) is very soluble in alcohols, benzene and ethers. Prolonged exposure of the ester (Xb) to air forms the corresponding boronic acid and boric acid. The nmr spectrum shows an H-C-B singlet at

δ 5.27 (1 H), a $\begin{array}{c} \text{H} \\ | \\ \text{C}-\text{C}-\text{C} \\ | \\ \text{O} \end{array}$ septet at δ 4.66 (2 H), a $\text{CH}_3\text{-C}$ doublet at δ 1.2 (12 H).

The result of elemental analyses of the 1,3-propandiol ester (IX) is not acceptable. This possibly is due to the contamination of the unreacted 1,3-propandiol. The boiling point of 1,3-propandiol is 214° (760 mm Hg), which is too close to that of the 1,3-propandiol ester (IX) to permit separation. The analytic data obtained is listed in Table II.

Table II. Results of elemental analyses.*

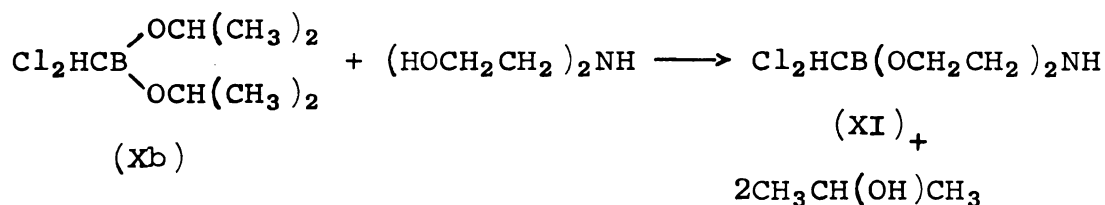
Formula		%C	%H	%N	%Cl
$\text{Cl}_2\text{HCB} \begin{cases} \text{OCH}(\text{CH}_3)_2 \\ \text{OCH}(\text{CH}_3)_2 \end{cases}$	Calcd	39.46	7.10		33.36
	Found	39.24	7.28		33.56
$\text{Cl}_2\text{HCB}(\text{OCH}_2\text{CH}_2)_2\text{NH}$	Calcd	30.33	5.10	7.07	35.89
	Found	30.31	5.23	6.86	35.51
$\text{Cl}_2\text{HCB}(\text{OCH}_2)_2\text{CH}_2$	Calcd	28.44	4.18		42.05
	Found	29.69	4.13		39.93

* Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tennessee.

Because it is very stable and can be obtained in good yield, the di-isopropyl dichloromethaneboronate was chosen in preference to the other boronates for exploratory studies of reactions of dichloromethaneboronate with bases.

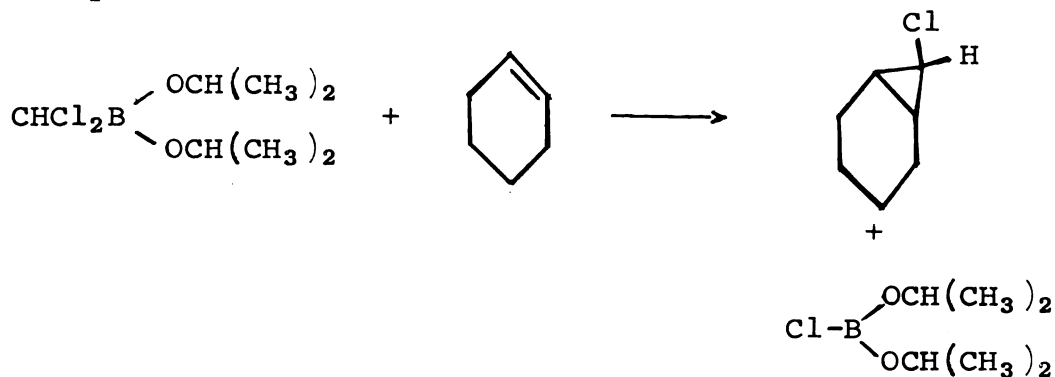
Although the acid derivative of diethanolamine (XI) was synthesized, the purity was unsatisfactory.¹

With a hope of synthesizing the pure acid derivative (XI), the reaction of di-isopropyl dichloromethaneboronate with diethanolamine was run at toom temperature.



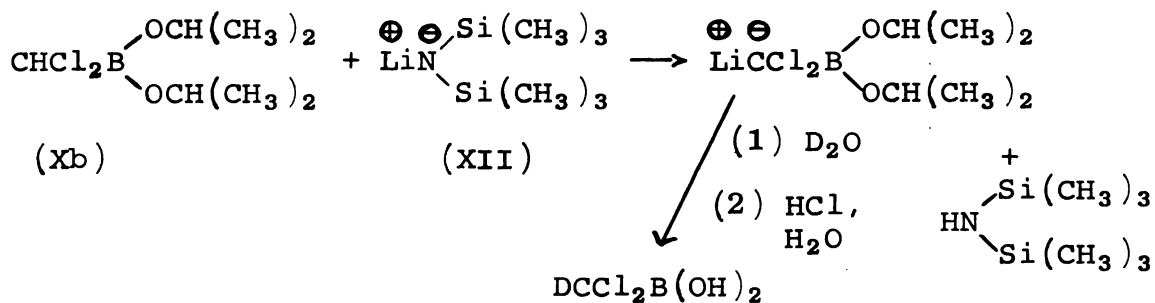
A white precipitate forms immediately after mixing an equivalent amount of diethanolamine and di-isopropyl dichloromethaneboronate (Xb) in tetrahydrofuran under nitrogen. After filtration there was obtained 0.90 g (90.9% yield) of pure $\text{CHCl}_2\text{B}(\text{OCH}_2\text{CH}_2)_2\text{NH}$, melting at $207 \sim 208^\circ$ with decomposition. The derivative (XI) obtained is a pure compound and further purification is unnecessary. With the exception of absorbing water, the derivative (XI) seems stable in air. Through prolonged contact with water the acid derivative (XI) undergoes hydrolytic cleavage to form the corresponding acid (I) and diethanolamine. Its melting point remains constant over a period of two days' exposure to air. The derivative is insoluble in ethers, chloroform, carbon tetrachloride and benzene, but does dissolve in alcohols, water and hot acetonitrile. The nmr spectrum shows an H-C-B singlet at δ 4.85, a C-N-C singlet centered at δ 4.15, a O-CH₂-C triplet centered at δ 3.35 and a C-CH₂-N triplet centered at δ 2.67 in D₂O.

It was thought that upon heating di-isopropyl dichloromethaneboronate possibly would undergo α -elimination to generate monochlorocarbene. The reaction of the boronate (Xb) with cyclohexene was desired as follows:



Excess cyclohexene was added to the boronate-benzene solution and the mixture was refluxed under nitrogen. Although the refluxing was continued for four hours, the nmr spectrum indicated no detectable reaction occurred.

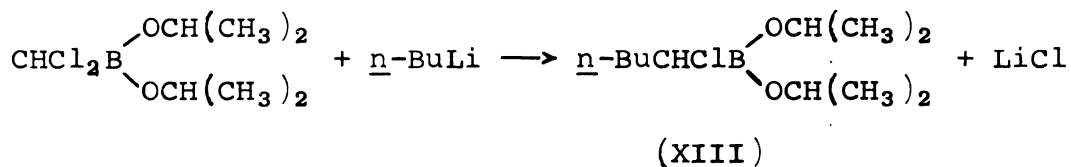
An attempt was made to remove the α -hydrogen of di-isopropyl dichloromethaneboronate. It was hoped that starting from the reaction of di-isopropyl dichloromethaneboronate with lithium bis-(trimethylsilyl)amide (XII) followed by addition of deuterated water and dilute hydrochloric acid, an α -deuterated dichloromethaneboronic acid might be obtained. The reaction scheme is shown as follows:



Reaction of stoichiometric quantities of di-isopropyl dichloromethaneboronate and lithium bis-(trimethylsilyl)amide (XII) was performed in tetrahydrofuran under nitrogen. The reaction mixture was stirred for 30 min at room temperature, then deuterated water followed by dilute hydrochloric acid was added. Extraction of the water layer and evaporation of the ether solvent afforded a white solid. The nmr spectrum shows that the ratio of the intensity of H-C-B signal to OH signal is one to two, which indicates no α -deuterated dichloromethaneboronic acid is obtained.

An attempt was also made to synthesize phenylacetic acid. Benzyl chloride was added to the reaction mixture of the dichloromethaneboronate (Xb) and lithium bis-(trimethylsilyl)amide (XII) and the mixture was then oxidized by hydrogen peroxide. However, no desired product was obtained.

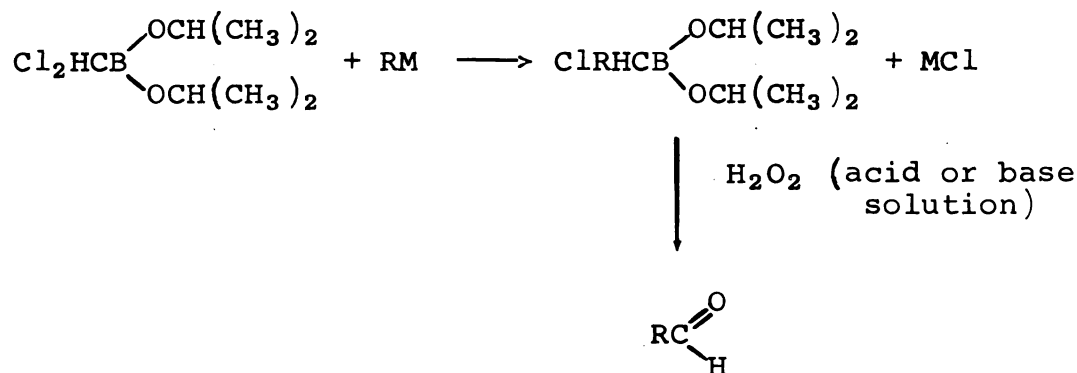
The reaction of di-isopropyl dichloromethaneboronate with n-butyllithium can be shown as follows:



An equivalent amount of n-butyllithium was rapidly added to di-isopropyl boronate-hexane solution at -78° under nitrogen. A white precipitate with a positive flame test for boron forms even at low temperature. After the reaction mixture was stirred for one hour at -78° and 14 hours at room temperature, a white precipitate with a negative flame

test for boron was filtered off and the filtrate was fractionally distilled under reduced pressure (10 mm Hg). This yielded 3.5 g of α -chloropentaneboronate (XIII), containing some impurities, at $96 \sim 97^\circ$. Purification by simple distillation is difficult. The best nmr spectrum shows an H-C-B triplet at δ 3.2.

It is hoped that the reaction of di-isopropyl dichloromethaneboronate (Xb) with bases followed by hydrogen-peroxide oxidation can provide a convenient route for the synthesis of aldehydes. In general, the reaction scheme is shown as follows:



Three typical reactions were run using n-butyllithium, t-butyllithium or phenylmagnesium bromide to react with di-isopropyl dichloromethaneboronate. All of the reactions produce the desired aldehyde isolated as the derivative of 2,4-dinitrophenylhydrazine, but the best reaction conditions differ greatly. The yields of the derivative are largely dependent on the solvent, reaction time and reaction temperature of the reaction of di-isopropyl dichloromethaneboronate with organometallic reagents. The results of the reactions are summarized as follows:

A mixture of di-isopropyl dichloromethaneboronate-anhydrous ethyl ether and n-butyllithium was stirred for one hour at -78° , then warmed to room temperature. At this time, a white precipitate with a positive flame test for boron forms. The mixture was then stirred for 15 hours at room temperature and finally a white precipitate with a negative flame test for boron forms. After removal of the solvent, 2,4-dinitrophenylhydrazine-hydrogen peroxide solution was added. When the mixture is stirred the white precipitate dissolves and a yellow precipitate of 2,4-dinitrophenylhydrazone forms. This was filtered and recrystallized from methanol. The yield of pentanal derivative is 72% melting at $105.5 \sim 106.5^{\circ}$, which agrees with the reported value of 106° . The nmr spectrum is also consistent with the assigned structure. The reaction can be run in hexane solution also.

At first, the reaction of di-isopropyl boronate (Xb) and phenylmagnesium bromide was run under the conditions similar to the above reaction, but no desired benzaldehyde derivative was obtained. Even if the reaction mixture was allowed to reflux for one day, only a few percent of benzaldehyde derivative was produced. This is insufficient to isolate. However, it was found that by running the reaction in tetrahydrofuran, good yields of benzaldehyde derivative could be obtained.

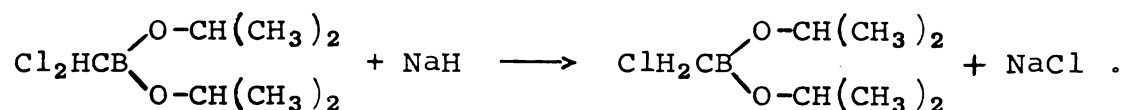
A mixture of phenylmagnesium bromide and di-isopropyl dichloromethaneboronate-tetrahydrofuran was stirred for

one hour at -78° under nitrogen, then allowed to reflux for 15 hours. When it was cooled a white precipitate with a negative flame test for boron forms. After removal of tetrahydrofuran, 2,4-dinitrophenylhydrazine-hydrogen peroxide solution was added. The white precipitate dissolves and a red-orange precipitate forms within 15 min. Recrystallization from methanol-ethyl acetate gives 1.06 g (in 74% yield) of benzaldehyde derivative melting at $237 \sim 238^{\circ}$, which is in accord with the literature value, 237° .

A similar run with the reaction mixture refluxed for 3 hours only gives the desired derivative in 30% yield.

It is found that a similar reaction starting from the reaction of t-butyllithium and di-isopropyl dichloromethane-boronate in tetrahydrofuran does not give any pivalaldehyde derivative. In anhydrous ethyl ether solution the reaction only gives a few percent of the derivative, which is insufficient to isolate. Even if the reaction mixture was refluxed for one day, the results still remained the same. However, if the reaction of di-isopropyl dichloromethane-boronate and t-butyllithium was run in pentane solution and the reaction mixture kept at $-15 \sim -20^{\circ}$ for seven hours, then warmed to room temperature and stirred overnight, 30% of pivalaldehyde derivative was obtained. The yellow derivative is very soluble in alcohol and more water is needed to induce the precipitation. Recrystallization from methanol gives a melting range of $205 \sim 206^{\circ}$, which agrees with the reported value, 206° .

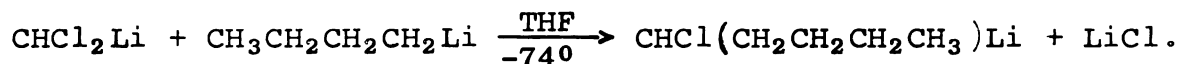
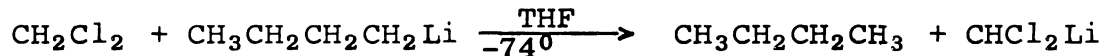
The reaction of di-isopropyl dichloromethaneboronate with sodium hydride was desired to occur according to the following equation.



A mixture of an equivalent amount of sodium hydride and di-isopropyl dichloromethaneboronate was allowed to reflux for four hours in tetrahydrofuran under nitrogen. The desired reaction did not occur as indicated by the nmr spectrum. Injection of water into the reaction mixture causes the evolution of hydrogen gas, which indicates that a lot of sodium hydride remains in the reaction mixture. Similar experiments using ethyl ether, diglyme and hexane as solvent also failed to cause the reaction to take place. Addition of 2,4-dinitrophenylhydrazine-hydrogen peroxide solution to the reaction mixture does not give the desired formaldehyde derivative.

DISCUSSION

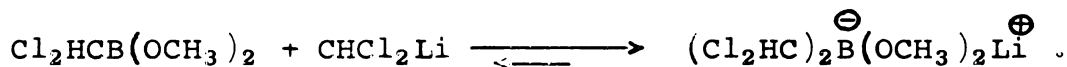
Dichloromethyl lithium (V) is very stable in tetrahydrofuran at -100° and can be stored for several hours without decomposition.^{13,14} Although the lithium compound (V) is also stable in tetrahydrofuran at -74° ,^{15,16} its preparation cannot be carried out at this temperature because at -74° dichloromethyl lithium (V) reacts with n-butyllithium to form $\text{CHCl}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{Li}$.^{15,16}



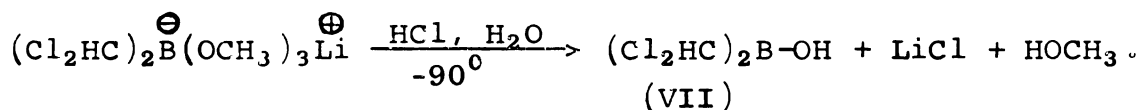
The side reaction decreases the yield of dichloromethyl lithium (V). Also, $\text{CHCl}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)\text{Li}$ can participate in subsequent reactions to form the by-product.¹⁶ It is found that these side reactions also occur at -90° in tetrahydrofuran. However, by running the reaction at -100° and using a small excess of methylene chloride, good yields of dichloromethyl lithium (V) can be obtained.

An oil-like material, which is obtained by the reaction of the dimethyl lithium (V) and trimethyl borate, is suggested to be $\text{Cl}_2\text{HCB}^{\ominus}(\text{OCH}_3)_3\text{Li}^{\oplus}$ (VI). Possibly, this lithium salt (VI) is quite stable at low temperature with

disproportionation to $\text{Cl}_2\text{HCB}(\text{OCH}_3)_2$ and LiOCH_3 being negligible. However, if the disproportionation does occur, further alkylation of $\text{Cl}_2\text{HCB}(\text{OCH}_3)_2$ by dichloromethyl lithium (V) would be fast. It is probable that the electron-withdrawing effects of the chlorine atoms attached to the α -carbon of $\text{Cl}_2\text{HCB}(\text{OCH}_3)_2$ accelerate the further alkylation by stabilization of the transition state. Indeed, the yields of the boronic acid (I) are largely dependent on the amount of trimethyl borate used and the reaction temperature of trimethyl borate and dichloromethyl lithium (V). It is thought that during the preparation of the boronic acid (I), side reactions possibly occur according to the following equations.



Thus, hydrolysis of the reaction mixture with dilute acid, bis-dichloromethaneborinic acid (VII) is obtained as one of the by-products.



The addition of the dichloromethyl lithium (V) to cooled trimethyl borate reduces the side reactions and is the proper procedure for the reaction. However, it is difficult to maintain the dichloromethyl lithium (V) at the proper low temperature.^{16,17} Consequently, the order of the addition was reversed. However, rapid introduction of excess

trimethyl borate to vigorously stirred dichloromethyl lithium (V) solution at -120° followed by gradually warming the reaction mixture to -100° produces the monoalkylated boron compound as the major product.

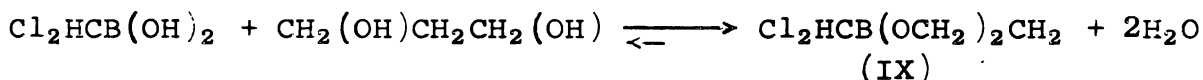
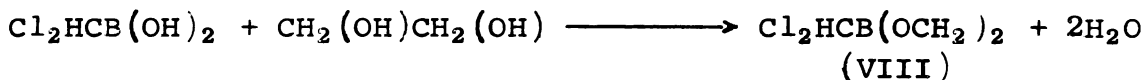
It is known that normal boron-carbon bonds are not easily broken by strong acids such as hydrochloric acid or sulfuric acid at room temperature. However, in order to avoid any side reactions such as the migration of the methoxy group from boron to carbon or the decomposition of the lithium compound¹⁸ (VI), the hydrolysis of the $\text{Cl}_2\text{HCB}(\text{OCH}_3)_3\text{Li}^{\oplus}$ (VI) with dilute hydrochloric acid was carried out at -90° .

It is found that the yields of the boronic acid (I) also depend on the rate of stirring of the reaction mixture. The presence of boric acid and the borinic acid (VII) in the crude boronic acid can explain the variable proton ratios of the nmr spectrum. These impurities are difficult to remove from the desired boronic acid (I) presumably because of similar solubility. Although purification by crystallization is impossible, the pure boronic acid (I) can be isolated in 50 ~ 58% yields as the diisopropyl ester (Xb). The boronic acid (I) is very soluble in polar solvents such as acetone, alcohols, tetrahydrofuran and water. Prolonged exposure of the boronic acid (I) to air causes autooxidation and leads to formation of boric acid.¹⁹

Since the α -halo boronic acid (I) is very sensitive to heat, the esterifications are performed below 110° . It is very convenient to remove the water formed as an

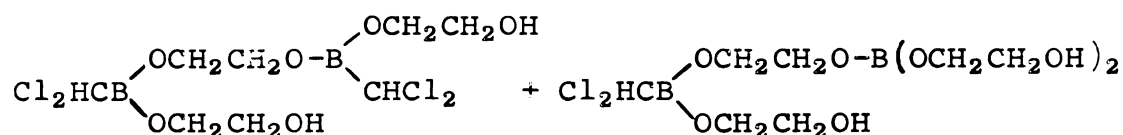
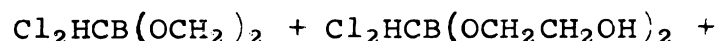
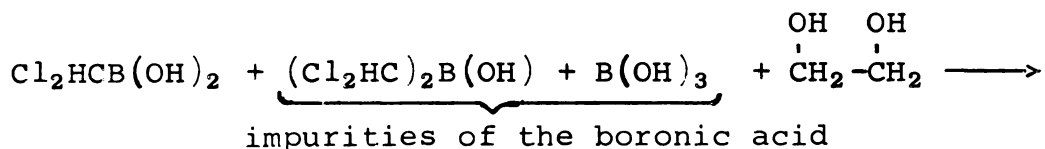
azeotrope, but for some of the esterifications which involve high boiling alcohols such as ethylene glycol, 1,3-propanediol, hexanol and 2-ethoxyethanol, the water-alcohol azeotropic distillation to remove the water formed is not appropriate. For the high boiling alcohols magnesium sulfate is used as drying agent and the reaction is run in acetone with care not to overheat the reaction mixture.

It was expected that the reaction of α -halo boronic acid (I) with ethylene glycol or 1,3-propandiol would produce the cyclic ester with the ring structure containing 5- or 6-members,²⁰ respectively. The reactions can be shown as follows:



For the second reaction, the equilibrium lies far in favor of the desired cyclic 1,3-propandiol ester (IX). Although the impurities of the crude α -halo boronic acid cause side reactions, the fractionation to separate the desired cyclic ester (IX) from the by-products, which result from the side reactions of the boric acid and the borinic acid (VII) with 1,3-propandiol, is possible. The desired portion, which is a two layer liquid, is contaminated with the unreacted diol. This is separated and the bottom layer yields the desired viscous ester (IX). The ester (IX) is quite stable and can be stored under nitrogen. Both the nmr spectrum and the mass spectrum agree with the assigned structure of the 1,3-propandiol ester (IX).

In contrast to the cyclic 1,3-propandiol ester (IX), the pure liquid of ethylene glycol ester (VIII) is not obtained. This difference probably concerns the steric requirements for ring formation and the preference of the ring size.²⁰ Many attempts to prepare the ethylene glycol ester (VIII) yielded similar solid products, which showed variable proton ratios in the nmr spectrum. This indicates that impurities form together with the desired ethylene glycol ester (VIII). Further purification by crystallization fails. The impurities could be the unreacted α -halo boronic acid, boric acid and borinic acid. It is also likely that during the esterification polymerization occurs to form a mixture of compounds according to the following equation:



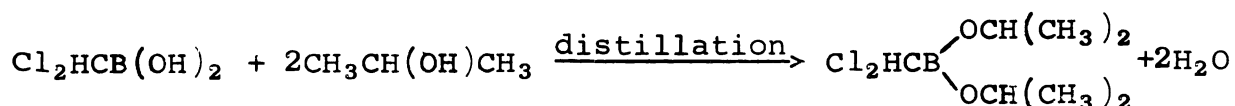
+ other possible products.

The reaction of α -halo boronic acid (I) with monohydroxyalcohols produces the desired ester. The by-products include the corresponding borate and borinate. Since boric acid and borinic acid (VII) are the impurities of the crude α -halo boronic acid, it is not certain whether the borate and the borinate

by-products arise from the reactions of the boric acid and the borinic acid with the alcohol or are the result of disproportionation of the corresponding boronate. However, the di-isopropyl ester (Xb) is isolated in pure form; repeated distillation in vacuum does not show any appreciable disproportionation. For the reaction of the α -halo boronic acid (I) with n-propanol, n-hexanol, or 2-ethoxyethanol, the separation of the α -halo boronate from the corresponding by-products by fractionation is impossible. This failure in separation can be rationalized by assuming that the desired boronate boils too close to the by-products or that the boronate disproportionates on heating in vacuum.

For alcohols with a boiling point lower than that of n-butanol, esterification produces a boronate with a boiling point between that of the corresponding borate and borinate, the borinate having the highest boiling point of the three. On the other hand, if the alcohol boils higher than n-butanol, fractionation of the esterified products gives the borinate as the lowest boiling component, with the boric ester as the highest boiling.

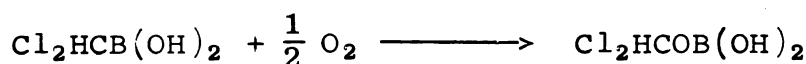
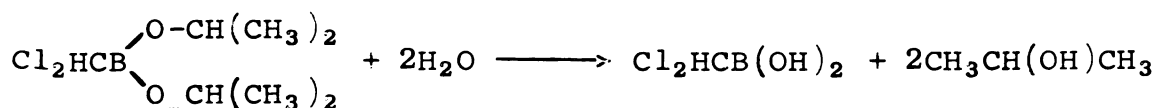
Useful quantities of pure di-isopropyl ester (Xb) are collected at 65° (10 mm Hg) according to the following equation.



The reaction is very slow and the azeotropic distillation takes almost five days to complete. Excess benzene is added

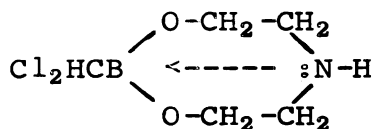
to remove the benzene-isopropanol azeotrope in order to avoid the di-isopropyl boronate (Xb) distilling together with the unreacted alcohol. Due to the di-isopropyl boronate (Xb) with a sufficient boiling point difference under reduced pressure from the corresponding boric ester, borinic ester and alcohol, the separation by fractionation is more facile in this case than for other boronic esters. The pure boronic ester (Xb) is obtained and may be redistilled without noticeable decomposition.

If one starts from the methylene chloride and n-butyllithium reaction, directly followed by hydrolysis and esterification with iso-propanol, the stable di-isopropyl dichloromethaneboronate (Xb) is obtained in 50 ~ 58% yields, based on the amount of the n-butyllithium utilized. Since the di-isopropyl ester (Xb) appears to be quite volatile, it is believed that the prolonged azeotropic distillation decreases the total yield of the ester (Xb). The ester (Xb) is very soluble in alcohols, benzene and ethers; and can be stored under nitrogen. Prolonged exposure of the ester (Xb) to air leads to the corresponding boronic acid (I) and boric acid, which probably forms according to the following equations:¹⁹



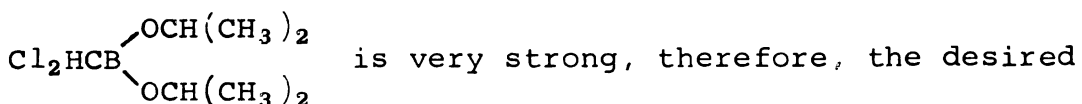
α -Haloalkaneboronic esters, especially dichloromethaneboronates, are potentially useful intermediates for the synthesis of a wide variety of new organofunctional boronic esters. Since di-isopropyl dichloromethaneboronate is very stable and can be obtained in good yield, it was chosen for synthetic studies.

The reaction of di-isopropyl dichloromethaneboronate and diethanolamine produces the desired acid derivative in pure form. The derivative is hygroscopic, but quite stable in air as indicated by its constant melting point at $207 \sim 208^\circ$ with decomposition. Prolonged contact with water causes hydrolysis and leads to the formation of the corresponding boronic acid and diethanolamine. The derivative is insoluble in ethers, chloroform, carbon tetrachloride and benzene, but does dissolve in alcohols, water and hot acetonitrile. The easy synthesis and high stability of the acid derivative of diethanolamine is probably due to the formation of the internal complex.^{21,22}



The nmr spectrum is consistent with the assigned structure of the acid derivative of diethanolamine.

Refluxing of di-isopropyl dichloromethaneboronate-cyclohexene-benzene solution does not cause any detectable reaction. It is probably because the carbon-boron bond of



α -elimination to generate the monochlorocarbene does not occur.

Lithium bis-(trimethylsilyl)amide (XII) fails to remove the α -hydrogen of di-isopropyl dichloromethaneboronate (Xb). Since the boron atom is very sensitive to attack by bases, the failure in removing the α -hydrogen is possibly because the lithium reagent (XII) has neither sufficient steric hindrance to reduce its basicity toward boron so that side reactions involving base attack on boron occur nor is the lithium reagent (XII) basic enough to remove the hydrogen.

It is known that nucleophilic displacement of halide ion from α -haloalkaneboronic ester is greatly facilitated by the neighboring boron atom. The reaction evidently proceeds through a tetravalent boron anion formed by attack of a nucleophile, which then migrates from boron to α -carbon with expulsion of the α -halide ion.^{5,10,11}

When warmed to $-10 \sim -20^\circ$ the reaction mixture of di-isopropyl dichloromethaneboronate and organometallic reagents, such as n-butyllithium, t-butyllithium or phenylmagnesium bromide, forms a white precipitate with a positive flame test for boron. This white precipitate seems soluble in tetrahydrofuran but insoluble in hexane and ethyl ether. It is very hygroscopic and turns to a viscous mass soon after it is isolated. However, through prolonged stirring of the reaction mixture of the boronate and n-butyllithium at room temperature a white precipitate with a negative flame test

for boron is obtained. It is thought that the white precipitate, which has a positive flame test for boron, possibly is an intermediate formed by attack of the base on the boron atom.

Migration of the n-butyl group from boron to the α -car-

bon of $\left[\begin{array}{c} \text{OCH(CH}_3)_2 \\ | \\ \text{Cl}_2\text{HCB-OCH(CH}_3)_2 \\ | \\ \text{n-Bu} \end{array} \right]^\ominus \text{Li}^\oplus$ seems easy to occur even at

low temperature; therefore, n-butyllithium-hexane solution is rapidly added to di-isopropyl dichloromethaneboronate-ether (or hexane) solution at -78° in order to minimize the

formation of $(\text{n-Bu})_2\text{HCB} \begin{array}{l} \text{OCH(CH}_3)_2 \\ \text{OCH(CH}_3)_2 \end{array}$. The failure to isolate

the pure product, di-isopropyl α -chloropentaneboronate, is probably due to the presence of di-isopropyl dichloromethaneboronate and isopropyl B-n-butyl-B-dichloromethaneborinate. These compounds boil too close together to permit separation.

Migration of the phenyl group from boron to the α -car-

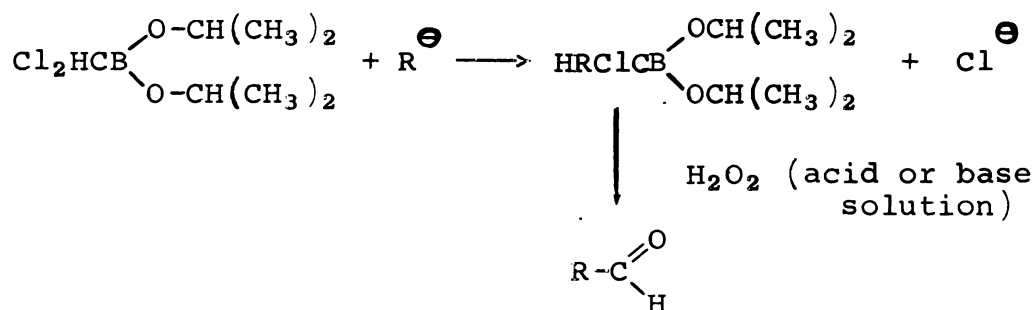
bon of $\left[\begin{array}{c} \text{OCH(CH}_3)_2 \\ | \\ \text{Cl}_2\text{HCB-OCH(CH}_3)_2 \\ | \\ \text{C}_6\text{H}_5 \end{array} \right]^\ominus \text{Li}^\oplus$ does not occur readily in

anhydrous ethyl ether. Even if the reaction mixture is refluxed for one day, the migration is still negligible. However, the migration does occur in tetrahydrofuran solution, after the reaction mixture is refluxed for ten hours.

Nucleophilic displacement of the chloride ion from di-isopropyl dichloromethaneboronate by t-butyl anion does not occur in tetrahydrofuran. In anhydrous ethyl ether solution, the reaction only occurs to a small extent. It

is probably because t-butyl anion is a strong base with a sufficient steric hindrance, therefore, its attack on the boron does not occur readily and side reactions involving the removal of the α -hydrogen of the ether solvent occur. However, if the reaction is run in hexane and the reaction mixture kept at $-15 \sim -20^\circ$ for 7 hours, the displacement reaction occurs to give 30% yield of the desired product.

Starting from the reaction of di-isopropyl dichloromethaneboronate with base followed by hydrogen peroxide oxidation provides a convenient route for the synthesis of aldehydes. The general scheme can be shown as follows:



To prove the formation of aldehydes, 2,4-dinitrophenylhydrazine solution was added. The yields of the aldehyde derivatives are largely dependent on the solvent, reaction time and reaction temperature of the reaction of di-isopropyl dichloromethaneboronate with nucleophiles.

Sodium hydride fails to react with di-isopropyl dichloromethaneboronate as a nucleophile, possibly because no proper solvent is found to dissolve the sodium hydride. This makes the reaction not occur readily.

EXPERIMENTAL

A. Preparation of Dichloromethaneboronic Acid (I)

The experimental apparatus consisted of a 500 ml round-bottomed, three-necked flask which was equipped with an efficient mechanical stirrer, a dropping funnel, and a mercury bubbler. The flask was placed in a dewar dish, containing a mixture of absolute ethanol-liquid nitrogen, in order to control the temperature of the contents of the flask.

The flask was flushed with nitrogen at 100° , then cooled to room temperature. Into the flask were placed 7 ml (110 mmoles) of methylene chloride and 200 ml of tetrahydrofuran. After the mixture was cooled to -110° , 63 ml (100 mmoles) of n-butyllithium in hexane was added dropwise via the dropping funnel to the vigorously stirred reaction mixture over a period of 40 min. An exothermic reaction ensued, but the temperature of the reaction mixture was kept between -100 and -105° by adjustment of the temperature bath. After complete addition of the n-butyllithium, the resulting suspension was allowed to warm to -95° and was stirred at this temperature for 30 min, to assure completion of the reaction. It was then cooled back to -120° .

At this time, 12.5 ml (110 mmoles) of trimethyl borate was introduced rapidly with vigorous stirring. Over the course of 30~40 min, the temperature rose to -90° . The reaction mixture was then hydrolyzed with dilute hydrochloric acid (9.2 ml HCl + 10.8 ml H_2O). The temperature of this solution was maintained at -90° for 20 min, and finally warmed to room temperature. The ethereal layer was separated and the aqueous layer was extracted twice with 25 ml portions of ether, which were combined with the main portion. The combined organic phase was concentrated on a steam bath. This afforded a viscous, reddish-brown mass which solidified on standing for several hours. The weight of the crude product was 15.5 g.

Difficulty was experienced in purifying the crude product; repeated crystallizations from various solvents gave a white solid which showed a wide melting range, $75 \sim 100^{\circ}$. The nmr spectrum showed a singlet at δ 5.25 (1 H) and a singlet at δ 6.15 (2 ~ 4 H) in tetrahydrofuran.

B. Preparation of Dichloromethaneboronic Esters

A number of esters of the dichloromethaneboronic acid were prepared by simply heating a mixture of alcohol with the crude boronic acid. The water formed in esterification, was removed either by drying agent or by water-solvent azeotropic distillation. All of the esters were obtained by vacuum distillation, with the exception of the ethylene glycol ester. The calculation of the number of moles of

the crude boronic acid used was based on the amount of n-butyllithium utilized in the preparation of the boronic acid.

1. Ethylene Glycol Ester (VIII)

Crude dichloromethaneboronic acid (1.3 g; 8.4 mmoles) was placed in a 50 ml round-bottomed flask, fitted with a distilling head, condenser and receiver; 0.66 ml (10 mmoles) of ethylene glycol and 30 ml of toluene were added under nitrogen, and the mixture was gently heated on an oil bath. Upon dissolution of the acid, the mixture was slowly distilled at atmospheric pressure. Fresh toluene was added to the reaction mixture at frequent intervals to maintain the original volume. After four hours, a total of 60 ml of distillate had been collected. The liquid residue was then cooled and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure over an oil bath left a solid residue. The residue was then recrystallized from anhydrous ethyl ether and gave a white solid with melting range of 98 ~ 100°. The nmr spectrum showed singlets at δ 5.3 (1 H), δ 4.6 ~ 5.0 (3 ~ 5H), δ 3.7 (4 ~ 7H) in variable proton ratios, which indicated that the solid product was not the expected ester. Further purification was unsuccessful.

Similar experiments in the presence of p-toluenesulfonic acid monohydrate, as catalyst, as well as other attempts using different combinations of solvents and drying agents gave the same undesired product.

2. n-Propanol Ester (Xa)

A 200 ml round-bottomed flask equipped with a fractionating column was charged with 15 g (100 mmoles) of crude dichloromethaneboronic acid and 100 ml of n-propanol, and was heated on an oil bath. With continued heating under nitrogen, the water-n-propanol azeotrope was distilled at 87.7°. After 70 ml of distillate was collected, the remaining yellowish solution was distilled under reduced pressure (31 mm Hg). Successively, fractionation yielded n-propanol, tri-n-propyl borate, di-n-propyl dichloromethaneboronate and n-propyl bis-dichloromethaneborinate. Although the distillation was carried out very carefully, the di-n-propyl dichloromethaneboronate, which was obtained at 106 ~ 107° in 46% yield based on the nmr spectrum, was contaminated with some of the corresponding borate and borinate. Several redistillations failed to separate these by-products. The best nmr spectrum of the boronate showed a single peak at δ 5.32 downfield from tetramethylsilane plus the characteristic n-propoxy pattern.

3. 1,3-Propandiol Ester (IX)

Into a 100 ml round-bottomed flask equipped with a reflux condenser were placed 12.07 g (80 mmoles) of crude dichloromethaneboronic acid, 6.4 ml (90 mmoles) of 1,3-propandiol, 10 g of anhydrous magnesium sulfate and 50 ml of acetone under nitrogen. The mixture was heated under reflux for three hours, then allowed to cool. After removal

of the magnesium sulfate by filtration and evaporation of the acetone solvent, the remaining clear viscous liquid was transferred to a small round-bottomed flask and distilled under reduced pressure (8 ~ 8.5 mm Hg). The desired boronic ester (IX) collected at 97 ~ 98°, was contaminated with a small amount of unreacted 1,3-propandiol, which boils at 214° (760 mm Hg). This was separated from the desired product (IX) and the bottom layer afforded the boronic ester (IX) in 52% (7g) yield, n_D^{25} 1.4758. The nmr spectrum showed a singlet at δ 5.28 (1 H), a triplet at δ 4.15 (4 H), a quintet at δ 2.05 (2 H). The mass spectrum showed the expected parent peak at m/e 168. Both of the spectra are consistent with the assigned structure.

4. Isopropanol Ester (Xb)

The crude dichloromethaneboronic acid (15 g; 100 mmoles) was placed in a 250 ml round-bottomed flask, fitted with a distilling head, condenser and receiver; 120 ml of benzene and 50 ml of isopropanol were added under nitrogen, and the mixture was gently distilled at atmospheric pressure. Fresh benzene and isopropanol were added to the reaction mixture at frequent intervals to maintain the slow distillation of. successively, the ternary (water-isopropanol-benzene) azeotrope at 66.5° and the binary (water-benzene) azeotrope at 69.3°. After the reaction mixture was distilled for five days, the water formed in the esterification was removed successfully. Further distillation gave the isopropanol-

benzene azeotrope at 71.9° . After removal of the unreacted isopropanol, the solution was decanted into a small round-bottomed flask and distilled under reduced pressure (10 mm Hg). Fractionation separated the excess benzene, tri-isopropyl borate and high-boiling impurities, and afforded 10.5 ~ 12.2 g of the desired boronic ester (Xb) (b.p. 65°), $n_D^{23} 1.4211$, in pure form. The ester (Xb) is a slightly fuming liquid and can be stored under nitrogen. The nmr spectrum showed an H-C-B singlet at δ 5.27 (1 H), a C-CH-C septet at δ 4.66 (2 H), a CH_3 -C doublet at δ 1.2 (12 H).
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5. Hexanol Ester (Xc)

A mixture of 6.5 g (43 mmoles) of crude dichloromethaneboronic acid, 8 ml (64 mmoles) of hexanol, 6 g of anhydrous magnesium sulfate and 20 ml of acetone was refluxed for two hours at $70 \sim 80^{\circ}$ under nitrogen. After the solution was cooled, the magnesium sulfate was removed by filtration and the filtrate was fractionally distilled under reduced pressure (0.5 mm Hg). Di-n-hexyl dichloromethaneboronate (Xc) (7.8 g), contaminated with some of the corresponding borate, which boiled slightly higher, was collected at $127 \sim 128^{\circ}$. The nmr spectrum showed an H-C-B singlet at δ 5.29.

6. 2-Ethoxyethanol Ester (Xd)

A mixture containing 6.5 g (43 mmoles) of crude dichloromethaneboronic acid, 5 ml of 2-ethoxyethanol, 6 g of anhydrous magnesium sulfate, and 20 ml of acetone was heated

on an oil bath at $75 \sim 80^{\circ}$ under nitrogen. After heating for two hours, the drying agent was removed by filtration, the solvent was removed by water aspirator and the remainder was then fractionally distilled. The portion at $143-144^{\circ}$ ($8.5 \sim 9$ mm Hg) yielded 8.06 g of boronic ester (Xd), contaminated with the corresponding borate by-product. The nmr spectrum showed an H-C-B singlet at δ 5.54.

C. Reactions of Di-isopropyl Dichloromethaneboronate (Xb)

1. The Reaction of Di-isopropyl Dichloromethaneboronate with Diethanolamine. Synthesis of Dichloromethaneboronic Acid Derivative of Diethanolamine (XI)

Diethanolamine (0.48 ml; 5 mmoles) was slowly added under nitrogen to a gently stirred solution of di-isopropyl dichloromethaneboronate (1 ml; 5 mmoles) in 15 ml of tetrahydrofuran at room temperature. During the course of addition a white precipitate formed immediately. After the resulting mixture was stirred for 15 min, the precipitate was filtered off and washed with 10 ml of cold tetrahydrofuran. This gave 0.90 g (in 90.9% yield) of $\text{Cl}_2\text{HCB}(\text{OCH}_2\text{CH}_2)_2\text{NH}$ melting at $207 \sim 208^{\circ}$ with decomposition. The derivative (XI) obtained was a pure compound and the further purification was unnecessary. The nmr spectrum, which was taken immediately after the derivative was dissolved in deuterated water, showed an H-C-B singlet at δ 4.85, a C-N-C singlet centered at δ 4.15, a $-\text{OCH}_2-\overset{\text{H}}{\underset{|}{\text{C}}}$ triplet centered at δ 3.35 and a C-CH₂-N triplet centered at δ 2.67.

2. An Attempt to Generate Carbene. The Reaction of Di-isopropyl Dichloromethaneboronate with Cyclohexene

Cyclohexene (2.56 ml; 25 mmoles) was slowly added under nitrogen to a gently stirred solution of 1 ml (5 mmoles) of di-isopropyl dichloromethaneboronate in 5.8 ml of benzene at room temperature. No apparent reaction was observed. The reaction mixture was then refluxed for four hours and cooled. The nmr spectrum indicated no detectable reaction occurred under the reaction conditions.

3. An Attempt to Remove the α -Proton of Di-isopropyl Dichloromethaneboronate. The Reaction of Di-isopropyl Dichloromethaneboronate with Lithium Bis-(trimethylsilyl)amide (XII)

a. Preparation of Lithium Bis-(trimethylsilyl)amide Solution. A 50 ml round-bottomed flask connected to a mercury bubbler was flushed with nitrogen at 100° and cooled to room temperature. Into the flask was placed 3.25 ml (5 mmoles) of n-butyllithium in hexane; then, 1.05 ml (5 mmoles) of hexamethyldisilazane was added dropwise under nitrogen. An exothermic reaction accompanied with a small amount of gas evolution was observed. The resulting clear solution was gently stirred for 10 min; and the solvent was removed by water aspirator via the mercury bubbler. A warm water bath was used to accelerate the evaporation of the rest of the solvent. In order to avoid getting mercury in the reaction vessel, care was taken in balancing the nitrogen pressure

therein. After removal of the solvent a white solid of lithium bis-(trimethylsilyl)amide was left. Tetrahydrofuran (5 ml) was then added to dissolve the solid and form a colorless solution.

b. Reaction of Di-isopropyl Dichloromethaneboronate with Lithium Bis-(trimethylsilyl)amide (XII). Di-isopropyl dichloromethaneboronate (5 mmoles) in 5 ml of tetrahydrofuran was slowly added to the solution of the lithium bis-(trimethylsilyl)amide obtained from the previous preparation at room temperature under nitrogen. When the two solutions were mixed, heat evolved and the color of the solution mixture turned to pale yellow. Over the course of stirring for 30 min at room temperature, 1 ml of deuterated water followed by 2 ml of 20% hydrochloric acid was added. Vigorous reaction occurred and the solution turned to colorless. After the solution was stirred for 30 min the water layer was separated and extracted twice with 10 ml portions of anhydrous ethyl ether, which were combined with the tetrahydrofuran portion. Evaporation of the ether solvent afforded a white solid of dichloromethaneboronic acid. The nmr spectrum indicated no α -deuterated dichloromethaneboronic acid formed.

4. Reaction of Di-isopropyl Dichloromethaneboronate with *n*-Butyllithium. Preparation of α -Chloropentaneboronic Ester (XIII)

A 100 ml round-bottomed flask connected to a mercury

bubbler was heated at 100° and cooled to room temperature under nitrogen. Into the flask were placed 5 ml (25 mmoles) of di-isopropyl dichloromethaneboronate and 60 ml of hexane. After the solution was cooled to -78° in an acetone-dry ice bath, 15.75 ml of n-butyllithium was added. The reaction mixture was stirred at -78° for one hour, then warmed to room temperature. At this time, a white precipitate formed. The reaction was then completed by stirring for 14 hours at room temperature. After filtration of the white precipitate and removal of the solvent, the remaining solution was distilled under reduced pressure (10 mm Hg). Di-isopropyl α -chloropentaneboronate (3.5 g) consisting of a small amount of impurities was collected at 96 ~ 97°. Further purification by fractional distillation failed. The best nmr spectrum showed the H-C-B triplet at δ 3.2, the $\text{C}-\overset{\overset{\text{O}}{\text{|}}}{\underset{\underset{\text{O}}{\text{|}}}{\text{CH}}}-\text{C}$ septet at δ 4.41 and the $\text{CH}_3-\overset{\overset{\text{O}}{\text{|}}}{\underset{\underset{\text{O}}{\text{|}}}{\text{C}}}-$ doublet overlapped the characteristic n-butyl pattern of $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-\overset{\overset{\text{O}}{\text{|}}}{\underset{\underset{\text{Cl}}{\text{|}}}{\text{C}}}-$ at δ 1.0 ~ 1.2 region.

5. Reaction of Di-isopropyl Dichloromethaneboronate with n-Butyllithium followed by Hydrogen Peroxide Oxidation. Preparation of n-Pentanal Isolated as Derivative of 2,4-Dinitrophenylhydrazine.

a. Preparation of Di-isopropyl α -Chloropentaneboronate (XIII). A 50 ml round-bottomed flask connected to a mercury bubbler was flame dried, flushed with nitrogen and cooled to room temperature. After these, the flask was charged with 1 ml of di-isopropyl dichloromethaneboronate

and 15 ml of anhydrous ethyl ether; then cooled in an acetone-dry-ice bath. While the cooling was continued, 3.25 ml of n-butyllithium was rapidly added. After the reaction mixture was stirred for one hour at -78° it was allowed to warm and stir for 15 hours at room temperature. At the end of the reaction, a white precipitate of lithium chloride formed. Removal of the ethyl ether concentrated the reaction product, di-isopropyl α -chloropentaneboronate (XIII).

b. Hydrogen Peroxide Oxidation and Pentanal Derivative Formation. A solution of 1 g of 2,4-dinitrophenylhydrazine in 6.5 ml of sulfuric acid, 12 ml of water and 28 ml of 95% ethanol was mixed with 10 ml of 30% hydrogen peroxide and added to the di-isopropyl α -chloropentaneboronate (XIII) solution obtained from the previous preparation at room temperature under nitrogen. When the reaction mixture was stirred the white precipitate of lithium chloride disappeared and a yellow precipitate formed within 10 min. After 20 min 5 ml of water was added to the stirred reaction mixture to cause more precipitation and the precipitate was then filtered. Recrystallization from methanol gave 0.96 g (in 72% yield) of 2,4-dinitrophenylhydrazone, melting at $105.5 \sim 106.5^{\circ}$. The nmr spectrum agreed with the assigned structure.

6. Reaction of Di-isopropyl Dichloromethaneboronate with Phenylmagnesium Bromide followed by Hydrogen Peroxide Oxidation. Preparation of Benzaldehyde Isolated as Derivative of 2,4-Dinitrophenylhydrazine.

a. Preparation of Phenylmagnesium Bromide Solution.

A 100 ml round-bottomed flask fitted with a reflux condenser was heated to 100° , then cooled to room temperature under nitrogen. Into the flask were placed 3 g (125 mmoles) of magnesium turnings and 7 ml of absolute ether; 0.5 ml of bromobenzene was then added. This mixture was continuously stirred to allow reaction to take place. After reaction had started in the vessel, the solution of 11.7 ml of bromobenzene in 43 ml of anhydrous ethyl ether was then added at a slow rate to maintain the reflux. Over the course of addition, stirring was continued for about one hour.

The concentration of phenylmagnesium bromide was determined by titration and phenolphthalein was used as the indicator.

b. The Reaction of Di-isopropyl Dichloromethaneboronate with Phenylmagnesium Bromide. Preparation of Chlorophenylmethaneboronate. The reaction was run at -78° with 5 mmoles (1.88 ml) of prepared phenylmagnesium bromide mixed with 5 mmoles (1 ml) of di-isopropyl dichloromethaneboronate in 15 ml of tetrahydrofuran under nitrogen. The mixture was stirred for one hour at -78° , then warmed to room temperature and refluxed for 15 hours. When the yellowish

solution was cooled a small amount of white precipitate of lithium chloride formed. The reaction product, di-isopropyl chlorophenylmethaneboronate, was concentrated by removal of the ether solvent.

c. Hydrogen Peroxide Oxidation and Benzaldehyde Derivative Formation. A solution of 1 g of 2,4-dinitrophenylhydrazine in 6.5 ml of sulfuric acid, 10 ml of water and 25 ml of 95% ethanol was mixed with 10 ml of 30% hydrogen peroxide and added to the previously prepared chlorophenylmethaneboronate solution under nitrogen. The white precipitate dissolved and an orange red precipitate formed within 15 min. After 25 min, 5 ml of water was added to the stirred reaction mixture and the precipitate was collected. Recrystallization from methanol-ethyl acetate gave 1.06 g of 2,4-dinitrophenylhydrazone melting at $237 \sim 238^{\circ}$ in 74% yield.

7. Reaction of Di-isopropyl Dichloromethaneboronate with *t*-Butyllithium followed by Hydrogen Peroxide Oxidation. Preparation of Pivalaldehyde Isolated as Derivative of 2,4-Dinitrophenylhydrazine.

a. Preparation of Di-isopropyl *t*-Butylchloromethaneboronate. The reaction was run at -20° with 4.02 ml (5 mmoles) of *t*-butyllithium slowly added to 1 ml (5 mmoles) of di-isopropyl dichloromethaneboronate in 15 ml of pentane under nitrogen. After 7 hours at $-15 \sim -20^{\circ}$, the stirred reaction mixture was then allowed to warm to room temperature

and stirred overnight. At this time, a white precipitate was observed. Removal of the solvent concentrated the reaction product, t-butylchloromethaneboronate.

b. Hydrogen Peroxide Oxidation and Pivaldehyde Derivative Formation. A similar 2,4-dinitrophenylhydrazine-hydrogen peroxide solution was prepared as above and was added to the previously prepared di-isopropyl t-butylchloromethaneboronate solution. The white precipitate dissolved and a yellow precipitate of 2,4-dinitrophenylhydrazone formed within 20 min. After the reaction mixture was stirred for 40 min. 7 ml of water was added and the yellow precipitate was filtered. Recrystallization from methanol gave 0.39 g of desired derivative melting at 205 ~ 206° in 30% yield.

8. Attempted Reaction of Di-isopropyl Dichloromethaneboronate with Sodium Hydride.

Di-isopropyl dichloromethaneboronate (1 ml; 5 mmoles) was added to the mixture of 10 ml of tetrahydrofuran and 0.23 g (5 mmoles) of sodium hydride-oil dispersion washed twice with 10 ml of tetrahydrofuran at room temperature under nitrogen. Upon stirring, no detectable reaction was observed. The mixture was then refluxed for 4 hours and cooled. The resulting mixture still contained a lot of unreacted sodium hydride as indicated by the reaction of the mixture with water. The nmr spectrum indicated no desired reaction product, monochloromethaneboronate, formed.

A similar reaction with the reaction mixture refluxed for 10 hours, followed by addition of 2,4-dinitrophenylhydrazine-hydrogen peroxide solution failed to give the desired formaldehyde derivative. Similar experiments using ethyl ether, diglyme and hexane as solvents were also unsuccessful.

CONCLUSION

Di-isopropyl dichloromethaneboronate is a potentially useful intermediate for organic synthesis and mechanistic studies. Starting from the reaction of n-butyllithium with methylene chloride to the esterification, it can be obtained in 50 ~ 58% yields. Its reactions with bases followed by hydrogen peroxide oxidation provide a convenient route for the synthesis of aldehydes. The yield of the aldehyde is largely dependent on the solvent used, reaction time and reaction temperature of the reaction of di-isopropyl dichloromethaneboronate with bases. The reaction of the isopropanol ester with base evidently proceeds through a tetracovalent boron anion formed by attack of the base, which then rearranges with expulsion of the chloride ion.

REFERENCES

REFERENCES

1. E. Y. Chao, "Synthesis of α -Haloorganoboron Compounds." M.S. Thesis, Michigan State University, East Lansing, Michigan.
2. D. S. Matteson, J. Amer. Chem. Soc., 82, 4228 (1960).
3. D. S. Matteson and J. D. Liedtke, Chem. and Ind. (London), 1241 (1963).
4. D. S. Matteson, R. A. Bowie, and G. Srivastava, J. Organometal. Chem., 16, 33 (1969).
5. D. S. Matteson and G. D. Schaumberg, J. Org. Chem., 31, 726 (1966).
6. (a) D. J. Pasto, J. Hickman and T. C. Cheng, J. Amer. Chem. Soc., 90, 6259 (1968).
(b) H. C. Brown and R. L. Sharp, J. Amer. Chem. Soc., 90, 2915 (1968).
7. D. S. Matteson, J. Org. Chem., 29, 3399 (1964).
8. D. S. Matteson and T. C. Cheng, J. Organometal. Chem., 6, 100 (1966).
9. D. S. Matteson and R. W. H. Mah, J. Org. Chem., 28, 2174 (1963).
10. D. S. Matteson and R. W. H. Mah, J. Amer. Chem. Soc., 85, 2599 (1963).
11. D. S. Matteson, Organometal. Chem. Rev., 1 (1966).
12. D. S. Matteson and R. W. H. Mah, J. Org. Chem., 28, 2171 (1963).
13. D. F. Hoeg, D. I. Lusk, and A. L. Crumbliss, J. Amer. Chem. Soc., 87, 4147 (1965).
14. G. Köbrich and K. Flory, Angew. Chem., 76, 536 (1964); Angew. Chem. internat. Edit., 3, 445 (1964).

15. G. Köbrich and H. R. Merkle, Chem. Ber., 99, 1782 (1966).
16. F. W. Hoffmann, Chem. Abs., 65, 7204g-7205b (1966).
17. Annual Surveys of Organometallic Chemistry, 3, 14 (1966).
18. G. Köbrich and H. R. Merkle, Chem. Ber. 100, 3375 (1967).
19. H. R. Snyder, J. A. Kuck and J. R. Johnson, J. Amer. Chem. Soc., 60, 105 (1938).
20. J. M. Sugihara and C. M. Bowman, J. Amer. Chem. Soc., 80, 2443 (1958).
21. M. E. D. Hillman, J. Amer. Chem. Soc., 84, 4716 (1962).
22. A. N. Nesmeyanov and R. A. Sokolik, Methods of Elemento-organic Chemistry, Volume 1, page 29 and page 230 (1967).

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