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THE PREPARATION AND REACTIONS OF ESTERS OF DICHLORO-METHANEBORONIC ACID

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Summary

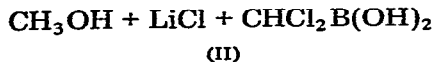
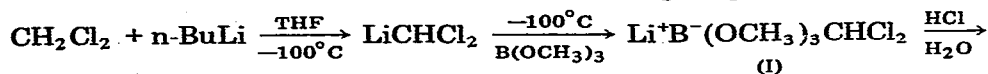
Dichloromethaneboronic acid is obtained in impure form from the reaction of dichloromethylithium with trimethylborate. Reaction with the appropriate alcohols furnishes the 1,3 propandiol ester and the diisopropyl ester. Diisopropyl-dichloromethaneboronate reacts with organolithium or organomagnesium reagents to give substitution products which can be oxidized to aldehydes.

Introduction

α -Haloalkylboron compounds are known to undergo facile substitution reactions with a variety of nucleophiles [1–4]. Consequently, they are potentially useful for the preparation of functionally substituted organoboron derivatives. Although chloromethaneboronic acid is available only with difficulty [5,6], dichloromethaneboronates should be readily obtained by reaction of dichloromethylithium [7] with boron esters. Using this method, we have prepared dichloromethaneboronic acid and studied the reaction of its isopropyl ester with a number of nucleophiles.

Results and discussion

Dichloromethaneboronic acid was prepared as outlined in the following equations. Material assumed to be the lithium salt I precipitates at the reaction

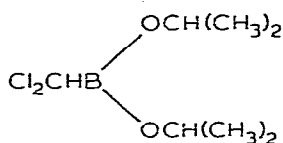


temperature and may be isolated as an impure white solid. Hydrolysis of the salt with dilute acid produces dichloromethaneboronic acid, II. The weight of II

corresponds to a yield of 95–100%. However, the material is difficult to purify and the proton NMR spectrum indicates the presence of considerable amounts of boric acid as impurity. The material is quite stable and may be exposed to the atmosphere for prolonged periods with no evidence of oxidation.

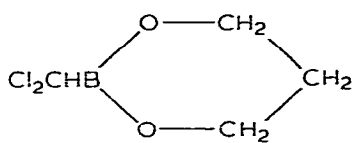
Normally the addition of borate esters to organolithium reagents produces major amounts of dialkylated products [8]. The good yield of monoalkylated product in the present procedure may be due to the electron-withdrawing effect of the dichloromethyl group, stabilizing the lithium salt, I, and slowing displacement of methoxide ion.

By reaction with the appropriate alcohol and removal of water, dichloromethaneboronic acid was converted into the following esters (yields are overall yields from methylene chloride and *n*-butyllithium):



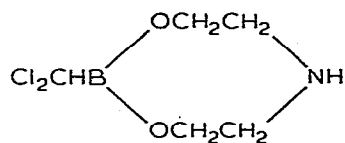
(III)

(60%)



(IV)

(52%)

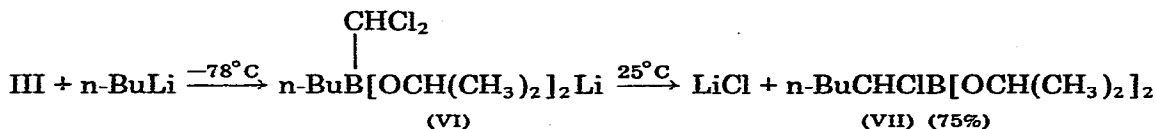


(V)

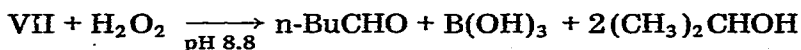
(55%)

All of the esters are stable to dry air, although moisture converts them to the boronic acid, II, and the corresponding alcohol.

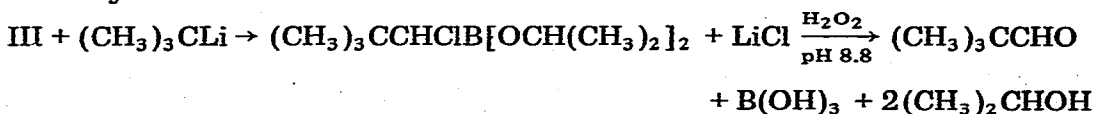
Addition of *n*-butyllithium to a solution of diisopropyl dichloromethaneboronate, III, in hexane at -78°C produces an immediate white precipitate which gives a positive flame test for boron and is presumed to be the boron salt VI. When the reaction mixture is allowed to reach room temperature, the pre-



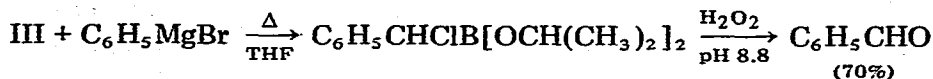
cipitate dissolves and a new precipitate of lithium chloride is slowly formed. The substitution product VII can be isolated from the reaction mixture in 75% yield. VII is oxidized with buffered hydrogen peroxide to *n*-pentanal.



A similar sequence with *t*-butyllithium produces 2,2-dimethylpropanal in 35% overall yield.

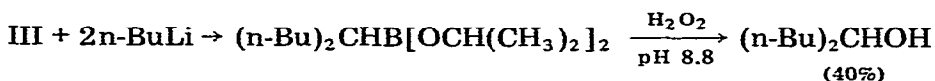


Reaction of III with phenylmagnesium bromide is more difficult. Reaction does not occur in ethyl ether solution but prolonged refluxing in tetrahydrofuran followed by oxidation produces a 70% yield of benzaldehyde.

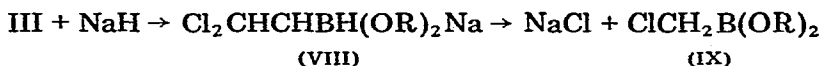


Although the time-consuming method for preparing III probably negates the use of these reactions as synthetic pathways to aldehydes for the present, it is interesting to note the ready displacement of halogen by reagents as bulky as *t*-butyllithium. A similar ease of substitution by a wide range of alkyl groups has been observed for other migration reactions from boron to carbon [1-4].

In all of these reactions, displacement of both halogens by the alkylating agent is apparently avoided by the initial formation of salts analogous to VI at low temperatures, which then undergo a much slower rearrangement with displacement of the halogen. However, if two equivalents of the alkylating agent are added, it is possible to obtain substitution of both halogens.



It was anticipated that III would react with sodium hydride to furnish a synthesis of chloromethylboronate esters, IX. Surprisingly, III is inert to sodium



hydride in a variety of solvents even after prolonged reflux. It is possible that the bulky isopropyl groups greatly slow the formation of the intermediate borohydride, VIII.

Experimental

Tetrahydrofuran was distilled from LAH and stored under a nitrogen atmosphere. Solutions of *n*-butyllithium (1.5 *M* in hexane), *t*-butyllithium (2 *M* in pentane) and phenylmagnesium chloride (3 *M* in THF) were obtained from Alpha Inorganics, Inc. All reactions were conducted under an atmosphere of nitrogen in flame-dried apparatus. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. The NMR spectra of reported compounds were obtained on a Varian T60 spectrometer with TMS as internal standard. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee.

Preparation of dichloromethanebornic acid (II)

A 500 ml, 3-neck round bottom flask equipped with mechanical stirring dropping funnel and mercury bubbler was immersed in an ethanol/liquid nitrogen bath maintained at -100°C . The flask was charged with a solution of methylene chloride (9.34 g, 110 mmol) in 200 ml of tetrahydrofuran. *n*-Butyllithium (63 ml, 100 mmol) was added dropwise over a period of 40 min. The resulting suspension of dichloromethylithium [7] was stirred and addition 0.5 h and then trimethylborate (12.5 ml, 110 mmol) was added all at once. After 0.5 h, the reaction mixture was hydrolyzed with 20 ml of 5 *N* hydrochloric acid. The solution was allowed to reach room temperature, the organic layer separated and the aqueous layer extracted with 2×25 ml of ether. The com-

bined organic layers were concentrated on the steam bath to obtain a viscous reddish-brown mass which solidified on standing.

The crude boronic acid is very soluble in ethanol, acetone, tetrahydrofuran and water and insoluble in methylene chloride, benzene, chloroform and acetonitrile. Repeated crystallization from acetone/water gave 15.5 g of an impure white solid, m.p. 75–100°C, proton NMR (tetrahydrofuran solution): singlet, δ 5.25 (1H); singlet, δ 6.15 ppm (2.6 H).

Preparation of diisopropyl dichloromethaneboronate (III)

The crude dichloromethaneboronic acid (15.0 g) obtained above was added to 120 ml of benzene and 50 ml of isopropyl alcohol. The solution was slowly distilled at atmospheric pressure to remove water as an azeotrope. Fresh alcohol and benzene were added periodically as required. After 2 days, no water was present in the distillate and the pot residue was fractionally distilled to obtain 12.2 g (60% overall yield) of diisopropyl dichloromethaneboronate as a clear liquid, b.p. 65°C/10 mm, n_D^{25} 1.4208, proton NMR (neat liquid): singlet, δ 5.27 (1H); septet, δ 4.66 (2H) and doublet, δ 1.2 ppm (12H). (Found: C, 39.24; H, 7.28; Cl, 33.56. $BC_7H_{15}O_2Cl_2$ calcd.: C, 39.46; H, 7.10; Cl, 33.36%.)

Preparation of 1,3 propandiol ester of dichloromethaneboronic acid (IV)

A sample of crude dichloromethaneboronic acid (12 g) was added to 1,3-propandiol (6.4 ml, 90 mmol) dissolved in 50 ml of acetone. Anhydrous magnesium sulfate (10 g) was added to remove the water and the mixture refluxed for 3 h. Filtration followed by vacuum distillation gave 7.2 g (52% overall yield) of the 1,3-propandiol ester as a colorless liquid, b.p. 97–98°C/8 mmHg; n_D^{25} 1.4758. Proton NMR spectrum (neat liquid): singlet δ 5.28 (1H), triplet δ 4.15 (4H), quintet δ 2.05 (2H). (Found: C, 28.54; H, 4.12; Cl, 41.90. $BC_4H_7O_2Cl_2$ calcd.: C, 28.44; H, 4.18; Cl, 42.05%.)

Preparation of diethanolamine ester of dichloromethaneboronic acid (V)

This compound forms rapidly (55% yield) upon mixing the reagents in tetrahydrofuran; however, it is most readily obtained in a pure state by starting with the diisopropyl ester, III.

Diethanolamine (0.48 ml, 5 mmol) was added to a solution of diisopropyl dichloromethaneboronate (1.05 g, 5 mmol) in 15 ml of tetrahydrofuran. The solution was stirred for 15 min and the white precipitate isolated by filtration. There was obtained 0.90 g (91% yield) of the diethanolamine ester, m.p. (with decomposition) 207–208°C. Proton NMR spectrum (D_2O solution): singlet δ 4.85 (1H), singlet δ 4.15 (1H), triplet δ 3.35 (2H), triplet δ 2.67 ppm (2H). (Found: C, 30.31; H, 5.23; N, 6.86; Cl, 35.59. $BC_5H_{10}O_2Cl_2N$ calcd.: C, 30.33; H, 5.10; N, 7.07; Cl, 35.89%.)

Reaction of diisopropyl dichloromethaneboronate with one equivalent of n-butyllithium

n-Butyllithium (15.8 ml, 25 mmol) was added dropwise to a solution of diisopropyl dichloromethaneboronate (5.25 g, 25 mmol) in 60 ml of hexane maintained at a temperature of –78°C. The solution was allowed to reach room temperature at which time a white precipitate of lithium chloride was formed.

Filtration followed by vacuum distillation gave 3.9 g (75%) of diisopropyl 1-chloropentaneboronate (VII) as a colorless liquid, b.p. 96°C/10 mmHg.

Oxidation with 30% hydrogen peroxide and a pH 8.8 phosphate buffer gave pentanal, 85% by GLPC analysis.

Reaction of diisopropyl dichloromethaneboronate with two equivalent of n-butyllithium

The reaction was conducted as described above except that two equivalents of n-butyllithium (31.6 ml, 50 mmol) were utilized. Oxidation of the reaction mixture with 30% hydrogen peroxide and phosphate buffer gave 5-nonanol (10 mmole, 40%) as indicated by GLPC analysis using internal standard.

Reaction of diisopropyl dichloromethaneboronate with t-butyllithium

t-Butyllithium (4.02 ml, 5.0 mmol) was added dropwise to a solution of diisopropyl dichloromethaneboronate (1.05 g, 5 mmol) in 15 ml pentane maintained at a temperature of -78°C. The solution was allowed to reach room temperature and stirred overnight. The reaction mixture was oxidized by addition of 2 ml of phosphate buffer all at once followed by dropwise addition of 1.0 ml of 30% hydrogen peroxide maintaining the temperature under 35°C. GLPC analysis of the organic phase established the presence of 2,2-dimethylpropanal (1.5 mmol, 30%).

Reaction of diisopropyl dichloromethaneboronate with phenylmagnesium bromide

Phenylmagnesium bromide (1.67 ml, 5.0 mmol) was added dropwise to a solution of diisopropyl dichloromethaneboronate (1.05 g, 5 mmol) in 15 ml of tetrahydrofuran maintained at -78°C. After complete addition, the solution was allowed to reach room temperature and then refluxed for 10 h. Oxidation with hydrogen peroxide and phosphate buffer gave 3.7 mmoles of benzaldehyde (75%), established by GLPC analysis with internal standard.

A similar reaction conducted in ethyl ether solution gave only traces of benzaldehyde.

Attempted reactions of diisopropyl dichloromethaneboronate with sodium hydride

Sodium hydride (0.11 g, 5 mmol) was added to a solution of diisopropyl dichloromethaneboronate in 10 ml of tetrahydrofuran. The reaction mixture was refluxed for 4 h with no evidence of reaction: NMR analysis of the solution indicated essentially complete recovery of III and addition of water caused evolution of the expected quantity of hydrogen gas (5.0 mmol). Analogous experiments in hexane or diglyme solution gave similar results.

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