Journal of Organometallic Chemistry, 114 (1976) 1—7

A NEW SYNTHESIS OF AN α-HALOALKANEBORONIC ESTER, 1-BROMO-1-ETHYLENEDIOXYBORYL-2-PHENYLETHANE, AND A SUPERVENIENT SYNTHESIS OF A 1,2-DIBORONIC ESTER, 1,2-BIS(ETHYLENEDIOXYBORYL)-1-PHENYLETHANE *

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(Received January 16th, 1976)

Summary

Conversion of tris(ethylenedioxyboryl)methane, $HC(BO_2C_2H_4)_3$ (I) to lithium bis(ethylenedioxyboryl)methide, $Li^+ HC(BO_2C_2H_4)_2$ (II), with methyllithium, followed by alkylation with benzyl bromide, has yielded 1,1-bis(ethylenedioxyboryl)-2-phenylethane, $PhCH_2CH(BO_2C_2H_4)_2$ (III). Reaction of III with one equivalent each of mercuric chloride and sodium methoxide in anhydrous methanol resulted in the selective replacement of one boron atom by mercury to form 1-chloromercuri-1-ethylenedioxyboryl-2-phenylethane (IV), which reacted with bromine in dichloromethane to yield 1-bromo-1-ethylenedioxyboryl-2-phenylethane, $PhCH_2CHBrBO_2C_2H_4$ (V). Several attempts to convert V to an aminoboronic acid were unsuccessful. In an attempt to find a more convenient route to III, the dihydroboration of phenylacetylene with borane in tetrahydrofuran followed by treatment with ethylene glycol unexpectedly yielded not III, but its isomer 1,2-bis(ethylenedioxyboryl)-1-phenylethane (VI), which is consequently the first 1,2-alkanediboronic ester to be easily made in substantial quantities.

Introduction

We first reported the synthesis of some α-haloalkaneboronic esters more than 15 years ago [1] and soon showed that the halide is displaced by nucleophiles with unusual facility, even permitting carbon—carbon bond formation by way of attack of a Grignard reagent on the boron atom [2], and that dehydrohalogenation is relatively difficult [3]. Attempts to find more general routes to α-halo-

* Supported by grant number CA-05513 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

alkylboron compounds met with limited success [4—7]. In general, successful syntheses are limited to those structures that can be made by free radical additions to alkenylboron compounds [1—5] or hydrogen halide additions to alkeneboronic esters bearing a methyl or other activating substituent on the same carbon as the boron [5,6], and halomethaneboronic esters have been solved as a special case [7]. This topic has been reviewed recently [8].

The synthetic utility of α-haloalkylboron compounds has been demonstrated for the trialkylborane series by Brown and coworkers, and the field is expanding so rapidly that only a few leading references can be supplied [9—14]. In spite of rapid progress, the general problem of constructing $RR'CXBZ_2$, where X is halogen and R, R' and Z are any desired groups, has only been solved for a restricted range of structures.

In the present work, we approached the α-haloalkaneboronic ester problem with a fundamentally new combination of synthons based on our recent work on boron-substituted carbanions and related chemistry [15—20].

$$R{-}X + Z{-}CH{-}B(OR')_2 \rightarrow R{-}\underset{Z}{CH}{-}B(OR')_2 \rightarrow R{-}\underset{X}{CH}{-}B(OR')_2$$

(R is alkyl, X is halogen, and Z is a replaceable group)

We chose R as benzyl at the suggestion of Lienhard, who has found that 2-phenylethaneboronic acid is an efficient chymotrypsin inhibitor [21] and suggested that 1-amino-2-phenylethane-1-boronic acid and its derivatives might be enzyme inhibitors. Replacement of the α-halogen by ammonia proved to be much more complicated than expected on the basis of previous work with amines [7], and definitive results will be reported later [22]. We chose Z as $B(OR')_2$ because our previous work indicated that the first dimethoxyboryl group of $CH_2[B(OCH_3)_2]_2$ is replaced 65 times faster than the second by mercuric chloride and $ClHgCH_2B(OCH_3)_2$ is easily isolated [20], and the chloromercuri group is easily replaced by bromine [23,24]. A cyclic boronic ester group was chosen because of our previous experience indicating that higher yields and improved stability result if $B(OR')_2$ is cyclic [17,18].

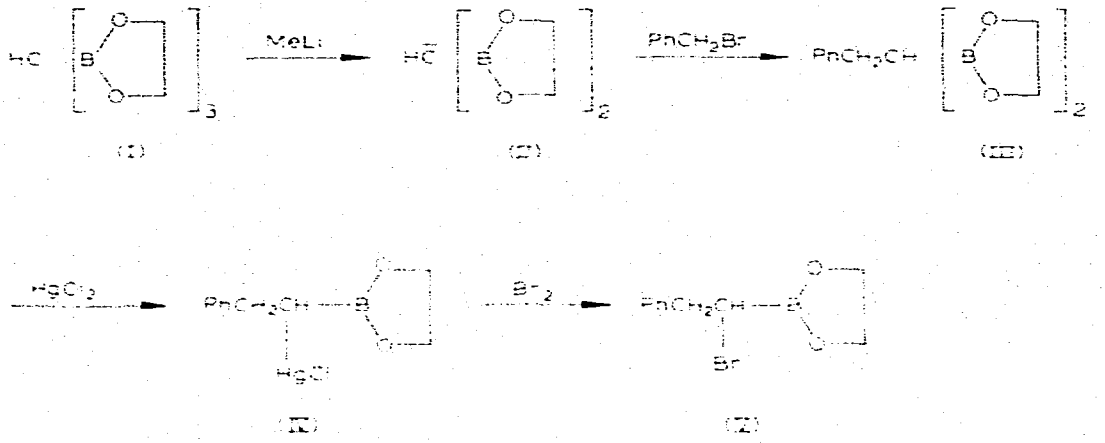
We arrived at the synthetic scheme outlined only after trying several obvious approaches based on addition of a suitable reagent to the double bond of a β-substituted styrene. The difficulties, as well as the unexpected formation of 1,2-diboryl-1-phenylethane as the major product of the dihydroboration of phenylacetylene, are described in the second part of the "Results and discussion".

Results and discussion

1. The boron-substituted carbanion route

Tris(ethylenedioxyboryl)methane (I) was converted to the carbanion II with methyllithium as previously described [17]. Benzyl bromide reacted with II to form 65—75% 1,1-bis(ethylenedioxyboryl)-2-phenylethane (III), a known compound [25] but obtained in crystalline form for the first time in this work. Reaction of III with mercuric chloride and sodium methoxide in anhydrous methanol gave 77% of 1-chloromercuri-1-ethylenedioxyboryl-2-phenylethane (IV). Bromination of IV in small batches in dichloromethane gave 45% of pure 1-

bromo-1-ethylenedioxyboryl-2-phenylethane (V), which proved to be somewhat sensitive to heat as well as to air and moisture. The structures of III, IV, and V were confirmed by 60 MHz proton NMR spectra. Attempts to make IV without



first rigorously drying the methanol solvent resulted in erratic yields and formation of 1,1-bis(chloromercuri)-2-phenylethane, $PhCH_2CH(HgCl)_2$, which was not obtained analytically pure, but showed properties typical of known compounds of the class $RCH(HgCl)_2$ [20,26].

We tried several different solvents and temperatures for the bromination of IV, including carbon tetrachloride, dichloromethane, ether, and acetic acid. It may be noted that these are solvents in which a radical mechanism usually predominates [23, 24]. We did not try pyridine, which would encourage direct electrophilic displacement of the mercury [23,24], but would probably displace bromide from V. The best conditions appeared to involve dichloromethane as solvent at 0°C, though differences in results were not great. The major problem was purification, since HgX_2 (X = Cl, Br) tends to codistil with V and perhaps contributes to its tendency toward instability during distillation. Separation was accomplished by extracting the product V into hexane, in which the mercury salts were insoluble. Simple distillation then led to pure V, a low-melting crystalline solid.

Neighboring boron normally activates halides toward displacement by alkoxides [2,5,27], and V reacted with sodium methoxide in methanol to form 1-methoxy-1-ethylenedioxyboryl-2-phenylethane. The NMR spectrum showed the expected phenyl (δ 7.18 ppm), OCH_2 (δ 4.12 ppm), and OCH_3 (δ 3.29 ppm) singlets, plus a nondescript CH_2CH multiplet (δ 3—4 ppm). However, no effort was made to purify the small amount of liquid product available.

2. Dihydroboration of phenylacetylene to a 1,2-diboronic ester and other unsuccessful routes to V

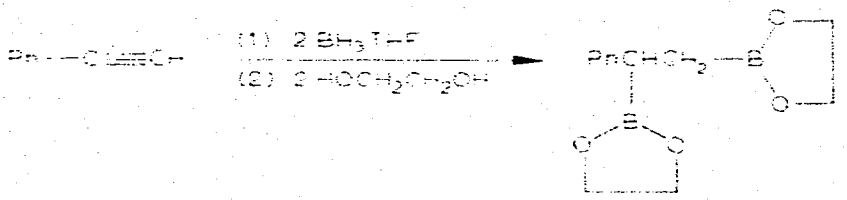
We undertook the successful synthesis of V described in the preceding subsection only after considerable frustration with attempts to start from various β-substituted styrenes or from phenylacetylene, which incidentally led to an unexpected and convenient synthesis of a 1,2-diboronic ester.

Hydroboration of β-bromostyrene would yield $PhCH_2CHBrBX_2$ in one step.

However, borane in tetrahydrofuran leads to reductive loss of the bromine [28], and we verified by NMR examination of the crude hydroboration product that useful amounts of bromo compound could not be obtained this way. Chloroborane in ether [29] proved no better. Dichloroborane [30] appeared unreactive.

Radical addition of hydrogen bromide to a β-styreneboronic ester, $PhCH{=}CHB(OR)_2$, was expected on the basis of our previous work [1,31] to be predominantly influenced by the phenyl group and therefore yield $PhCH_2CHBrB(OR)_2$, though Pasto and coworkers had reported that the opposite orientation prevails [25]. To reinvestigate, we prepared 2-methyl-2,4-pentanediyl β-styreneboronate and dimethyl β-styreneboronate. Reaction of either of these with hydrogen bromide under ultraviolet irradiation [31] at temperatures between −70 and 25°C with or without dichloromethane as solvent and azobisisobutyronitrile or benzophenone as possible photosensitizers invariably gave 1-bromo-1-phenylethane, confirmed by NMR, as the only identifiable and isolable product. Pasto and coworkers presented convincing evidence that they obtained the product of polar hydrogen bromide addition, $PhCHBrCH_2BO_2C_2H_4$, as an unstable component of crude reaction mixtures [25], and although we were unable to confirm this observation directly, our results suggest cleavage of the analogous β-bromo boronic esters to styrene followed by polar addition of HBr to form $PhCHBrCH_3$.

Since $PhCH_2CH(BO_2C_2H_4)_2$ (III) was already a known compound [25], made by a hydroboration route we had previously developed [26], we decided to try the ultimately successful route from III to V, but first we attempted a shortcut to III. Direct dihydroboration of phenylacetylene appeared to be obviously the most convenient possible route to III. The literature indicates that hydroboration of vinylboranes or dihydroboration of therminal acetylenes preferentially places both boron atoms on the terminal carbon [25,26,32]. An early paper by Pasto suggesting substantial formation of 1,2-diboryl compound in the dihydroboration of phenylacetylene [33] was later questioned by Zweifel and Arzoumanian [32] and agreed to be inconclusive by Pasto and coworkers [34]. It therefore was a considerable surprise to obtain a 55% yield of crystalline 1,2-bis(ethylenedioxyboryl)-1-phenylethane (VI), the "wrong" isomer, from the dihydroboration of phenylacetylene with two moles of borane in tetrahydrofuran followed by treatment with ethylene glycol.



(VI)

This unexpected synthesis of VI is much more convenient than the sterically controlled hydroboration route designed by Pasto and coworkers [25] and makes VI the most readily available 1,2-diboronic ester known at present. The general synthesis of 1,2-diboryl compounds based on addition of diboron tetrachloride to olefins [35] suffers from the considerable inconvenience of preparing the reagent.

Perhaps the unexpected directing influence of the BH_2 group on hydroboration is somehow dependent on B—H—B bridge bonding, which might make hyperconjugative π-electron donation possible or might involve the incoming BH_3 in a cyclic transition state. No attempt has been made to find out whether the directing influence observed here has some generality or is unique to PhCH=CHBH$_2$.

Having discovered an excellent solution to the wrong problem, we turned to the known synthesis of III [25]. Dimethyl β-styreneboronate happened to be already available and was used in place of the n-butyl ester [25], and the product was about 80% the desired compound, 1,1-bis(dimethoxyboryl)-2-phenylethane. Presumably, greater attention to detail should lead to the higher regioselectivity described by Pasto and coworkers [25], but it was clear that there would be an isomer separation problem. It was also clear that the labor required to make a 50-g batch of a β-styreneboronic ester was comparable to that required to make a similar amount of tris(ethylenedioxyboryl)methane (I), in spite of the 25% yield faced in the first step of preparing I [15,17,19]. Consequently, the absolute regiospecificity inherent in the alkylation of the carbanion II with benzyl bromide was appealing, and the immediate success in obtaining pure III by this route was decisive in its favor.

Experimental

1,1-Bis(ethylenedioxyboryl)-2-phenylethane (III)

A 4.5-g portion of tris(ethylenedioxyboryl)methane [17] suspended in 25 ml of rigorously dried tetrahydrofuran was stirred under argon at −70°C during the dropwise addition of 12 ml of 1.6 *M* methyllithium in ether. The mixture was warmed to 0°C, 3.4 g of benzyl bromide was added, and the mixture was stirred 4 h at 25°C. Distillation yielded 3.4 g (69%) of III, b.p. 115—120°C 0.2 mm Hg (lit. [25] b.p. 115—117°C/0.04 mm Hg crystallized at −15°C overnight, m.p. 29—31°C, proton NMR same ($\delta \pm 0.04$ ppm) as reported [25].

1-Chloromercuri-1-ethylenedioxyboryl-2-phenylethane (IV)

A solution of 5.4 g of mercuric chloride and 4.9 g of 1,1-bis(ethylenedioxyboryl)-2-phenylethane in ~ 50 ml of rigorously dried methanol (distilled from magnesium methoxide) was stirred under argon at 25°C during the dropwise addition of a solution of sodium methoxide prepared from 0.45 g of sodium metal and 50 ml of anhydrous methanol. Stirring was continued 5 h and the solution was concentrated under vacuum. The gummy white residue was extracted with anhydrous ether (100—200 ml), leaving an insoluble residue of 1,1-bis(chloromercuri)-2-phenylethane and other by-products, and the ether solution was concentrated, which led to crystallization of IV, 77%, m.p. 115—117°C, NMR (DMSO-d_6): δ(ppm) 7.2 (s, 5, $C_6\underline{H}_5$), 4.05 (s, 4, O—C$\underline{H}_2$), 3.4 (m, 3, C$\underline{H}_2$C$\underline{H}$). (Found: C, 29.00; H, 3.39; B, 2.77; Cl, 8.24; Hg, 48.76. $C_{10}H_{12}BClHgO_2$ calcd.: C, 29.20; H, 2.92; B, 2.64; Cl, 8.63; Hg, 48.82%.)

1-Bromo-1-ethylenedioxyboryl-2-phenylethane (V)

A solution of 4.1 g of 1-chloromercuri-1-ethylenedioxyboryl-2-phenylethane (IV) in 150 ml of dichloromethane was stirred at 0°C during the dropwise addi-

tion of 1.6 g of bromine in 25 ml of methylene chloride. After the addition was complete, the mixture was stirred at 25°C until the bromine color was discharged. The solvent was removed under vacuum and the residue was extracted with three 25-ml portions of hexane, leaving the mercury chlorobromide as an insoluble residue. Concentration of the hexane solution followed by short path distillation at ~100°C/0.1 mm Hg yielded 45% of the bromo compound V as an oil which solidified on storage at −15°C overnight. The analytical sample was redistilled; m.p. 33°C; mass spectrum *m/e* 254 and 256 (parent ion), 183 and 185 (loss of $BO_2C_2H_3$); NMR (CCl_4): δ(ppm) 7.1 (s, 5, $C_6\underline{H}_5$), 4.1 (s, 4, O—$C\underline{H}_2$), 3.2 (m, 3, $C\underline{H}_2C\underline{H}$). (Found: C, 46.80; H, 4.71; B, 4.02; Br, 31.43. $C_{10}H_{12}BBrO_2$ calcd.: C, 47.11; H, 4.71; B, 4.24; Br, 31.37%.)

1,2-Bis(ethylenedioxyboryl)-1-phenylethane (VI)

A sample of phenylacetylene was hydroborated by adding it to two molar equivalents of borane in tetrahydrofuran (Aldrich Chemical Co.) under argon at 25°C. The theoretical amount of ethylene glycol was added dropwise with stirring, which resulted in immediate hydrogen evolution. The product VI distilled at 130—140°C/0.5 mm Hg and crystallized on standing, 55% yield, recrystallized from carbon tetrachloride, m.p. 111—112°C (Lit. [25] m.p. 115—117°C), NMR same (within 0.2 ppm) as reported [25], further confirmed by satisfactory C, H and B analyses.

2-Methyl-2,4-pentanediyl β-styreneboronate

This compound was prepared by the addition of β-styrylmagnesium bromide in tetrahydrofuran to 2-butoxy-4,4,6-trimethyl-1,3,2-dioxaborinane [36] at −70°C, followed by pyrolysis of the precipitated magnesium salt at 250—300°C under vacuum, 30—45%, b.p. 101—104°C/0.2 mm Hg. NMR similar to other β-styreneboronic esters [17,25], 15—20% *cis* isomer present. (Found: C, 72.83; H, 8.31; B, 4.38. $C_{14}H_{19}BO_2$ calcd.: C, 73.11; H, 8.27; B, 4.70%.)

Dimethyl β-styreneboronate

20 g of β-styreneboronic acid (*cis—trans* mixture, m.p. 137—138°C) [37] was esterified by fractionally distilling a solution in 100 ml of 2,2-dimethoxypropane in the presence of 0.1 g of zinc chloride [38], b.p. 74—78°C/0.2 mm Hg, 71%, NMR (CCl_4): δ(ppm) 3.6 (2, 6, $OC\underline{H}_3$), 5.5 (d, *J* 15 Hz, 0.1, *cis*-CH=C$\underline{H}$—), 6.1 (d, *J* 18, 0.9, *trans*-CH=C$\underline{H}$—), 7.25 (m, 6, $C_6\underline{H}_5C\underline{H}$=). The *cis* isomer disappeared from a redistilled sample. (Found: C, 68.14; H, 7.65; B, 6.27. $C_{10}H_{13}BO_2$ calcd.: C, 68.26; H, 7.39; B, 6.14%.)

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