Organoboranes. 22. Light-Induced Reaction of Bromine with Alkylboronate Esters. A Convenient Synthesis of α-Bromoalkylboronate Esters

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Received April 15, 1977

In the presence of light, bromine reacts rapidly with trimethylene esters of alkylboronic acids possessing a tertiary or benzylic hydrogen α to boron to give high yields of the corresponding α-bromoalkylboronate esters. This procedure permits a facile entry into the highly versatile but relatively inaccessible class of α-substituted organoboron derivatives.

Some of the most promising synthetic routes based on organoboranes are postulated to proceed through α-haloorganoboranes.[2] A notable example is the alkoxide-induced alkylation and arylation of α-halo esters, ketones, and nitriles with organoboranes (eq 1).

$$BrCH_2CO_2Et \xrightarrow{KOC(CH_3)_3} Br\bar{C}HCO_2Et \xrightarrow{R_3B} R_3\bar{B}CHBrCO_2Et \longrightarrow R_2BCHRCO_2Et \xrightarrow{HOC(CH_3)_3} RCH_2CO_2Et + R_2BOC(CH_3)_3 \quad (1)$$

However, characterization and chemical exploration of this important class of compounds has been sparse, due in part to their high reactivity and lack of convenient routes for their synthesis.[3] To our knowledge, only three α-haloalkyldialkylboranes have been isolated and characterized.[4–6] These compounds exhibit extraordinary reactivity, undergoing very fast rearrangement with mild heat, various electrophiles, and nucleophiles as weak as tetrahydrofuran or water (eq 2).[4–7]

$$CH_3CH(Br)B(CH_2CH_3)_2 \xrightarrow[<1\ min]{H_2O,\ 0\ ^\circ C} CH_3CH(CH_2CH_3)B(OH)CH_2CH_3 + HBr \quad (2)$$

On the other hand, α-haloalkylboronate esters are much less reactive.[3,8,9] These compounds may be distilled at moderate temperatures (~120 °C) without rearrangement. They may be formed in tetrahydrofuran. It has even proved possible to hydrolyze the ester linkages while leaving the α-halogen intact. Nevertheless, the α-haloalkylboronate esters exhibit fascinating potentiality for mechanistic studies and useful synthetic transformations.[3,10,11] Unfortunately, the available synthetic routes for their preparation are relatively few and limited in scope.[3,9]

Through the pioneering efforts of Matteson, α-haloalkylboronate esters may be formed by additions of polyhalomethanes (eq 3) or hydrogen halides (eq 4) across the double bond of alkenylboronate esters.[3,9]

$$CH_2{=}CHB(OC_4H_9)_2 + Cl_3CBr \xrightarrow[initiator]{radical} Cl_3CCH_2CH(Br)B(OC_4H_9)_2 \quad (3)$$

$$CH_2{=}C(CH_3)B(OC_4H_9)_2 + HBr\ (liquid) \xrightarrow{-60\ ^\circ C} (CH_3)_2C(Br)B(OC_4H_9)_2 \quad (4)$$

However, the starting alkenylboronate esters are somewhat troublesome to make and the direction of the addition of hydrogen halide across the double bond is highly sensitive to structural features of the alkenylboronate esters and reaction conditions. Radical additions of polyhalomethanes result in the presence of an extraneous feature normally not desired—a fully halogenated γ carbon.

The base-induced reaction of hindered borinic esters with α,α-dichloromethyl methyl ether constitutes a valuable procedure for the synthesis of α-chloroalkylboronate esters (eq 5).[8]

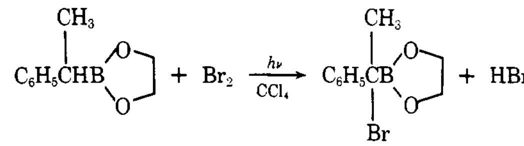
$$R_2BOR' + CHCl_2OCH_3 + LiOCEt_3 \xrightarrow{THF} R_2C(Cl)B(OCH_3)OR' + LiCl + HOCEt_3 \quad (5)$$

Unfortunately, this synthetic method precludes the formation of simpler α-haloalkylboronate esters, such as α-halobenzyl-, -cyclopentyl-, or -norbornylboronate esters, $RCHClB(OR')_2$. Esters of dichloromethylboronic acid are available in 52–60% yield by the reaction of dichloromethyllithium with trimethyl borate (eq 6).[12]

$$Cl_2CHLi + B(OCH_3)_3 \xrightarrow[-110\ ^\circ C]{THF} Cl_2CHB(OCH_3)_2 \xrightarrow[ROH]{HCl} Cl_2CHB(OR)_2 \quad (6)$$

Treatment of these with organometallics provides a route to such α-chloroalkylboronic esters.[12]

Based on our needs for certain α-bromoalkylboronate esters not available by the previously discussed methods, we decided to explore the possibility of forming these compounds by the direct halogenation of alkylboronate esters. Preliminary studies along these lines indicate mixed results. Chlorination of di-*tert*-butyl methylboronate gives impractically small amounts of $ClCH_2B(OR)_2$.[3,9] Pasto reports that bromination of ethylene 1-phenylethyl- or 1-methylpentylboronate provides high yields of the α-bromoalkylboronates (eq 7).[13,14]



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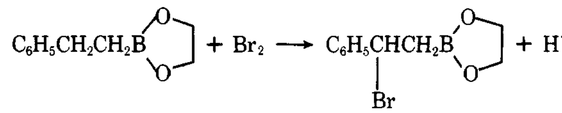
However, he reports that hexylboronate esters are inert to bromine, while ethylene 2-phenylethylboronate gives β-bromination predominantly (eq 8).[13,14]



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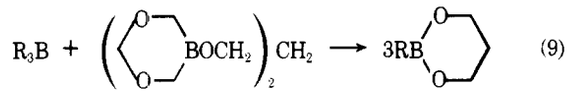
We decided to explore the generality of this bromination procedure in hopes of developing a practical procedure which would permit applying the α-bromoalkylboronate esters as convenient synthetic intermediates. Since the 2-alkyl-1,3,2-dioxaborinanes (trimethylene alkylboronate esters) are stable to disproportionation and readily available from the



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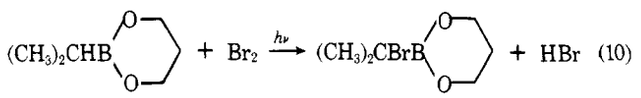
clean, quantitative, and general redistribution of trialkylboranes with trimethylene borate (eq 9),[15] we decided to explore the reaction of bromine with these compounds.

Results and Discussion

In the presence of light, bromine reacts readily and cleanly with alicyclic derivatives such as trimethylene, 1-methylpropyl or 1-methylethyl boronate to give trimethylene α-bromoalkylboronate esters. Although the reaction in methylene chloride or pentane proceeds at a moderate rate under normal laboratory lighting, a 275-W sunlamp greatly accelerates the reaction. Complete decolorization of the bromine takes place in 1–10 min and simple distillation gives the trimethylene



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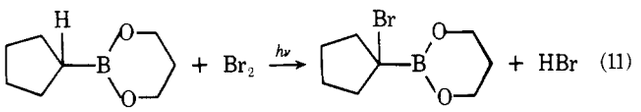
α-bromoalkylboronate esters in high yield and purity (eq 10).

The reaction is also applicable to trimethylene cyclohexyl- and cyclopentylboronate esters. This permits the first synthesis of cyclic α-bromoalkylboronate esters (eq 11).



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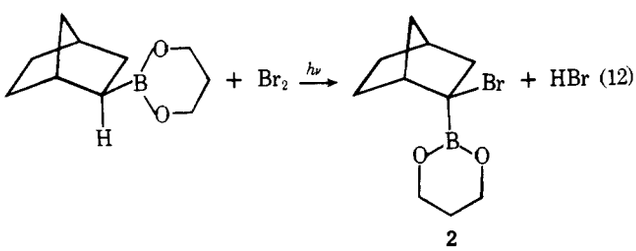
Previous attempts to prepare isolable α-halonorbornylorganoboranes via hydroboration of 2-halonorbornenes have failed.[16,17] Yet trimethylene 2-bromonorbornylboronate is readily obtained by the current procedure (eq 12). Although



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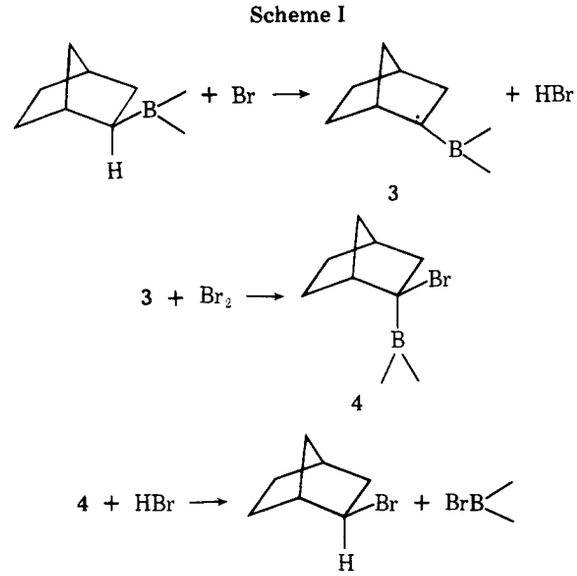
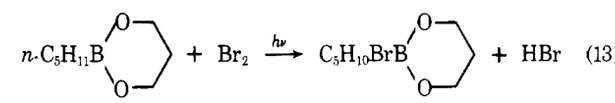
we have not yet established the stereochemistry of the α-bromonorbornylboronate ester (**2**), the bromine is presumably in the exo configuration. This would be consistent with the previously reported results that the free radical bromination of tri-*exo*-norbornylborane and *B*-*exo*-norbornyl-9-borabicyclo[3.3.1]nonane followed by hydrogen bromide cleavage of the boron–carbon bond produces >99% *exo*-2-bromonorbornane.[18,19] This has been interpreted[20] as indicating that bromine attacks the α-boranorbornyl free radical (**3**) from the least sterically hindered exo side to give α-bromo-*endo*-norbornylborane intermediates (**4**). The subsequent hydrogen bromide cleavage then proceeds with clean retention of configuration to produce stereochemically pure *exo*-2-bromonorbornane (Scheme I).

The alkylboronate esters, such as trimethylene or dimethyl butyl- or pentylboronate esters, are not inert to bromine, as

Scheme I



previously reported.[13,14] In carbon tetrachloride, methylene chloride, or pentane, they react somewhat sluggishly with bromine. However, although an equivalent of bromine is decolorized in 30–50 min in the presence of a sunlamp, some 60–80% of starting material is unreacted. For example, treatment of trimethylene pentylboronate with 1 equiv of bromine in carbon tetrachloride in the presence of a sunlamp results in decolorization of the bromine in 30 min. ^{1}H NMR analysis of the reaction mixture shows two overlapping triplets for the trimethylene protons α to oxygen at δ 3.93 and 4.03 and overlapping quintets for the trimethylene protons β to oxygen at δ 1.90 and 1.97. The remainder of the spectrum is complex, showing multiplets at δ 4.3–4.6, 3.1–3.5, and 0.8–2.6. The area ratio of the trimethylene protons to the rest of the protons is approximately 6:10, which stoichiometrically corresponds to incorporation of one bromine into the *n*-pentyl moiety (eq 13).



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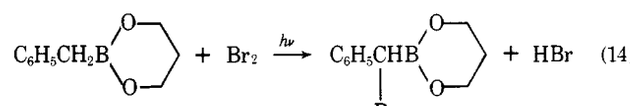
However, GLC analysis shows a complicated reaction mixture containing 70–80% of unreacted trimethylene pentylboronate. Distillation gives 67% of recovered starting material. Only a 16% yield of trimethylene 1-bromopentylboronate could be isolated from the complex mixture.

The results indicate that bromine does not attack the trimethylene ester group, but instead polybrominates the *n*-alkyl moieties. This interesting observation was beyond the scope of our research objectives and we did not pursue it further.[21]

Apparently, when the alkylboronate esters possess a tertiary hydrogen α to boron, reaction with bromine results in clean substitution of the α-hydrogen by bromine (eq 10–12). With alkylboronate esters possessing secondary α-hydrogens, such as butyl- and pentylboronate esters, the reaction does not proceed as desired. Free radical halogenation of methylboronate esters also fails to provide useful amounts of α-halomethylboronate esters.[3,9] However, we found activation by a phenyl group permits the bromination to be carried out



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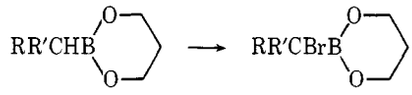
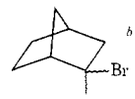
successfully (eq 14). The results of this study are summarized in Table I.

Table I. Preparation of Trimethylene α-Bromoalkylboronate Esters by the Light-Induced Bromination of Trimethylene Alkylboronate Esters



RR'CH–	Registry no.	RR'CHBr–	Registry no.	Isolated yield,[a] %	Bp, °C (mm)
Isopropyl	62930-27-2	$(CH_3)_2CBr$–	62930-29-4	96	51 (0.9)
sec-Butyl	30169-72-3	$CH_3CH_2C(CH_3)Br$–	62930-30-7	84	62 (0.1)
Cyclopentyl	30169-74-5		62930-31-8	88	75–76 (0.1)
Cyclohexyl	30169-75-6		62930-32-9	89	85–87 (0.05)
exo-Norbornyl	30154-25-7		62930-33-0	85	81–82 (0.1)
n-Butyl	30169-71-2	$CH_3(CH_2)_2CHBr$–	62930-34-1	20[c]	60–62 (0.1)
Benzyl	62930-28-3	C_6H_5CHBr–	62930-35-2	73	130–140 (0.3)

[a] All compounds gave satisfactory ^1H NMR spectra and correct elemental analysis for C, H, B, Br. [b] Stereochemistry was not established. [c] 60–80% of starting material recovered.

Summary

It is evident that the facile light-induced reaction of bromine with alkylboronate esters provides an important synthetic procedure for the preparation of a wide variety of α-bromoalkylboronate esters. Some of these compounds are difficult to obtain by previously reported procedures.

The α-halogen of such compounds is easily substituted by a number of nucleophiles.[3,9] This suggests that the α-haloalkylboronate esters are promising intermediates for synthetic applications. We are actively pursuing such possibilities.

Experimental Section

General Comments. General procedures for solvent purification and laboratory manipulation of air-sensitive compounds have been presented.[2] Bromine, ACS Reagent, was used as received from the Fisher Scientific Co. The pure trimethylene alkylboronate esters were prepared by the procedure of Brown and Gupta[15] except for trimethylene 1-methylethyl- and benzylboronate esters, which were prepared by esterification of the respective boronic acids with propane-1,3-diol.[22] ^1H NMR spectra were recorded on a Varian T-60 (60 MHz) in $CDCl_3$ and chemical shifts are relative to tetramethylsilane (δ0). Products gave ^1H NMR in agreement with the indicated structures. Microanalyses were performed by the Purdue Microanalytical Laboratories and the results were within the accepted limits (±0.2%). Boiling points were uncorrected.

Preparation of Trimethylene 2-Bromo-2-methylethylboronate [α-Bromoisopropyl Boronate (1)]. The following procedure for the preparation of trimethylene α-bromoisopropylboronate is representative. A dry 500-mL flask, equipped with a septum inlet, magnetic stirrer, and reflux condenser topped with a connecting tube was flushed with nitrogen and maintained under a static pressure of the gas. By means of a hypodermic syringe, 200 mmol (25.6 g) of trimethylene 2-methylethylboronate was added to the flask followed by 200 mL of dry, olefin-free pentane (or methylene chloride). Then, 200 mmol (10.4 mL) of bromine was introduced all at once with an all-glass syringe with a Teflon needle and a Sears 275-W sunlamp was directed about 1 in. from the reaction flask. An exothermic reaction ensued with reflux of the reaction mixture and evolution of hydrogen bromide gas, which should be vented to a trap containing aqueous sodium hydroxide. Within 3 min, the bromine color disappeared and the solvent was removed immediately by aspirator vacuum. The residual liquid was transferred to a dry, nitrogen flushed distillation apparatus by a double-ended needle. Simple distillation gave 39.8 g (a 96% yield) of the trimethylene α-bromoisopropylboronate, bp 51 °C (0.9 mm). The ^1H NMR showed signals at δ 1.72 (s, 6 H, *gem*-dimethyl), 1.97 (quintet, J = 6 Hz, 2 H, trimethylene β-methylene), and 4.07 (t, J = 6 Hz, 4 H, trimethylene α-methylenes). The ^{11}B NMR (32.1 MHz, $CDCl_3$, $BF_3{\cdot}OEt_2$ = δ 0) showed a singlet at δ −27.8.

Anal. Calcd for $C_6H_{12}BBrO_2$: C, 34.83; H, 5.85; B, 5.22; Br, 38.63. Found: C, 35.04; H, 5.98; B, 5.09; Br, 38.78.

The trimethylene α-bromoalkylboronate esters undergo no apparent change in several months and were stored in a cold room and protected from light, air, and moisture.

Registry No.—Bromine, 24959-67-9.

References and Notes

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