ORGANOBORANES

XVI. TRIETHYLMETHANOL ESTERS OF tert-ALKYLFLUOROBORONIC ACIDS: A NEW CLASS OF ORGANOBORANE INTERMEDIATE REMARKABLY STABLE TO OXIDATION AND ALKALINE HYDROLYSIS

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SUMMARY

Secondary and hindered trialkylboranes react with chlorodifluoromethane quantitatively under the influence of lithium triethylmethoxide to produce highly hindered triethylmethanol esters of tert-alkylfluoroboronic acids. These hindered intermediates differ from all previously known boronic acid derivatives in being remarkably stable to oxidation of the tert-alkyl group by oxygen, alkaline hydrogen peroxide, or trimethylamine-*N*-oxide and to basic hydrolysis of the triethylmethoxy group. The boronic half esters can be cleaved under strongly acidic conditions using methanesulfonic acid or sulfuric acid and the resulting unhindered intermediates then are readily oxidized with alkaline hydrogen peroxide to give excellent yields of the corresponding trialkylmethanol compounds.

INTRODUCTION

We recently reported[1] that the reaction of tri-n-butylborane with a variety of trihalomethanes under the influence of lithium triethylmethoxide produces tri-n-butylmethanol on oxidation with alkaline hydrogen peroxide [eqn. (1)]. This reaction promised to provide a convenient route under mild conditions for conversion of
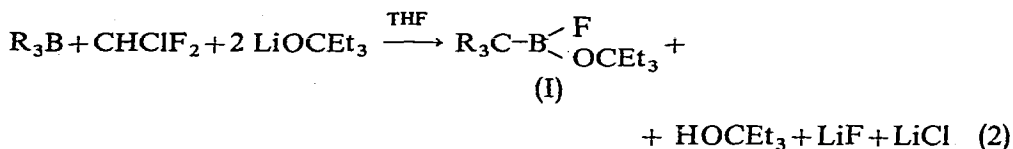
$$\text{n-Bu}_3\text{B} + \text{HCX}_3 + 2\text{ LiOCEt}_3 \xrightarrow[]{\text{THF} \quad [O]} \text{n-Bu}_3\text{COH} \tag{1}$$
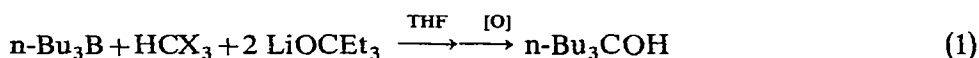
trialkylboranes to the corresponding trialkylmethanol compounds to supplement the carbonylation reaction[2] of organoboranes and the reaction of trialkylcyanoborates with trifluoroacetic anhydride[3]. Chlorodifluoromethane appeared especially promising since essentially quantitative yields (98 %) of tri-n-butylmethanol were obtained. Extension of the reaction of chlorodifluoromethane with secondary trialkylboranes, however, resulted in poor yields of the corresponding trialkylmethanol on oxidation. This led to the isolation and discovery of a new class of highly hindered organoborane intermediates which are remarkably stable to oxidation and basic hydrolysis. The only other fluoroboronic esters previously reported are relatively unhindered primary

alkylfluoroboronic esters, prepared by redistribution reactions[4]. We wish to describe here the preparation and properties of these new triethylmethanol esters of tert-alkylfluoroboronic acids.
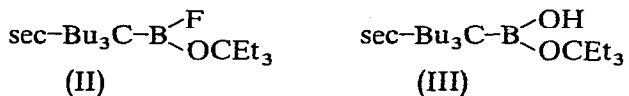
RESULTS AND DISCUSSION

Preparation of triethylmethanol esters of tert-alkylfluoroboronic acids

The reaction of trialkylboranes with chlorodifluoromethane ($CHClF_2$) under the influence of lithium triethylmethoxide produced the triethylmethanol esters of tert-alkylfluoroboronic acids, (I), in nearly quantitative yields [eqn. (2)]. The reaction required two equivalents of lithium triethylmethoxide and was complete

$$R_3B + CHClF_2 + 2\,LiOCEt_3 \xrightarrow{\text{THF}} R_3C-B\overset{F}{\underset{OCEt_3}{\diagdown}} +$$

$$(I)$$

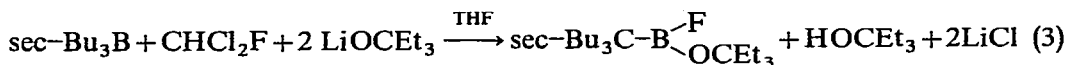$$+ HOCEt_3 + LiF + LiCl \quad (2)$$

after 1 h at reflux in tetrahydrofuran (THF) in all cases studied. When the organoborane contained simple normal alkyl groups, the resulting intermediates could be oxidized readily with sodium acetate and 30 % hydrogen peroxide. This is demonstrated by the 98 % yield of tri-n-butylmethanol obtained by this procedure from tri-n-butylborane[1]. However, when the alkyl groups were secondary or substituted primary, such as isobutyl, the intermediate fluoroboronic esters, (I), proved to be remarkably stable to oxidation and basic hydrolysis, presumably a consequence of the greater steric hindrance around the boron atom. Thus, the reaction of tri-sec-butylborane with $CHClF_2$ and 2 equivalents of lithium triethylmethoxide proceeded cleanly to give the intermediate, (II), after 1 h at reflux in THF as revealed by GLC examination of the reaction mixture. Oxidation with sodium acetate and 30% hydrogen peroxide, however, failed to give tri-sec-butylmethanol. Moreover, treatment in ethanolic solution at 50° with a 6-fold excess of sodium hydroxide and 30% hydrogen peroxide produced only a 21 % yield of the desired trialkylmethanol. The remainder of the intermediate was converted to the boronic half ester, (III), but resisted further oxidation or hydrolysis even under these unusually vigorous conditions.

$$sec\text{-}Bu_3C-B\overset{F}{\underset{OCEt_3}{\diagdown}} \qquad sec\text{-}Bu_3C-B\overset{OH}{\underset{OCEt_3}{\diagdown}}$$

$$(II) \qquad\qquad (III)$$

The intermediate, (II), was isolated in 92 % yield by vacuum distillation, b.p. 109–111°/1 mmHg. (II) was characterized by mass spectral analysis, revealing a weak parent ion at m/e 328, base ion at m/e 99, and other strong ions at m/e 173, 71, 57, 43 and 41. Further supporting evidence was the finding of only 1 equivalent of triethylmethanol and 1 equivalent each of lithium fluoride and lithium chloride in the reaction mixture. ^{11}B NMR using acetone-d_6 as internal standard gave a shift of δ −30.0 ppm. Treatment of (II) with acid resulted in cleavage of the triethylmethoxy group to produce 3-ethyl-2-pentene, and subsequent oxidation of the intermediate produced tri-sec-butylmethanol in 99 % yield. The boronic half ester, (III), was isol-

ated by GLC and characterized by mass spectral analysis. (III) gave no parent ion, a base ion at m/e 99 and other strong ions at m/e 171, 87, 71, 57 and 28. Proton NMR showed a singlet downfield at δ 3.9 ppm for BOH integrating 1/42.5 (ca. 1/42). An infrared spectrum of (III) showed O–H stretch at 3680 cm^{-1}.

Reaction of dichlorofluoromethane ($CHCl_2F$) with tri-sec-butylborane and 2 equivalents of lithium triethylmethoxide produced an intermediate identical with (II) after reflux for 1 h in THF but in lower yield [eqn. (3)]. Thus, in the reactions of

$$sec\text{–}Bu_3B + CHCl_2F + 2\ LiOCEt_3 \xrightarrow{\text{THF}} sec\text{–}Bu_3C\text{–}B\diagdown_{OCEt_3}^{F} + HOCEt_3 + 2LiCl \quad (3)$$

both $CHClF_2$ and $CHCl_2F$ with trialkylboranes the reaction product contains one atom of fluorine attached to boron. Oxidation with alkaline hydrogen peroxide of the intermediate obtained from the reaction of $CHCl_2F$ with tri-sec-butylborane following treatment with methanesulfonic acid to cleave the triethylmethoxy group resulted in only a 75 % yield of tri-sec-butylmethanol. It is possible that formation of the intermediate (II) is less satisfactory in the reaction with $CHCl_2F$, as compared to $CHClF_2$.

Attempts to prepare the triethylmethanol ester of a tert-alkylchloroboronic acid by reacting chloroform with 2 equivalents of lithium triethylmethoxide and tri-sec-butylborane failed. Many side products were formed in the reaction and oxidation, following treatment with methanesulfonic acid, resulted in only a 27 % yield of the desired tertiary methanol. Evidently the base-induced reactions of tri-sec-butylborane with these haloforms decrease in effectiveness in the order: $CHClF_2 > CHCl_2F \gg CHCl_3$. This is in contrast to the relatively similar results involving the reaction of these three haloforms with tri-n-butylborane.

Oxidation and hydrolysis of the triethylmethanol esters of tert-alkylfluoroboronic acids

Attempts to oxidize the highly hindered intermediate, (II), obtained from the reaction of tri-sec-butylborane with $CHClF_2$ and $CHCl_2F$ without removal of the triethylmethoxy group by treatment with acid gave poor results. This is in sharp

TABLE 1

OXIDATION OF THE REACTIONS OF n-Bu$_3$B AND sec-Bu$_3$B WITH TRIHALOMETHANES AND LiOCEt$_3$

Trihalomethane	Yield R_3COH from R_3B upon oxidation of the intermediate (%)^a		
	Direct oxidation		Oxidation after treatment with MeSO$_3$H
	n-Bu$_3$B^b	sec-Bu$_3$B^c	sec-Bu$_3$B
Chloroform	85	33	27
Dichlorofluoromethane	81^d	25	75
Chlorodifluoromethane	98	21	90

^{a} By GLC analysis. ^{b} Oxidation performed with sodium acetate and 30% hydrogen peroxide. ^{c} Oxidation in ethanolic solution with 6-fold excess of sodium hydroxide and 20-fold excess of 30% hydrogen peroxide. ^{d} Accompanied by 16% yield of 5-nonanone.

contrast to the ease of oxidation of the intermediates produced in the corresponding reactions of organoboranes containing only primary, normal alkyl groups, such as tri-n-butylborane. Table 1 shows a comparison of the reactions of tri-n-butylborane and tri-sec-butylborane. Even treatment in ethanolic solution at 50° with a 6-fold excess of sodium hydroxide and a 30-fold excess of 30 % hydrogen peroxide failed to oxidize (II) to any appreciable extent after 4 h. We have never previously encounter-ed an organoborane derivative which could resist such vigorous conditions. (II) could be handled conveniently in the air with little oxidation.

Trimethylamine-N-oxide has been demonstrated to oxidize readily tert-alkyl groups on boron[5]. However, refluxing (II) with trimethylamine-N-oxide for 14 h in THF, followed by stirring at room temperature for 7 days, resulted in oxidation of only 58 % of the intermediate.

We thought that if the bulky triethylmethoxy group could be cleaved from the molecule, oxidation could then be accomplished with ease using standard conditions. The ethylene glycol esters of the tert-alkylboronic acids obtained in the carbonyl-ation reaction of organoboranes[2] are readily oxidized by ethanolic sodium hydroxide and hydrogen peroxide. Attempts to replace the bulky triethylmethoxy group with ethylene glycol by heating the intermediate in refluxing ethylene glycol for 14 h failed to achieve any significant exchange.

Hydrolysis of (II) was then attempted. Whereas most boronic esters undergo hydrolysis rapidly[6] in water or in mild base, the alkoxy group of (II) was resistant to alkaline hydrolysis. Thus, treatment of (II) at reflux in 95 % ethanol with a 6-fold excess of sodium hydroxide converted the B–fluoro intermediate, (II), fairly rapidly into the B–hydroxy compound, (III). In the absence of such strongly basic conditions (II) is quite stable to water. Further hydrolysis in the presence of the base removed the triethylmethoxy group of (III) very slowly. After 24 h at reflux, only 55 % of the triethylmethoxy groups in the intermediate had been hydrolyzed. The resulting boronic acid oxidized readily with hydrogen peroxide to give tri-sec-butylmethanol, but the unhydrolyzed intermediate resisted the oxidation.

Reaction with strong acids provided a solution to the problem. It was observed that 37 % hydrochloric acid was relatively ineffective for removing the triethyl-methoxy group. However, treatment of (II) with methanesulfonic acid achieved facile cleavage of the alkoxy group. Thus, addition of 1.1 equivalents of methanesulfonic acid to the neat intermediate, followed by heating to 50° for 1 h, resulted in complete loss of the triethylmethoxide group. Destruction of the intermediate was conveniently followed by GLC. Subsequent oxidation with alkaline hydrogen peroxide produced a 99 % yield of tri-sec-butylmethanol based on (II). Alternatively, treatment with 1.1 equivalents of concentrated sulfuric acid was somewhat more rapid, being complete in 40–45 min at 50°. Oxidation then resulted in a 96 % yield of the tertiary methanol. When only 10 mole % of sulfuric acid was used, cleavage of (II) was apparently com-plete by GLC in 1 h at 70°, but only a 66.5 % yield of tri-sec-butylmethanol was ob-tained on oxidation. The use of methanesulfonic acid generally gave more consistent results than did sulfuric acid for cleavage of the triethylmethoxy groups from the boronic esters and was the reagent of choice for these transformations.

The more hindered the tertiary alkyl group on boron, the more difficult the transformation of the fluoroboronic ester intermediates proved to be. The inter-mediate obtained from tri-isobutylborane was converted easily with 1 equivalent

of methanesulfonic acid in 2 h at room temperature, whereas the transformation of the intermediate from tri-*exo*-norbornylborane was not complete after 2 days and had to be completed by heating for an hour at 70°.

Representative organoboranes were reacted with $CHClF_2$ and 2 equivalents of lithium triethylmethoxide. The reactions went very cleanly to give the highly hindered fluoroboronic ester intermediates as evidenced by GLC of the reaction mixtures and the excellent yields of tertiary methanol compounds obtained on oxidation after treatment with methanesulfonic acid. Table 2 presents the results.

TABLE 2

REACTION OF REPRESENTATIVE ORGANOBORANES WITH $CHClF_2$ UNDER THE INFLUENCE OF LITHIUM TRIETHYLMETHOXIDE
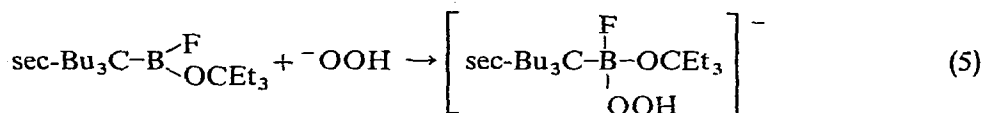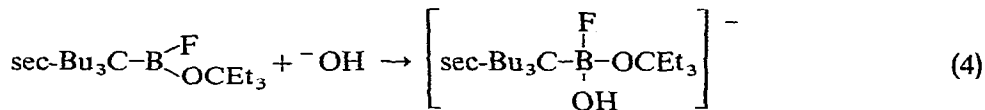
Organoborane	Oxidation product after treatment with $MeSO_3H$	Yield $R_3COH(\%)$[a]
Tri-sec-butylborane	Tri-sec-butylmethanol	90[b]
Tri-isobutylborane	Tri-isobutylmethanol	93
Tricyclopentylborane	Tricyclopentylmethanol	90
Tricyclohexylborane	Tricyclohexylmethanol	80
Tri-*exo*-norbornylborane	Tri-*exo*-norbornylmethanol	84

[a] By GLC analysis. [b] Isolated yield by distillation, b.p. 60–61°/2 mmHg. Purity checked by GLC. NMR and IR compared with an authentic sample obtained from the carbonylation of sec-Bu_3B. n_D^{20} 1.4556, lit.[7] n_D^{20} 1.4558.

CONCLUSIONS

The reactions of organoboranes derived from internal or substituted terminal olefins with $CHClF_2$ and lithium triethylmethoxide provide a new class of highly hindered organoborane intermediates. These triethylmethanol esters of tert-alkyl-fluoroboronic acids show remarkable stability toward oxidation and alkaline hydrolysis. In fact the tertiary alkyl group cannot be oxidized to any appreciable extent even by heating in a strongly alkaline ethanolic solution with a 30-fold excess of 30% hydrogen peroxide to 50° for 4 h. These hindered intermediates can be handled in the air with little oxidation. Hydrolysis of the triethylmethoxy group is very sluggish under strongly alkaline conditions, but it may be cleaved readily with a strong acid such as methanesulfonic acid.

Attack on boron to produce the tetracoordinate complexes necessary for basic hydrolysis [eqn. (4)] and alkaline hydrogen peroxide oxidation [eqn. (5)] must be extremely difficult with the bulky tertiary groups around boron. The fluorine

$$\text{sec-Bu}_3\text{C-B}\underset{\text{OCEt}_3}{\overset{\text{F}}{\diagup}} + {}^-\text{OH} \rightarrow \left[\text{sec-Bu}_3\text{C-}\underset{\text{OH}}{\overset{\text{F}}{\underset{|}{\overset{|}{\text{B}}}}}\text{-OCEt}_3 \right]^- \tag{4}$$

$$\text{sec-Bu}_3\text{C-B}\underset{\text{OCEt}_3}{\overset{\text{F}}{\diagup}} + {}^-\text{OOH} \rightarrow \left[\text{sec-Bu}_3\text{C-}\underset{\text{OOH}}{\overset{\text{F}}{\underset{|}{\overset{|}{\text{B}}}}}\text{-OCEt}_3 \right]^- \tag{5}$$

is only displaced readily by hydroxide under strongly alkaline conditions. Treatment with acid, however, involves attack on oxygen α to boron and does not require a tetra-coordinate boron species. Thus, cleavage of the triethylmethoxy group occurs readily.

The reactions of trialkylboranes with $CHClF_2$ and lithium triethylmethoxide go cleanly to produce the fluoroboronic ester intermediates in high yield as evidenced by the excellent yields of the corresponding trialkylmethanol compounds obtained on oxidation after acid treatment.

It is interesting to note that our work was initially directed towards the conversion of trialkylboranes into trialkylmethanol compounds. The difficulty in oxidizing these intermediates was a temporary setback, but led to the discovery of a new class of highly hindered organoborane intermediates remarkably stable to basic hydrolysis and oxidation.

EXPERIMENTAL

Materials

All glassware was dried in an oven, assembled hot, and cooled by flushing with dry nitrogen. THF was distilled from lithium aluminium hydride and stored under nitrogen prior to use. Chlorodifluoromethane and dichlorofluoromethane were obtained from Matheson Gas Products. Chloroform was Mallinckrodt Spectrar grade. Triethylmethanol was obtained from Chem Samples and n-butyllithium from Alpha Inorganics as a solution in hexane.

Lithium triethylmethoxide was prepared by addition of a stoichiometric amount of triethylmethanol to n-butyllithium in hexane at $0°$. Solutions of lithium triethylmethoxide were standardized prior to use by titration of hydrolyzed aliquots with standard acid to a phenolphthalein end point.

Trialkylboranes were prepared by hydroboration[8] of the respective olefins with a solution of borane (BH_3) in THF prepared according to the procedure of Brown and Sharp[9]. Commercial tri-n-butylborane and tri-isobutylborane (Callery) were distilled under reduced pressure prior to use. Tri-sec-butylborane was prepared by hydroboration of cis-2-butene (Matheson) and distilled under reduced pressure prior to use (b.p. $63–64°/3.0$ mmHg). All other trialkylboranes were prepared and used as solutions in THF.

Trimethylamine-N-oxide (Eastman) was sublimed to remove water of hydration prior to use.

Small amounts (10 mmoles) of gaseous reactants were added conveniently by volume using a simple 250 ml gas syringe designed by G. W. Kramer[10].

Analyses

Infrared spectra were taken on a Perkin–Elmer Model 700 instrument and calibrated with polystyrene film. NMR spectra were recorded on a Varian Associates T-60 instrument and a Varian Associates XL-100 with ^{11}B probe. Mass spectra were taken on an Hitachi RMU-6A instrument. GLC analyses were performed on a Hewlett Packard 5750 instrument using 6 ft. × 1/4 in. stainless steel columns packed with 10 % Carbowax 20M or 10 % SE-30 on Chromosorb W. A 2 ft. × 1/4 in. column packed with 10 % XE-6^0 on Chromosorb W was used for analysis of high boiling compounds.

Preparation of tri-n-butylmethanol from tri-n-butylborane

In an oven dried 100 ml flask fitted with septum inlet, reflux condenser, magnetic stirrer and maintained under a nitrogen atmosphere were placed 10 ml THF and 1.82 g (10 mmoles) tri-n-butylborane. This solution was cooled to 0° and 10.3 ml of a 1.93 M solution of lithium triethylmethoxide (20 mmoles) were added at once followed by the slow addition of 12 mmoles (by volume or weight) chlorodifluoromethane over 15 min. The solution was then heated to reflux for 1 h. The reaction mixture was cooled to 0° and oxidized by the addition of 6 ml 3 M sodium acetate and careful addition of 6 ml 30 % hydrogen peroxide followed by heating to 50–60° for 1 h. The aqueous phase was saturated with potassium carbonate. 1.56 g (10 mmoles) undecane were added as internal standard and the organic phase was separated, dried over anhydrous potassium carbonate and analyzed by GLC. GLC analysis indicated a 98 % yield of tri-n-butylmethanol.

Preparation of (II)

In an oven dried 100 ml flask fitted with septum inlet, reflux condenser, magnetic stirrer and maintained under a nitrogen atmosphere were placed 24 ml THF and 7.28 g (40 mmoles) tri-sec-butylborane. The solution was cooled to 0° and 41.44 ml of a 1.93 M solution of lithium triethylmethoxide in hexane (80 mmoles) were added at once. Then 4.33 g (50 mmoles) $CHClF_2$ were added via a syringe needle inserted below the surface of the solution over a period of ≈ 1 h. The reaction was stirred at 0° for 1 h followed by reflux for 1 h. The solvents were then r moved leaving a mixture of the desired intermediate, Et_3COH and lithium salts. The mixture was fractionally distilled under vacuum yielding 4.8 g (41.3 mmoles) Et_3COH, b.p. 40–42°/4.5 mmHg and 12.1 g (36 mmoles, 92 %) (II), b.p. 109–111°/1 mmHg. The lithium salts remaining in the pot were washed with pentane, dried and weighed. 2.71 g of LiCl and LiF were obtained (ca. for 40 mmoles LiCl plus 40 mmoles LiF = 2.73 g).

Mass spectral analysis of the intermediate gave conclusive evidence for the structure of the intermediate.

Acid treatment and oxidation of the triethylmethanol esters of tert-alkylfluoroboronic acids

A representative procedure is given for the preparation of tri-isobutylmethanol. In an oven dried 100 ml flask fitted with septum inlet, reflux condenser, magnetic stirrer and maintained under a nitrogen atmosphere were placed 10 ml THF and 1.82 g (10 mmoles) i-Bu₃B. The solution was cooled to 0° and 10.3 ml 1.93 M solution of lithium triethylmethoxide (20 mmoles) were added at once. $CHClF_2$ [12 mmoles (by volume or weight)] were added slowly through a syringe needle below the surface of the reaction mixture over 15 min. After addition the reaction was heated to reflux for 1 h. GLC analysis at this stage showed the reaction had proceeded cleanly to give the hindered fluoroboronic ester intermediate. The solvents were removed under aspirator vacuum and the residue taken up in 30 ml pentane. The insoluble lithium salts were removed by filtration and the pentane removed from the filtrate under vacuum. The residue was treated with 1.06 g (11 mmoles) of methanesulfonic acid at 25° for 2 h. (Note: the more hindered cases require more vigorous conditions. Use of 1–2 equivalents of methanesulfonic acid with heating to 50–60° for several hours is commonly required. Transformation of the intermediate is conveniently followed by

GLC). When all of the intermediate had been converted, oxidation was accomplished by addition of 10 ml 95 % ethanol plus 2.8 g sodium hydroxide followed by the careful addition of 15 ml 30 % hydrogen peroxide at 0° and heating to 50–60° for $1\frac{1}{2}$ h. The aqueous phase was saturated with potassium carbonate. 10 mmoles undecane were added as internal standard plus 10 ml THF to insure homogeneity of the organic phase. The organic phase was then separated, dried over anhydrous potassium carbonate and analyzed by GLC. GLC analysis indicated 9.3 mmoles, 93 %, tri-isobutyl-methanol.

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