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IODOMETHANEBORONIC ESTERS AND AMINOMETHANEBORONIC ESTERS

Donald S. Matteson* and Debesh Majumdar

Department of Chemistry, Washington State University, Pullman, Washington 99164 (U.S.A.)

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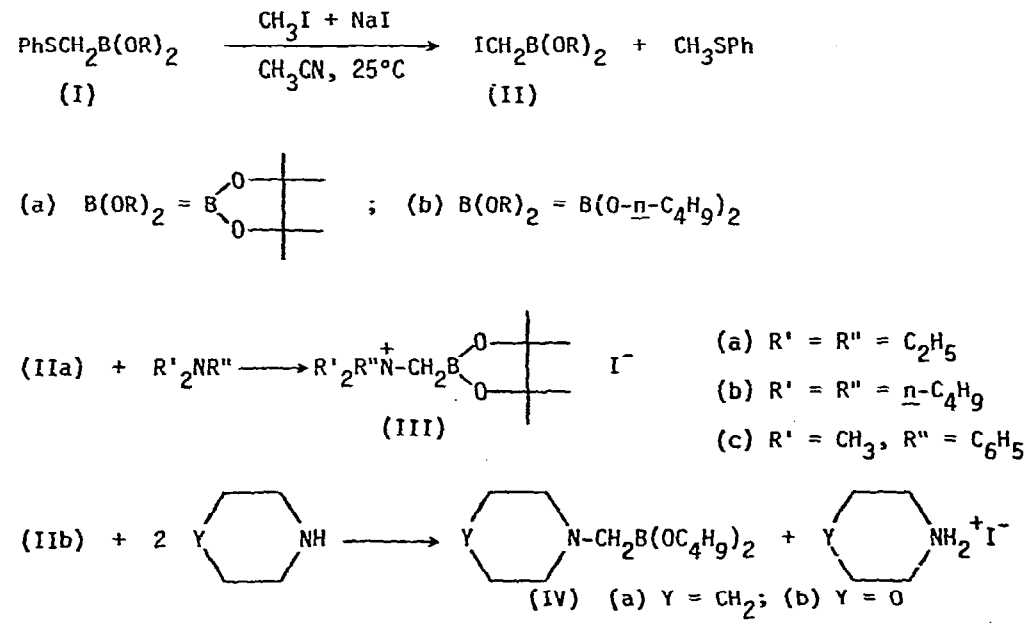
Summary

An efficient preparation of pinacol iodomethaneboronate and dibutyl iodomethaneboronate from the respective (phenylthio)methaneboronic esters has been devised, using the reaction with methyl iodide. Pinacol iodomethaneboronate reacts efficiently with tertiary amines to form the crystalline quaternary ammonium salts. Dibutyl iodomethaneboronate reacts with excess piperidine or morpholine in ether to precipitate piperidine or morpholine hydriodide and yield the distillable piperidino- or morpholinomethaneboronic ester. Benzylamine failed to yield a stable product.

We have previously reported the synthesis of dibutyl iodomethaneboronate (IIb) by a laborious route from iodomethylmercuric iodide [1]. Several reactions of (IIb) with nucleophiles were reported, including two reactions with secondary amines to form aminomethaneboronic esters (IV). More recently, Lindquist and Nguyen have used (IIb) as a source of benzamidomethaneboronic acid, which is a chymotrypsin inhibitor [2].

When we tried to extend this chemistry to prepare an α-aminoalkaneboronic ester from pinacol 1-iodo-2-phenylethane-1-boronate, $Me_4C_2O_2B\text{-}CHICH_2Ph$ [3], we met with persistant failure. For example, this iodo compound fails to undergo nucleophilic displacement in ether saturated with ammonia at 25°C (unchanged iodo compound recovered), and in liquid ammonia under pressure at 25°C the reaction that occurs ultimately leads to phenylethylammonium salts, $PhCH_2CH_2NH_3^+$, as shown by the characteristic symmetrical $-CH_2CH_2-$ multiplet near δ 3 in the NMR [

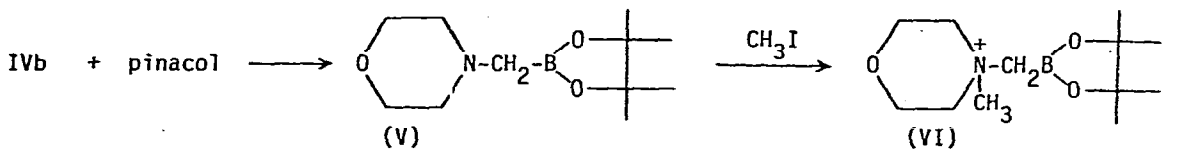
Since our previous work was limited in scope [1] and perhaps open to question in view of our repeated failure to extend it, we thought it desirable to reinvestigate. Also, our recent synthesis of (phenylthio)methaneboronic esters (I) [3] has made possible a much easier route to iodomethaneboronic esters (II). We now report this route and the preparation of several well-defined amine derivatives.



The reported method for converting (phenylthio)alkanes to iodoalkanes requires excess methyl iodide and sodium iodide in dimethylformamide [5]. We have found that acetonitrile is a more convenient solvent, especially when nonaqueous work-up is required, since it is easier to distill from the products. Pinacol iodomethaneboronate (IIa) and dibutyl iodomethaneboronate (IIb) were easily obtained in good yields.

Quaternary ammonium salts (III) were readily obtained from reaction of the pinacol ester (IIa) with triethylamine, tri-n-butylamine, and N,N-dimethylaniline. However, we were unable to obtain satisfactory results from reactions of (IIa) with secondary amines, and turned to the butyl ester (IIb) in the hope that our previously reported work [1] would prove correct.

Reaction of (IIb) with excess piperidine or morpholine in ether precipitated the amine hydriodide and yielded a distillable residue of the aminomethaneboronic ester (IV).. Transesterification of the morpholino compound (IVb) with pinacol yielded the pinacol ester (V), confirming that the B-C-N linkage is stable to hydroxyl groups at least under mild conditions. The presence of a basic amino group in (V) was confirmed by reaction with methyl iodide to form the methiodide (VI).



(V) (VI)

Reexamination of our NMR data then showed that (V) had indeed been formed from pinacol iodomethaneboronate (IIa) and morpholine, but that recrystallization had failed to yield pure material. From the analytical results, which indicated that the product was high in boron and low in nitrogen content, as well as the extra pinacol borate ester peak in the NMR, it appears likely that some deboronation had occurred as a side reaction, analogous to the deboronation which occurs as the major reaction of pinacol 1-iodo-2-phenylethane-1-boronate with ammonia. In contrast, the clean butyl esters (IV) obtained from dibutyl iodomethaneboronate (IIb) indicated negligible deboronation.

Liquid ammonia failed to react with (IIb) at atmospheric pressure. Benzylamine at first appeared to react normally with (IIb) under the same conditions used with piperidine, precipitating amine hydriodide, but the product decomposed on attempted distillation. Redistillation yielded a mixture that was mostly benzylamine mixed with a little benzylmethylamine on the basis of its NMR spectrum, and a fraction at 55°C (0.1 Torr) having the characteristic NMR spectrum of tributyl borate. Further investigation will be required in order to determine whether compounds of the general structure $RNHCH_2B(OR')_2$ can be prepared and isolated.

We have made several attempts to deprotonate the $N-CH_2-B$ group of (IIIa) and (V) under conditions similar to those used for deprotonating the (phenylthio)-methaneboronic ester (Ia) [3], but have been unable to obtain any evidence that deprotonation occurs.

Experimental

Reactions were run in an argon atmosphere. Acetonitrile was distilled from calcium hydride. (Phenylthio)methaneboronic acid and its pinacol ester were prepared as described previously [3]. 60 MHz proton NMR spectra were recorded on a Varian EM-360 instrument with internal tetramethylsilane as the reference. Microanalyses were by Galbraith Laboratories, Knoxville, Tennessee.

Pinacol iodomethaneboronate (IIa)

A mixture of 12.5 g (0.05 mol) of pinacol (phenylthio)methaneboronate (Ia) [3], 35.5 mL (0.5 mol) of methyl iodide, and 11.25 g (0.075 mol) of sodium iodide (not quite all soluble) in 250 mL of acetonitrile was stirred 48 h at 25°C. Methyl iodide and acetonitrile were recovered by fractional distillation at atmospheric pressure, and vacuum distillation yielded 5.5 g (95%) of thioanisole, bp 34°C (0.2 Torr), and 9.4 g (70%) of pinacol iodomethaneboronate (IIa), bp 64-65°C (0.2 Torr); NMR ($CDCl_3$) δ 1.30 (s, 12, CCH_3), 2.20 (s, 2, ICH_2B). Found: C, 31.52; H, 5.28; B, 4.20; I, 47.29. $C_7H_{14}BIO_2$: calcd.: C, 31.88; H, 5.25; B, 4.03; I, 47.36%.

Dibutyl (phenylthio)methaneboronate (Ib)

The water was removed from 16.8 g (0.1 mol) of (phenylthio)methaneboronic acid [3] and 18.3 mL (0.2 mol) of n-butyl alcohol by refluxing 3 h in benzene using a Dean-Stark trap. Distillation yielded 25.4 g (91%) of dibutyl (phenylthio)methaneboronate, bp 124-125°C (0.1 Torr); NMR ($CDCl_3$) δ 0.90 (t, 6, CH_2CH_3), 1.50 (m, 8, $(CH_2)_2$), 2.46 (s, 2, SCH_2B), 3.95 (t, 4, OCH_2CH_2), 7.40 (m, 5, C_6H_5). Found: C, 65.67; H, 8.90; B, 3.90; S, 10.81. $C_{15}H_{25}BO_2S$ calcd.: C, 65.75; H, 8.62; B, 3.69; S, 10.97%.

Dibutyl iodomethaneboronate (IIb)

The procedure described for pinacol iodomethaneboronate (IIa) was followed, using dibutyl (phenylthio)methaneboronate (Ib) in place of the pinacol ester (Ia), and yielded 74% of dibutyl iodomethaneboronate (IIb), bp 78-80°C (0.2 Torr) (reported bp 61-63°C (0.1 Torr) on fractionation [1]); NMR ($CDCl_3$) δ 0.95 (t, 6, CH_2CH_3), 1.46 (m, 8, $(CH_2)_2$), 2.16 (s, 2, ICH_2B), 3.95 (t, 4, OCH_2), same as that of an authentic sample [1].

[(Tetramethylethylenedioxyboryl)methyl]trialkylammonium iodides (III)

A solution of 1.34 g (5 mmol) of pinacol iodomethaneboronate (IIa) in 8 mL of dichloromethane was added to a solution of 5 mmol of the tertiary amine in 5 mL of dichloromethane at 0°C and stirred 1 h at 0°C. Addition of 50 mL of cold ether precipitated the crystalline product (III), which was filtered, washed with cold ether, and dried under vacuum. From triethylamine, the yield of (IIIa) was 1.7 g (93%), mp 235-237°C; NMR ($CDCl_3$) δ 1.30 (s, 12, CCH_3), 1.50 (t, 9, NCH_2CH_3), 3.16 (s, 2, NCH_2B), 3.70 (q, 6, NCH_2CH_3). Found: C, 42.45; H, 7.87; B, 3.09; I, 34.58; N, 3.74. $C_{13}H_{29}BINO_2$ calcd.: C, 42.30; H, 7.92; B, 2.92; I, 34.38; N, 3.79%. From tributylamine, the yield of (IIIb) was 2.1 g (91%), mp 143-144°C; NMR ($CDCl_3$) δ 1.03 (t, 9, CH_2CH_3), 1.33 (s, 12, $C(CH_3)_2$), 1.73 (m, 12, $(CH_2)_2$), 3.26 (s, 2, NCH_2B), 3.63 (t, 6, NCH_2CH_2). Found: C, 50.34; H, 9.11; B, 2.49; I, 28.40; N, 3.12. $C_{19}H_{43}BINO_2$ calcd.: C, 50.35; H, 9.12; B, 2.38; I, 28.10; N, 3.09%. From dimethylaniline, the yield of (IIIc) was 1.5 g (76%), mp 189-191°C; NMR ($CDCl_3$) δ 1.00 (s, 12, CCH_3), 4.13 (s, 6, NCH_3), 4.33 (s, 2, NCH_2B), 7.75 + 8.20 (m, 3 + 2, C_6H_5). Found: C, 46.24; H, 6.53; B, 2.79; I, 32.80; N, 3.52. $C_{15}H_{25}BINO_2$ calcd.: C, 46.30; H, 6.47; B, 2.77; I, 32.61; N, 3.60%.

Dibutyl piperidinomethaneboronate (IVa)

2.55 g (30 mmol) of piperidine was added to 2.84 g (10 mmol) of dibutyl iodomethaneboronate (IIb) in 30 mL of ether at 0°C and stirred 1 hr at 0°C. The precipitated piperidine hydriodide was filtered. The filtrate was concentrated and distilled, yielding 2.26 g (89%) of (IVa), bp 90-92°C (0.2 Torr); NMR ($CDCl_3$) δ .95 (t, 6, CH_2CH_3), 1.50 (m, 14, $(CH_2)_2$ and $(CH_2)_3$), 2.00 (s, 2, NCH_2B), 2.36 (t, 4, NCH_2CH_2), 3.86 (m, 4, OCH_2). Found: C, 65.75; H, 11.75; B, 4.06; N, 5.38. $C_{14}H_{32}BNO_2$ calcd.: C, 65.88; H, 11.84; B, 4.23; N, 5.48%.

Dibutyl morpholinomethaneboronate (IVb)

Morpholine was used in place of piperidine in the procedure described in the preceding paragraph, yield of (IVb) 2.10 g (82%), bp 96-98°C (0.2 Torr); NMR ($CDCl_3$) δ .95 (t, 6, CH_2CH_3), 1.50 (m, 8, $(CH_2)_2$), 2.10 (s, 2, NCH_2B), 2.45 (t, 4, NCH_2CH_2), 3.85 (m, 8, OCH_2). Found: C, 60.48; H, 10.74; B, 4.13;

N, 5.60. $C_{13}H_{88}BNO_3$ calcd.: C, 60.71; H, 10.97; B, 4.20; N, 5.44%. Morpholine hydriodide was also isolated (93%), mp 202-205°C (not previously reported); NMR (D_2O) δ 3.66 (t, $OC\underline{H}_2$), 4.46 (t, NCH_2), 5.36 (s, HDO).

Pinacol morpholinomethaneboronate (V)

A solution of 2.57 g (10 mmol) of dibutyl morpholinomethaneboronate (IVb) and 1.18 g (10 mmol) of anhydrous pinacol in 50 mL of ether was stirred overnight at 25°C. Distillation yielded 2.2 g (97%) of the pinacol ester (V), bp 80-82°C (0.2 Torr); solidified, mp 38-39°C; recrystallized twice from petroleum ether, mp 48-49°C; NMR ($CDCl_3$) δ 1.28 (s, 12, $CC\underline{H}_3$), 2.16 (s, 2, $NC\underline{H}_2B$), 2.50 (t, 4, $NC\underline{H}_2CH_2$), 3.83 (t, 4, $CH_2C\underline{H}_2O$). Found: C, 58.04; H, 9.90; B, 4.52; N, 6.32. $C_{11}H_{22}BNO_3$ calcd.: C, 58.17; H, 9.76; B, 4.75; N, 6.16%. An impure sample of (V) was obtained from the reaction of 5 mmol of (IIa) with 10 mmol of morpholine in 6 mL of ether mixed at 0°C and kept at 25°C overnight. The precipitate was filtered, the solution was concentrated, and the residue was recrystallized from ether-pentane, yield 0.5 g (44%), mp 55-59°C, NMR spectrum similar to (V) but with extra peaks at δ 1.16 and 2.73. Found: C, 50.15; H, 9.54; B, 6.21; N, 4.24%.

Methiodide of pinacol morpholinomethaneboronate (VI)

Reaction of 1.13 g (5 mmol) of pinacol morpholinomethaneboronate (V) with 0.63 mL (10 mmol) of methyl iodide in 10 mL of ether 3 h at 0°C precipitated 1.16 g (96%) of the methiodide (VI), mp 198-200°C; NMR ($CDCl_3$) δ 1.33 (s, 12, $CC\underline{H}_3$), 3.73 (s, 3, $NC\underline{H}_3$), 3.86 (s, 2, $NC\underline{H}_2B$), 3.90 + 4.10 (m, 4 + 4, $N(C\underline{H}_2C\underline{H}_2)_2O$). Found: C, 39.17; H, 6.99; B, 3.14; I, 34.20; N, 3.94. $C_{12}H_{25}BINO_3$ calcd.: C, 39.05; H, 6.82; B, 2.92; I, 34.38; N, 3.79%.

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