Interactions of carborane-containing electrophiles with triethyl phosphite. Synthesis of new carborane-containing phosphonates*

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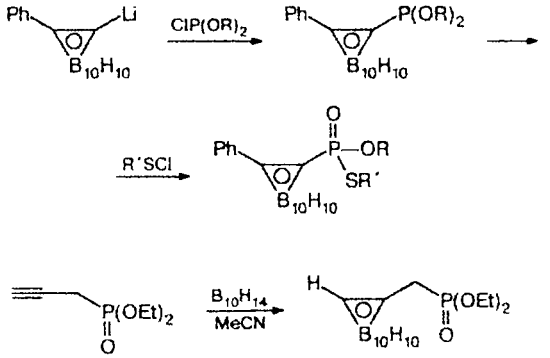
The reactions of *o*-carboran-1-ylethyl mesylates with triethyl phosphite and sodium diethyl phosphite were studied. Carborane-containing phosphonates were synthesized. The reaction of *o*-carboranylacetyl chloride with triethyl phosphite afforded *O,O*-diethyl (*E*)-2-(*o*-carboran-1-yl)-1-(*o*-carboran-1-ylacetoxy)vinylphosphonate rather than oxo phosphonate.

Key words: carborane-containing mesylates, acid chlorides and phosphonates, triethyl phosphite.

Carborane derivatives that can be selectively incorporated into tumor cells are of great importance in boron neutron-capture therapy of cancer.[1] Therefore, the synthesis of carborane-containing phosphonates (compounds containing the phosphonate group accumulate in bone tissues[2]) is of interest. Several examples of the synthesis of these compounds were reported in the literature.[3–5]

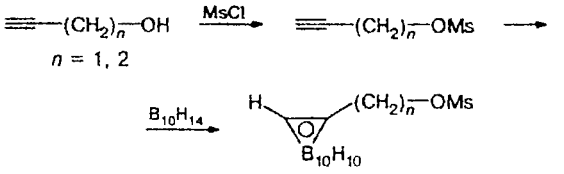


The available methods have particular drawbacks. The first method allows one to prepare primarily compounds in which the phosphonate group is directly bound to the carborane polyhedron. In this case, it is difficult to synthesize phosphonates that have no substituents at the second carbon atom of the *o*-carborane nucleus. The starting alkynylphosphonates used in the second method are difficultly accessible, and in the stage of their interaction with decaborane, yields of the target products are low.

In this work, we studied the possibility of the synthesis of carborane-containing phosphonates with the use of carborane-containing electrophilic synthons, such as carboranylalkyl mesylates, carboranylethyl iodide, and carboranylacetyl chloride, in the Arbuzov and Michaelis—Becker reactions.

Results and Discussion

Carboranylalkyl sulfonates as synthons. It is common knowledge that alkyl sulfonates readily enter into the Arbuzov and Michaelis—Becker reactions[6] to give reaction products in higher yields compared to those obtained under the action of alkyl halides. Carboranylalkyl mesylates can be prepared by the reaction of decaborane with the corresponding alkynyl mesylates. The last-mentioned compounds can be readily prepared from the corresponding alcohols in high yields.



1 (n = 1)
2 (n = 2)

* Dedicated to the memory of Academician M. I. Kabachnik on his 90th birthday.

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The structures of the synthesized compounds were established by NMR spectroscopy and elemental analysis.

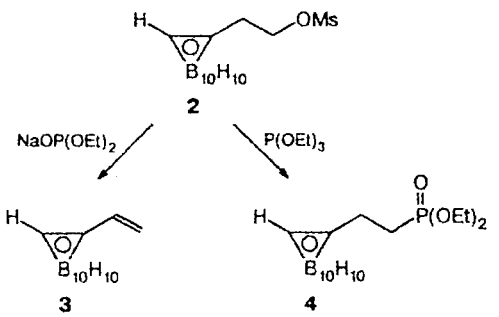
In spite of the fact that the mesylate is a good leaving group, the reactivity of sulfonate **1** in reactions of nucleophilic substitution is low, as in the case of bromomethyl-*o*-carborane,[7,8] due to the strong σ-electron-withdrawing effect of the *o*-carborane nucleus. Because of this, compound **1** does not react with triethyl phosphite and sodium diethyl phosphite. Moreover, replacement by iodine according to the Finkelstein reaction does not occur under the standard conditions. Therefore, the reactivities of the resulting *o*-carboranyl mesylates in the Arbuzov and Michaelis—Becker reactions were studied using mesyloxyethylcarborane **2** as an example because the MsO group in **2** is more remote from the carborane nucleus and should be more labile.

Note that the Arbuzov reaction often affords a by-product due to the interaction of the alkyl halide that formed with triethyl phosphite.[9] Moreover, elimination of hydrogen halide can be a competitive process in the Arbuzov and Michaelis—Becker reactions. In the case of compound **2**, this process is highly probable because in the resulting vinyl-*o*-carborane the conjugation of the double bond with the carborane polyhedron is energetically favorable.[10]

Actually, when sulfonate **2** was used in the Michaelis—Becker reaction, elimination of MsOH occurred exclusively although the basicity of $NaP(O)(OEt)_2$ is low. The structure of the resulting compound **3** was established based on the data of ^1H NMR spectroscopy and elemental analysis as well as from a comparison of its melting point with the literature value (see the Experimental section).[14]

However, when sulfonate **2** reacted with triethyl phosphite, elimination was not observed and the target carboranylethylphosphonate **4** was formed in a rather high yield (62%) (Scheme 1).

Scheme 1



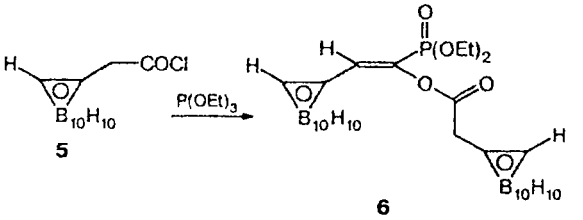
The structure of phosphonate **4** was established based on the ^1H, ^{13}C, and ^{31}P NMR spectral data.

It should be noted that, unlike mesylate **2**, analogous iodide $HCB_{10}H_{10}(CH_2)_2I$ reacted with $P(OEt)_3$ to give a mixture of vinylcarborane **3** and phosphonate **4** in a ~1 : 1 ratio (^1H NMR data).

Interaction of triethyl phosphite with carboranylacetyl chloride. We also studied the reaction of *o*-carboranylacetyl chloride with $P(OEt)_3$. Generally, the reactions of $P(OEt)_3$ with carboxylic acid chlorides give the corresponding acylphosphonates in high yields.[11]

However, the reaction of *o*-carboranylacetyl chloride with $P(OEt)_3$ afforded exclusively *O,O*-diethyl (*E*)-2-(*o*-carboran-1-yl)-1-(*o*-carboran-1-ylacetoxy)vinylphosphonate (Scheme 2).

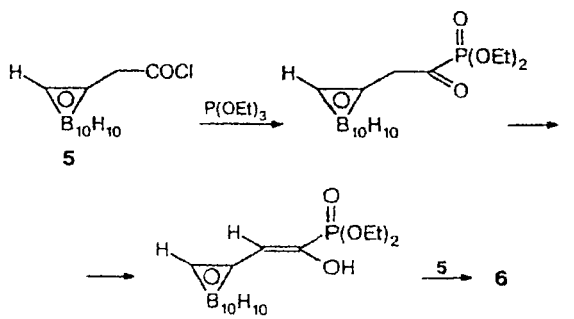
Scheme 2



The reaction is exothermic and proceeded at a high rate. Note that this reaction afforded exclusively product **6** with both 2 : 1 or 1 : 1 acid chloride **5** to $P(OEt)_3$ molar ratios.

The structure of compound **6** was established from the spectral data. The IR spectrum has absorption bands at 2590, 1716, and 1241 cm^{-1}, which correspond to the B—H, C=O, and P=O groups, respectively, and bands at 1154 and 1020 cm^{-1}, which are assigned to the P—O—Et group. The Raman spectrum has a band at 1662 cm^{-1} typical of C=C bonds. Unfortunately, the assignment of the signals in the ^{11}B NMR spectrum presents difficulties because of their overlapping. In the ^1H NMR spectrum, the signal of the vinyl proton at δ 6.27 occurs as a doublet with the constant J_{H-P} = 11 Hz, which confirms the *E* configuration of the resulting compound.[12] The formation of product **6** is attributable to enolization of oxo phosphonate followed by the reaction of enol with the second molecule of acid chloride. This result confirms once again the high tendency to formation of a double bond conjugated with the carborane substituent, which has been reported previously[10] (Scheme 3).

Scheme 3



To summarize, we studied the possibility of the synthesis of carborane-containing phosphonates starting from the corresponding electrophilic synthons.

Experimental

The reagents were purchased from Aldrich and Fluka and used without additional purification. Tetrahydrofuran was distilled over sodium benzophenone ketyl. Acetonitrile and dichloromethane were distilled over P_2O_5. Pyridine was distilled over NaOH. Acid chloride **5** was prepared according to a procedure reported previously.[13] The ^1H, ^{13}C, ^{11}B, and ^{31}P NMR spectra were recorded on a Bruker AMX-400 instrument operating at 400.13, 100.61, 128.2, and 161.98 MHz, respectively. The chemical shifts (the δ scale) are given relative to TMS (internal standard), $BF_3 \cdot OEt_2$, and H_3PO_4 (external standards). The IR spectra were recorded on a Specord M-80 instrument. The melting temperatures were measured in an open capillary.

But-3-ynyl methanesulfonate. A solution of MsCl (16 mL, 140 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of but-3-yn-1-ol (17 mL, 140 mmol) and Py (13 mL, 117 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 3 h. The reaction mixture was filtered off from a precipitate of pyridine hydrochloride and washed with water (2×50 mL). The aqueous extracts were extracted with CH_2Cl_2 (40 mL). The combined organic extracts were dried with Na_2SO_4. The solvent was evaporated. The residue was distilled *in vacuo* to give 14.9 g (85%) of the title compound, b.p. 84 °C (0.5 Torr). ^1H NMR ($CDCl_3$), δ: 4.27 (t, 2 H, O—CH_2, J = 6.1 Hz); 3.03 (s, 3 H, CH_3—S); 2.61 (dt, 2 H, CH_2—C≡CH, J = 2.6, 6.1 Hz); 2.05 (t, 1 H, HC≡C, J = 2.6 Hz). Found (%): C, 40.42; H, 5.53; S, 21.72; $C_5H_8O_3S$. Calculated (%): C, 40.53; H, 5.44; S, 21.64.

Prop-2-ynyl methanesulfonate was prepared analogously. The yield was 82%, b.p. 76 °C (0.5 Torr). ^1H NMR ($CDCl_3$), δ: 4.77 (d, 2 H, CH_2—O, J = 3.6 Hz); 3.09 (s, 1 H, CH_3—S); 2.78 (t, 1 H, C≡CH, J = 3.6 Hz). Found (%): C, 35.65; H, 4.52; S, 24.01. $C_4H_6O_3S$. Calculated (%): C, 35.81; H, 4.51; S, 23.90.

2-Methanesulfonyloxyethyl-*o*-carborane (2). MeCN (5.7 mL, 110 mmol) was added to a solution of decaborane (6.8 g, 55 mmol) in benzene (150 mL). The resulting solution was purged with argon and heated to boiling. Then a solution of but-3-ynyl mesylate (7.5 g, 50 mmol) in benzene was added. The reaction mixture was boiled for 20 h until liberation of hydrogen ceased. The resulting solution was passed through a column with silica gel. The solvent was evaporated *in vacuo*. A colorless crystalline compound was obtained in a yield of 5.8 g (42%), m.p. 89 °C. Found (%): C, 22.34; H, 6.72; B, 40.54; S, 12.11. $C_5H_{18}B_{10}O_3S$. Calculated (%): C, 22.55; H, 6.81; B, 40.58; S, 12.04. ^1H NMR ($CDCl_3$), δ: 4.30 (t, 2 H, OCH_2, J = 6.3 Hz); 3.71 (s, 1 H, CH of carborane); 3.05 (s, 3 H, CH_3SO_2); 2.69 (t, 2 H, CH_2—carborane, J = 6.3 Hz); 0.5—3.9 (m, 10 H, B—H). ^{13}C NMR ($CDCl_3$), δ: 70.8 ($\underline{C}$—CH_2); 66.0 (CH_2—O); 60.6 (CH of carborane); 37.7 (CH_3—S); 37.2 (CH_2—carborane). ^{11}B NMR ($CDCl_3$), δ: −2.3 (1 B), −4.4 (1 B), −9.5 (2 B), −12.2 (2 B), −13.0 (4 B).

Methanesulfonyloxymethyl-*o*-carborane (1) was prepared analogously. The yield was 45%, m.p. 56 °C. Found (%): C, 18.9; H, 6.29; B, 42.72; S, 12.55. $C_4H_{16}B_{10}O_3S$. Calculated (%): C, 19.04; H, 6.39; B, 42.84; S, 12.71. ^1H NMR ($CDCl_3$), δ: 4.59 (s, 2 H, $\underline{CH_2}$OS); 3.89 (s, 1 H, CH of carborane); 3.09 (s, 3 H, CH_3S); 0.5—4.0 (m, 10 H, BH). ^{11}B NMR ($CDCl_3$), δ: −2.2 (1 B), −5.6 (1 B), −9.6 (2 B), −12.8 (4 B), −13.2 (2 B).

Reaction of sodium diethyl phosphite with 2-methanesulfonyloxyethyl-*o*-carborane (2). Sulfonate **2** (0.54 g, 2.06 mmol) was added to sodium diethyl phosphite prepared by the reaction of sodium (0.0523 g, 2.27 g-at.) and $HOP(OEt)_2$ (0.29 mL, 2.27 mmol). The reaction mixture was boiled for 3 h. The solvent was evaporated. The residue was recrystallized from hexane. Vinyl-*o*-carborane **3** was obtained in a yield of 0.32 g as white crystals. M.p. 76 °C (*cf.* Ref. 14: 76—77 °C). ^1H NMR ($CDCl_3$), δ: 5.90, 5.62, 5.44 (3 H, ABX system, CH_2=CH).

***O,O*-Diethyl 2-(*o*-carboran-1-yl)ethylphosphonate (4).** A mixture of sulfonate **2** (4 g, 14.9 mmol) and $P(OEt)_3$ (2.55 mL, 14.9 mmol) was heated at 160 °C for 32 h. One equivalent of $P(OEt)_3$ (14.9 mmol) was added to the reaction mixture every 8 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and then hexane was added. The product that precipitated was filtered off and dried in air. A resinous compound was obtained in a yield of 2.86 g (62%). Found (%): C, 31.07; H, 8.05; B, 35.16; P, 9.92. $C_8H_{25}B_{10}O_3P$. Calculated (%): C, 31.16; H, 8.17; B, 35.06; P, 10.04. ^1H NMR ($CDCl_3$), δ: 4.13 (m, 4 H, 2 CH_2—O); 3.65 (s, 1 H, CH of carborane); 1.75 (m, 2 H, CH_2—P); 2.51 (m, 2 H, CH_2—carborane); 1.35 (m, 6 H, 2 $\underline{CH_3}$). ^{13}C NMR ($CDCl_3$), δ: 62.3 (O—CH_2); 61.5 (CH of carborane); 31.4 ($\underline{C}H_2$—CH_2—P); 26.0 (CH_2—P); 16.2 (O—CH_2—$\underline{C}H_3$). ^{11}B NMR ($CDCl_3$), δ: −2.5 (1 B), −5.8 (1 B), −9.6 (2 B), −12.5 (4 B), −13.1 (2 B).

2-Iodoethyl-*o*-carborane. A solution of sodium iodide (1.5 g, 8 mmol) in MeCN was added to a solution of sulfonate **2** (2.0 g, 7.5 mmol) in MeCN (75 mL). The resulting solution was boiled for 8 h. The precipitate that formed was filtered off and washed with CH_2Cl_2. The combined filtrates were concentrated. The residue was recrystallized from heptane. A colorless crystalline compound was obtained in a yield of 1.87 g (85%), m.p. 131.5 °C (*cf.* Ref. 15: 130.5—131 °C). Found (%): C, 16.05; H, 5.11; B, 36.15; I, 42.53. $C_4H_{15}B_{10}I$. Calculated (%): C, 16.11; H, 5.07; B, 36.25; I, 42.56. ^1H NMR ($CDCl_3$), δ: 3.62 (s, 1 H, CH of carborane); 3.15 (t, 2 H, CH_2I, J = 7.4 Hz); 2.73 (t, 2 H, CH_2—carborane, J = 7.4 Hz); 4.1—3.6 (m, 10 H, B—H). ^{11}B NMR ($CDCl_3$), δ: −2.5 (1 B), −5.6 (1 B), −9.6 (2 B), −12.8 (4 B), −13.1 (2 B).

Reaction of triethyl phosphite with 2-iodoethyl-*o*-carborane. A mixture of 2-iodoethyl-*o*-carborane (1.55 g, 5.2 mmol) and $P(OEt)_3$ (3.1 mL, 18.5 mmol) was heated on an oil bath at 160 °C for 12 h. Then an excess of $P(OEt)_3$ was evaporated *in vacuo*. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. It was established that the reaction afforded a mixture of vinylcarborane and *O,O*-diethyl 2-(*o*-carboranyl)ethylphosphonate in a ratio of ~1 : 1.

***O,O*-Diethyl (*E*)-2-(*o*-carboran-1-yl)-1-(*o*-carboran-1-ylacetoxy)vinylphosphonate (6).** Acid chloride **5** (2.8 g, 12.6 mmol) was added portionwise to $P(OEt)_3$ (1.1 mL, 6.3 mmol) over 30 min. The reaction mixture was stirred for 1 h. The mixture crystallized out. The product was recrystallized from hexane. A colorless crystalline compound was obtained in a yield of 2.6 g (84%), m.p. 86 °C. Found (%): C, 28.79; H, 7.23; B, 43.03; P, 6.09. $C_{12}H_{35}B_{20}O_5P$. Calculated (%): C, 28.45; H, 6.96; B, 42.68; P, 6.11. ^1H NMR ($CDCl_3$), δ: 1.34 (td, 6 H, 2 CH_3, J_{CH} = 7.1, J_{P-H} = 0.7 Hz); 4.13 (m, 4 H, 2 CH_2O); 3.45 (s, 2 H, CH_2CO); 3.76 and 4.50 (both s, 2 H, CH of carborane); 6.27 (d, 1 H, CH=CP, $J_{H,P}$ = 11 Hz); −0.5—4.0 (m, 20 H, BH). ^{13}C NMR

($CDCl_3$), δ: 16.1 (CH_3); 63.7 (CH_2O); 40.7 ($\underline{C}H_2CO$); 58.9, 66.5, 60.8, 67.1 (all C of carborane); 164.1 (C=O); 127.7 ($\underline{C}H$=CP, J_{C-P} = 29 Hz); 143.9 (CH=$\underline{C}$P, J_{C-P} = 218 Hz). ^{31}P NMR ($CDCl_3$), δ: 5.7.

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