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I.P. Beletskaya on Her Jubilee

Reactivity of 1-Bromomethyl-2-lithio-*o*-carborane and Syntheses Based Thereon

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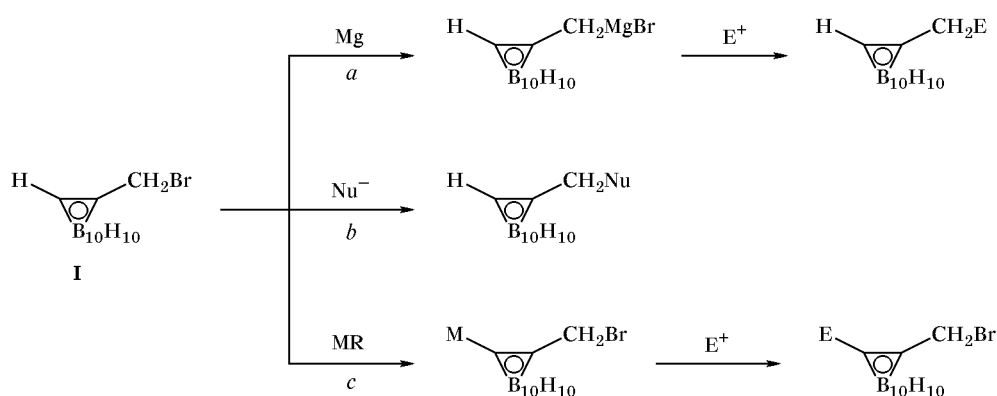
Abstract—1-Bromomethyl-*o*-carborane reacts at low temperature with lithium diisopropylamide to form 1-bromomethyl-2-lithio-*o*-carborane in quantitative yield. Reactions of the latter with various electrophiles give disubstituted carboranes in good yields.

Despite the fact that the chemistry of carboranes exists as long as 40 years, problems concerning their organic reactions remain urgent. Of specific interest are syntheses of carboranes having various functional groups. 1-Bromomethyl-*o*-carborane (**I**) is one of the most readily accessible derivatives of this series [1]. Three ways of its further modification are known (Scheme 1). Pathway *a* includes synthesis of the corresponding Grignard compound, followed by reaction with electrophiles. This route makes it possible to obtain various polyfunctional derivatives, e.g., carboxylic acids [2], nitriles [3], and phosphines [4]. Pathway *b* implies nucleophilic replacement of the bromine atom. The scope of application of this way of functionalization of carborane **I** is limited, for the *o*-carboranyl substituent exerts a strong negative inductive effect on the methylene group [5]. Only the

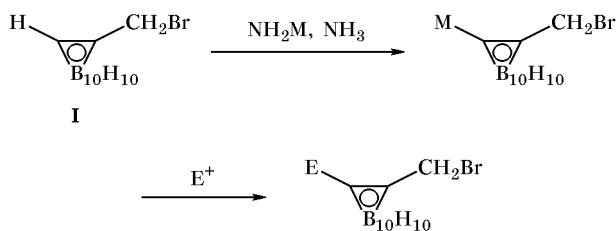
reaction of **I** with 3-cyanopyridinethiones leads to formation of substitution products in good yields [6].

The most interesting is pathway *c* which involves metalation of the CH group. It opens the way to carboranes having various active functional groups. However, only a few examples of such reactions have been reported. According to Zakharkin *et al.* [2], reactions of carborane **I** with organolithium and organomagnesium compounds lead to formation of mixtures of products. Successful selective metalation of the CH group was effected with the use of alkali and alkaline-earth metal amides in liquid ammonia [7, 8] (Scheme 2). On the other hand, only a limited set of electrophiles can be involved in the proposed procedure, and the yields are generally low. Moreover, our attempts to synthesize 1-bromomethyl-2-methyl-*o*-carborane (M = Na, E = MeI) from compound **I**

Scheme 1.



Scheme 2.

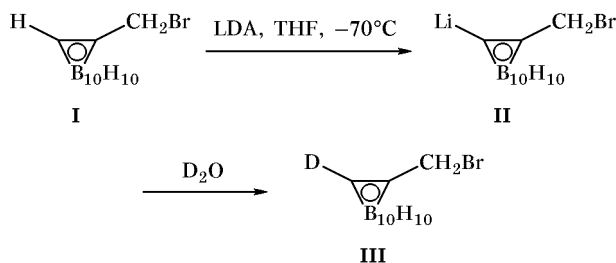


M = Li, Na, K, Ca; E = alkyl halides, carbonyl compounds.

resulted in formation of mixtures of products, and the yield of the target product was 26 rather than 68% as reported in [7].

We were the first to examine the reaction of 1-bromomethyl-*o*-carborane (**I**) with lithium diisopropylamide (LDA). Compound **I** reacted with LDA in THF at -70°C to give 1-bromomethyl-2-lithio-*o*-carborane (**II**) as the only product. Treatment of **II** with deuterium oxide at -70°C afforded 1-bromomethyl-2-deutero-*o*-carborane (**III**) in quantitative yield (Scheme 3).

Scheme 3.

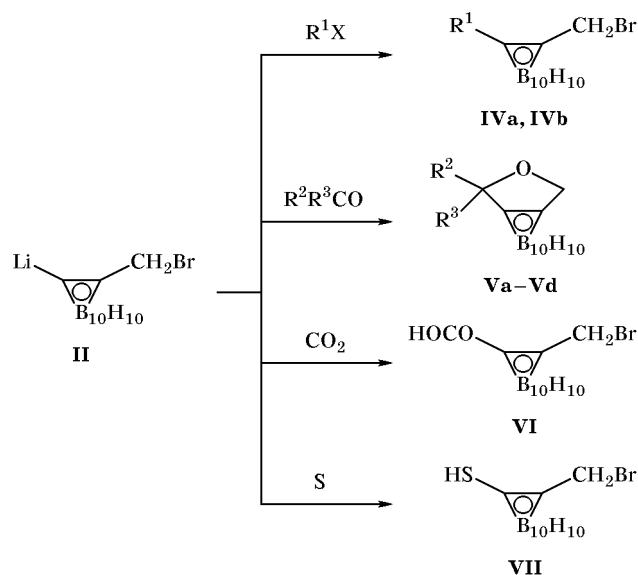


According to the ^1H NMR data, the degree of H–D exchange in the CH group is 95% (D_2O contained 97% of deuterium). This means that the reaction of **I** with LDA occurs with high regioselectivity and that the conversion is almost 100%.

We studied reactions of lithium derivative **II** with various electrophiles (Scheme 4). Reactions of **II** with such alkyl halides as methyl iodide and benzyl bromide gave the corresponding 1-bromomethyl-2-alkyl-*o*-carboranes in 75–82% yield. With less active alkyl halides, e.g., ethyl bromide, butyl bromide, etc., the reaction is slower. The structure of products **IVa** and **IVb** was confirmed by the ^1H and ^{13}C NMR spectra (see Experimental). Compound **II** reacted with carbonyl compounds (aldehydes and ketones) to give cyclic ethers **Va–Vd** rather than alcohols. Depending on the R^2 and R^3 substituents, the yields of ethers **V** were 52–90%. Their cyclic structure was proved by the ^1H NMR and IR data. The ^1H NMR spectra of

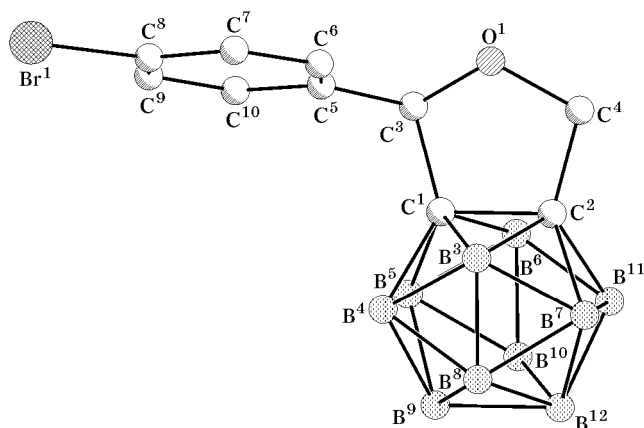
Va–Vd contain no signal assignable to hydroxy proton. Compounds **Va** and **Vb** show in the ^1H NMR spectra signals from two nonequivalent vicinal protons. Such signals are typical of substituted dihydrofurans having a chiral carbon atom in position 2 (doublet of doublets at δ 4.4 and 4.5 ppm, $J \approx 8.2$ Hz). The IR spectra of **Va–Vd** lack absorption bands in the region $3650\text{--}3200\text{ cm}^{-1}$, which is characteristic of stretching vibrations of hydroxy group. These data also support the cyclic structure of compounds **V**.

Scheme 4.



IV, $\text{R}^1 = \text{Me}$, X = I (**a**); $\text{R}^1 = \text{CH}_2\text{Ph}$, X = Br (**b**); **V**, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{H}$ (**a**); $\text{R}^2 = 4\text{-BrC}_6\text{H}_4$, $\text{R}^3 = \text{H}$ (**b**); $\text{R}^2 = \text{R}^3 = \text{Ph}$ (**c**); $\text{R}^2\text{R}^3 = (\text{CH}_2)_5$ (**d**).

The crystalline structure of compound **Vb** was studied by the X-ray diffraction method. It thus became the first representative of 3,4-(*o*-carborano)-dihydrofurans characterized by structural data. A unit cell of **Vb** contains two independent molecules differing by the angle of rotation of the phenyl group relative to the five-membered ring. The main geometric parameters of molecule **Vb** (see figure) approach expected values. The dihydrofuran ring has an *envelope* conformation with the oxygen atom (O^1) deviating by ~ 0.40 Å from the plane formed by the other ring atoms. The dihedral angles between the planes of the envelope base and phenyl ring are 74 and 69° for the two independent molecules. It is surprising that the $\text{C}^1\text{--C}^2$ bond in the polyhedron is considerably shorter than might be expected, $1.578(8)\text{--}1.587(8)$ Å. This shortening cannot be explained by the presence of fused five-membered

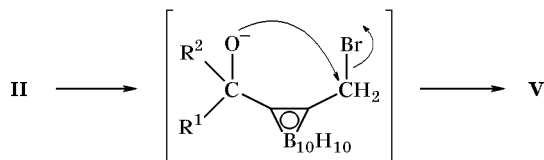


Structure of the molecule of 2-(4-bromophenyl)-3,4-(*o*-carborano)-2,5-dihydrofuran.

ring, for the corresponding bonds in structurally related 5-methyl-1,2-dicarbadodecaboracyclopentan-3-ol [9] and 1-phenyl-3,4-(*o*-carborano)dihydrophosphole [10] are much longer, ~ 1.630 and 1.655 Å, respectively. Analysis of the crystal packing showed that all intermolecular distances correspond to usual van der Waals contacts.

Presumably, cyclic products are formed via intramolecular nucleophilic substitution of the bromine atom in intermediate alkoxide (Scheme 5).

Scheme 5.



According to published data, nucleophilic substitution of bromine in 1-bromomethyl-*o*-carborane by the action of alkoxides usually does not occur. Probably, in our case the process is facilitated due to its intramolecular character.

The reaction of lithium derivative **II** with carbon dioxide afforded previously unknown 2-bromomethyl-*o*-carboranecarboxylic acid (**VI**). Its ^1H NMR spectrum contains a signal at δ 8.31 ppm from the acid proton, and in the ^{13}C NMR spectrum a signal from the carbonyl carbon atom is present at δ_{C} 163.4 ppm. Finally, compound **II** reacted with elemental sulfur to give 2-bromomethyl-*o*-carboranethiol (**VII**). Newly synthesized compounds **VI** and **VII** are among the first representatives of poorly known difunctional carboranes.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of solutions in CDCl_3 were recorded on a Bruker AMX-400 spectrometer at 400.13 and 100.61 MHz, respectively. The chemical shifts were measured relative to tetramethylsilane or deuterated solvent as internal reference. The IR spectra were measured on a Specord M80 instrument. The melting points were determined in an open capillary. All reactions, except for the synthesis of **Vb**, were carried out under argon. Butyllithium (a 1.6 N solution) from Merck and 4-bromobenzaldehyde from Lancaster were used; diethyl ether and tetrahydrofuran were distilled over sodium diphenylketyl.

1-Bromomethyl-2-lithio-*o*-carborane (II). A solution of 1.51 g (6.36 mmol) of 1-bromomethyl-*o*-carborane (**I**) in 5 ml of THF was added dropwise at -75°C to a solution of lithium diisopropylamide in THF (prepared from 4.3 ml of a 1.6 M solution of butyllithium in hexane and 0.91 ml of diisopropylamine in 10 ml of THF). The mixture was stirred for 1 h at -75°C . Product **II** separated from the solution.

1-Bromomethyl-2-methyl-*o*-carborane (IVa) was synthesized from equimolar amounts of compound **II** and methyl iodide (0.43 ml, 7.00 mmol). The mixture was poured into hydrochloric acid under stirring, and the product was extracted with several portions of diethyl ether. The combined extracts were dried over sodium sulfate and evaporated, and the residue was recrystallized from cold hexane. Yield 1.22 g (75%), mp $124\text{--}125^\circ\text{C}$; published data [8]: mp $125\text{--}127^\circ\text{C}$. ^1H NMR spectrum, δ , ppm: 2.08 s (3H, CH_3), 1.5–3.2 m (10H, BH), 3.99 s (2H, CH_2Br). ^{13}C NMR spectrum, δ_{C} , ppm: 22.9 (CH_3), 29.8 (CH_2Br), 74.8 and 77.4 (C_{carb}). Found, %: C 18.98; H 6.01. $\text{C}_4\text{H}_{15}\text{B}_{10}\text{Br}$. Calculated, %: C 19.13; H 6.02.

1-Benzyl-2-bromomethyl-*o*-carborane (IVb) was synthesized from equimolar amounts of compound **II** and benzyl bromide (0.8 ml, 7.00 mmol). Yield 1.71 g (82%), mp $69\text{--}70^\circ\text{C}$. ^1H NMR spectrum, δ , ppm: 1.5–3.2 m (10H, BH), 3.51 s (2H, CH_2Ph), 4.11 s (2H, CH_2Br), 7.21 and 7.34 m (5H, Ph). ^{13}C NMR spectrum, δ_{C} , ppm: 30.3 (CH_2Br), 40.8 (CH_2Ph), 76.5 and 79.2 (C_{carb}), 128.2 (C^4), 128.6 (C^3 , C^5), 130.2 (C^2 , C^6), 134.4 (C^1). Found, %: C 34.49; H 5.46. $\text{C}_{10}\text{H}_{19}\text{B}_{10}\text{Br}$. Calculated, %: C 34.51; H 5.47.

2-Phenyl-3,4-(*o*-carborano)-2,5-dihydrofuran (Va) was synthesized from equimolar amounts of compound **II** and benzaldehyde (0.76 ml, 7.25 mmol). Yield 1.45 g (80%), mp $90\text{--}92^\circ\text{C}$; published data [8]: mp $123\text{--}125^\circ\text{C}$. ^1H NMR spectrum, δ , ppm: 1.5–

3.0 m (10H, BH), 4.40–4.50 d.d (2H, CH₂O, $J = -8.2$ Hz), 5.55 s (1H, PhCH), 7.30 m and 7.38 m (5H, Ph). ¹³C NMR spectrum, δ_C , ppm: 73.1 (CH₂O), 78.6 and 83.1 (C_{carb}), 84.15 (CHO), 125.7 (C⁴), 128.4 (C³, C⁵), 129 (C², C⁶), 135.1 (C¹). Found, %: C 45.67; H 6.90. C₁₀H₁₈B₁₀O. Calculated, %: C 45.78; H 6.92.

2-(4-Bromophenyl)-3,4-(*o*-carborano)-2,5-dihydrofuran (Vb) was synthesized from equimolar amounts of compound **II** and 4-bromobenzaldehyde (9.7 g, 52.5 mmol). Yield 15.41 g (90%), mp 148°C. ¹H NMR spectrum, δ , ppm: 1.5–3.0 m (10H, BH), 4.41–4.49 d.d (2H, CH₂O, $J = -8.2$ Hz), 5.51 s (1H, CHO), 7.20 d.d and 7.53 d.d (4H, H_{arom}, $J = 8.1$, 8.4 Hz). ¹³C NMR spectrum, δ_C , ppm: 73.1 (CH₂O), 78.5 and 82.5 (C_{carb}), 83.5 (CHO), 123.3 (C⁴), 127.2 (C³, C⁵), 131.8 (C², C⁶), 134.1 (C¹). IR spectrum (mineral oil), ν , cm⁻¹: 1600 (C=C_{arom}); 2542, 2567, 2595 (BH). Found, %: C 35.17; H 5.01. C₁₀H₁₇B₁₀BrO. Calculated, %: C 35.20; H 5.02.

2,2-Diphenyl-3,4-(*o*-carborano)-2,5-dihydrofuran (Vc) was obtained from equimolar amounts of compound **II** and benzophenone (1.31 g, 7.10 mmol). Yield 1.22 g (52%), mp 208°C. ¹H NMR spectrum, δ , ppm: 1.5–3.0 m (10H, BH), 4.41 s (2H, CH₂O), 7.25–7.33 d.t and 7.67 d (10H, H_{arom}). ¹³C NMR spectrum, δ_C , ppm: 70.8 (CH₂O), 80.7 and 87 (C_{carb}), 89.5 (CHO), 125.5 (C⁴), 127.9 (C³, C⁵), 128.3 (C², C⁶), 141.8 (C¹). IR spectrum (mineral oil), ν , cm⁻¹: 1590, 1600 (C=C_{arom}); 2575, 2590, 2620 (BH). Found, %: C 56.68; H 6.52. C₁₆H₂₂B₁₀O. Calculated, %: C 56.78; H 6.55.

2,2-Pentamethylene-3,4-(*o*-carborano)-2,5-dihydrofuran (Vd) was synthesized from equimolar amounts of compound **II** and cyclohexanone (0.65 ml, 6.72 mmol). The product was recrystallized from hexane. Yield 1.21 g (73%), mp 75–77°C; published data [8]: mp 76–77°C. ¹H NMR spectrum, δ , ppm: 1.5–3.0 m (10H, BH), 1.52 m (2H, CH₂CH₂CH₂C), 1.64 m (4H, CH₂CH₂C), 2.07 m (4H, CH₂C), 4.12 s (2H, CH₂O). ¹³C NMR spectrum, δ_C , ppm: 22.8 (CH₂CH₂CH₂C), 24.7 (CH₂CH₂C), 36.5 (CH₂C), 71.1 (CH₂O), 79.3 and 83.9 (C_{carb}), 87.1 (CHO). IR spectrum (mineral oil), ν , cm⁻¹: 2595, 2650 (BH). Found, %: C 42.47; H 8.62. C₉H₂₂B₁₀O. Calculated, %: C 42.50; H 8.72.

2-Bromomethyl-*o*-carborane-1-carboxylic acid (VI) was synthesized from equimolar amounts of compound **II** and carbon dioxide. Yield 1.35 g (76%). ¹H NMR spectrum, δ , ppm: 1.5–3.2 m (10H, BH),

4.18 s (2H, CH₂Br), 8.31 s (1H, COOH). ¹³C NMR spectrum, δ_C , ppm: 30.6 (CH₂Br), 72.1 and 77.3 (C_{carb}), 163.4 (COOH). Found, %: C 17.04; H 4.66. C₄H₁₃B₁₀BrO₂. Calculated, %: C 17.09; H 4.66.

2-Bromomethyl-*o*-carborane-1-thiol (VII) was synthesized from equimolar amounts of compound **II** and elemental sulfur (0.22 g, 6.88 mmol). Yield 1.4 g (80%), mp 123–126°C. ¹H NMR spectrum, δ , ppm: 1.5–3.2 m (10H, BH), 3.73 s (1H, SH), 4.22 s (2H, CH₂Br). ¹³C NMR spectrum, δ_C , ppm: 29.9 (CH₂Br), 79.9 (C_{carb}CH₂Br), 75.5 (C_{carb}SH). Found, %: C 13.03; H 4.79; S 11.64. C₃H₁₃B₁₀BrS. Calculated, %: C 13.39; H 4.87; S 11.91.

X-Ray diffraction study of compound Vb. Monoclinic crystals, C₁₀H₁₇B₁₀BrO. Unit cell parameters (110 K): $a = 21.822(8)$, $b = 7.162(4)$, $c = 21.979(12)$ Å; $\beta = 113.718(9)^\circ$; $V = 3145(3)$ Å³; $Z = 8$; $M = 341.25$; $d_{\text{calc}} = 1.441$ g/cm³; space group $P2_1/n$; $\mu(\text{MoK}\alpha) = 26.01$ cm⁻¹; $F(000) = 1360$. Intensities of 16609 reflections were measured on a Smart 1000 CCD diffractometer at 110 K [$\lambda(\text{MoK}\alpha) = 0.71073$ Å], ω -scanning, step 0.3°, exposition 20 s, $2\theta < 54^\circ$]; 6762 independent reflections were used in the subsequent refinement. Absorption by the sample was taken into account semiempirically using equivalent reflections. The structure was solved by the direct method and was refined by the full-matrix least-squares method with respect to F^2 in anisotropic-isotropic approximation. The refinement led to a high value of the R factor (32%) because of twinning observed for all crystals of **Vb**. By taking a correction for twinning (TWIN 0 0 1 0 1 0 1 0 0), the R factor was considerably reduced, and hydrogen atoms were localized from the Fourier synthesis of electron density. The positions of hydrogen atoms in the carborane polyhedron were refined in the isotropic approximation, and the other hydrogen atoms were refined using the rider model. The final divergence factors were $wR_2 = 0.1160$ and $\text{GOF} = 1.105$ for all independent reflections [$R_1 = 0.0718$ was calculated from F for 3977 reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.1 software package.

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