A solvent-free regioselective iodination route of *ortho*-carboranes

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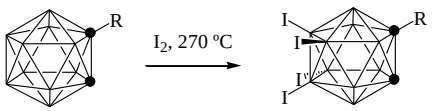
Tetraiodo-*ortho*-carborane based X-ray contrast agents can be readily produced in a high yield, fast, clean, regioselective fashion by a solvent-free reaction of *ortho*-carboranes with iodine in sealed tubes.

The quest for more efficient and environmentally friendly transformations is nowadays essential for the sustainability of chemical synthesis in the 21st century.[1] In this line, an excellent solution is the replacement of volatile organic solvents for alternative reaction media, mainly supercritical fluids, ionic liquids, water or absence of a solvent.[2] The latter option is the best known of them, widely employed in petrochemical industry with remarkable waste minimization.[2] Despite such advantages, only recent advances in solventless solid-state reactions are showing the ability to selectively produce high value substances, providing successful results in organic and organometallic synthesis.[3]

Highly iodinated molecular species receive great interest in medical applications[4] and materials science. Highly iodinated *ortho*-carboranes with metal-based X-ray contrast agents,[5] are called to be a new generation of advanced radiopaques for clinical purposes. They represent a great increase in iodine percentage by weight compared to the iodinated organic compounds used in X-ray contrast agents. Clean and effective synthetic methods are still the critical issue for the consideration of highly iodinated *ortho*-carboranes as promising candidates for X-ray diagnosis.[6]

ortho-Carborane, 1,2-$C_2B_{10}H_{12}$, and its derivatives, have been typically iodinated under electrophilic conditions, requiring the use of Lewis or Brönsted acid catalysts. Thus, three methods have been developed for the transformation of B-H vertices to B-I ones: i) elemental iodine in the presence of alumminum trichloride[7] or a mixture of acetic, nitric and sulfuric acids to yield diiodinated compounds,[8] ii) iodine monochloride and triflic acid to transfrom eight B-I vertices[6a] and recently, iii) a sequential combination of nucleophilic and electrophilic reactions to generate the highest boron iodinated *ortho*-carboranes: 3,4,5,7,8,9,10,11,12-I_9-*closo*-1,2-$C_2B_{10}H_3$ and 3,4,5,6,7,8,9,10,11,12-I_{10}-1,2-*closo*-$C_2B_{10}H_2$.[9] Their extremely high iodine content (around 90%), should make them of interest to build new high performance X-ray contrast agents, but complications in the synthetic route are still a problem.

This work aims at establishing new competitive preparations of polyiodinated *ortho*-carboranes in the absence of any solvent. Our strategy aims at exploring the reactivity of *ortho*-carboranes with I_2 under thermal treatment in sealed tubes, but in the absence of any strong acid, in order to attain cleaner and more practical pathways for neutral molecular inorganic X-ray contrast agents.



Scheme 1 General tetraiodination of 1-R-1,2-*closo*-$C_2B_{10}H_{11}$ by reaction with iodine in sealed tubes. For R = H, t = 4 h. For R = Me or Ph, t = 3.5 h.

Regioselectively tetraiodinated *ortho*-carborane 8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_8$ (**1**) was easily obtained in a solvent-less reaction just by heating 1,2-*closo*-$C_2B_{10}H_{12}$ with four equivalents of I_2 at 270±2 ºC for 24 hours in a sealed tube. After the reaction is complete, the Pyrex tube is opened and gaseous IH is immediately evaporated leaving a solid. The crude product contained *ca.* 25% of 8,9,12-I_3-1,2-*closo*-$C_2B_{10}H_9$ and 75% of 8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_8$, based on $^1H\{^{11}B\}$ NMR spectroscopy. Longer reaction times did not improve substantially this result. Experiments with higher iodine ratio were indeed much quicker and more selective; heating 1,2-*closo*-$C_2B_{10}H_{12}$, now with ten equivalents of I_2 at 270±2 ºC for 4 hours in a sealed tube produced a solid containing *ca.* 93% of 8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_8$, 2% of 8,9,12-I_3-1,2-*closo*-$C_2B_{10}H_9$ and 4% of higher iodinated *ortho*-carboranes. Almost all of the excess iodine, 95%, could be effectively recovered from the mixture by sublimation under reduced pressure as a crystalline solid, avoiding its quenching with sodium metabisulfite and allowing further re-utilisation. The residual solid was recrystallized from 1:1 ethanol/water, giving pure **1** in a high yield. The $^{11}B\{^1H\}$-NMR shows a pattern 2:2:4:2 in which the resonances at higher and lower field do not split in the ^{11}B-NMR

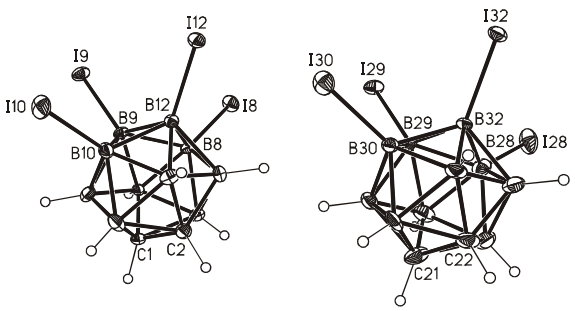


Fig. 1. Perspective view of the asymmetric unit of **1** with 30% ellipsoids. Selected bond lengths (Å): C(1)-C(2) 1.599(10), C(21) – C(22) 1.611(12), B-I 2.139(10) – 2.164(8) Å.

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confirming that four boron atoms have one *exocluster* iodine. The ^{1}H NMR spectrum of **1** reveals a singlet at 5.57 ppm. assigned to the two C-bonded H atoms, *ca*. 2 ppm. to high frequency relative to that in 1,2-*closo*-$C_2B_{10}H_{12}$, suggesting greater protonic character for these H atoms in the tetraiodo species. To confirm the structure of **1**, colourless crystals were grown by the slow evaporation of a hexane/dichloromethane solution and a single-crystal *X*-ray diffraction analysis[10] (Figure 1) was undertaken.

The synthesis of **1** had been reported in low yield by using chlorinated solvents and long workup procedures.[6b,11] Therefore the preparation and isolation of **1** described here is a much more convenient and efficient route.

To prove the versatility of the method, C-alkyl- and C-aryl- substituted *ortho*-carboranes were iodinated under similar conditions. Slightly shorter reaction times were needed for the same degree of substitution. After heating 1-R-1,2-*closo*-$C_2B_{10}H_{11}$ (R = Me, Ph) with I_2 at 270±2 ºC for 3.5 hours in a sealed tube, the corresponding 1-R-8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_7$ (R = Me, **2**; Ph, **3**) derivatives were selectively produced in high yields (>75%). It is noteworthy that in the iodination of 1-Ph-1,2-*closo*-$C_2B_{10}H_{11}$, only B-H vertices from the cluster have been activated, and in no case C-I substitution in the aromatic ring has been observed. These data have been obtained by ^{1}H or ^{13}C{^{1}H} NMR spectroscopy. To unambiguously prove such reactivity, good crystals of **3** were grown by slow evaporation of a hexane/dichloromethane solution and X-ray analysis was undertaken (Figure 2).[12]

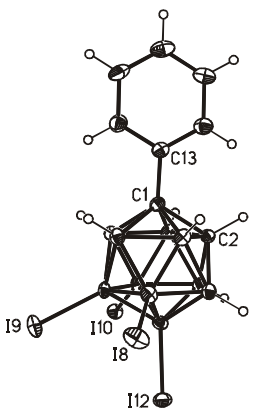

Fig. 2. Perspective view of **3** with 30% ellipsoids. Selected bond lengths (Å): C(1)-C(2) 1.659(9), C(1) – C(13) 1.501(9), B-I 2.147(7) – 2.155(7) Å.

The C-disubstituted counterparts, 1,2-R_2-1,2-*closo*-$C_2B_{10}H_{10}$ (R = Me, Ph) were iodinated in a parallel way and the crude products obtained were analysed by ESI-MS. The 1,2-Ph_2-1,2-*closo*-$C_2B_{10}H_{10}$ achieved tetraiodination rather selectively after 3.5 hours too, whereas the 1,2-Me_2-1,2-*closo*-$C_2B_{10}H_{10}$ showed to be more susceptible to electrophilic substitution and only 2.5 hours were enough for completion of the reaction. It agrees with the theoretical[13] and experimental results[14] reported by Lipscomb that electron donating methyl groups bonded to the $C_{cluster}$ atoms cause a rather uniform increase in electron density on the B atoms while keeping inalterable the sequence of substitution.

Once the feasibility of the method to selectively produce tetraiodinated *ortho*-carboranes has been proven, further experiments regarding temperature have been done to tune the degree of substitution. Increasing the temperature, and even the reaction time to several days, did not produce satisfactory results in terms of selectivity, as mixtures of highly iodinated *ortho*-carboranes were always generated. Nevertheless, by limiting the temperature to 170±2 ºC, a reagents mixture of 1,2-*closo*-$C_2B_{10}H_{12}$ and I_2 in 1:10 ratio produced after 4 hours in the oven a crude product containing 9,12-I_2-1,2-*closo*-$C_2B_{10}H_{10}$ (85%), 8,9-I_2-1,2-*closo*-$C_2B_{10}H_{10}$ (13%) and 8,9,12-I_3-1,2-*closo*-$C_2B_{10}H_9$ (2%), based on ^{1}H and ^{1}H{^{11}B} NMR spectroscopy.

As a conclusion, our targeted synthesis and processing of tetraiodinated *ortho*-carboranes with a solvent-free, high yield, fast, clean and regioselective method has been achieved. Additionally, the procedure does not require any futher solvent-based workup and excess of iodine is recovered and re-utilized. Work is now underway to study the reported iodinated compounds as X-ray contrast agents on methyl methacrylate poymerization for bone cements and as building blocks for supramolecular chemistry.

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10 Crystal data. **1**: $C_2H_8B_{10}I_4$, M = 647.78, monoclinic, space group $P2_1/c$ (no. 14), a = 15.0422(5), b = 14.8814(5), c = 14.3581(5) Å, β = 110.378(2)º, U = 3012.90(18) Å^3, Z = 8, D_c = 2.856 g cm^{-3}, μ(Mo-Kα) = 8.235 mm^{-1}, T = 173 K. F(000) = 2256. 18481 reflections measured, 6563 unique (R_{int} = 0.0581). $R1(F_o)$ = 0.0417 [$wR2(F_o^2)$ = 0.0855] with a goodness-of-fit of 1.049.

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12 Crystal data. **3**: $C_8H_{12}B_{10}I_4$, M = 723.88, monoclinic, space group $P2_1/n$ (no. 14), a = 10.0569(4), b = 15.2555(5), c = 13.0206(5) Å, β = 99.686(2)º, U = 1969.18(13) Å^3, Z = 4, D_c = 2.442 g cm^{-3}, μ(Mo-Kα) = 6.314 mm^{-1}, T = 173 K, F(000) = 1288. 11228 reflections measured, 4181 unique (R_{int} = 0.0432). $R1(F_o)$ = 0.0390 [$wR2(F_o^2)$ = 0.0744] with a goodness-of-fit of 1.053.

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