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

Albert Vaca,‡[a] Francesc Teixidor,[a] Raikko Kivekäs,[b] Reijo Sillanpää[c] and Clara Viñas*[a]

Received 29th August 2006, Accepted 6th September 2006
First published as an Advance Article on the web 15th September 2006
DOI: 10.1039/b612465h

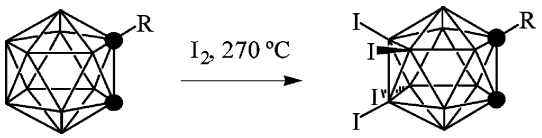
Tetraiodo-*ortho*-carborane based X-ray contrast agents can be readily prepared in a high yield, fast, clean, regioselective fashion by a solvent-free reaction of *ortho*-carboranes with iodine in sealed tubes.

Highly iodinated molecules have been of interest in materials science and medical applications[1] including the potential use of iodinated *ortho*-carboranes as next-generation radiopaque contrast agents for X-ray diagnostic imaging.[2] These compounds have a much greater proportion of iodine in the structures compared to the iodinated organic compounds currently used in X-ray contrast agents. However, clean and effective syntheses are still the critical issue for the consideration of highly iodinated *ortho*-carboranes as realistic candidates for X-ray contrast agents.[3]

ortho-Carborane, 1,2-$C_2B_{10}H_{12}$, and its derivatives, can be iodinated under electrophilic conditions using Lewis or Brønsted acid catalysts. Three methods have been developed for the transformation of B–H vertices to B–I ones: (i) elemental iodine in the presence of aluminium trichloride,[4] or a mixture of acetic, nitric and sulfuric acids to yield diiodinated compounds,[5] (ii) iodine monochloride and triflic acid to transform eight B–I vertices[3a] 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*-$C_2B_{10}H_2$.[6] Their extremely high iodine content (around 90%) makes these compounds of particular interest, but complications in the established syntheses of these compounds still presents problems.

The development of atom efficient, environmentally friendly transformations which generate minimal waste is essential in order to support sustainability of chemical synthesis through the 21st century.[7,8] Solvent-free synthesis is one approach which has shown value in organic and organometallic synthesis[9] for the selective preparation of high value materials, and as an effective means of waste minimization.

This work establishes new competitive syntheses of polyiodinated *ortho*-carboranes under solvent-free conditions. We have explored the reactivity of *ortho*-carboranes with I_2 under solvent-free conditions in the absence of strong acids at high temperature in sealed tubes (Scheme 1). The goal being to develop cleaner, more practical pathways to 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 °C for 24 h in a sealed tube. After the reaction is complete, the Pyrex™ tube was opened and gaseous HI removed by evaporation leaving the crude product as a solid which contained *ca.* 25% of 8,9,12-I_3-1,2-*closo*-$C_2B_{10}H_9$ and 75% of **1**, based on $^1H\{^{11}B\}$ NMR spectroscopy. Longer reaction times did not improve substantially this result. Increasing the iodine ratio led to greater reactivity and selectivity; heating 1,2-*closo*-$C_2B_{10}H_{12}$ with ten equivalents of I_2 at 270 ± 2 °C for 4 h in a sealed tube produced a solid containing 2% of 8,9,12-I_3-1,2-*closo*-$C_2B_{10}H_9$, *ca.* 93% of **1**, and 4% of higher iodinated *ortho*-carboranes. Almost all of the excess iodine (95%) could be recovered from the mixture by sublimation under reduced pressure avoiding the need for quenching with sodium metabisulfite and allowing further reuse of reagents. The remaining solid was recrystallized from 1 : 1 ethanol/water to give 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 confirming that the four iodine atoms are exocluster on four adjacent boron atoms. The ^1H NMR spectrum of **1** reveals a singlet at 5.57 ppm assigned to the two C-bonded H atoms. This signal is shifted to a higher frequency by *ca.* 1 ppm 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] (Fig. 1) was undertaken.

The synthesis of **1** had previously been reported as a low yield product 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 explore 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 compared to **1**. Heating 1-R-1,2-*closo*-$C_2B_{10}H_{11}$ (R= Me, Ph) with I_2 at 270 ± 2 °C for 3.5 h gave the corresponding 1-R-8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_7$ (R= Me, **2**; Ph, **3**) derivatives selectively in high yields (>75%). These were

[a]*I.C.M.A.B. (C.S.I.C.), Campus U.A.B., 08193, Bellaterra, Spain. E-mail: clara@icmab.es; Fax: +34 3580 5729; Tel: +34 3580 1853*
[b]*Department of Chemistry, P.O. Box 55, University of Helsinki, FIN-00014, Helsinki, Finland*
[c]*Department of Chemistry, University of Jyväskylä, FIN-40351, Jyväskylä, Finland*

† Electronic supplementary information (ESI) available: Synthesis and characterization of **1**–**5**. See DOI: 10.1039/b612465h

‡ Albert Vaca is enrolled in the PhD program of the UAB, Spain.

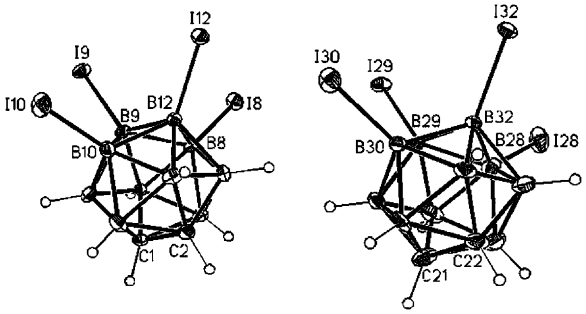


Fig. 1 Perspective view of the asymmetric unit of **1** with 30% ellipsoids. Selected bond lengths (Å): C(1)–C(2) 1.599(10), C(21)–C(22) 1.611(12), B–I 2.139(10)–2.164(8).

identified by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy and, for **3**, by X-ray analysis (Fig. 2) from crystals obtained by recrystallization from hexane/dichloromethane.[12] 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 has C–I substitution in the aromatic ring been observed.

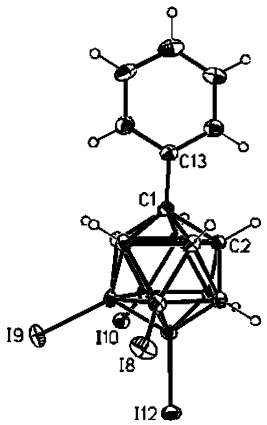


Fig. 2 Perspective view of **3** with 30% ellipsoids. Selected bond lengths (Å): C(1)–C(2) 1.659(9), C(1)–C(13) 1.501(9), B–I 2.147(7)–2.155(7).

The C-disubstituted counterparts, 1,2-R_2-1,2-*closo*-$C_2B_{10}H_{10}$ (R= Me, Ph) were iodinated in an analogous way and the crude products obtained were analysed by ESI-MS. 1,2-Ph_2-1,2-*closo*-$C_2B_{10}H_{10}$ underwent tetraiodination selectively after 3.5 h, whereas 1,2-Me_2-1,2-*closo*-$C_2B_{10}H_{10}$ was more susceptible to electrophilic substitution and only 2.5 h were required for completion of the reaction. This is consistent with both theoretical[13] and experimental results[14] reported by Lipscomb and co-workers which showed that the electron donating effect of methyl groups bonded to the $C_{cluster}$ atoms causes a uniform increase in electron density on the B atoms while having little, or no effect on the sequence of substitution.

Having proven that this solvent-free approach to the iodination of *ortho*-carboranes is feasible and appears to be fairly generic for the synthesis of tetraiodinated products, we set out to study whether the degree of substitution could be further tuned by controlling the reaction temperature. Increasing the temperature, and even the reaction time to several days, did not produce satisfactory results in terms of selectivity. In each system investigated, mixtures of highly iodinated *ortho*-carboranes were always generated. Nevertheless, when the temperature was reduced to 170 ± 2 °C, after 4 h, a reagent mixture of 1,2-*closo*-$C_2B_{10}H_{12}$ and I_2 in 1 : 10 ratio produced a crude product containing 9,12-I_2-1,2-*closo*-$C_2B_{10}H_{10}$ (*ca.* 85%), 8,9-I_2-1,2-*closo*-$C_2B_{10}H_{10}$ (*ca.* 13%) and 8,9,12-I_3-1,2-*closo*-$C_2B_{10}H_9$ (*ca.* 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 further solvent-based workup and an 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 polymerization for bone cements and as building blocks for supramolecular chemistry.

Notes and references

1 P. J. Ell and S. Gambhir, in *Nuclear Medicine in Clinical Diagnosis and Treatment*, 3rd edn, Churchill Livingstone, Oxford, UK, 2004.
2 (*a*) S.-B. Yu and A. D. Watson, *Chem. Rev.*, 1999, **99**, 2353.
3 (*a*) R. R. Srivastava, D. K. Hamlin and D. S. Wilbur, *J. Org. Chem.*, 1996, **61**, 9041; (*b*) *PCT Int. Appl.*, WO9526353, 1995; *Eur. Pat. Appl.*, EP0700918, 1996.
4 J. Li, C. F. Logan and M. Jones, Jr., *Inorg. Chem.*, 1991, **30**, 4866.
5 A. S. Batsanov, M. A. Fox, J. A. K. Howard, A. K. Hughes, A. L. Johnson and S. J. Martindale, *Acta Crystallogr., Sect. C*, 2003, **C59**, o74.
6 (*a*) G. Barberà, F. Teixidor, C. Viñas, R. Sillanpää and R. Kivekäs, *Eur. J. Inorg. Chem.*, 2003, 1511; (*b*) G. Barberà, F. Teixidor, C. Viñas, R. Sillanpää and R. Kivekäs, *Inorg. Chem.*, 2006, **45**, 3496.
7 (*a*) R. Noyori, *Chem. Commun.*, 2005, 1807; (*b*) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez and J. C. Palacios, *Angew. Chem., Int. Ed.*, 2006, **45**, 3904; (*c*) M. Jansen and J. C. Schön, *Angew. Chem., Int. Ed.*, 2006, **45**, 3406.
8 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792.
9 (*a*) G. Kaupp, *Top. Curr. Chem.*, 2005, **254**, 95; (*b*) K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; (*c*) G. W. V. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2001, 2159; (*d*) G. Rothenberg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am. Chem. Soc.*, 2001, **123**, 8701; (*e*) V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *Chem. Commun.*, 2002, 1606; (*f*) V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *J. Am. Chem. Soc.*, 2002, **124**, 6244.
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)°, 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. CCDC reference number 611426. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612465h.
11 L. I. Zakharkin, V. I. Stanko and A. I. Klimova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966, **11**, 1946.
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)°, 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. CCDC reference number 611427. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612465h.
13 (*a*) M. D. Newton, F. P. Boer and W. N. Lipscomb, *J. Am. Chem. Soc.*, 1966, **88**, 2353; (*b*) F. P. Boer, J. A. Potenza and W. N. Lipscomb, *Inorg. Chem.*, 1966, **5**, 1301.
14 J. A. Potenza and W. N. Lipscomb, *Inorg. Chem.*, 1966, **5**, 1483.