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Synthesis of Unsymmetrical C-disubstituted *para*-Carboranes: Access to Functionalized Carboranyl-boronic acid and Carboranol.

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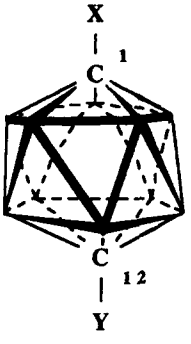
Abstract : After lithiation of *para*-carborane and subsequent reaction with diethyl phenyl orthoformate, the monoacetal **4** can be obtained in preparative yields; this was followed by a boration/hydroxylation sequence to yield C-disubstituted *p*-carborane derivatives. © 1997 Elsevier Science Ltd.

Carboranes [1] are useful building blocks in supramolecular chemistry [2,3] and these boron-rich icosahedra have also been attached to biomolecular vectors for boron neutron capture therapy to enable delivery of high boron concentrations to malignant cells.[4] Thus, there is a need for derivatization of carboranes and present work focusses on unsymmetrical difunctionalization of *para*-carborane **1**, for which a limited number of examples are known.[5]



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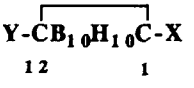
Symbolysed as : 

1 : X=Y=H
2 : Y=H (monofunctionalized)
3 : X ≠ Y (unsymmetrically difunctionalized)

The preparation of *para*-carborane derivatives of type **3** can be achieved by two successive substitutions (at C-1 then C-12), which requires an efficent monofunctionalization to be carried out as the first step. Unfortunately, for such a goal, the elegant procedures used for *ortho* -carborane [6] based on temporary shielding of one carbon with a bulky substituent, cannot be of help in the *para*- series; this is because in **1** the methines point out in opposite directions.[7] Since after metallation of *para*-carborane, the ratio of mono- *vs* di-substituted products (**2** : **3**) has been shown to strongly depend on the stoechiometry of the reaction partners, [8] experimental work was carried out to optimize the production of monosubstituted **2**, as detailed below.

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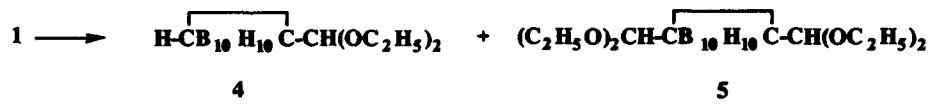
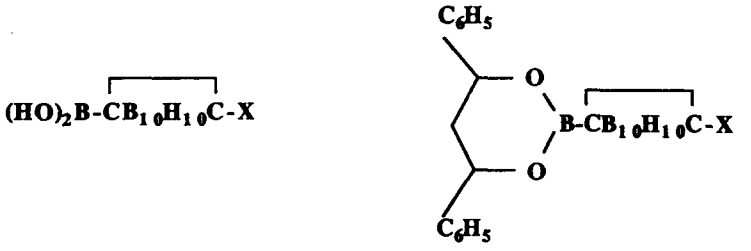
In view of its synthetic potential, the first functional group to be introduced on **1** was the formyl moiety; [9] its introduction under a protected form was preferred as this would allow metallation at the other carbon acidic site (C-12) without further manipulation. When **1** is treated with *n*-butyllithium then condensed with diethyl phenyl orthoformate according to literature, [10] a 1.3/1 ratio (**4**:**5**) is observed. This ratio could be raised to 2.1/1 (n.-BuLi 1.06 eq., formate 1.27 eq., 80°C, 10 hrs) but with **4** being obtained in low (26 %) yield. Conditions were then found [11] to isolate **4** in preparative yield (71 %), formation of the di-substituted product **5** having been minimized (8%), the ratio being now 9/1.



4 **5**

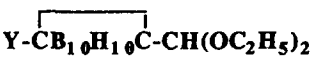
An efficient monofunctionalization of **1** having been achieved, the preparation of hitherto unknown *para*-carboranylboronic acid derivatives, [12] was considered. Thus **4** was lithiated and reacted with an excess of trimethyl borate to give **6** in 88 % yield [13] which could be quantitatively protected as boronate **7** by reaction with *d,l*-1,3-diphenylpropane-1,3-diol; [14] the aldehyde group could then be selectively unmasked (CF_3COOH - 95 %) to give **8**; similarly **9** (96 %) was obtained from **6**.

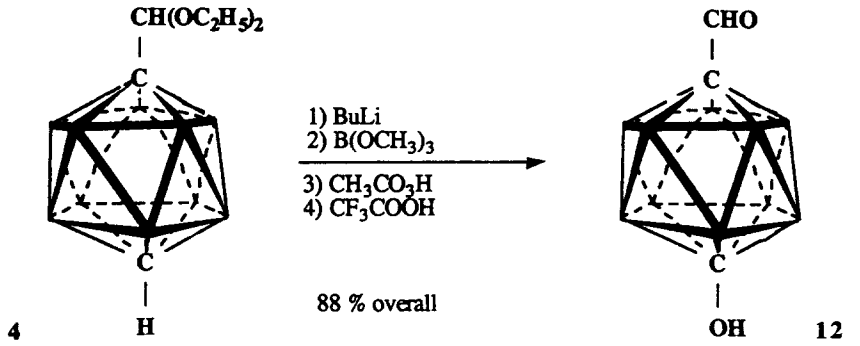


6 : X = $CH(OC_2H_5)_2$ **7** : X = $CH(OC_2H_5)_2$
9 : X = CHO **8** : X = CHO

No *para*-carboranol derivative has yet been prepared ; lithiation of **4**, followed by reaction with *t*–butyl peroxide or benzoyl peroxide [15] did not allow isolation of hydroxylation products. Quenching with freshly prepared trimethylsilylperoxide [16] gave **10** but in low (*ca.* 30 %) yield. To C-hydroxylate a *para*-carborane, [17] advantage was taken of the availability of **6** as the boration/hydroxylation sequence is a known preparation of phenols. [18] Thus **6** was oxidized with peracetic acid [19] which gave **11** (97%).[20]

10 : Y = $(CH_3)_3SiO$-
11 : Y = HO-





It was then found that the reaction sequences converting **4** to **11** could be carried out (91%) without isolation of intermediates. 1-Formyl *para*-carboranol **12** [21] was then obtained by acidic deprotection of **11** and the excellent overall yield obtained for the whole conversion (63 % from *para*-carborane **1**) makes **12** a suitable carborane building block for further synthetic elaborations.

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References and notes

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11) To a stirred solution of *para*-carborane (1.65g, 11.44 mmol) in dry C_6H_6 (20mL) was added dropwise a solution of *n*-BuLi (1.56M in hexane, 8.1mL, 12.64 mmol), under Ar at r.t. Stirring is pursued for 30 min. before the dropwise addn of diethyl phenyl orthoformate (3mL, 15.50 mmol). The reaction mixture was heated under Ar at 80°C for 36hrs and filtered after cooling, the residue being thoroughly washed with hexane.After evaporation to dryness of the filtrate, the residue obtained was chromatographed over deactivated neutral alumina (10% water w/w ; elution : cyclohexane/dichloromethane 9/1) to yield **4** (2.0g - 71%). m.p.=75°C (hexane); litt.(10): 74-75°C; ^{1}H NMR (300MHz, $CDCl_3$): 1.1 (t, J=7.5, 6H, CH_3); 1.2- 3.3 (M, $B_{10}H_{10}$); 2.7 (1 s, $\underline{H}CB_{10}H_{10}$); 3.3-3.4 and 3.5-3.6(2*m, 4H, CH_2); 4.01(s,1H,$C\underline{H}(OC_2H_5)_2$); ^{13}C NMR (75MHz, $CDCl_3$): 14.7 (CH_3); 60,8 ($HCB_{10}H_{10}$); 65,4 (CH_2); 87,2 ($B_{10}H_{10}\underline{C}$-$CH(OEt)_2$); 101.9 ($\underline{C}H(OC_2H_5)_2$); ^{10}B NMR (96.3MHz $CDCl_3$, ext. ref. : $BF_3{\cdot}Et_2O$ in $CDCl_3$): -13.9 (1 s); -15.6 (1 s). Elution with CH_2Cl_2 then afforded **5** (8 %) m.p.=80°C (hexane); litt.(10): 80-81°C.

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20) **11** was acetylated conventionally : ^{1}H NMR (300MHz, $CDCl_3$): 1.1 (t, J=6.9, 6H, $CH_2C\underline{H}_3$); 1.2-3.3 (M, $B_{10}H_{10}$); 1.9 (s, $COCH_3$); 3.3-3.4 and 3.5-3.6 (2*m, 4 H, CH_2); 4.14 (s, 1H, $C\underline{H}(OC_2H_5)_2$); ^{13}C NMR (75MHz, $CDCl_3$): 14.7 ($OCH_2\underline{C}H_3$); 21.1 ($CO\underline{C}H_3$); 65.5 ($O\underline{C}H_2CH_3$); 78.5 ($B_{10}H_{10}\underline{C}CH$); 101.2 (CH); 103.6 ($O\underline{C}B_{10}H_{10}$); 165.6 (C=O); ^{10}B NMR (96.3MHz, $CDCl_3$,external ref. : $BF_3{\cdot}Et_2O$ in $CDCl_3$): -14.0 (1 s); -16.2 (1 s).

21) The value observed in the ^{13}C-NMR spectrum (δ=109.9) for the carborane carbon attached to oxygen is in agreement with those observed for *ortho*-carboranol derivatives, see : Morin, C.; Ramburrun, M. *Curr. Topics Boron Chem.*, **1994**, 228-231.

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