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Dimethoxyethane as a Solvent for the Synthesis of C-Monosubstituted *o*-Carborane Derivatives

Clara Viñas,*,† Rajae Benakki,‡
Francesc Teixidor,† and Jaume Casabó‡

Institut de Ciència de Materials de Barcelona (CSIC) and
Departament de Química, Universitat Autonoma de
Barcelona, 08193 Bellaterra, Spain

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To synthesize new *o*-carborane-derived materials such as asymmetric macrocycles, compounds for boron–neutron capture therapy,[1] and asymmetric catalysts, monosubstituted precursors are required. Unfortunately there are not many methods available to prepare such compounds as was recently stressed.[2] The reaction of terminal alkynes with $B_{10}H_{12}L_2$ suffers from the scarcity of appropriate alkynes, and monolithiation of 1,2-$C_2B_{10}H_{12}$ at carbon competes unfavorably with dilithiation which leads to complex mixtures.

With the aim of getting a high-yield, reliable, one-pot, and comparatively inexpensive route to monosubstituted *o*-carborane derivatives, the following research was started. This paper discusses the results obtained as well as the advantages and difficulties of this procedure. Furthermore a plausible explanation of the mechanism is presented.

Results and Discussion

The synthesis of 1-SH-$C_2B_{10}H_{11}$ in almost a 100% yield was of utmost importance to our development of new materials containing thioether groups bonded to the carborane cluster. The synthesis of this compound has been reported[3] in aromatic solvents, but the conversion was found to be too low for our purposes. We expected that ether solvents would enhance the yield and would provide a more convenient reaction system. The main problem in this medium is the dilithiation of *o*-carborane rather than the desired monolithiation, leading to disubstituted compounds. This problem was recently solved by blocking one of the C-positions[2] in *o*-carborane with a $-Si(Me)_2CMe_3$ (TBDMS) group; effecting the desired reaction in the other C site; and subsequently deprotecting the original C-position with *n*-Bu_4NF.

Several attempts to synthesize 1-SH-2-TBDMS-1,2-$C_2B_{10}H_{10}$ by treatment of 1-TBDMS-1,2-$C_2B_{10}H_{11}$ with BuLi and S in diethyl ether were unsuccessful, yielding only the starting material. The recovery of reagents and thus the lack of reaction were considered the consequence of steric crowding in the neighborhood of the reactive nucleophilic carbon.

It is well-known that crown ethers have been developed for Li and other alkali metal coordination, most of them containing $-OCH_2CH_2O-$ units.[4] A similar Li or Na coordination sphere could be obtained if a chelating solvent containing this unit, e.g. dimethoxyethane, $CH_3OCH_2CH_2OCH_3$ (dme), is present in solution. In this way, dilithiation could be prevented because of the steric constraints caused by the bulky Li(dme) moiety. The postulated monolithiated compound is shown in Figure 1.

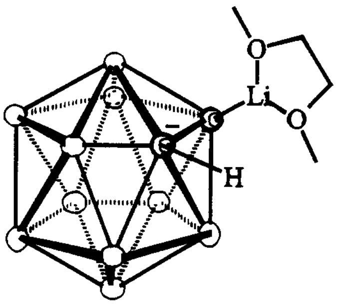

Figure 1. Proposed monolithiated compound in dimethoxyethane.

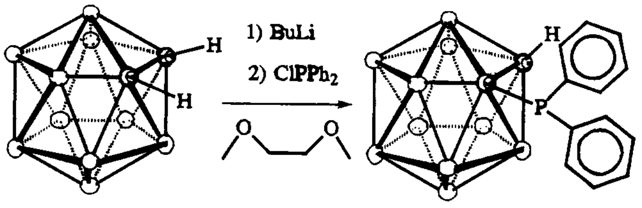

Figure 2. Reaction leading to the Ph_2P-monosubstituted *o*-carborane derivative.

The reaction of 1 equiv of *o*-carborane with 1 equiv of BuLi in dimethoxyethane is presumed to give only 1-Li-1,2-$C_2B_{10}H_{11}$. Upon reaction of this compound with sulfur powder, or suitable X–R compounds, $BrCH_2Ph$, $ClPPh_2$, and $Br(CH_2)_3CH_3$, monosubstituted 1-R-1,2-$C_2B_{10}H_{11}$ compounds are obtained in high to very high yields. Figure 2 describes the reaction with $ClPPh_2$.

The nature of the resulting compounds has been assigned by ^{11}B-NMR comparison with authentic samples. Yields of the desired monosubstituted compounds are in the range 76–91% based on the starting *o*-carborane. In addition, a minor amount of the disubstituted species is usually formed, except in the case of $Br(CH_2)_3CH_3$, where the disubstituted compound is found in 30% yield. Normally about 5% *o*-carborane is recovered unreacted.

We believe higher glymes, e.g. $H_3COCH_2CH_2OCH_2CH_2OCH_3$, may not be as favorable for monolithiation due to the higher chelating capacity of such ethers which might even favor dilithiation.

Dimethoxyethane has been previously used in C-arylation and C-heteroarylation of icosahedral carboranes via their copper(I) derivatives. Monosubstitution of *o*-carborane was achieved,[5] e.g. for 1-(3-$NO_2C_6H_4$)-1,2-$C_2B_{10}H_{11}$ and 1-(4-$NO_2C_6H_4$)-1,2-$C_2B_{10}H_{11}$, though the reagent ratio to diarylation was used. The chelating capacity of dimethoxyethane can explain the observed monosubstitution in these cases too. We consider that the effect of oxygen chelating solvents in promoting monosubstitution is very strong for Li and Na and maybe even for larger alkaline metal ions. In fact, the synthesis of 1-SH-1,2-$C_2B_{10}H_{11}$ from NaH and 1,2-$C_2B_{10}H_{12}$ in dimethoxyethane has previously been reported[6] although in a lower yield than that reported here. Although dme can be considered of quite general use for monosubstitution, some exceptions have appeared. We have found that the reaction of *o*-carborane with 1 equiv of BuLi in dme and $Br(CH_2)_3Br$, produces a 50/50 mixture of the disubstituted species, and unreacted carborane. In that case, the formation of a very stable ring overcomes the blocking capacity of the Li(dme) unit; however the desired compound may be successfully prepared by blocking one of the C-positions with TBDMS.[2]

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† Institut de Ciència de Materials de Barcelona.

‡ Departament de Química.

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Conclusions

The synthesis of C-monosubstituted 1,2-$C_2B_{10}H_{12}$ derivatives is possible via a fast, high-yield, reliable, comparatively inexpensive, one-pot reaction when the lithiated species is prepared in dimethoxyethane. This is probably due to the bulky Li(dme) group blocking the attack of a second BuLi unit at the neighboring C atom. We suspect that di or trichelating glymes show the opposite effect, and favor disubstitution. Furthermore, we believe that diethyl ether is a better choice of solvent when the C-monosubstituted compound is used as starting material and a second substitution is sought via a lithiated intermediate. The method described above is less successful when C,C′-thermodynamically stable rings can be formed, in which case the protecting group strategy, e.g. using TBDMS, may be a more appropriate pathway.

Experimental Section

General Methods. Commercial *o*-carborane was purified by sublimation at 0.01 mmHg. A 1.6 M solution of *n*-butyllithium in hexane (Fluka) was used as received. Dimethoxyethane was dried with Na/benzophenone.

All organic and inorganic salts were Fluka or Aldrich analytical reagent grade and were used as received. The solvents were reagent grade.

All reactions were carried out under a dinitrogen atmosphere employing Schlenk techniques. Microanalyses were performed in our analytical laboratory by using a Perkin-Elmer 240B microanalyzer. IR spectra were obtained as KBr pellets on a Nicolet 710-FT spectrophotometer. The ^{1}H-NMR, ^{11}B-NMR, and ^{31}P-NMR spectra were recorded on a Bruker AM 400WB instrument.

Preparation of 1-SH-1,2-$C_2B_{10}H_{11}$. To a solution of 7 mmol (1 g) of 1,2-$C_2B_{10}H_{12}$ in 25 cm^3 of dimethoxyethane at 0 °C was added 7.04 mmol of butyllithium. The suspension was stirred at this temperature for 0.5 h, then maintained at 25 °C for the same period, and cooled again to 0 °C, at which point 7 mmol (0.225 g) of sulfur powder was slowly added over a period of 0.5 h. The resulting solution was stirred at 25 °C (0.5 h). Solvent and volatiles were removed in vacuo, and 25 cm^3 of diethyl ether was added. To the 0 °C solution was added a 6-fold excess of 1 M HCl. The mixture was thoroughly shaken, and the two layers separated. The diethyl ether layer was washed with 1 M HCl (3 × 15 cm^3), and the aqueous layer, with diethyl ether (15 cm^3). The combined organic solutions were dried over $MgSO_4$. The filtrate was evaporated to yield 1.20 g (98% yield) of a practically pure yellowish compound containing 93% 1-SH-1,2-$C_2B_{10}H_{11}$, 5% *o*-carborane, and 2% 1,2-$(SH)_2C_2B_{10}H_{10}$. The pure compound was obtained upon sublimation. The purity of the samples was compared with data in the literature on 1-SH-1,2-$C_2B_{10}H_{11}$[7] and 1,2-$(SH)_2$-1,2-$C_2B_{10}H_{10}$.[8]

Preparation of 1-PPh_2-1,2-$C_2B_{10}H_{11}$ and 1-CH_2Ph-1,2-$C_2B_{10}H_{11}$. The procedures are analogous to that described above for 1-SH-$C_2B_{10}H_{11}$. $ClPPh_2$ (7 mmol) and $BrCH_2Ph$ (7 mmol) were used instead of sulfur powder, respectively. Following addition of the halogenated reagents, the mixture was stirred at 0 °C for 0.5 h and refluxed for 1 h ($ClPPh_2$) or stirred at room temperature overnight ($BrCH_2Ph$). Acidification of the reaction products was not used in the workup. The yields of the impure compounds obtained were as follows: 1-PPh_2-1,2-$C_2B_{10}H_{11}$, 1.82 g of a solid (80%); 1-CH_2Ph-1,2-$C_2B_{10}H_{11}$, 1.54 g (95%) of a semisolid. The composition of the samples was determined by ^{11}B-NMR; for 1-PPh_2-1,2-$C_2B_{10}H_{11}$ it was 93% 1-PPh_2-1,2-$C_2B_{10}H_{11}$,[9] 4% *o*-carborane, and 3% 1,2-$(PPh_2)_2C_2B_{10}H_{10}$,[10] and for 1-CH_2Ph-1,2-$C_2B_{10}H_{11}$ it was 90% 1-CH_2Ph-1,2-$C_2B_{10}H_{11}$,[2] 6% *o*-carborane, and 4% 1,2-$(CH_2Ph)_2C_2B_{10}H_{10}$.[2]

Preparation of 1-$CH_2CH_2CH_2CH_3$-1,2-$C_2B_{10}H_{11}$. To a solution of 7 mmol (1 g) of 1,2-$C_2B_{10}H_{12}$ in 25 cm^3 of dimethoxyethane at 0 °C was added 7.05 mmol of BuLi. The suspension was stirred for 0.5 h (0 °C) and then maintained at 25 °C for the same period. After the mixture was cooled to −15 °C, 7 mmol (0.98 g) of $Cl(CH_2)_3CH_3$ was added and the resulting mixture was stirred for 2.5 h at −15 °C and 0.5 h at 25 °C. Solvent and volatiles were removed in vacuo, and 25 cm^3 of diethyl ether and 75 cm^3 of water were added. Workup was as before. The filtrate was evaporated to dryness. Chloroform (10 cm^3) was added, and a white solid appeared which was discarded. Upon evaporation of the solvent, 1.33 g of a yellow oil was obtained (96% yield if the compound was considered pure) which consisted of 70% 1-$CH_2CH_2CH_2CH_3$-1,2-$C_2B_{10}H_{11}$,[2] 15% 1,2-$(CH_2CH_2CH_2CH_3)$-1,2-$C_2B_{10}H_{10}$,[2] and 15% *o*-carborane determined by ^{11}B-NMR comparison with authenticated samples. The compounds were separated by preparative silica TLC using H_2CCl_2/hexane, 1/9, as elutant.

Reaction of $Br(CH_2)_3Br$ with 1,2-$C_2B_{10}H_{12}$. The experiment was performed as with the halogenated examples cited above with the aim of preparing 1,1′-(1,3-$CH_2CH_2CH_2$)(1,2-$C_2B_{10}H_{10}$)$_2$, using 2/1 molar ratios of 1,2-$C_2B_{10}H_{10}$ and $Br(CH_2)_3Br$, respectively. The ^{11}B-NMR showed that 1/1 mixtures of 1,2-$(CH_2)_3$-1,2-$C_2B_{10}H_{10}$[11] /*o*-carborane were obtained in all cases.

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