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Synthesis of *Closo*-1,7-Carboranyl Alkyl Amines

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Abstract

Of the three *closo*-carborane isomers (C₂B₁₀H₁₂), *closo*-1,2-carborane has been used most widely in the synthesis of carboranyl amines. However, *closo*-1,2-carboranes are prone to deboronation to *nido*-7,8-carborane under various conditions including attack by basic amino groups. In order to overcome this problem, *closo*-1,7-carboranyl ethyl-, propyl-, and butylamine were synthesized, which should be more stable towards basic deboronation than their *closo*-1,2-carboranyl counterparts. These *closo*-1,7-carboranyl amines (**5**, **18** and **19**) were synthesized using two different methods, both starting from the corresponding *closo*-1,7-carboranyl alkyl iodides (**3**, **14** and **15**). One of the carboranyl alkyl amine (**5**) was conjugated with folic acid to form a *closo*-1,7-carborane-folic acid bioconjugate (**20**).

Keywords

m-closo-carborane; *closo*-1,7-carborane; carboranyl amine

The hydrophobic dicarba-*closo*-dodecaboranes present a group of three isomers with the chemical formula C₂B₁₀H₁₂. Depending on the position of the two carbons in the cage, the isomers are designated as *closo*-1,2 (*ortho*)-, *closo*-1,7 (*meta*)-, and *closo*-1,12 (*para*)-carborane. Nucleophilic deboronation of these *closo*-carboranes produces the corresponding negatively charged, hydrophilic dicarba-*nido*-undecaboranes 7,8-C₂B₉H₁₂[−], 7,9-C₂B₉H₁₂[−], and 2,9-C₂B₉H₁₂[−] (Figure 1).¹

Numerous types of carboranyl amines have been described.^{2–18} In most cases, *closo*-1,2- or *nido*-7,8-carborane were used for their synthesis. Many *closo*-1,2- and *nido*-7,8-carboranyl amines were synthesized for conjugation with pre-existing biomedical molecules, such as the epidermal growth factor (EGF),¹⁹ cyanocobalamin,⁶ and pyropheophorbide.¹⁷ These bioconjugates were prepared for use in Boron Neutron Capture Therapy (BNCT). Similarly, Tolmachev et al. prepared dextran conjugates of *nido*-7,8-carboranyl propyl amines for tumor imaging studies.^{20,21} Only very few reports are available describing *mcloso*-1,7-, *nido*-7,9-, and *closo*-1,12-carboranyl amines.^{14–16}

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Supplementary Material

Supporting Information include the following: (S3) General Information, (S5) Experimental section, (S16) Spectral characterization data.

Among the three *closo*-carboranyl isomers, *closo*-1,2-carborane is the most susceptible to deboronation by bases, such as alkoxides and amines.¹ Deboronation of *closo*-1,2-carborane derivatives has even been reported under physiological and neutral aqueous conditions such as wet DMSO.^{22,23} In addition, Schinazi et al. observed intracellular *nido*-formation of 5-*closo*-1,2-carboranyl-2'-deoxyuridine *in vitro*.²⁴ Therefore, *nido*-7,8-carboranes may not be suitable for biomedical applications which rely on the lipophilic character of a neutral *closo*-carborane cluster, as may the case for compounds that enter cells via passive diffusion.²⁵ In addition, degradation of *closo*-1,2-carborane under physiological condition²⁴ or during synthetic procedures involving carboranyl amines²³ is generally not desirable when a *closo*-carboranyl compound is the desired target compound. To the best of our knowledge, deboronation of 1,7- and 1,12-carboranes under neutral aqueous conditions has not yet been reported and both clusters are in general far more stable than *closo*-1,2-carborane. In contrast to *closo*-1,7-carborane, *closo*-1,12-carborane is very expensive and has not been readily available in recent years in larger quantities. Therefore, *closo*-1,7-carboranes may be the best candidate for the synthesis of *closo*-carboranyl alkyl amines to be used in the preparation of *closo*-carboranyl bioconjugates that are stable under physiological conditions.

In this paper, we discuss the synthesis of *closo*-1,7-carboranyl ethyl-, propyl-, and butyl amine using two different synthetic strategies. To the best of our knowledge, the synthesis of 1,7-carborane-containing amines with spacers between amino group and cluster has not been described yet. In the first approach, *closo*-1,7-carboranyl propyl amine (**5**) was synthesized using a method that was previously reported for the preparation of the corresponding *closo*-1,2-carboranyl propyl amine (Scheme 1).²¹ The synthesis of **5** was initiated by reacting *closo*-1,7-carborane with butyl lithium in anhydrous tetrahydrofuran (THF) at -78°C for 2 hrs (Scheme 1). Subsequently, oxetane was added at 0°C followed by stirring at room temperature overnight to produce 1-(3-hydroxypropyl)-*closo*-1,7-carborane (**1**) and 1,7-bis-(3-hydroxypropyl)-*closo*-1,7-carborane in 55% and 20% yields, respectively.²¹ Compound **1** was then reacted with carbon tetrabromide (CBr_4) in presence of triphenyl phosphene (TPP) at 0°C to produce 1-(3-bromopropyl)-*closo*-1,7-carborane (**2**) in 95% yield. Conversion to 1-(3-iodopropyl)-*closo*-1,7-carborane (**3**) in 95% yield was accomplished by refluxing **2** with sodium iodide (NaI) in anhydrous acetone. N-alkylation of **3** was achieved using di-*tert*-butyliminodicarboxylate (diBoc amine) in a phase transfer catalyzed reaction.²⁶ Compound **3**, diBoc amine, tetrabutylammonium hydrogen sulfate, and sodium hydroxide solution (2M) were refluxed (50°C) in dichloromethane to produce N-[3-*closo*-1,7-carboranyl propyl]-N,N-diBoc amine (**4**) in 70% yield.²¹ Formation of *nido*-carborane was not observed under these reaction conditions. Finally, removal of the Boc protective groups using 70% trifluoroacetic acid in dichloromethane at room temperature afforded a white precipitate of target compound **5** in 90% yield.

In the second approach, *closo*-1,7-carboranyl ethyl amine (**18**) and *closo*-1,7-carboranyl butyl amine (**19**) were synthesized adapting a procedure previously described by Soloway et al. for the preparation of *closo*-1,2-carboranylethyl amine (Scheme 2).³ Commercially available haloalkoxy-*tert*-butyl-dimethylsilane (**6/7**) was used for reaction with *closo*-1,7-carborane instead of oxetane. *closo*-1,7-Carborane was dissolved in anhydrous diethylether:benzene (2:1 mixture v/v), butyl lithium was added at 0°C , and the reaction mixture was stirred for 2 hrs. Following this, **6/7** was added to produce 1,7-carboranyl ethoxy-*tert*-butyl-dimethylsilane (**8**) and 1,7-carboranyl ethoxy-*tert*-butyl-dimethylsilane (**9**) in 43% and 49% yield, respectively. Compound **8** and 1,7-carborane have similar R_f values (0.60 hexanes), and only partial purification of **8** was achieved to get 1,7-carborane-contaminated **8** (~30% *m*-carborane). The TBDMS protective groups of **8** and **9** were removed with a solution of 10% HCl in methanol to give 1,7-carboranyl ethanol (**10**) and 1,7-carboranyl butanol (**11**) in 79% and 84% yield, respectively.

Using the same procedure as described for the synthesis of *closo*-1,7-carboranyl propanol (**1**, Scheme 1), bromoethyl-*closo*-1,7-carborane (**12**) and bromobutyl-*closo*-1,7-carborane (**13**) were synthesized in 48% and 53% yield. A reaction time of exactly two hrs was crucial for an optimal yield of ~50%. Increased reaction times resulted in reduced yields and increased formation of impurities. Unreacted **10/11** were recovered by column chromatography and used again to further improve the yield. Longer reaction times resulted in increased formation of uncharacterized side products, which were difficult to separate from **12/13**.

Compounds **12** and **13** were converted in yields of 100% to the corresponding iodo-analogues **14** and **15**, as described in Scheme 1 for compound **3**. In contrast to iodopropyl-*closo*-1,7-carborane (**3**),²¹ the iodoalkyl-*closo*-1,7-carboranes **14** and **15** did not react with diBoc amine. To the best of our knowledge, the corresponding *ortho*-carboranyl analogues were never synthesized using this method. However, in the case of N-protected 4-(2-bromoethyl)- and 4-(4-bromobutyl)piperidines, for example, amination with diBoc amine proceeded without problems to the desired products.²⁷ Therefore, compounds **14/15** were reacted with sodium azide in DMF at room temperature overnight to produce the *closo*-1,7-carboranyl ethyl azides **16** and **17** (both 100% yield).³ Finally, **16/17** were reduced with H₂/PdC (10%) to the target compounds *closo*-1,7-carboranyl ethyl amine (**18**) and *closo*-1,7-carboranyl butyl amine (**19**) in 54% and 63% yield, respectively. All compounds were purified by silica gel column chromatography and analyzed by proton and carbon NMR spectroscopy as well as high-resolution mass spectrometry.

Finally, the *closo*-1,7-carboranyl propyl amine, **5**, was conjugated with folic acid to yield the *closo*-1,7-carborane-folic acid bioconjugate, **20** (Scheme 3). Cellular uptake of folic acid and its bioconjugates is mediated by the folate receptor, which is overexpressed in various types of human cancer cells.^{28,29} In the past, boronated folic acid derivatives have been synthesized for BNCT studies.²⁹ Cage-radiohalogenated forms of **20** could also be used for tumor imaging and the radiotherapy of cancer.²⁸

Compound **20** was synthesized by reacting folic acid with **5** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) as the coupling reagent and pyridine as the base in DMSO at room temperature overnight (Scheme 3). The reaction mixture was added to a mixture of methanol and ether (1/4, v/v). The resulting precipitate was collected and purified by preparative RP18 HPLC to yield **20** in 53% yield. NMR-spectroscopic analysis indicated that **20** was a mixture of ~ 60% γ -amide (**20a**) and ~ 40 % α -(**20b**). The formation of **20** demonstrates the feasibility of *closo*-1,7-carboranyl amines to react with biomolecules.

In summary, three *closo*-1,7-carboranyl alkyl amines (**5**, **18** and **19**) were successfully synthesized using two different methods without observing *nido*-formation during preparation. The overall yield for *closo*-1,7-carboranyl propyl amine (**5**) was the highest with 45%. On the other hand, the overall yields for *closo*-1,7-carboranyl ethyl amine (**18**) and 1,7-carboranyl butyl amine (**19**) were 9 and 14%, respectively, due to comparatively lower yields in the first two reaction steps. As an example, **5** was conjugated with folic acid to form the *closo*-1,7-carborane-folic acid bioconjugate, **20**. The described carboranyl amines could also be used for the conjugation to other biomedically active molecules, such as nucleosides to be used in BNCT.²⁵ Preliminary biological studies in our laboratory with several *closo*-1,7-carboranyl amine bioconjugates indicated no cage degradation under physiological conditions. Additionally, the intermediate *closo*-1,7-carboranyl alcohols (**1**, **10** and **11**) and iodides (**3**, **14** and **15**) could also be used in the synthesis of biologically-active compounds, as has been described previously for the corresponding *closo*-1,2-carboranyl derivatives.^{13,17}

Supplementary Material

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Figure 1.
Deboronation of *closo*-1,2-, *closo*-1,7-, and *closo*-1,12-dicarba-dodecaboranes to corresponding *nido*-7,8-, *nido*-7,9- and *nido*-2,9-dicarba-undecaboranes, respectively.

Scheme 1.
Synthesis of 1-(3-aminopropyl)-1,7-dicarba-*closo*-dodecaborane (**5**)

Scheme 2.

Synthesis of 1-(2-aminoethyl)-1,7-dicarba-*closo*-dodecaborane (**18**) and 1-(4-aminobutyl)-1,7-dicarba-*closo*-dodecaborane (**19**).

Scheme 3.
Synthesis of a *closo*-1,7-carborane-folic acid bioconjugate, (20).