SYNTHESIS OF NOVEL CARBORANE HYBRIDS BASED ON A TRIAZINE SCAFFOLD FOR BNCT

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ABSTRACT

Cyanuric chloride has been used as a scaffold for the synthesis of chemical constructions containing a carborane, a saccharidic moiety and an amino acid as potential agents for BNCT. Such compounds allow, in principle, the use of a combinatorial approach to more complex derivatives as it is possible to introduce different oligosaccharides and to insert the compounds in bioactive peptides.

Introduction

Boron neutron capture therapy (BNCT) is a therapy for tumors treatment based on the selective irradiation with thermal neutrons of molecules containing 10B atoms, which has a large capture cross section relative to the more abundant endogenous nuclei (^{1}H, ^{12}C, ^{31}P, ^{14}N).[1]

BNCT is referred to as a binary therapy because the individual components (i.e. the boron atoms and the thermal neutrons) by themselves are not efficacious. In combination, however, they have the potential to create a highly selective therapy. The interaction between the nucleus of boron atom and the neutron produces an α particle and a ^{7}Li ion with about 2.4 MeV energy which dissipates before travelling one cell diameter so that the destructive effect is highly localized to boron loaded tissues. In order to be therapeutically useful, an ideal boronated candidate should have the following properties: high tumor targeting selectivity; low cytotoxicity; high water solubility: required for intra-arterious administration of the BNCT agent; high uptake by cancer cells.

As boron moiety, our attention has been focused mainly on carboranes, icosahedral clusters containing ten boron atoms. Such boron containing structures allow to obtain chemical constructions that bring a large number of boron atoms per molecule. On the other hand, carboranes are highly hydrophobic compounds, which require their conjugation with hydrophilic counterparts in order to have molecules with adequate water solubility for their administration. Among the different systems able to give the desired solubility properties to the carborane containing derivatives, carbohydrates are particularly interesting compounds[2] as they could also target specific receptors found on the surface of tumor cells, and usually show low toxicities.

On the other hand, the introduction of an amino acid unit can allow the incorporation of carboranes into peptides. To date only few examples of carborane derivatives containing both a sugar and an amino acid appeared in literature, and usually their synthesis is quite laborious.[3]

We then chose to exploit trichlorotriazine as a scaffold for the easy introduction of a carborane, a sugar and an amino acid on the same molecule. Such a scaffold, thanks to the different reactivity of the chlorine atoms, allows a sequential introduction of various substituents, opening the way to introduce diversity into the products. Trichlorotriazine, in fact, has been used in combinatorial synthesis.[4]

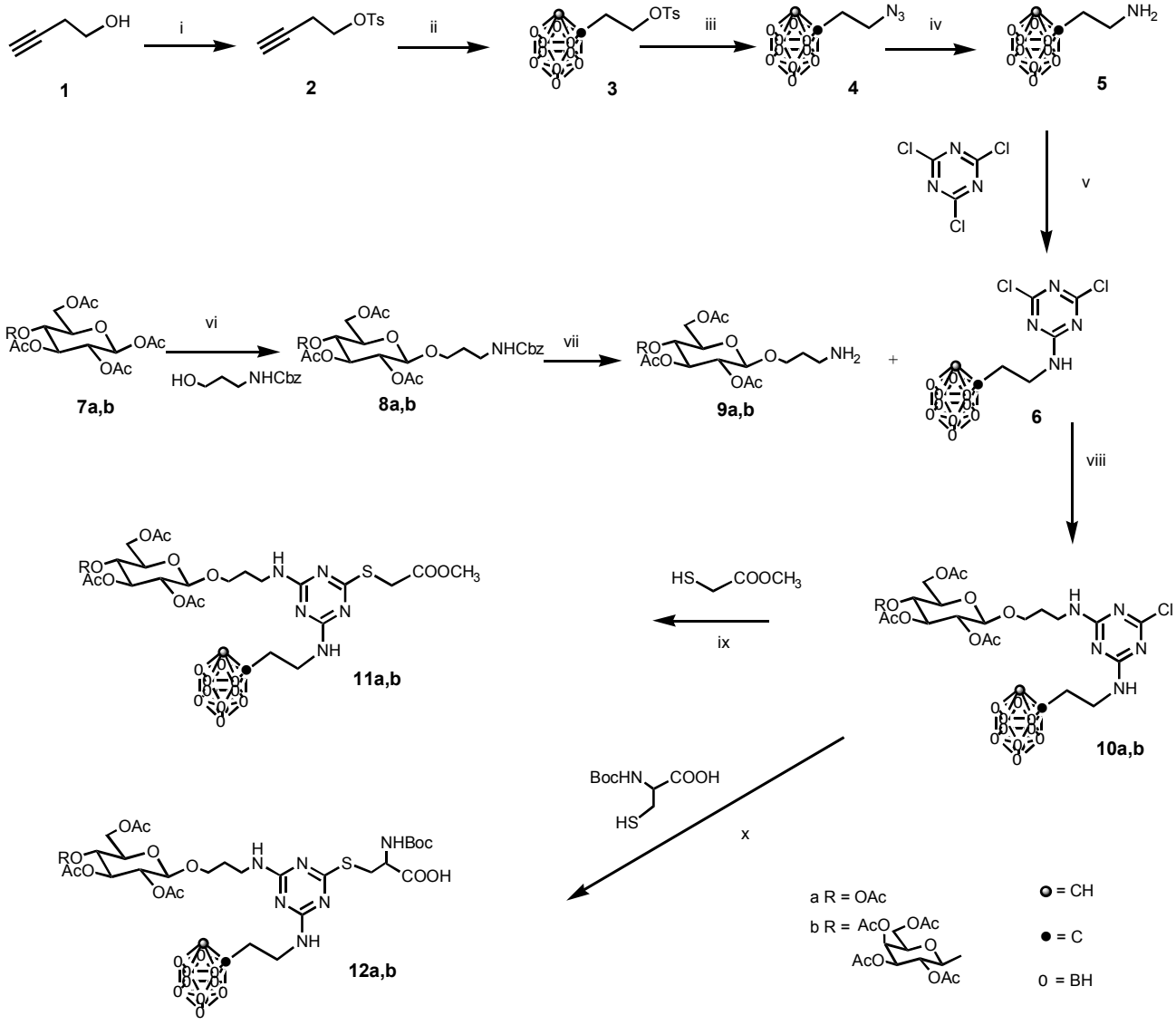
It has to be noted that, to the best of our knowledge, only one example of triazine derived carboranes appeared in literature.[5] They showed that it is possible to directly join the carborane cage to triazine, but the other substituents were only simple secondary amines. It is remarkable that, in their reactions, the carborane cage seems to be quite resistant to the presence of secondary amines,

as they did not notice any degradation of the *closo* form with formation of the corresponding anionic *nido* derivatives.

Results and discussion

In order to verify the possibility of generating differently functionalysed triazines, we prepared 2-carboranyl ethylamine as well as protected glucose and lactose 3-aminopropyl glycosides.

The preparation of the carborane derivative was performed according to a literature procedure, [6] with a modification of the azide reduction step. Tosylation of 3-butynol, carborane formation by treatment with decaborane-acetonitrile complex and substitution with azide anion gave 2-carboranyl azido ethane **4**. The azido function was converted into the corresponding amino group with H_2-Pd/C in dry THF.



Scheme 1. Reagents and conditions: i) Ts Cl, pyridine, dry CH_2Cl_2, 90%; ii) $B_{10}H_{14}$, dry CH_3CN, dry toluene, reflux , 78%; iii) NaN_3, acetone, reflux, 72%; iv) H_2, Pd/C, dry THF; v) DIPEA, cyanuric chloride, 85% for two steps; vi) BF_3OEt_2, dry CH_2Cl_2, 47% for **8a**, 41% for **8b**; vii) H_2, Pd/C, dry THF; viii) DIPEA, dry THF, 0°C to r.t., 88% for **10a**, 60% (not optimized) for **10b**; ix) NaH, dry CH_3CN, 80°C, 75% for **11a**, 71% for **11b**; x) NaH, dry CH_3CN, 80°C, 72% for **12a**, 70% for **12b**.

Excess of trichlorotriazine (3 eq.) and Hünigs' base were directly added into the hydrogenation reaction mixture containing the amine **5**, smoothly affording the desired monosubstituted triazine **6** in good yield (Scheme 1).

The protected aminopropyl glycosides were obtained by conventional Lewis acid catalysed glycosylation of commercially available peracetylated β-D-glucose **7a** and β-D-lactose **7b** with 3-benzyloxycarbonylamino propanol. Although the yields were not very high, the product was obtained in a single step.

Benzyloxycarbonyl protecting group of compounds **8a** (or **8b)** was removed by catalytic hydrogenolysis. The reaction mixture containing the free amino derivative **9a** (or **9b** respectively) was directly added to a solution of compound **6** and Hünigs' base in THF at 0°C, and the mixture was allowed to warm to room temperature. We were pleased to observe the clean formation of the disubstituted triazines **10a** and **10b** both with glucose and lactose derivatives.

The displacement of the third chlorine atom is usually more difficult: in our hands any attempt to attach the ε-amino group of the side chain of the Z-α-L-lysine failed. So we decided to exploit a better nucleophile such as a thiolate anion for this substitution. In order to verify the reaction conditions we initially employed the thiolate of methyl thioglycolate, generated with sodium hydride in acetonitrile. After addition of compound **10a** (or **10b**), the reaction mixture was refluxed overnight. Work-up and flash chromatography purification afforded the desired trisubstituted compound **11a** and **11b** respectively in 70-75% yield. The newly introduced carboxylic function would make this molecule disposed to conjugation to biopolymers.

Encouraged by such results we decided to try the third substitution reaction with cysteine. This amino acid moiety allowed us to generate a compound which could not only be easily joined to a protein, but also inserted into a synthetic peptide.

Thus, the reaction was repeated essentially in the same conditions employed for methyl thioglycolate, using N-Boc-*L*-cysteine and 2 eq. of sodium hydride. Again we were pleased to observe the formation of the expected compounds **12a** and **12b** in comparable yield with respect to the previous reaction.

In conclusion, this communication describes a simple and effective way to introduce a carborane, a sugar and a carboxylic acid or an aminoacid onto a triazine scaffold.

The obtained compounds open the possibility to generate easily a remarkable diversity. It is in fact possible to introduce various oligosaccharidic structures as well as to use this class of derivatives for the synthesis of biologically relevant peptides.

Work is in progress to extend the scope of the procedure to more complex derivatives directly involved in tumor cell surface recognition and endocytosis phenomena.

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