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Designing dendritic frameworks using versatile building blocks suitable for Cu^I-catalyzed alkyne azide 'click' chemistry

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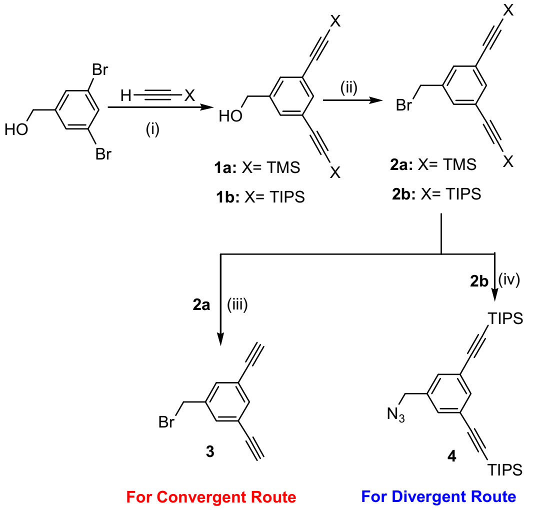
ABSTRACT

Synthesis of molecular building blocks that incorporate azide and alkyne-terminated functionalities suitable for Cu^I-catalyzed cycloaddition between alkynes and azides is reported. Their utility in constructing dendritic frameworks with 4, 6, or 12 peripheral acetylene groups using either the convergent or divergent methodology, and their functionalization with desirable end groups are demonstrated.

Dendrimers constitute key components in the quest to build smart nanodevices for applications in a diverse range of areas including biology and medicine.[1] The synthesis of these monodisperse macromolecules has attracted the imagination of scientists, and it has already generated a large library with varied backbones.[2] A major contribution to this increasing interest in dendrimer synthesis has been made by one of the highly efficient 'click' reactions that involves Cu^I-catalyzed coupling of an alkyne with an azide (CuAAC).[3] The versatility of this methodology lies in the design of appropriate alkyne and azide-terminated molecular units which can then be 'clicked' together under a variety of mild reaction conditions. We report herein the synthesis of highly versatile AB_2 (A: N_3; and B: C≡CH) building blocks that can be used to perform CuAAC 'click' chemistry to construct dendrimers using either the divergent or the convergent synthetic methodology. We demonstrate that the scope and utility of this 'greener' approach to the synthesis of dendrimers can be easily elaborated by designing such building blocks. We used these molecular units to construct dendritic frameworks which contain 4, 6, or 12 peripheral alkynes using 'click' chemistry. The potential of surface active acetylene groups in these dendrimers is demonstrated by coupling functional molecules of interest[4] such as a fluorescent dye (BODIPY PM 605) and positively charged amine centers leading to water-soluble dendrimers.

For the dendrimer synthesis using CuAAC 'click' chemistry, we envisioned a molecular unit that will incorporate a primary azide and two protected acetylenes which could be made active at the desired stage. The synthetic elaboration was begun using 3,5-dibromobenzyl alcohol, and to which trimethylsilylacetylene (**1a**) or triisopropylsilylacetylene (**1b**) was linked through bromo position using Sonogashira coupling (Scheme 1). It was subsequently followed by bromination of the benzylalcohol group (**2a** and **2b**). The building blocks **2a** and **2b** provide versatile platforms to construct dendrimers using either (i) the convergent methodology,[2f] in which dendrons are built separately, and then as a final step their focal point is activated and used to anchor the dendron onto the appropriate core or (ii) the divergent methodology,[2h] inside-out approach that employs an iterative build-up starting from the core molecule.

For the convergent construction of dendrimers, the protective (TMS) groups of **2a** were removed using a mild deprotection process with K_2CO_3. The two acetylene arms in **3** are now available for performing CuAAC click reaction, while the bromo-benzyl consti-



Scheme 1. Synthesis of building blocks for convergent and divergent routes to dendritic frameworks. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$/CuI (cat.), NEt_2H, reflux, overnight, **1a**: 89%, **1b**: 90%; (ii) CBr_4/TPP, THF 2 h, **2a**: 72%, **2b**: 87%; (iii) K_2CO_3, H_2O/acetone, overnight, **3**: 89%; (iv) NaN_3, DMF, room temperature (rt), 2 h, **4**: 96%.

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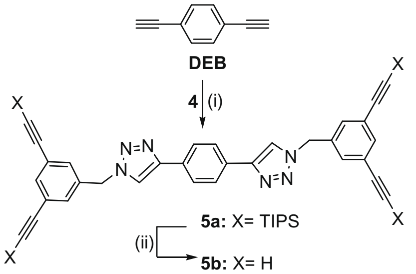
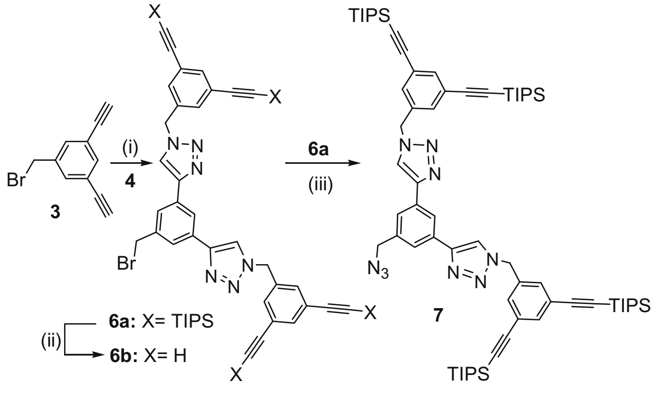


Scheme 2. Model reaction. Reagents and conditions: (i) $CuSO_4{\cdot}5H_2O$/sodium ascorbate, DMF/H_2O/THF, rt, overnight; (ii) Bu_4NF, THF, **5a**: 92%, **5b**: 89%.

tutes a focal point that can be activated later by converting it to an azide for coupling to core molecules of interest.

For the divergent synthesis, we converted the bromide arm of **2b** to an azide (**4**) by a simple azidation reaction using NaN_3 in DMF. Compound **4** is used in performing CuAAC click reaction with acetylene-terminated core molecules such as 1,4-diethynylbenzene (**DEB**) with two acetylene arms and 1,3,5-triethynylbenzene (**TEB**) with three acetylenes, using the divergent methodology, as will be demonstrated below. Interestingly, azidation of **2a**, and its subsequent use in divergent synthesis with CuAAC click reaction, in the presence of the more labile TMS protective groups, did not proceed very well, and yielded a mixture of products. We believe that it was mainly due to a premature deprotection of the TMS groups in situ under the CuAAC reaction conditions. This was confirmed by the appearance of the acetylene protons in its ^{1}H NMR. Thus, the TMS-protected acetylenes are not ideal silent partners in CuAAC 'click' chemistry.

As a model reaction, compound **4** was first reacted with a divalent core (**DEB**) using the 'click' reaction with copper sulfate pentahydrate ($CuSO_4{\cdot}5H_2O$) and sodium ascorbate (Scheme 2) to give a four-arm structure with protected acetylene groups (**5a**). The removal of TIPS groups was then achieved using Bu_4NF (**5b**). It should be noted that in this general procedure the sequence of adding the reactants and solvents is highly crucial to ensure a complete reaction. All reactants, except $CuSO_4{\cdot}5H_2O$, were dissolved in a minimal amount of DMF, followed by the addition of $CuSO_4{\cdot}5H_2O$ as an aqueous solution, and then finally THF was added to the mixture. Varying the solvent mixture or the order of addition led to incomplete reactions and lower yields. Thus, we followed the general procedure described above throughout the work reported here for building dendritic frameworks, with only slight variation of temperature and the time of reaction.



Scheme 3. Reagents and conditions: (i) $CuSO_4{\cdot}5H_2O$/sodium ascorbate, DMF/H_2O/THF, rt, overnight, **6a**: 97%; (ii) Bu_4NF, THF, **6b**: 72%; (iii) NaN_3, DMF, rt, 2 h, **7**: 89%.

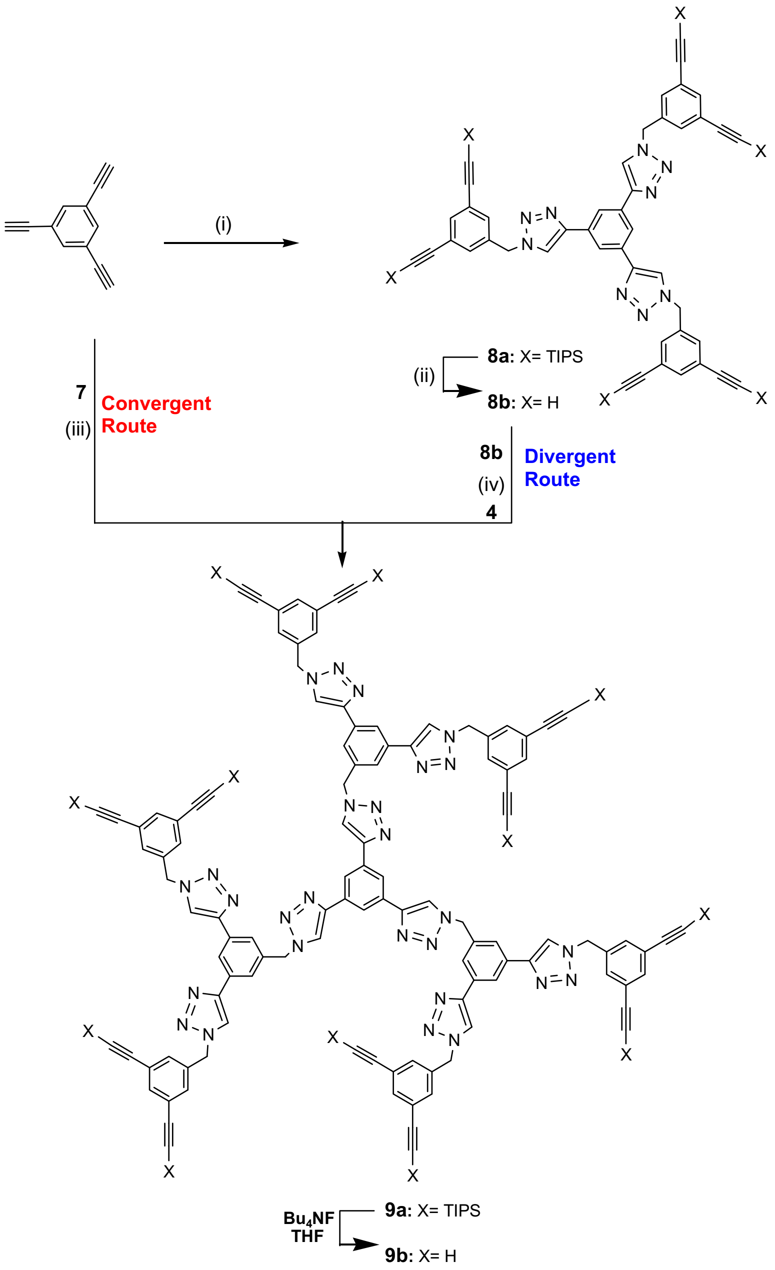
For the convergent synthesis of dendrimers, dendrons using building blocks **3** and **4** were prepared (Scheme 3). The CuAAC click reaction was carried out using a similar procedure as described above for the construction of **5a**, and it yielded a second generation dendron with four TIPS-protected arms (**6a**). The TIPS protective groups can be easily removed to give free acetylene arms (**6b**), made available for further click reaction, to build higher generation dendrons. Alternatively, the bromine focal point of dendron **6a** can be activated by converting it to an azide, which could be covalently linked to a core molecule while keeping the acetylene peripheries protected. It is important to mention here that the deprotection of **6a** with Bu_4NF gave lower yield than expected. This was due to the fact that Bu_4NF deprotection is also accompanied by the substitution of Br with F at the focal point, as confirmed by ^{1}H NMR, and mass spectroscopies. The fluoro-substituted core does not yield to subsequent azidation.

The synthesis of the first generation dendrimer with six TIPS-protected acetylenic arms (**8a**) was achieved using the divergent methodology (Scheme 4), in which the trivalent core **TEB** was reacted with compound **4**. Subsequent removal of the protective groups using Bu_4NF yields the first generation dendrimer with six free acetylenes (**8b**) available for functionalization with any azide-terminated molecule of interest. To demonstrate this possibility, and the feasibility of building higher dendrimer generations, **8b** was reacted with compound **4** to give the second generation dendrimer with 12 TIPS-protected acetylene arms (**9a**) as shown in Scheme 4. The reaction was performed using the general procedure described in the synthesis of **5a**, however it was left to proceed for 48 h instead of overnight to ensure complete reaction of compound **4** with all the available six acetylene arms of the first generation dendrimer (**8b**).

We believe that the increasing polarity of the system with an increase in generation number, and steric crowding at the periphery, slows down the reaction, and thus requires longer time for completion.

Alternatively, the TIPS-protected second generation dendrimer (**9a**) can also be synthesized using the convergent methodology by reacting the previously prepared dendron **7** with the trivalent TEB core (Scheme 4). The reaction conditions were similar to those employed in the divergent methodology, however, heating at 40 °C was necessary for complete substitution. The TIPS protective groups of the second generation dendrimer, from both convergent and divergent routes, were then removed using Bu_4NF to give the second generation dendrimer with 12 acetylene peripheral groups (**9b**).

It is worth mentioning that in all the 'click' reactions reported here, we used slight excess of azide-terminated molecules to ensure completion to almost quantitative yields (>90%). The removal of excess azide-terminated compound was found to be very easy via flash column chromatography, due to a clear difference in polarity and solubility, as more polar triazole ring-containing products are formed. The lower polarity of the starting materials facilitated their removal using low polarity solvent mixtures, except in the case of the protected second generation dendrimer **9a**, in which the presence of 12 triisopropylsilyl groups enhanced its solubility to a great extent, and it could be flushed down a short column with hexanes, while the excess of the starting material stayed on the column. The synthetic elaboration of the dendrimers was monitored by TLC, ^{1}H and $^{13}C\{^1H\}$ NMR spectroscopy. The latter were found to be diagnostic since there is a clear shift in the ^{1}H and $^{13}C\{^1H\}$ NMR signals as the triazole rings were formed. Interestingly, all compounds reported here were found to be soluble in most organic solvents with the exception of **5b** and **9b**, in which upon removal of the protective TIPS groups the compounds were



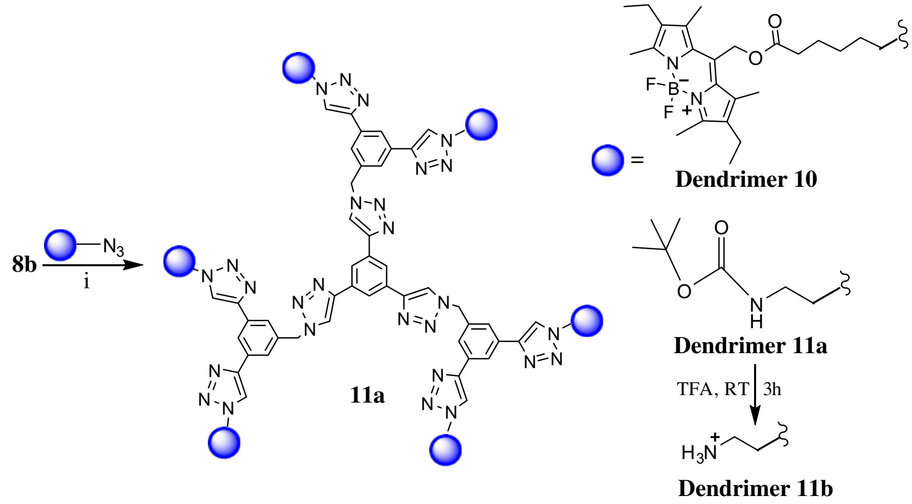
Scheme 4. Convergent and divergent syntheses of dendritic frameworks. Reagents and conditions: (i) $CuSO_4{\cdot}5H_2O$/sodium ascorbate, DMF/H_2O/THF, rt, overnight, **8a**: 96%; (ii) Bu_4NF, THF, **8b**: 95%; (iii) and (iv) $CuSO_4{\cdot}5H_2O$/sodium ascorbate, DMF/H_2O/THF, rt, 48 h; **9a**: 90%, **9b**: 89%.

found to be soluble only in DMF and DMSO. This is intriguing, and we are currently investigating the relationship between the number of triazole rings and free acetylene groups in the structure, on the solubility of these dendrimers.

The potential of these dendrtic frameworks in coupling desired functional groups at the periphery was successfully demonstrated by performing the 'click' reaction with two different azide-terminated molecules. For example, dendrimer **8b** containing six terminal acetylene groups was reacted with azide-functionalized BODIPY dye (pyrromethene 605) in the presence of copper sulfate pentahydrate ($CuSO_4{\cdot}5H_2O$) and sodium ascorbate (Scheme 5). It led to the formation of dendrimer **10** with six covalently linked imaging dye molecules. In a similar manner, dendrimer **8b** was coupled with azide-functionalized *t*-BOC-protected amine to form dendrimer **11a**.

The deprotection of six periphery situated *t*-BOC-protected amines in **11a** using trifluoroacetic acid (TFA) gave a water-soluble dendrimer **11b** containing six terminal NH_3^+ groups. These reactions were easily monitored using FT-IR spectroscopy, as the acetylene peak at 2104 cm^{-1} in **8b** disappeared upon peripheral coupling (**10** and **11a**).

In summary, we have demonstrated that by designing appropriate building blocks for highly efficient CuAAC click reaction, one could tailor the synthesis to create a small series of dendritic frameworks with different valencies for further functionalization. Recent reports in the literature have suggested that it is easier and more practical to build the dendritic frameworks, and then introduce suitable surface functionalities as the final step.[2b,5] The free acetylene groups at the periphery of compounds **5b**, **8b**, and **9b** provide this opportunity, and can be used to couple a diverse range of azide-ter-



Scheme 5. Reagents and conditions: (i) $CuSO_4{\cdot}5H_2O$/sodium ascorbate, DMF/H_2O/THF, rt, 48 h, **11a** BOC-NH–CH_2–CH_2–: 82%, **11b** NH_3^+–CH_2–CH_2–: 86%.

minated molecules of interest including fluorescent dyes and charged centers leading to water-soluble dendrimers.

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Supplementary data

Supplementary data (detailed synthetic and characterization data for all the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.061.

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