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Monofunctionalization of Dendrimers with Use of Microwave–Assisted 1,3-Dipolar Cycloadditions

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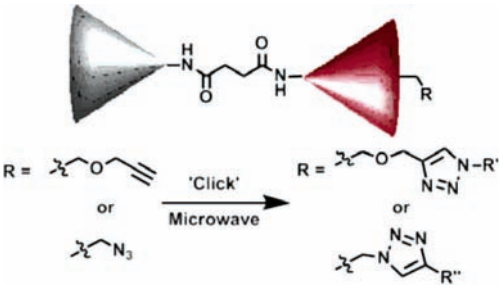
ABSTRACT



Monofunctionalized polyamide-based dendrimers containing either a terminal azide or alkyne moiety have been designed and synthesized via a convergent synthetic approach. The monofunctionalization allows for the single attachment of a functional moiety in quantitative yields by using 1,3-dipolar cycloadditions, thereby opening the possibility for targeted dendrimer functionalization.

Dendrimers are important materials for biological applications as a result of their unique features such as the precise control of size and shape, uncommon physical properties, and the placement of numerous functional groups on the periphery and/or core.[1] Polyamide-based dendrimers are of particular interest because they are based solely on a peptide like amide backbone and have demonstrated low toxicities and non-immunogenicities.[2] Accordingly, polyamide- and polyamidoamine-based dendrimers have been used extensively as biomaterials in gene and drug delivery[3] and for nanoparticle encapsulation[4] in imaging.[5] Although dendrimers containing a single functionality have been reported,[6] few of these examples are using the important polyamide backbone. Furthermore, one desired property that has not been realized to date for dendrimers is the possibility to monofunctionalize them selectively in quantitative yields thereby allowing for the single attachment of biological specific targeting and recognition moieties onto the dendrimer surface. Such a strategy would allow for the transportation of the dendrimer to the biological target of interest via a specific binding process and the targeted delivery of drugs or imaging moieties. The main prerequisite for such a

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functionalization is that the chemical handle for the attachment has to be high yielding and chemoselective. Furthermore, the transformation of choice must allow for the reaction to take place under physiological conditions. One chemical transformation that fulfills these requirements is the 1,3-dipolar cycloaddition between an azide and an alkyne.[7,8] Herein, we present the first synthesis of polyamide-based dendrimers that contain a single alkyne or azide group on the dendrimer surface and can be monofunctionalized via 1,3-dipolar cycloaddition chemistry in quantitative yields.[9]

Our research design is based on the convergent synthetic approach and some recent building block developments by the Newkome group.[10] Newkome and co-workers reported the syntheses of the nonfunctionalized dendrons **C** and **D** shown in Figure 1 (building block **C** is also known as

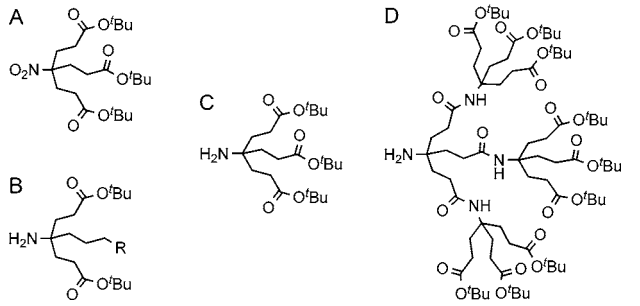
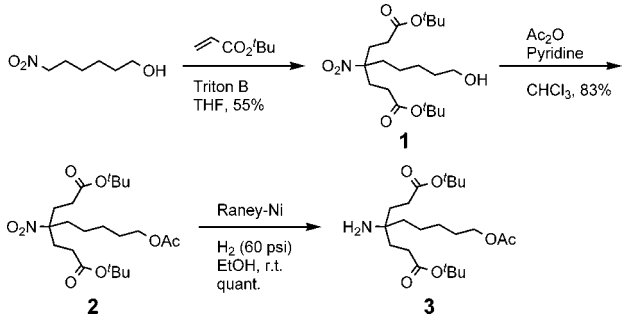


Figure 1. Newkome type monomers; **1** → (**2** + **1**) *C*-branching monomer (**A**), monofunctionalized monomer (**B**), and the first (**C**) and the second (**D**) generation of nonfunctionalized monomers.

Behera's amine).[11] Furthermore, they introduced **1** → (**2** + **1**) *C*-branching monomers and monofunctionalized dendron monomers that are ideal for our purpose to prepare monofunctionalized dendrimers with peptide like amide backbones and a single chemoselective handle (Figure 1).

The key building block in our design that will introduce the single functionality onto the dendrimer surface, monomer **3**, was prepared by a Michael-type addition with use of 6-nitrohexanol[12] and an excess of *tert*-butyl acrylate in the presence of Triton-B to provide monomer **1** in 55% yield (Scheme 1) followed by the protection of the hydroxyl group

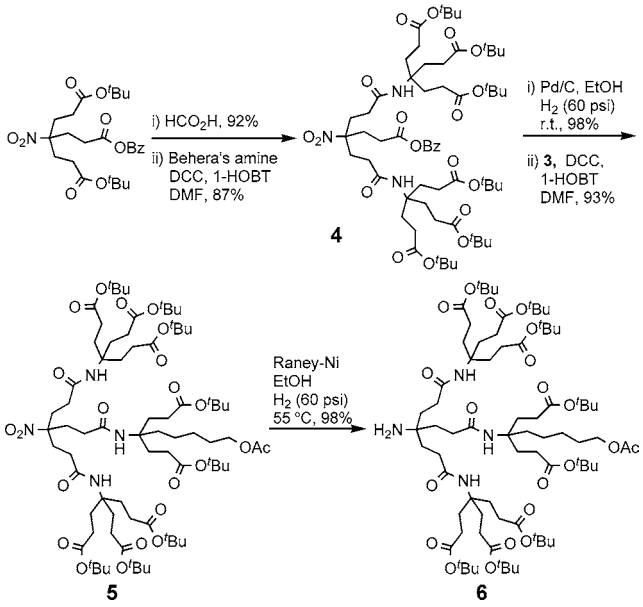
Scheme 1. Synthesis of Monofunctionalized G1 Dendron



with Ac_2O in pyridine and the catalytic reduction of the nitro group under 60 psi of hydrogen in EtOH. The quantitative reduction of the nitro group to the corresponding amine was supported by the chemical shift (^{13}C NMR) for the nitro-carbon from 92.8 to 52.5 ppm, respectively. Other building blocks (**A**, **C**, and **D**) were prepared as reported by Newkome and co-workers.[10,11]

With the basic building blocks in hand, we prepared the second generation of the monofunctionalized dendrons via the selective deprotection of the *tert*-butyl groups of **A** followed by the amidation coupling with 2 equiv of **C** (Scheme 2) to afford compound **4** in 87% isolated yield. After the deprotection of the benzyl ester group with use of Pd/C under 60 psi of hydrogen at room temperature for 12

Scheme 2. Synthesis of Monofunctionalized G2 Dendron



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(8) For some recent examples of the use of 1,3-dipolar cycloaddition in polymer chemistry see: (a) Helms, B.; Mynar, J. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020−15021. (b) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15−54. (c) Hoogenboom, R.; Moore, B. C.; Schubert, U. S. *Chem. Commun.* **2006**, *38*, 4010−4012. (d) Wang, X-Y.; Kimyonok, A.; Weck, M. *Chem. Commun.* **2006**, *37*, 3933−3935. (e) Quemener, D.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. *Chem. Commun.* **2006**, *48*, 5051−5053. (f) Opsteen, J. A.; Van Hest, J. C. M. *Chem. Commun.* **2005**, *1*, 57−59.

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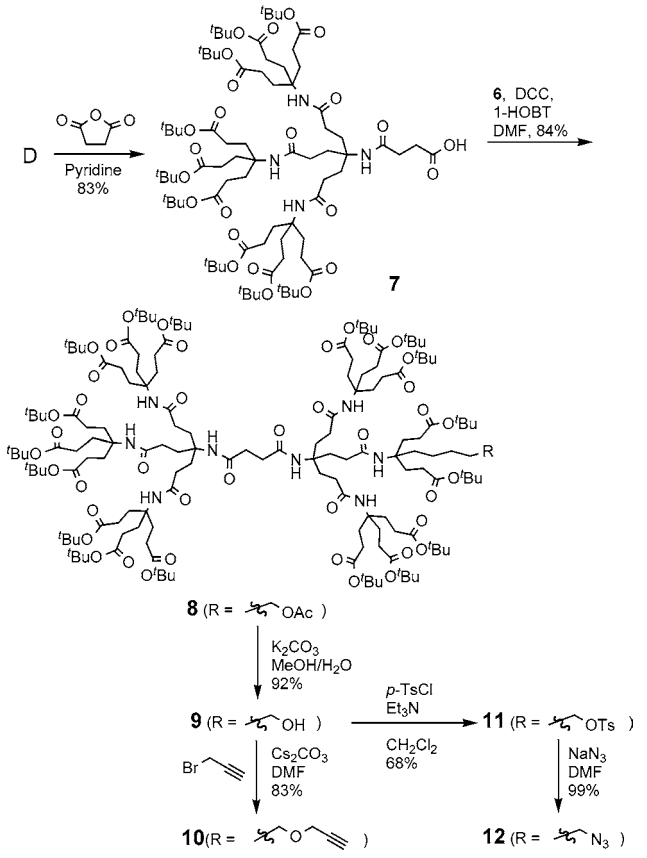
(10) Newkome, G. R.; Kim, H. J.; Moorefield, C. N.; Maddi, H.; Yoo, K.-S. *Macromolecules* **2003**, *36*, 4345−4354.

(11) (a) Newkome, G. R.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem.* **1991**, *56*, 7162−7167. (b) Newkome, G. R.; Yoo, K. S.; Moorefield, C. N. *Des. Monomers Polym.* **2002**, *5*, 67−77.

Scheme 3. Synthesis of Monofunctionalized Dendrimers (G2)



h, subsequent amidation reaction of the monoacid species with **3** yielded **5** in 93% yield. The nitro group reduction of **5** with Raney-Ni at 55 °C for 24 h under 60 psi of hydrogen provided the desired second generation dendron **6** in 98% yield, which was identified by the chemical shift change for C^{4° moiety from 92.5 to 52.6 ppm as well as the molecular ion peak (HRMS MALDI-TOF) at *m*/*z* 1439.9455 $[M + H]^+$. The overall yield of dendron **6** from its building blocks was 72%.

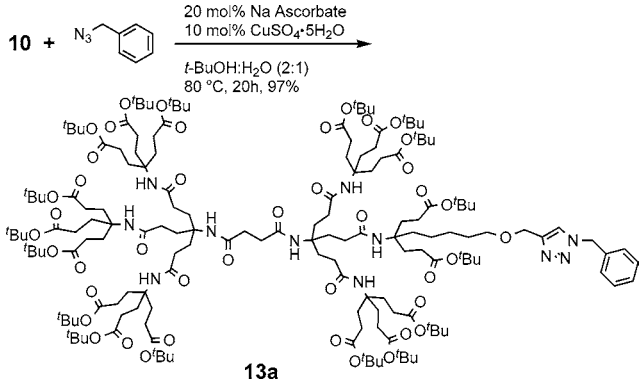
Scheme 3 outlines the synthesis of the monofunctionalized dendrimers **10** and **11** containing the single chemical handle. The synthesis commences with the stepwise incorporation of **D** and **6** onto the core molecule. The treatment of **D** with succinic anhydride in pyridine afforded the half shell of dendrimer **7** with an acid moiety at the core. Dendron **6** was then coupled onto the core by using DCC and 1-HOBT to provide the protected monofunctionalized dendrimer **8** in 84% yield. Deprotection with K_2CO_3 in a mixture of MeOH and H_2O (10:1) at room temperature for 2 h provided the hydroxyl dendrimer **9** in 92% yield.

For our purposes, both acetylene and azide were introduced onto the dendrimer at the hydroxyl moiety. Dendrimer **9** was treated with propargyl bromide in the presence of Cs_2CO_3 in DMF at 80 °C for 3 days to afford the desired acetylenic dendrimer **10** in 83% isolated yield. The transformation was demonstrated by the observation of a new ^{1}H NMR signal at 2.54 ppm for the terminal acetylene proton and two new ^{13}C NMR signals at 75.7 and 77.8 ppm for acetylene carbons.

To obtain the target azide dendrimer **12**, **9** was tosylated and subsequently treated with sodium azide in DMF to give **12** in quantitative yields. The conversions were confirmed by the observation of the chemical shift change (^{1}H NMR) for the methylene protons (CH_2R) from 3.60 ppm (R = OH) to 3.97 ppm (R = OTs) and 3.26 ppm (R = N_3).

The establishment of an easy protocol for the monofunctionalization is key to our research strategy. Therefore, we investigated the functionalization of dendrimers **10** and **12** using 1,3-dipolar cycloadditions between an azide and an alkyne moiety. Unlike the typical 1,3-dipolar cycloaddition conditions at moderate temperature, our preliminary study using acetylene dendrimer **10** and benzyl azide under the "typical" reaction conditions showed incomplete conversions and temperatures of 80 °C for 20 h were needed to obtain quantitative yields (Scheme 4). To reduce the reaction time

Scheme 4. 1,3-Dipolar Cycloaddition Functionalization with Use of Conventional Heating Conditions



and to have less harsh reaction conditions, we investigated the monomodal microwave reactor assisted 1,3-dipolar cycloaddition-based functionalization of our dendrimers. 1,3-Dipolar cycloadditions can be assisted by microwave irradiation to reduce the reaction time significantly and to provide near-perfect regioselectivity.[13] The microwave-assisted 1,3-dipolar cycloadditon has been utilized for biological systems including the attachment of peptides onto dendritic molecules[14] and the conjugation of oligonucleotides and carbohydrates.[15]

For the microwave experiments, **10** was treated with benzyl azide[16] under typical 1,3-dipolar cycloaddition conditions, using Na ascorbate and $CuSO_4 \cdot 5H_2O$ in a 1:1 mixture

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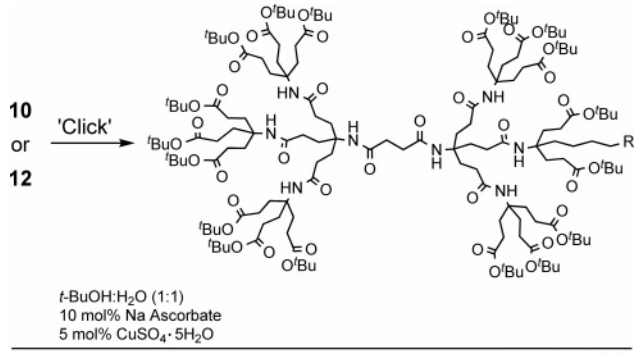
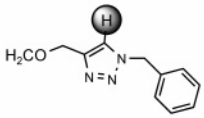
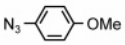
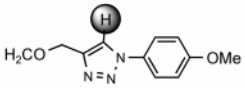
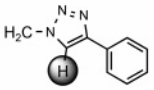
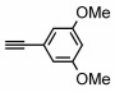
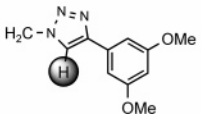
Table 1. Microwave-Assisted 1,3-Dipolar Cycloadditions of **10** and **12**[a]



dendrimer	reactant	product (R =)	^{1}H NMR (δ)[b]/ yield
10		**13a** 	7.62 ppm 98%
10		**13b** 	8.07 ppm 95%
12		**13c** 	7.93 ppm 98%
12		**13d** 	7.87 ppm 97%

[a] Reaction conditions: *t*-BuOH:H_2O (1:1), 10 mol % Na ascorbate, 5 mol % $CuSO_4$·$5H_2O$. Microwave setting: power-time control method, 100 W, 10 min, P_{max} = 65 psi, and T_{max} = 100 °C. [b] Chemical shift for the newly formed triazole protons.

of *t*-BuOH and H_2O, in a sealed glass vial. The microwave reactor was set up by using the power-time control method at 100 W irradiation power and a shut-off temperature of 100 °C.[14] The reaction was terminated after 10 min to afford the desired triazole product **13a** in 98% isolated yields. While the yields are similar to the ones described above with conventional heating methods, the microwave irradiation significantly cuts down the reaction time from hours to minutes. Table 1 summarizes the microwave-assisted 1,3-dipolar cycloaddition reactions that were carried out on dendrimers **10** and **12**. For all reactions studied under microwave conditions, we obtained excellent isolated yields (95−98%). Furthermore, when comparing the alkyne functionalized dendrimer (**10**) with the azide functionalized one (**12**), we did not detect any significant reactivity differences.

In conclusion, we have prepared monofunctionalized dendrons and dendrimers containing either a single alkyne or azide moiety. The resulting dendrimers containing a single chemical handle can be functionalized via 1,3-dipolar cycloadditon in outstanding yields. Along with the attachment of biological moieties on a single chemical handle, further functionalizations are available for these dendrimers via a deprotection of the *tert*-butyl esters on the periphery and subsequent reaction with the terminal carboxylic acids. The employed convergent approach potentially allows for the introduction of a second orthogonal functionality on the surface of the dendrimers. Such studies are currently under investigation.

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Supporting Information Available: Experimental details and characterization data (^{1}H and ^{13}C NMR, MS, and EA) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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