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Controllable, Selective Per-Functionalization of Dendritic Oligoamines

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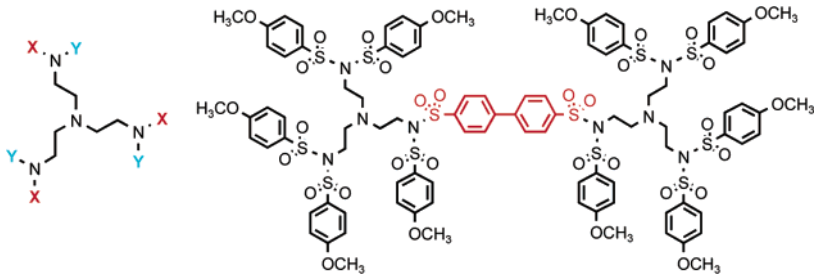
ABSTRACT



A method allowing for an unprecedented controllable functionalization of oligoamines via N,N-bis-sulfonylation with various sulfonyl chlorides has been developed. Depending on the nature of the sufonyl chloride and reaction conditions such as base, time of reaction, and temperature, each amino group can be selectively mono- or bis-sufonylated. The procedure was investigated in detail with the model substance tris(2-aminoethyl)amine and applied for the preparation of dumbbell-shaped coupled dendrons and second-generation sulfonimide-decorated dendrimers.

Dendritic molecules[1] are defined as repeatedly oligo- or polybranched compounds with a certain degree of perfection that is related to the symmetry and dispersity of the species. Dendritic molecules can be divided into low- and high-molecular weight species. The former category encompasses multifunctional compounds that can be used as central branching points (cores) and dendrimers[1] that are composed of a core unit and dendrons radiating out of it, while the latter class includes hyperbranched and dendronized polymers.[2] The interest in studying dendritic molecules is based on the fact that they are inherently different from their linear (polymer) analogues, and it is this constitutional difference that leads to many vivid changes in their physical properties.[1] One of the most stunning areas of dendrimer research is associated with their applications in diagnostics and healing, e.g., as in vivo contrast agents in X-ray and magnetic resonance imaging,[3,4] as gene delivery agents,[5] and as materials for antibodies and for repairing corneal wounds.[6]

Selective mono- or oligo-functionalization of the low-weight dendritic species at a core, periphery, or at the branching points between has been highlighted by many

(1) (a) Definitions of dendrimers, dendrons, and branched polymers were discussed by numerous experts during the 3rd International Dendrimer Symposium, September 17−20, Berlin, Germany. The term "dendritic molecules" seems to be suitable for all types of branched species. (b) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Syntheses, Perspectives*; VCH: Weinheim, 1996. (c) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons: Concepts, Syntheses, Applications*; Wiley-VCH: New York, 2001. (d) *Dendrimers and Other Dendritic Polymers*; Frechet, J. M. J., Tomalia, D. A., Eds.; Wiley: New York, 2001.

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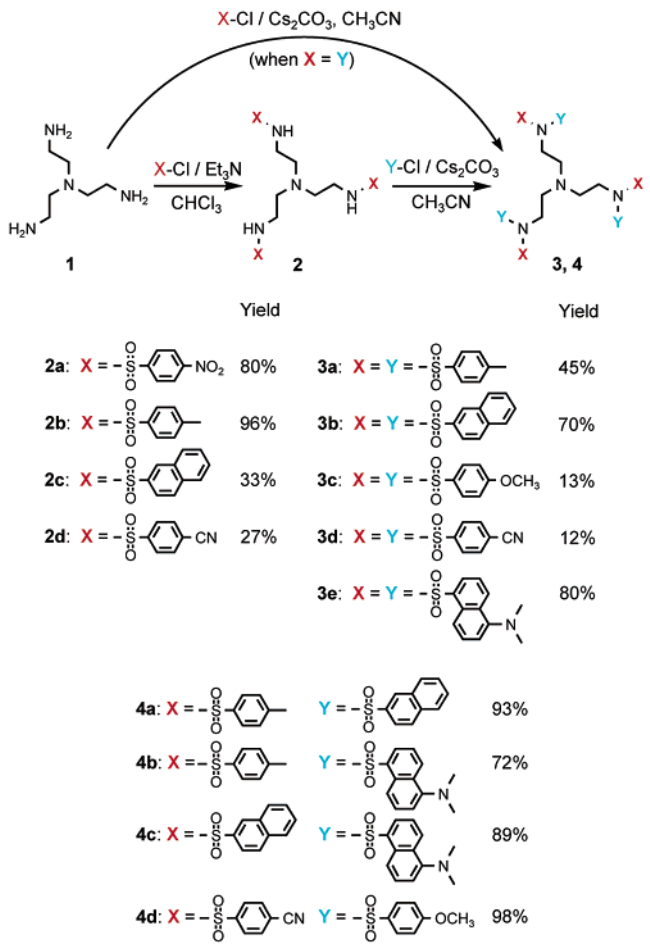
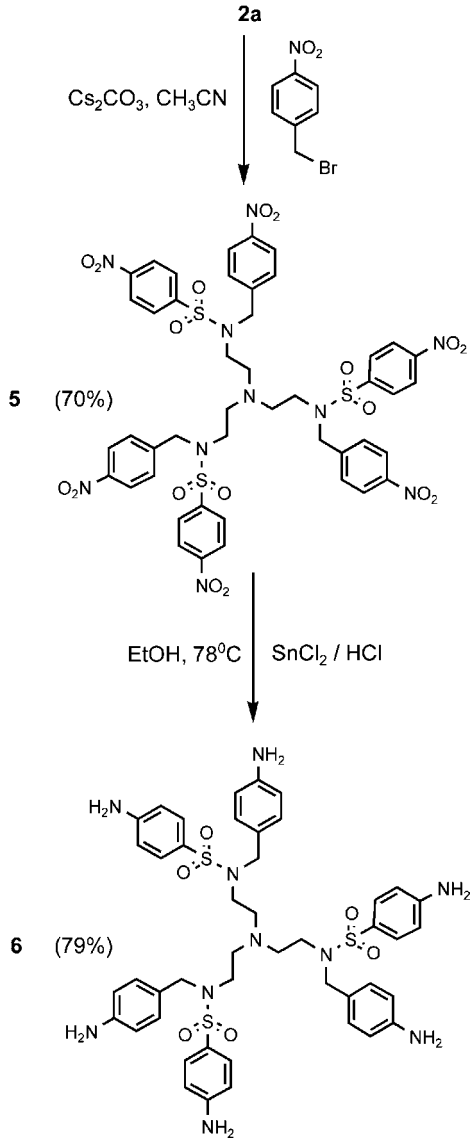
Scheme 1



authors[7] to be of high importance for precisely modifying the properties of the target material. Preparation of dendrons[1,8] for a convergent synthesis of more elaborate dendritic species is also inevitably associated with a need for a selective monofunctionalization.

Scheme 2



Oligo-amines and POPAM[9] and PAMAM[10] dendrimers have often been decorated at their periphery with diverse groups[9,11,12] aiming at the introduction of a specific function and consecutive dendrimer growth. This was usually restricted to the complete functionalization at each of the peripheral amino groups, e.g., a Michael-type addition,[9−11] by isocyanate addition[12] or by acylation.[12,13] The drawbacks of such functionalization often lie in the lack of both selectivity and a monodisperse product.

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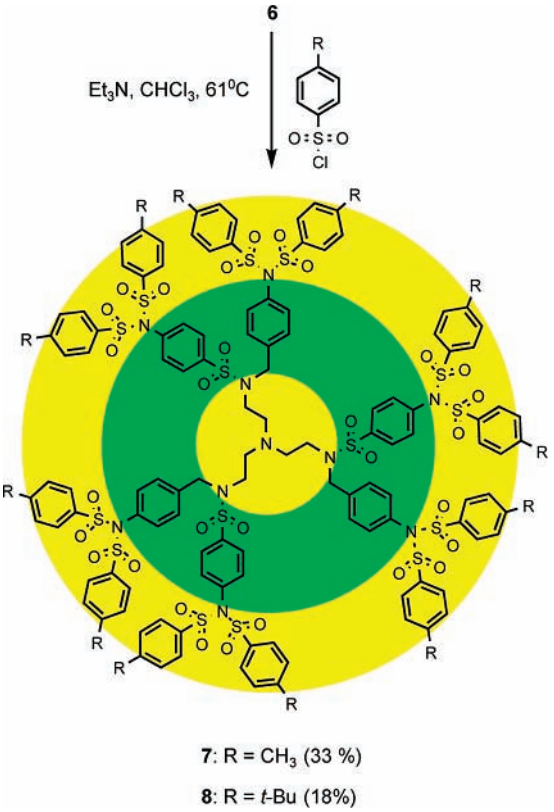
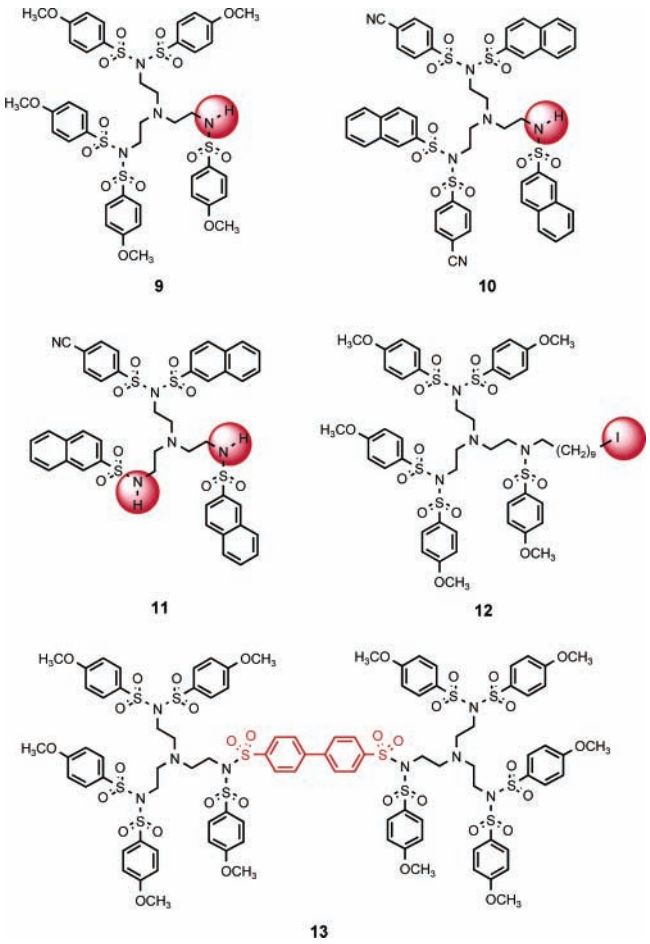
Scheme 3



Here we report an N,N-bis-functionalization that has advantages of being sequence-specific and regioselective and, in addition, represents a novel and efficient 1→2 branching method[14] of dendrimer growth. The reaction sequences based on the consecutive series of amine sulfonylation have been worked out and tested for their sufficiency by using tris(2-aminoethyl)amine **1** as a model starting material and also applied for the preparation of second-generation sulfonimide dendrimers.

Reaction of **1** with different arylsulfonyl chlorides in CH_2Cl_2 or $CHCl_3$ in the presence of Et_3N at room temperature as depicted in Scheme 1 gives rise to sulfonamides of type **2** in which each nitrogen is monosulfonylated. Yields of this 1→1 branching step range from 27 to 96%. If cesium carbonate is used as a base, tris(2-aminoethyl)-amine **1** can also be persulfonylated, resulting in sulfonimides **3a**−**e** with 12 to 80% yields depending on the sulfonyl chloride nature. Further sulfonylation of sulfonamides **2a**−**d** in the presence of cesium carbonate (Scheme 1) with other arylsulfonyl chlorides affords (72−98%) sulfonimides **4a**−**d** bearing pairs of two different arylsufonyl groups at each nitrogen.

This interesting possibility of new sulfonimide-type 1→2 branching prompted us to attempt sulfonylation of higher oligoamines. For this purpose we prepared hexaamine **6** by alkylating **2a**[15] with *p*-nitrobenzyl bromide followed by reduction of the intermediate hexanitro compound **5** (Scheme 2). Scheme 3 shows that sulfonylation of **6** with tosyl chloride and *p*-*t*-Bu-benzenesulfonyl chloride in the presence of Et_3N unexpectedly led to a one-step N,N-bis-sulfonylation of outer amino groups resulting in second-generation dendritic sulfonimides **7** and **8**, respectively. The enhanced acidity of amino group protons in aromatic hexaamine **6** compared to that of **1** seems to be responsible for its lack of stepwise sulfonylation. Despite the fact that only persulfonylation of **6** can be carried out, it represents a novel convenient technique of the 1→2 branching of dendritic aromatic amines producing chemically stable and conformationally robust sulfonimide branches.



We have been intrigued by how small structural and electronic effects govern the selectivity of the persulfonylation of oligoamines. Our next step was, therefore, the detailed study of the persulfonylation of **1** as a model substance. First we repeated series of persulfonylation reactions of **1** as shown in Scheme 1 leading to sulfonimides **3a**−**e**. This time the reactions were performed at room temperature and continuously followed by TLC analysis. It turned out that, in most cases, reaction proceeds quickly, resulting in the corresponding hexasulfonylated products and no products of partial substitution that can be easily detected or isolated. However, an interesting exception was found for

(14) Nomenclature of 1→*n* branching was suggested by G. R. Newkome. See ref 1b,c for details.

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the reaction of **1** with *p*-methoxybenzene-sulfonyl chloride. In the latter case, the introduction of the last sulfonyl unit proceeds very slowly, and a mixture of equal amounts of hexasulfonylated **3c** and pentasulfonylated **9** derivatives could be isolated and easily separated on silica gel. Even more interesting results were found controlling the persulfonylation of sulfonamides **2a**−**d** in the presence of cesium carbonate. Like in the previous case, the hexasulfonylated products were formed quickly from sulfonamides **2a**, **2b**, and **2d**. However, sulfonylation of **2c** with *p*-cyanobenzenesulfonyl chloride was found to proceed smoothly at room temperature and only mono- and bis-sulfonimides **10** and **11** were isolated, with yields of 41 and 21%, respectively, while the complete persulfonylation of **2c** could be accomplished in boiling acetonitrile.

Selectively functionalized compounds **9**−**11**, which contain different functional groups (NH, CN, OCH_3), could all be reacted under certain conditions in a controlled way. These species are undoubtedly suitable dendrons or cores for preparation of a diversity of dendritic architectures possessing selectively functionalized branches. To demonstrate to some extent the potential of the selectively persulfonylated species we attempted coupling of two units of monosulfonamide **9** via reaction with bifunctional linkers such as 1,10-diiododecane and 4,4′-biphenyldisulfonyl chloride. The reaction of **9** with 1,10-diiododecane (taken in a 2:1 molar ratio) in the presence of cesium carbonate in boiling acetonitrile led to dendron **12**, reflecting an insufficient spacer length for the attachment of the second unit of **9**. Similar reaction of **9** with 4,4′-biphenyldisulfonyl chloride readily yields a dumbbell-shaped[16] product of coupling **13**.

In summary, the described methods of complete and selective sulfonylation of oligoamines offer new reliable approaches for controlled branching and preparation of constitutionally novel dendritic species, e.g., sulfonimide dendrimers such as **7** and **8** and core-linked dendritic assemblies such as **13**. The reported studies outline a good starting point for exploring the functionalization selectivity on the periphery of POPAM dendrimers of higher generations. Moreover, the synthetic strategy can also be of advantage for the selective branching of linear polyamines.

Acknowledgment. Our planned Graduiertenkolleg network is acknowledged for stimulating discussions. O.L. thanks Alexander von Humboldt Foundation for a fellowship.

Supporting Information Available: Experimental procedures and full characterization for compounds **2**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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