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# Synthesis of sulfonimide-based dendrimers and dendrons possessing mixed $1 \rightarrow 2$ and $1 \rightarrow 4$ branching motifs

Mykola Kolotylo<sup>a</sup>, Volodymyr Holovatiuk<sup>b</sup>, Julia Bondareva<sup>c</sup>, Oleg Lukin<sup>c,\*</sup>, Vladimir Rozhkov<sup>a,\*</sup>

<sup>a</sup> Institute of Organic Chemistry, National Academy of Science, 5 Murmanskaya St., Kiev 02660, Ukraine

<sup>b</sup> Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences, 50 Kharkovskoye Shosse, Kiev 02660, Ukraine

<sup>c</sup> Skolkovo Institute of Science and Technology, 3 Nobel St., 143026 Moscow, Russia

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#### Introduction

The first series of "cascade molecules" was synthesized by Vögtle and co-workers in 1978 [1,2]. The term "cascade" was chosen because it evokes analogies to the repetitive branching of the arms and with some justification this type of molecule could have been called dendritic. These molecules were synthesized divergently utilizing two branching motifs. In 1985 Tomalia and coworkers developed branched poly(amidoamines) (PAMAM), coined, and propagated the name "dendrimer" [3,2]. PAMAM dendrimers were obtained by a divergent method involving the  $1 \rightarrow 2$ branching motif, which means every branching point is capable of attaching two branches or terminal groups. Fréchet and Hawker described the first convergent synthesis of dendrimers. They constructed poly(arylether) architectures "from the outside inwards" applying again the  $1 \rightarrow 2$  branching type [4]. Newkome and coworkers, in turn, presented a divergent synthetic route to watersoluble, highly branched "arborol systems" with terminal hydroxyl groups. In this case, the  $1 \rightarrow 3$  branching motif was utilized [5]. Percec and co-workers described an original convergent synthesis of four generations of dendrons with the  $1 \rightarrow 3$  branching motif based on the AB<sub>3</sub> building block methyl 3,4,5-trishydroxybenzoate

\* Corresponding authors.

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#### ABSTRACT

The synthesis of dendrimers and a chlorosulfo-dendron possessing a unique combination of  $1 \rightarrow 2$  and  $1 \rightarrow 4$  branching types is described. The procedure consists of a two-step preparation of 3,5-dinitrobenzene-1-sulfonyl chloride, which was used for the persulfonylation of *p*-toluidine and 4-(benzylthio)aniline. The obtained tetranitro compounds were reduced to the corresponding tetraamines. The latter were decorated with eight 4-toluene sulfonyl groups each to furnish the corresponding dendrimers. Oxidation of the dendrimer possessing a 4-(benzylthio)phenylene core with *N*-chlorosuccinimide resulted in the formation of a dendron with a sulfonyl chloride functionality at the focal point.

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[6]. Müllen and co-workers reported the four-fold Diels–Alder reaction of functionalized tetraphenylcyclopentadienone (the so-called A<sub>4</sub>B building block) with tetraethynylbiphenyl leading to the first and thus far only type of dendrimer with a  $1 \rightarrow 4$  branching motif [7].

Herein, we describe an alternative approach to the branched architectures involving combined  $1 \rightarrow 2$  and  $1 \rightarrow 4$  divergent growth type.

#### **Results and discussion**

The key compound for the preparation of the highly branched dendrons described in this work is 3,5-dinitrobenzene-1-sulfonyl chloride **2** (Scheme 1). Examination of the literature revealed that compound **2** could be obtained from 3,5-dinitroaniline *via* reaction with NaNO<sub>2</sub> with subsequent treatment of the diazonium salt with SO<sub>2</sub> [8]. However, this method has some drawbacks. Applying gaseous SO<sub>2</sub> onto the diazonium salt solution complicates the synthesis. Additionally, 3,5-dinitroaniline is a rather expensive reagent.

We developed a new two-step synthetic pathway to sulfonyl chloride **2** starting from 1,3,5-trinitrobenzene (**TNB**) (**CAUTION**: **TNB is an explosive and should be handled with great care**), the product of the primary processing of 2,4,6-trinitrotoluene. As shown in Scheme 1, in the first step the nucleophilic displacement of one nitro group in 1,3,5-trinitrobenzene with benzyl thiol in the presence of  $K_2CO_3$  takes place [9]. The process of the substitution

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*E-mail addresses:* o.lukin@skoltech.ru (O. Lukin), vladimir\_rozhkov@mail.ru (V. Rozhkov).

M. Kolotylo et al./Tetrahedron Letters xxx (xxxx) xxx



**Scheme 1.** Synthesis of 3,5-dinitrobenzene-1-sulfonyl chloride. Reagents and conditions: (i) K<sub>2</sub>CO<sub>3</sub>, DMF, rt; (ii) *N*-chlorosuccinimide, HCl, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C.

has been previously studied in detail and product **1** was obtained in 87% isolated yield [9]. Compound **1** readily reacts with *N*-chlorosuccinimide in the presence of concentrated aqueous HCl giving sulfonyl chloride **2** in nearly quantitative yield. Notably, since our last report on this type of reaction [10] we optimized the conditions which resulted in improved yields and shorter reaction times. The reaction was carried out in a homogeneous solution of both reagents in a 1:1 mixture of AcOH and  $CH_2Cl_2$  (Scheme 1). The overall isolated yield of **2** over the two steps was 83%.

The sulfonyl chloride was attached to p-toluidine to form persulfonylated nitro compound 3. The reaction was carried out in CH<sub>2</sub>Cl<sub>2</sub> in the presence of Et<sub>3</sub>N (Scheme 2). Tetranitro compound **3** precipitated from the reaction mixture. The product was filtered and washed with hot i-PrOH. Upon drying a colorless solid was obtained in 75% isolated yield. The use of p-toluidine is justified on account of its ready availability, higher reactivity in the persulfonylation reaction compared with aliphatic amines, and the ease of <sup>1</sup>H NMR interpretation of its derivatives. Four nitro groups of **3** were reduced to the amino groups with SnCl<sub>2</sub>·2H<sub>2</sub>O to furnish amine **4** which was obtained as a yellow solid in 23% isolated yield. The obtained amine is a stable compound and can be stored at ambient conditions for a long time without any detectable decomposition. Most likely, the relatively low yield of tetraamine 4 is due to its poor solubility in the extracting solvent (CH<sub>2</sub>Cl<sub>2</sub>) at the isolation stage. Finally, tetraamine **4** was treated with *p*-toluenesulfonyl chloride (12 eq.) to give dendrimer 5 in 41% isolated yield. The reaction was heated at reflux in CH<sub>2</sub>Cl<sub>2</sub> in the presence of Et<sub>3</sub>N for 72 h and the product was obtained as a creamy solid (Scheme 2).

Similarly, as depicted in Scheme 3, a convenient synthesis of "superbranched" sulfonyl chloride **10** was carried out. In this synthesis 4-(benzylthio)aniline **6** was first persulfonylated with sulfonyl chloride **2** in the presence of  $Et_3N$  in  $CH_2Cl_2$  to give tetranitro compound **7**. Notably, intermediate **7** did not precipitate



**Scheme 2.** Synthesis of dendrimer **5** utilizing the  $1 \rightarrow 4$  branching motif. Reagents and conditions: (i) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux; (ii) SnCl<sub>2</sub>·2H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>–MeOH (1:1), HCl, reflux; (iii) TsCl, Et<sub>4</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux.



**Scheme 3.** Synthesis of superbranched sulfonyl chloride **10**. Reagents and conditions: (i) Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux; (ii) SnCl<sub>2</sub>·2H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>–MeOH (1:1), HCl, reflux; (iii) TsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux; (iv) *N*-chlorosuccinimide, HCl, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C.

from the reaction mixture after reaction completion. Consequently, the solvent was evaporated and the residue was triturated with water (to remove triethylamine hydrochloride) and then with *i*-PrOH. The product was obtained as a white solid in 71% isolated yield. Analogous to the preparation of 4, tetranitro compound 7 was reduced to tetraamine 8 in 32% isolated yield. As in the case of tetraamine 4 the yield of 8 was moderate. This confirmed our assumption regarding the low solubility of amines in CH<sub>2</sub>Cl<sub>2</sub> at the isolation stage. The use of other reducing reagents such as Fe/NH<sub>4</sub>Cl, Zn/AcOH, and N<sub>2</sub>H<sub>4</sub>/FeCl<sub>3</sub>-C gave complex mixtures of products. In contrast to tetraamine 4, compound 8 was unstable and fully decomposes within 24 h. Therefore, compound 8 was used in the persulfonylation reaction immediately after its isolation. The tetraamine **8** was characterized only by <sup>1</sup>H NMR. In spite of eight reaction centers, amine 8 was persulfonylated in one step with tosyl chloride in the presence of triethylamine giving superbranched sulfonimide 9 which was successfully converted into sulfonyl chloride 10 using N-chlorosuccinimide as a chlorinating reagent (Scheme 3). The symmetrical structure of compound 10 is reflected in its simple <sup>1</sup>H NMR spectrum that can be unambiguously assigned (see ESI).

Dibutylamine was reacted with sulfonyl chloride **10** in MeCN in the presence of NaHCO<sub>3</sub> as a scavenger to give compound **11** (Scheme 4) proving that the reactivity of dendron **10** is comparable to that of regular arylsulfonyl chlorides.



Scheme 4. Synthesis of superbranched sulfonamide 11. Reagents and conditions: Bu<sub>2</sub>NH, NaHCO<sub>3</sub>, MeCN, rt.

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#### Conclusion

A divergent method for the synthesis of dendrimers and dendrons with a sulfonyl chloride functionality at the focal point possessing mixed  $1 \rightarrow 2$  and  $1 \rightarrow 4$  branching motifs was achieved. The key compound involved in the synthesis of these dendritic architectures is symmetrical trinitrobenzene (TNB) in which one nitro group can selectively be displaced by nucleophiles. It also was shown that the prepared dendritic sulfonyl chloride reacts as a typical aromatic sulfonyl chloride despite its considerable steric size.

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#### Appendix A. Supplementary data

Supplementary data (experimental procedures and spectral data) to this article can be found online at https://doi.org/10. 1016/j.tetlet.2018.12.052.

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