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Facile Synthesis of Aryl Ether Dendrimer from Unprotected AB_2 Building Blocks Using Thionyl Chloride as an Activating Agent

Natsuko Yamazaki, Isao Washio, Yuji Shibasaki, and Mitsuru Ueda*

Department of Organic and Polymeric Materials, Graduate School of Science and Engineering, Tokyo Institute of Technology, 2-12-1-H120 O-okayama, Meguro-ku, Tokyo 152-8552, Japan

mueda@polymer.titech.ac.jp

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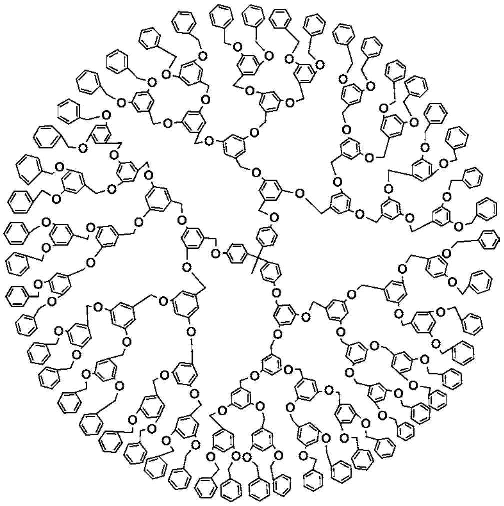
ABSTRACT



A novel, rapid, inexpensive, and highly efficient convergent approach for the synthesis of a Fréchet- type aryl ether dendrimer using thionyl chloride has been developed. In this method, the purification of each dendron and a dendrimer occurs by recrystallization, extraction, and precipitation. The MALDI-TOF MS spectrum supported the formation of the G2, G3, and G4 dendrons and the star-shaped G4 dendrimer.

Dendrimers are highly branched macromolecules consisting of a multifunctional core from which successive branched repeating units extend radially outward. A large number of reactive end groups at the periphery of dendrimers easily react with kinds of reagents giving dendrimers with various functionalities at their periphery. Therefore, they have received a great deal of attention as new polymeric materials for applications in areas such as molecular light harvesting,[1] catalysts,[2] liquid crystals,[3] molecular encapsulation,[4] and drug delivery systems.[5] Contrary to these useful prospects, a high level of synthetic control is required to prepare dendrimers. The general formation of dendrimers via divergent[6] or convergent[7] route involves reiterative growth strategies. In the divergent method, the molecule is assembled from the core to the periphery, while in the convergent method, the dendrimer is synthesized beginning from the outside and terminating at the core. In either method, it requires a

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stepwise process: attaching one generation to the last, purifying, and then changing functional groups for the next stage reaction. Several methods such as double-stage,[8] double-exponential growth,[9] hypermonomers,[10] and orthogonal coupling strategies[11] have been reported to shorten the time for these tedious syntheses by diminishing the number of steps.[12] These approaches, however, still require multiple steps to obtain high generation dendrimers. Recently, a one-pot, multiple-addition convergent synthesis of polycarbonate dendrimers was reported, in which the second-generation dendrimer was obtained by sequential activation of an alcohol with 1,1-carbonyldiimidazole and an AB_2 triol.[13] Quite recently, we have demonstrated a rapid synthesis of a perfectly branched third-generation polyamide dendrimer by a convergent method without repetitive protection−deprotection procedures.[14] This method consists of the direct condensation of a carboxylic acid and an unprotected AB_2 building block using the condensing agent, diphenyl(2,3-dihydro-2-thioxo-3-benzoxazolyl)phosphonate (DBOP),[15] and later using the more versatile activating reagent thionyl chloride.[16]

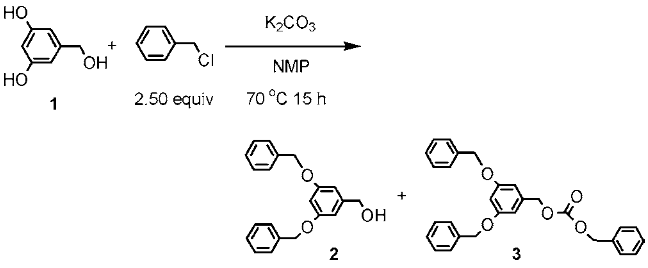
The Fréchet-type aryl ether dendrimer[7] is one of the most accepted macromolecules in various fields such as biology, although its synthesis is still difficult.[12b] Several methods have been reported to avoid the most difficult step of the bromination in the Fréchet process. Utilization of the Mitsunobu reaction and of the solid support system was developed.[17,18] They are, however, still tedious to prepare the high-quality dendrimer in a practical scale.

Thionyl chloride is the most attractive reagent for the chlorination of benzyl alcohols due to the short reaction time, low reaction temperature, and low price.[19] Percec et al. have reported utilization of thionyl chloride as a chlorination agent of benzyl alcohols and demonstrated that benzyl chloride is sufficient for the synthesis of aryl ether dendrimers.[20] However, they have used 3,5-dihydroxymethylbenzoate as a protected building block instead of 3,5-dihydroxybenzyl alcohol, which is conventionally used for preparation of aryl ether dendrimers. Therefore, the methyl benzoate group needed two-step reactions, reduction and chlorination, to prepare the benzyl chloride of each generation dendron.

Here, we present a successful rapid synthesis of a perfectly branched fourth generation (G4) Fréchet-type dendrimer (**7**) from unprotected AB_2 building block 3,5-dihydroxylbenzyl alcohol (**1**) by a convergent method using thionyl chloride as an activating agent. In our method, each generation dendron and dendrimer can be prepared in one pot: no isolation of intermediate chlorinated dendrons is required. Furthermore, the purification of every dendritic molecule requires only precipitation, recrystallization, and solvent extraction.

First-generation (G1) dendron **2** was initially prepared by the condensation of benzyl chloride with **1** in the presence of K_2CO_3 in 1-methyl-2-pyrrolidinone (NMP) at 70 °C for 18 h under nitrogen atmosphere. The products, however, contained only a few percent of 3,5-bis(benzyloxy)benzylbenzyl carbonate **3**, which was isolated by column chromatography and characterized by FT-IR, ^{1}H NMR, and MS spectroscopy (Scheme 1). We found that carbonate **3** was easily converted to the G1 dendron **2** and benzyl alcohol in the presence of K_2CO_3 in NMP at 140 °C for 3 h.

Scheme 1. Synthesis of G1 Dendron **2**



Thus, the preparation of G1 dendron **2** was carried out with an excess amount of K_2CO_3 in NMP at 120 °C for 1.5 h and then 140 °C for 8 h under nitrogen atmosphere

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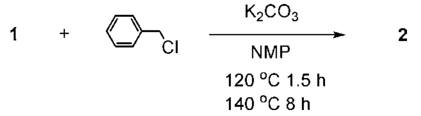
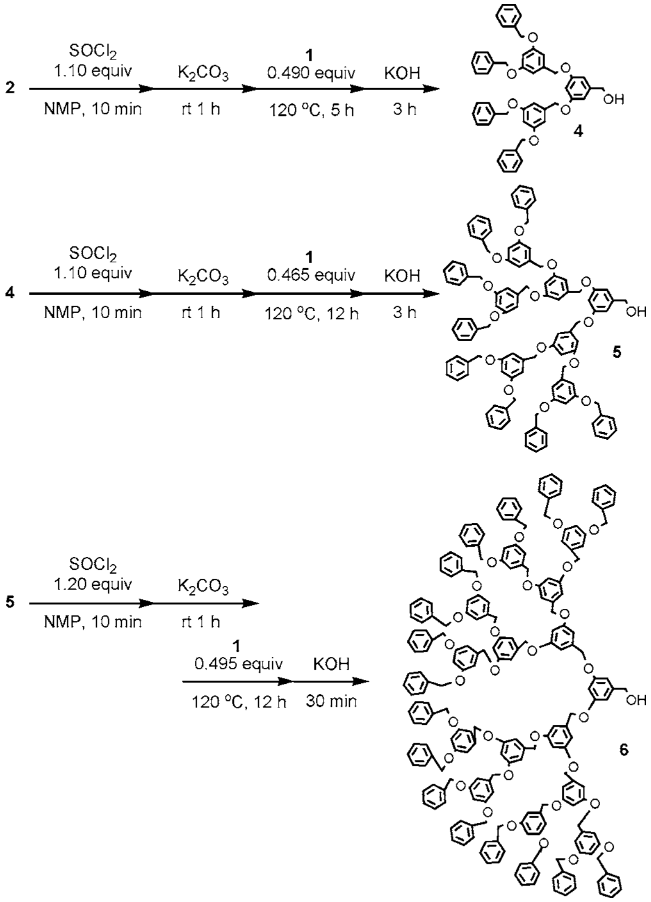
Scheme 2. Improved Synthesis of G1 Dendron **2**



(Scheme 2). The reaction mixture was poured into water, and the precipitate was collected and dried. Recrystallization from toluene/hexane gave the G1 dendron **2** in 85%.

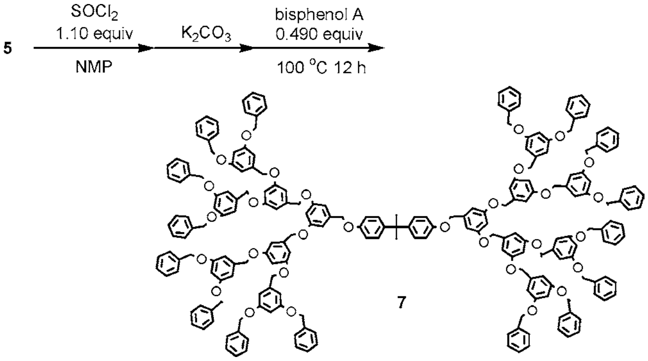
One-pot synthesis of G2 dendron **4** was then prepared from G1 dendron **2** and **1**. G1 dendron **2** was activated with 1.10 equiv of $SOCl_2$ in NMP at 0 °C for 10 min and then reacted with 0.50 equiv of **1** to G1 dendron **2** at 140 °C for 3 h under nitrogen atmosphere. The product was, however, only 3,5-bis(benzyloxy)benzyl chloride. The condensation of 3,5-bis(benzyloxy)benzyl chloride with **1** was completely prohibited with sulfurous acid generated from SO_2 and water because the isolated 3,5-bis(benzyloxy)benzyl chloride quantitatively reacted with **1** in the presence of K_2CO_3 in NMP. To remove HCl and remaining $SOCl_2$, an excess amount of K_2CO_3 was added to the solution before the condensation with **1** at 120 °C for 5 h. Desired G2 dendron **4** was produced with a small amount of similar carbonate compound formed in the synthesis of G1 dendron **2**. This carbonate was easily hydrolyzed with KOH. G2 dendron **4** was purified simply by reprecipitation to remove G1 dendron **2** and obtained in 80% yield as a white powder (Scheme 3). G3 dendron **5** and G4 dendron **6** were prepared by the same method in 82% and 73% yield,respectively (Scheme 3). The formation of the G2 dendron **4**, the G3 dendron **5**, and G4 dendron **6** was confirmed by ^1H NMR and MALDI-TOF MS spectroscopy (see the Supporting Information).

Scheme 3. Synthesis of G2 (**4**), G3 (**5**), and G4 (**6**) Dendrons



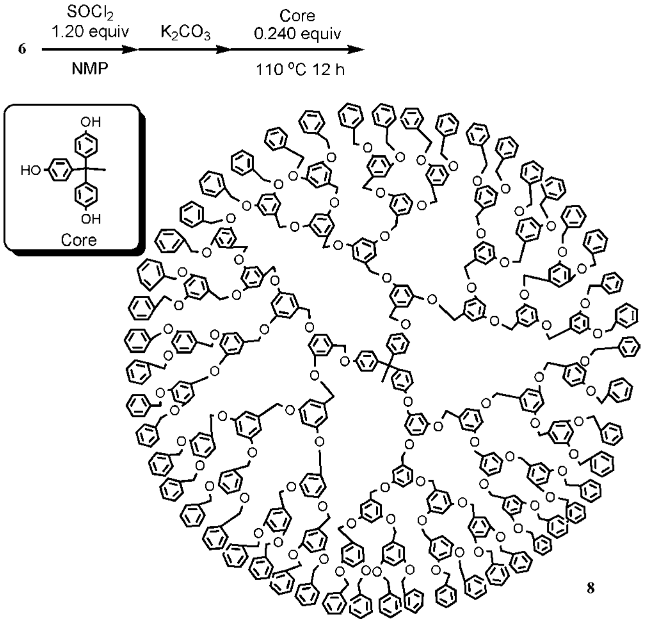
A coupling reaction of **5** and bisphenol A was performed to obtain a dumbbell-shaped G3 dendrimer **7** (Scheme 4).

Scheme 4. Synthesis of Dumbbell-Shaped G3 Dendrimer **6**



This reaction was performed using a two-step method similar to the syntheses for the G2, G3, and G4 dendrons. Activation of **5** was conducted using 1.10 equiv of $SOCl_2$, and a condensation reaction was carried out at 100 °C for 12 h. The resulting solution was diluted with toluene and washed with aqueous NaOH, aqueous HCl, and water. The organic part was concentrated, dissolved in a small amount of ethyl acetate, and poured into 2-methoxyethanol/ethyl acetate (10/1

Scheme 5. Synthesis of Star-Shaped G4 Dendrimer **8**



volume ratio). Dendrimer **7** was obtained in 76% yield and characterized by IR, NMR, and MALDI-TOF MS measurements and elemental analysis (see the Supporting Information).

Finally, a star-shaped G4 dendrimer **8**, which is expected to be a larger spherical shape, was prepared from **6** and 1,1,1-tris(4′-hydroxyphenyl)ethane in the same manner as the synthesis of G3 dendrimer **7** (Scheme 5). The resulting solution was poured into 1 M hydrochloric acid/methanol (1/1 in volume ratio). G4 dendrimer **8** was purified by washing with 2-methoxyethanol using a Soxhlet extractor. The yield of dendrimer **8** was 73%. IR, ^{1}H NMR, and MALDI-TOF MS measurements and elemental analysis were performed for the characterization of the dendrimer **8**. Figure 1 shows the MALDI-TOF MS spectrum of the dendrimer **8** (calcd mass 10127.7). A single signal was observed at *m*/*z* ($[M + Na]^+$) = 10149.4, indicating the formation of the star-shaped G4 dendrimer.

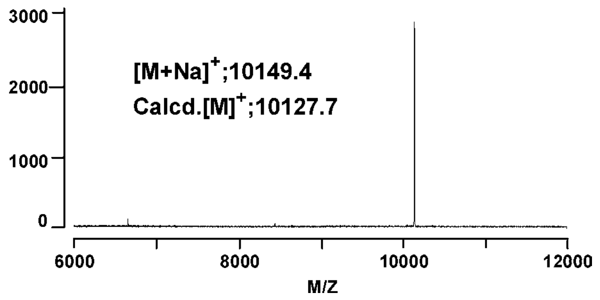


Figure 1. MALDI-TOF MS spectrum of G4 dendrimer.

In summary, a novel, very simple, inexpensive, and highly efficient convergent approach for the synthesis of the Fréchet-type aryl ether dendrimer using thionyl chloride has been developed. In this method, the purification of each dendron and a dendrimer are only extraction, recrystallization and precipitation. The MALDI-TOF MS spectrum supported the formation of the each dendron, the dumbell-shaped G3 dendrimer, and the star-shaped G4 dendrimer. The simplicity and experimental ease of this novel convergent route of the Fréchet-type dendrimer would make it extremely attractive for preparation of dendrimers both for laboratory and industrial scale.

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Supporting Information Available: Synthesis and characterization of each dendron and the star-shaped G4 dendrimer. This material is available free of charge via the Internet at http://pubs.acs.org.

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