ORGANIC LETTERS

2003
Vol. 5, No. 22
4159−4161

Facile Synthesis of Polyamide Dendrimers from Unprotected AB$_2$ Building Blocks

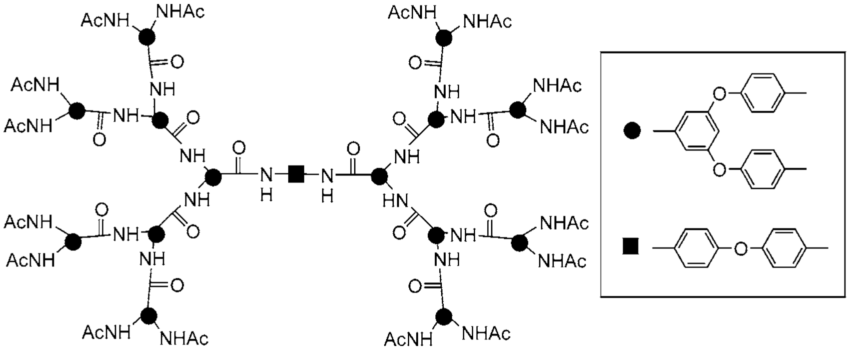
Isao Washio, Yuji Shibasaki, and Mitsuru Ueda*

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

mueda@polymer.titech.ac.jp

Received August 25, 2003

ABSTRACT



A fast, inexpensive, and highly efficient synthesis of aromatic polyamide dendrimers without the need for protection and deprotection steps has been developed. Dendrons and third-generation polyamide dendrimers were easily prepared by a convergent approach involving activation of a focal point with thionyl chloride, followed by condensation with unprotected AB$_2$ building blocks.

Dendrimers present a palette of unique properties, with applications in fields ranging from chemistry, catalysis, and material science to biology. However, syntheses of these macromolecules are tedious and provide poor yields due to the large number of steps involving repetitive protection−deprotection and purification processes in each generation. Although several groups have reported shortened syntheses[1] using double-stage, double-exponential growth, hypermonomer, and orthogonal coupling strategies, no effective methods have been developed for synthesizing polyamide dendrimers.[2]

Recently, we reported the rapid synthesis of a perfectly branched third-generation polyamide dendrimer by the convergent method without repetitive protection−deprotection procedures, involving direct condensation of a carboxylic acid and an unprotected AB$_2$ building block, 3,5-bis(4-aminophenoxy)benzoic acid (**1**), using the condensing agent diphenyl (2,3-dihydro-2-thioxo-3-benzoxazolyl)phosphonate (DBOP).[3] DBOP is very useful for producing amides and esters from carboxylic acids and amines or phenols in quantitative yields;[4] however, DBOP is an expensive reagent, especially for industrial large-scale synthetic use. Therefore,

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[1] For reviews, see, for example: (a) *Dendrimers and Dendrons, Concepts, Syntheses, Applications*; Newcome, G. R., Moorfield, C. N., Vögtle, F., Eds.; VCH: Weinheim, Germany, 2001. (b) *Dendrimer and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; VCH: Weinheim, Germany, 2002. (c) Grayson, M. S.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819.

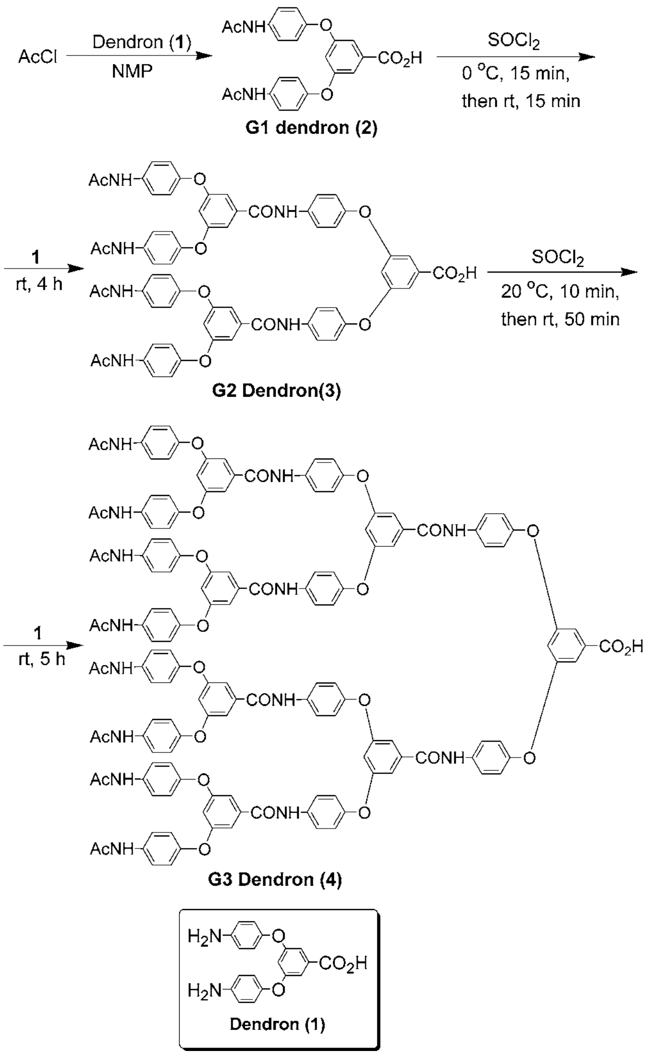
[2] (a) Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1990**, *2*, 346. (b) Bayliff, P. M.; Feast, W. J.; Parker, D. *Polym. Bull.* **1992**, 265. (c) Backson, S. C. E.; Bayliff, P. M.; Feast, W. J.; Kenwright, A. M.; Parker, D.; Richards, R. W. *Macromol. Symp.* **1994**, *77*, 1. (d) Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules* **2000**, *33*, 3202. (e) Rannard, S. P.; Davis, N. J.; McFarland, H. *Polym Int*. **2000**, *49*, 1002.

[3] Okazaki, M.; Washio, I.; Shibasaki, Y.; Ueda, M. *J. Am. Chem. Soc.* **2003**, *125*, 8120.

[4] (a) Ueda, M.; Kameyama, A.; Hashimoto, K. *Macromolecules* **1988**, *21*, 19. (b) Okazaki, M.; Hyakawa, T.; Ueda, M.; Takeuchi, K.; Asai, M. *J. Polym. Sci. Polym. Part A: Polym. Chem.* **2001**, *38*, 78.

10.1021/ol035595s CCC: $25.00

Scheme 1. Synthesis of Dendrons



finding a substitute for DBOP is important to expand the scope of this dendrimer synthesis.

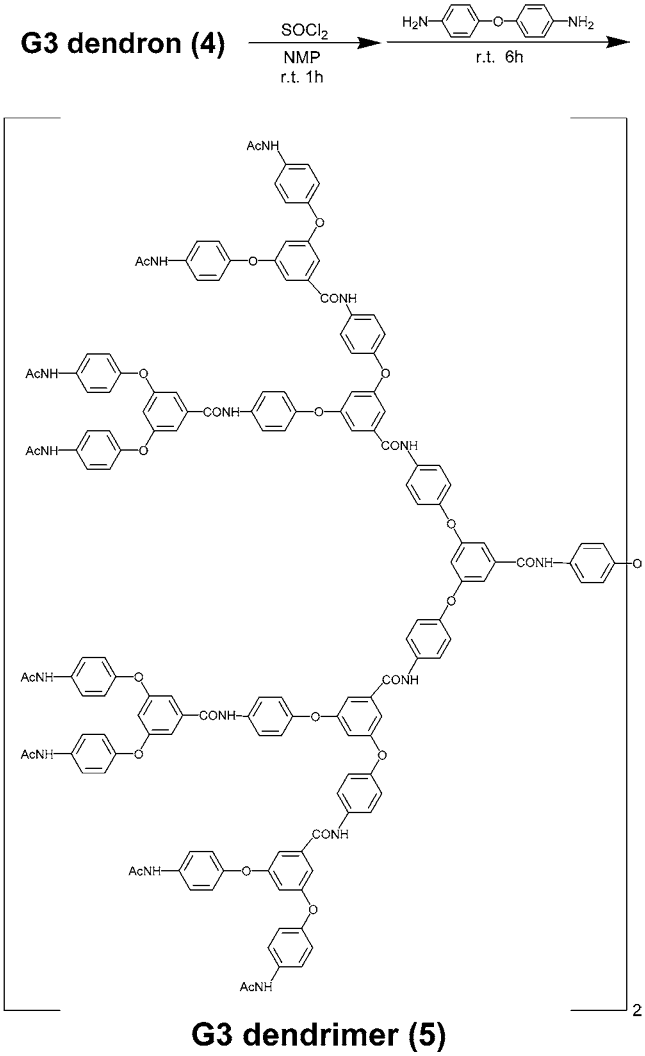
An inexpensive, commercially available reagent, thionyl chloride, is well-known as an activating agent for preparation of amides as well as acid chlorides from carboxylic acids.[5] Previously, we reported that thionyl chloride is effective for polyamide[6] and polyester[7] syntheses, after which no difficult purification procedures were necessary because the only byproducts were gases such as SO_2 and HCl.

Here, we present a facile synthesis of a perfectly branched third-generation polyamide dendrimer from unprotected **1** as an AB_2-building block by the convergent method using thionyl chloride as a versatile and common condensing reagent.

The coupling reaction for dendron synthesis was carried out by a two-step method involving (1) activation of carboxylic acids by thionyl chloride and (2) condensation with **1**. The molar ratio of thionyl chloride to the carboxyl group is very important for quantitative activation and prevention of unfavorable reactions such as self-condensation of **1** and reaction of thionyl chloride with amines. Thus, the reaction of 4-*t*-butylbenzoic acid with 4-phenoxy aniline was performed to determine the optimum molar ratio of thionyl chloride and a carboxylic acid in 1-methyl-2-pyrrolidinone (NMP). The reaction of 1.04 equiv of thionyl chloride to 4-*tert*-butyl benzoic acid provided the corresponding amide in quantitative yield. Then, the condensation of 4-*tert*-butylbenzoic acid with **1** in the presence of 1.04 equiv of thionyl chloride to the carboxylic acid was employed. Quantitative formation of the corresponding amide was observed.

The syntheses of G1, G2, and G3 dendrons are shown in Scheme 1. Dendron **1** was reacted with acetyl chloride to yield G1 dendron **2** in 98% yield after addition of the solution into water. The structure of **2** was characterized by IR, NMR, and elemental analyses. The IR spectrum of **2** showed strong absorptions at 1697 and 1658 cm^{-1}, characteristic of the C═O stretching of carboxyl acid and amide groups, respec-

Scheme 2. G3 Dendrimer Synthesis



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(5) Normant, J. F.; Deshayes, H. *Bull. Soc. Chim. Fr.* **1972**, 2854.

(6) Ueda, M.; Aoyama, S.; Konno, M.; Imai, Y. *Makromol. Chem.* **1978**, *179*, 2089.

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tively. Further evidence of the formation and isolation of **2** was obtained in the ^{1}H NMR spectrum.

G2 (**3**) and G3 (**4**) dendrons were prepared by the two-step method as mentioned above, in which thionyl chloride was employed as the condensing agent. The activation time of the carboxylic acid and the time for condensation were independently set depending on the dendron as shown in Scheme 1. In the case of G3 dendron synthesis, 2.0 equiv of thionyl chloride with respect to the G2 dendron was required. We assume that thionyl chloride decomposed during activation because of the hygroscopic nature of the amides in the G2 dendron. When the same reaction was conducted after drying **3** at 150 °C under reduced pressure, 1.1 equiv of thionyl chloride was sufficient to obtain **4**.

Each dendron was purified simply by reprecipitation to remove the parent dendron. G2 and G3 dendrons were isolated by reprecipitation with MeOH/water and EtOH in 92 and 72% yields, respectively, followed by characterization by IR, NMR, MALDI-TOF MS, and elemental analyses. The MALDI-TOF MS spectra of **3** and **4** showed the expected $[M + Na]^+$ peaks at 1163.0 and 2606.3, respectively. These findings clearly indicate the successful formation and isolation of the desired dendrons. The elemental analysis showed the contamination of a small amount of water in these dendrons even after the high-temperature dehydration under the reduced pressure. Thus, the accurate yields of G2 and G3 were determined by elemental analysis.

Finally, a dumbbell-shaped dendrimer (**5**) was synthesized from **4** and 4,4′-oxydianiline (Scheme 2). The reaction of **4** with 4,4′-oxydianiline was performed using 1.50 equiv of thionyl chloride with respect to the G3 dendron. The reaction mixture was poured into water and the precipitate collected and dried. The crude product was dissolved in *N*,*N*-dimethylformamide and the resulting solution reprecipitated with THF, giving dendrimer **5** in 74% yield. This value was also calculated on the basis of water contamination determined by elemental analysis. IR, NMR, MALDI-TOF MS, and elemental analyses were performed for the characterization of **5**. Figure 1 shows the MALDI-TOF MS spectrum of G3 polyamide dendrimer **5** (calcd mass 5329.39). A single signal was observed at M/Z ($[M + Na]^+$) = 5354.3, indicating the formation of the G3 dendrimer.

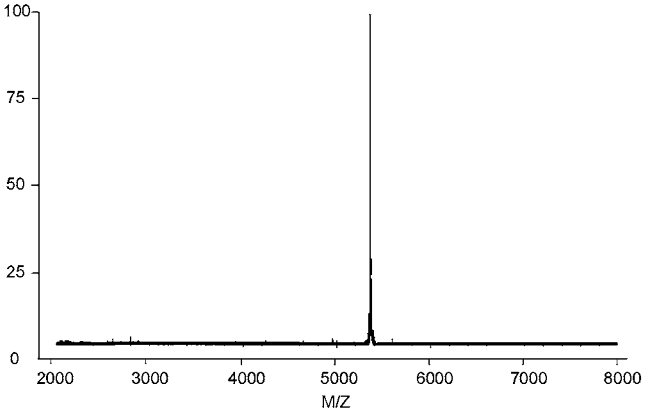

Figure 1. MALDI-TOF MS spectrum of the G3 dendrimer (**5**).

In conclusion, we have demonstrated a simple and highly efficient convergent approach for the synthesis of aromatic polyamide dendrimers using the inexpensive reagent thionyl chloride. In this method, the purification of each dendron and dendrimers requires only precipitation. The MALDI-TOF MS spectra supported the formation of the G2 and G3 dendrons and the G3 dendrimer. The methodology allows the large-scale and facile synthesis of dendrimers.

Acknowledgment. This work was financially supported by the New Energy and Industrial Technology Development Organization (NEDO) for the project of nanostructure polymers.

Supporting Information Available: Synthetic details and the characterization of each dendron and the G3 dendrimer. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035595S