

# Communications

## Synthesis of Dendrimers by Homocoupling of Alkyne-focal Fréchet Type Dendrons

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Received May 6, 2009, Accepted July 7, 2009

**Key Words:** Alkyne, Click chemistry, Dendrimer, Homocoupling

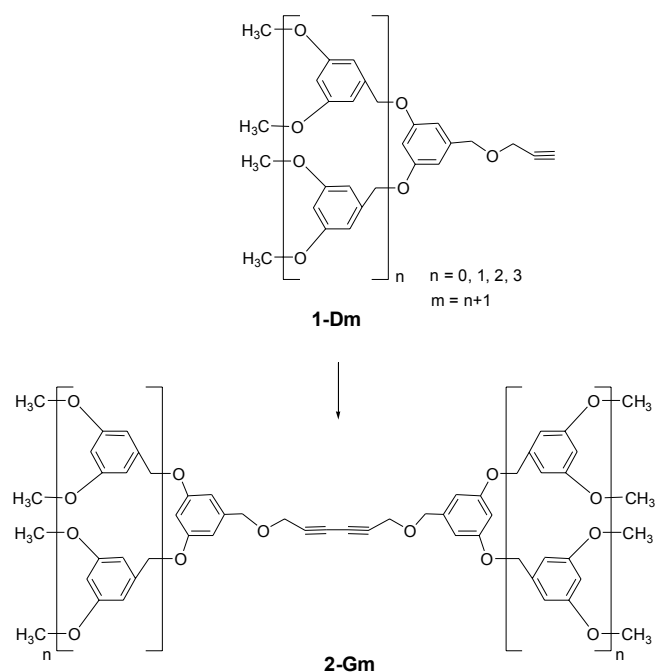
Terminal alkynes are versatile intermediates in synthetic organic and material chemistry due to their characteristic reactions such as metal-catalyzed coupling reactions including sonogashira coupling reaction and oxidative homocoupling, and so on.<sup>1</sup> Another important viewpoint in synthetic chemistry is 1,3-dipolar cycloaddition reaction with organoazides to provide heterocyclic five membered rings. The Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction between alkynes and azides is one of the prototype reactions in click chemistry.<sup>2</sup> This click chemistry is a modular approach that uses the most practical and reliable chemical transformations and has found in many applications in organic and material chemistry.<sup>3</sup> In continuation with our research on the synthesis of dendrimers *via* click chemistry using alkyne derivatives,<sup>4</sup> we are fascinated to develop the new click chemistry for the construction of dendrimers using oxidative homocoupling reaction of the terminal acetylene. In this paper, we report a feasible route to synthesize the symmetric Fréchet type dendrimers from Fréchet type dendrons containing alkyne moiety at their focal point by oxidative homocoupling of terminal alkyne.

Because dendrimers contain three distinct structural parts that are the core, end-groups, and branched units connecting core and periphery, we became interested in the synthesis of self-emissive dendrimer with a fluorescent probe in core region. A relatively few applications using the alkynyl-dendrimer in dendrimer synthesis have been reported. The palladium-catalyzed coupling of terminal acetylenes to aromatic bromides or iodides in basic amines have been well known since 1975.<sup>5</sup> In the investigation of the reaction between 9,10-dibromoanthracene and alkyne-dendrimer, we observed that the homocoupling of alkyne-dendrons was facilitated to provide the dimerized product. Therefore, we turned our attention into the synthesis of dendrimer by oxidative homocoupling of terminal alkyne. To the best of our knowledge, there is no report to synthesize dendrimers using oxidative homocoupling of terminal alkyne.

The synthetic strategy for Fréchet-type dendrimers, linked by 1,3-diynes, utilized a convergent method using the alkyne-functionalized Fréchet-type dendrons **1-Dm** (Scheme 1). The alkyne-functionalized Fréchet-type dendrons **1-Dm** was synthesized by the propargylation of the corresponding dendritic benzyl alcohols with propargyl bromide.<sup>4c</sup> To demonstrate the

effectiveness of oxidative homocoupling of alkyne-functionalized dendron **1-D1** (Scheme 1), we have screened with several conditions in different solvents and/or temperature with or without the additive in the presence of (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>/CuI. We have found that the reaction conducted from THF in the presence of (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>/CuI catalyst system with diisopropyl ethyl amine under heating afforded the desired product.

With this basic result, we began our study by establishing the validity of the chemistry in the synthesis of dendrimers. The reaction of alkyne-functionalized dendron **1-D1** in THF (0.1 M) in the presence of 0.025 equiv of (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>/0.015 equiv of CuI and 3 equiv of diisopropyl ethyl amine for 10 h at 40 °C afforded the desired product **2-G1** in yield of 94%.<sup>6</sup> The disappearance of **1-D1** and the appearance of new spot were observed from TLC analysis. The dendrimer **2-G1** was purified



**Scheme 1.** Synthetic strategy of dendrimers by oxidative homocoupling of alkyne-functionalized dendron. Reagents and conditions: (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>/CuI, diisopropyl ethyl amine, THF, 40 °C

by column chromatography and the structure of dendrimer was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, IR spectroscopy, and FAB mass spectra. The proton peak in terminal alkyne did not show at 2.47 ppm in the  $^1\text{H}$  NMR spectrum of dendrimer and the carbon peaks for the ethynylene carbons of dendrimer are at 72.2 and 75.8 ppm which are shielded relative to those for the dendron. IR data also confirmed that neither  $3286\text{ cm}^{-1}$  for the  $\text{H}-\text{C}\equiv$  bond stretching frequency nor  $2115\text{ cm}^{-1}$  for the  $\text{C}\equiv\text{C}$  bond stretching absorption remain in the final dendrimer. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. Reactions of dendron **1-D2** and **1-D3** afforded the dendrimers **2-G2** and **2-G3** in yields of 90 and 88% after 12 and 14 h, respectively, which were separated by column chromatography. In case of **1-D4**, the dendrimer **2-G4** was obtained in 85% yield after 17 h. For completion of the reaction, the higher generation dendron takes longer time than the lower generation dendron. This observation led us to imagine that the reaction was kinetically controlled by the accessibility of acetylide due to the steric hindrance (bulkiness) of dendron. This comparative efficiency of the new click methodology is emphasized by the synthesis of the symmetric dendrimers with 1,3-diynes at core. Therefore this approach may provide new methodological insight into introduction of multi-ynes at core of dendrimer and would greatly contribute to researches on the application side.

From their  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ ), the peaks of the methylene protons of core and the inside benzylic protons in dendrimers **2-Gm** were found at 4.52 and 4.55 ppm for **2-G1**, 4.24 and 4.54 ppm for **2-G2**, 4.23 and 4.53 ppm for **2-G3**, and 4.19 and 4.49 ppm for **2-G4**, respectively. As the dendrimer generation increased, the peaks of the discussed protons showed up-field shift which may be influenced by the dendritic micro-environment effect. The IR spectra show the disappearance of the  $\text{H}-\text{C}\equiv$  bond stretching frequencies around  $2115\text{ cm}^{-1}$  and the  $\text{C}\equiv\text{C}$  bond stretching absorptions around  $3286\text{ cm}^{-1}$  in the final dendrimer. Analysis of the dendrimers by FAB or MALDI mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling. As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values ( $\text{PDI} = 1.01 - 1.02$ ).

In summary, the convergent synthesis of dendrimers has been described by the oxidative homocoupling of terminal alkyne. The oxidative homocoupling reaction of the alkyne-functionalized Fréchet-type dendrons **1-Dm** was allowed to provide first through fourth generation dendrimers **2-Gm** with 1,3-diynes at core. Selection of appropriately functionalized terminal alkynes and dendrons will likely lead to the synthesis of new nanoscopic materials.

**Acknowledgments.** This research was supported by the Dong-A University Research Fund.

## References and Notes

- (a) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (b) Zhang, W.; Moore, J. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 4416. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632. (d) Moreno-Mañas, M.; Pleixats, R. *Acc. Chem. Res.* **2003**, *36*, 638.
- (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
- Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.
- (a) Lee, J. W.; Kim, B. K. *Bull. Korean Chem. Soc.* **2005**, *26*, 658. (b) Lee, J. W.; Kim, B. K.; Jin, S. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 833. (c) Lee, J. W.; Kim, B. K.; Kim, J. H.; Shin, W. S.; Jin, S. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1790. (d) Lee, J. W.; Kim, B. K. *Synthesis* **2006**, 615. (e) Lee, J. W.; Kim, J. H.; Kim, B. K.; Shin, W. S.; Jin, S. H. *Tetrahedron* **2006**, *62*, 894. (f) Lee, J. W.; Kim, B. K.; Kim, H. J.; Han, S. C.; Shin, W. S.; Jin, S. H. *Macromolecules* **2006**, *39*, 2418. (g) Lee, J. W.; Kim, J. H.; Kim, B. K. *Tetrahedron Lett.* **2006**, *47*, 2683. (h) Lee, J. W.; Kim, B. K.; Kim, J. H.; Shin, W. S.; Jin, S. H. *J. Org. Chem.* **2006**, *71*, 4988. (i) Lee, J. W.; Kim, J. H.; Kim, B. K.; Kim, J. H.; Shin, W. S.; Jin, S. H. *Tetrahedron* **2006**, *62*, 9193. (j) Lee, J. W.; Kim, J. H.; Kim, B. K.; Kim, J. H.; Shin, W. S.; Jin, S. H.; Kim, M. *Bull. Korean Chem. Soc.* **2006**, *27*, 1795. (k) Lee, J. W.; Kim, J. H.; Kim, H. J.; Han, S. C.; Kim, J. H.; Shin, W. S.; Jin, S. H. *Bioconjugate Chem.* **2007**, *18*, 579. (l) Lee, J. W.; Han, S. C.; Kim, J. H.; Ko, Y. H.; Kim, K. *Bull. Korean Chem. Soc.* **2007**, *28*, 1837. (m) Lee, J. W.; Kim, H. J.; Han, S. C.; Kim, J. H.; Jin, S. H. *J. Polym. Sci. Part A: Polym. Chem.* **2008**, *46*, 1083. (n) Lee, J. W.; Kim, H. J.; Han, S. C.; Kim, J. H.; Jin, S. H. *J. Nanosci. Nanotechnol.* **2008**, *8*, 4635. (o) Lee, J. W.; Kim, B.-K.; Han, S. C.; Lee, U. Y.; Kim, J. H.; Oh, J.; Jin, S. H. *Mol. Cryst. Liq. Cryst.* **2008**, *491*, 164. (p) Lee, J. W.; Kang, H.-S.; Han, S. C.; Sung, S. R.; Kim, J. H.; Oh, J.; Jin, S. H. *Mol. Cryst. Liq. Cryst.* **2008**, *492*, 139. (q) Lee, J. W.; Lee, U. Y.; Han, S. C.; Kim, J. H.; Jin, S. H. *Polymer (Korea)* **2009**, *33*, 67. (r) Lee, J. W.; Kim, B.-K.; Han, S. C.; Kim, J. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 157.
- (a) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Cassar, I. *J. Organomet. Chem.* **1975**, *93*, 253. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (d) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605. (e) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
- Typical experimental procedure.** A solution of alkyne-functionalized dendron **1-D1** (0.1 mmol),  $(\text{PPh}_3)_2\text{PdCl}_2$  (2.5 mol%), CuI (1.5 mol%), and diisopropyl ethyl amine (3 equiv) in THF (1 mL) was stirred at  $40^\circ\text{C}$  for the desired time until complete consumption of starting material as judged by TLC. After the usual workup, the residue was purified by flash column chromatography (hexane/ethyl acetate system) to give **2-G1**. FAB spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu. Spectral data for **2-G1**: IR 2936, 2839, 1597, 1458, 1204, 1153,  $1053\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.80 (s, 12H), 4.25 (s, 4H), 4.55 (s, 4H), 6.40 (t,  $J = 1.8\text{ Hz}$ , 2H), 6.51 (d,  $J = 1.9\text{ Hz}$ , 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  55.7, 58.0, 71.0, 72.2, 75.8, 100.6, 106.2, 139.8, 161.4; MS (FAB):  $m/z$  410.90 [ $\text{M}^+$ ]; HRMS (FAB) Calcd for  $\text{C}_{24}\text{H}_{26}\text{O}_6$ : 410.1729. Found: 411.1805 [ $\text{M}^+ + \text{H}$ ]. PDI: 1.01.