

## Synthesis of Dendrimers *via* Sonogashira Coupling Reaction of Alkyne-focal Fréchet Type Dendrons

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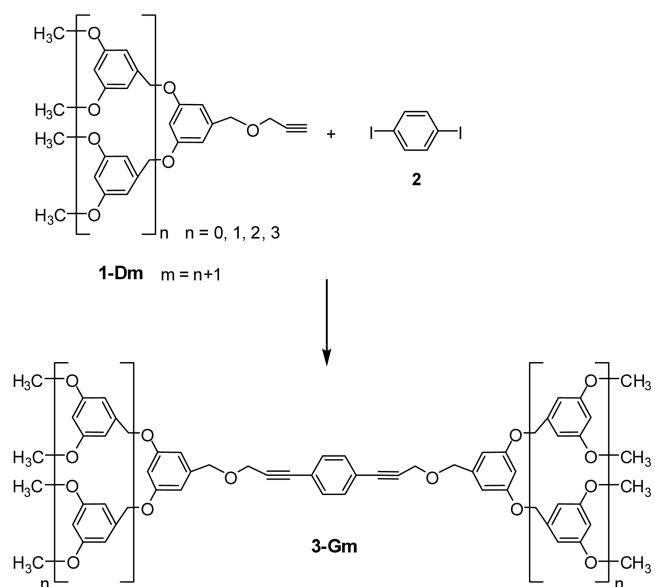
Dendrimers, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies, are highly branched and regular macromolecules with well-defined structures and have served as functional objects in nanotechnology and nanoscience.<sup>1</sup> The Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction between alkynes and azides is one of the prototype reactions in click chemistry.<sup>2</sup> We have developed the fusion and stitching methods for the convergent synthesis of dendrimers using click chemistry between an alkyne and an azide.<sup>3</sup> 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>4</sup> In continuation with our research on the synthesis of dendrimers *via* click chemistry using alkyne derivatives,<sup>5</sup> we are fascinated to develop the new click chemistry for the construction of dendrimers using Sonogashira coupling reaction of the terminal alkyne.

Although many methods for the convergent synthesis of various dendrimers were developed, there is still a demand to develop a simple, convenient, and efficient method for functional dendrimer. 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. The palladium-catalyzed coupling of terminal acetylenes to aromatic bromides or iodides in basic amines have been well known since 1975.<sup>6</sup> To the best of our knowledge, there is no report to synthesize dendrimers using Sonogashira coupling reaction. Herein we report a preliminary result to synthesize the symmetric dendrimers from the alkyne-focal Fréchet type dendrons and 1,4-diiodobenzene by the Sonogashira coupling reaction (Scheme 1).

The synthetic strategy for Fréchet-type dendrimers, linked by 1,4-diethynylbenzene, 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> The 1,4-diiodobenzene **2** was chosen to present

iodo functionalities available for dendrimer growth *via* sonogashira reaction with the alkyne dendrons. To find the most suitable conditions for the reaction of dendrons **1-D1** and 1,4-diiodobenzene **2**, we have screened with several conditions in different solvents, amine bases such as piperidine, triethylamine, diisopropylamine, piperazine and 1,8-diazabicycloundec-7-ene (DBU), and palladium catalysts in the presence of CuI. From these conditions the basicity of amine bases was a crucial factor to get high yield of product. Finally we have found that the reaction conducted from DMF as solvent, DBU as base, and Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst in the presence of CuI afforded the desired product in high yield.

With this basic result, we began our study by establishing the validity of the chemistry in the synthesis of dendrimers. The reaction of 1,4-diiodobenzene **2** and 2 equiv of alkyne-functionalized dendron **1-D1** in DMF (0.1 M) in the presence of 0.2 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>/0.05 equiv of CuI and 1.5 equiv of DBU for 2 h at room temperature afforded the desired product **3-G1** in yield of 93%.<sup>7</sup> The disappearance of



**Scheme 1.** Synthetic strategy of dendrimers by Sonogashira coupling reaction of alkyne-functionalized Dendron. *Reagents and conditions:* Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, DBU, DMF, rt.

**1-D1** and 1,4-diiodobenzene **2** and the appearance of new spot were observed from TLC analysis. The dendrimer **3-G1** was purified by column chromatography and the structure of dendrimer was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, IR spectroscopy, and mass spectra.<sup>7</sup> 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 86.0 and 86.9 ppm which are deshielded relative to those for the dendron. IR data also confirmed that neither  $3286\text{ cm}^{-1}$  for the  $\text{H-C}\equiv$  bond stretching frequency nor  $2115\text{ cm}^{-1}$  for the  $\text{C}\equiv\text{C}$  bond stretching absorption remain in the final dendrimer. The mass spectrum exhibited very good correlation with the calculated molecular masses.

Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. The same condition as first generation dendron **1-D1** was adapted for second generation dendron **1-D2**. Reaction of 1,4-diiodobenzene **2** and dendron **1-D2** afforded the dendrimer **3-G2** in yield of 90% which was separated by column chromatography. But we could not obtain the dendrimers **3-G3** and **3-G4** in satisfactory yields from the dendrons **1-D3** and **1-D4** with same condition as first generation dendron **1-D1**. Therefore we endeavored to find the optimum stoichiometric amount for palladium catalysts and CuI and the reaction time. Reactions of 1,4-diiodobenzene **2** and 2 equiv of alkyne-functionalized dendron **1-D3** and **1-D4** in DMF (0.1 M) in the presence of 0.4 equiv of  $\text{Pd}(\text{PPh}_3)_4$ /0.4 equiv of CuI and 1.5 equiv of DBU for 2 days at room temperature afforded the desired product **3-G3** and **3-G4** in yields of 84% and 80%, respectively. 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 transmetalation of copper acetylide to the palladium and 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 dendrimers with the tailor-made core unit. Therefore this approach may provide new methodological insight into introduction of various functional cores and would greatly contribute to researches on the application side. We are now investigating for self-emissive dendrimer with a fluorescent probe in core region.

In summary, the convergent synthesis of dendrimers has been demonstrated for the first time using the Sonogashira coupling reaction. The Sonogashira coupling reaction of the alkyne-functionalized Fréchet-type dendrons **1-Dm** with 1,4-diiodobenzene was allowed to provide first through fourth generation dendrimers **3-Gm**. Selection of appropriate fluorescent probe with multi-iodide will likely lead to the synthesis of new self-emissive dendrimer with a fluorescent probe in core region.

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- Typical Experimental Procedure.** A solution of 1,4-diiodobenzene (0.1 mmol) and alkyne-functionalized dendron **1-D1** (0.2 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (0.2 mol %), CuI (0.05 mol %), and DBU (0.15 mmol) in DMF (1 mL) was stirred at room temperature for 2 h. The reaction mixture was poured slowly into cold brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL  $\times$  3). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$  and filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:5) to afford the dendrimer **3-G1**. 93% yield; IR 2997, 2937, 2839, 1597, 1458, 1352, 1205, 1155,  $1066\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.80 (s, 12H), 4.40 (s, 4H), 4.61 (s, 4H), 6.41 (s, 2H), 6.55 (d,  $J$  = 2.0 Hz, 4H), 7.40 (s, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 55.3, 57.8, 71.7, 86.0, 86.9, 100.0, 105.7, 122.7, 131.6, 139.7, 160.9; MS (EI):  $m/z$  486 [ $\text{M}^+$ ]; HRMS (EI) Calcd for  $\text{C}_{30}\text{H}_{30}\text{O}_6$ : 486.2042. Found: 486.2047 [ $\text{M}^+$ ], 487.2077 [ $\text{M}^+$  + H]. PDI: 1.01. Mass datas were obtained from Korea Basic Science Institute (KBSI) in Daegu.