

Staudinger/Aza-Wittig Click Chemistry for Synthesis of Dendrimers Using Fréchet Type Dendritic Benzyl Azides

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Received January 31, 2009, Accepted March 19, 2009

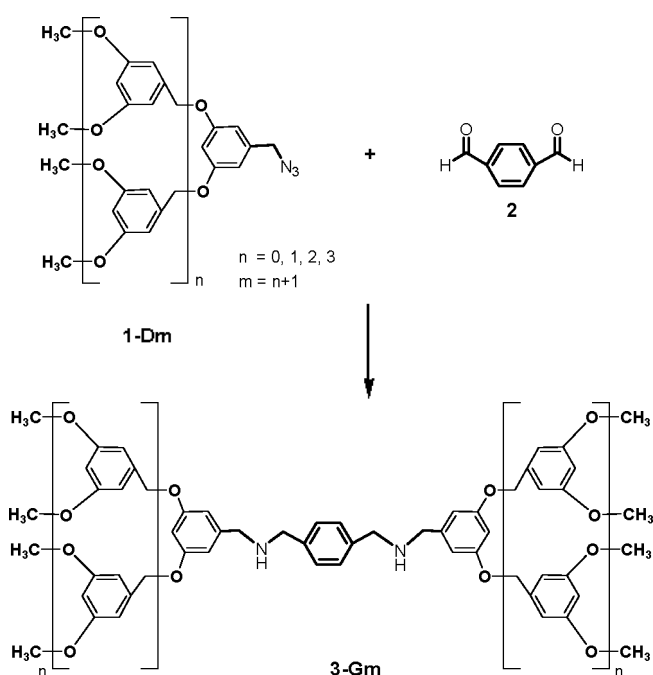
Key Words: Azide, Click chemistry, Dendrimer, Staudinger/aza-Wittig reaction

Secondary or tertiary amine derivatives were synthesized by N-alkylation reaction of primary amine with alkyl halides or reductive alkylation reaction of primary amine with carbonyl compounds.¹ Although the N-alkylation of amines is deceptively simple, this method has some drawback due to the formation of overalkylation products such as secondary amines, tertiary amines, and quaternary ammonium salts. There is also limitation due to stability of primary amine and availability and isolation problem for multiple amines derivatives. On the other hand, azides have proven to be useful as a kind of protecting group and precursor of amine compound in chemical synthesis.² In addition, azides are among the most stable 1,3-dipoles and generally can be stored for indefinite time without significant decomposition. Recently the well-known click chemistry which is the Cu(I)-catalyzed Huisgen [2 + 3] dipolar cycloaddition reaction between an organic azide and a terminal alkyne,³ has found in many applications in organic and material chemistry.⁴ In continuation with our research on the synthesis of dendrimers via click chemistry using azide derivatives,⁵ we are fascinated to develop the new click chemistry for the construction of dendrimers using Staudinger/aza-Wittig reactions.⁶ In this paper, we report a feasible route to synthesize dendrimers via sequential Staudinger/aza-Wittig reaction between an azide and an aldehyde.

Staudinger/aza-Wittig reactions are a powerful tool in organic synthetic strategies directed towards the preparation of nitrogen-containing compounds.⁷ To the best of our knowledge, there is no report to synthesize dendrimers using Staudinger/aza-Wittig reactions. We decided to apply this methodology for the synthesis of dendrimer. The synthetic strategy for Fréchet-type dendrimers, linked by the secondary amines, utilized a convergent method using the azide-functionalized Fréchet-type dendrons **1-Dm** and the di-aldehydes (Scheme 1). The azide-functionalized Fréchet-type dendrons **1-Dm** was synthesized by the azidation of the corresponding dendritic benzyl alcohols⁸ and/or the reaction of 5-(azido-methyl)-1,3-dihydroxybenzene with the dendritic benzyl bromide.^{5c} The benzene-1,4-dicarbaldehyde **2** was chosen to present aldehyde functionalities available for dendrimer growth via new click reaction with the dendrons. Our strategies in the synthesis of dendrimers are *in-situ* Staudinger/aza-Wittig reactions using an azido-dendron and aldehydes in the presence of triphenylphosphine and followed by the reduction

of imine intermediates.

To demonstrate the effectiveness of Staudinger/aza-Wittig reactions of benzene-1,4-dicarbaldehyde **2** and azide-dendron **1-D1** (Scheme 1), we have screened with several conditions in different solvents and/or temperature. We have found that the reaction conducted from toluene in the presence of triphenylphosphine for 24 h under reflux afforded the imine intermediate. The disappearance of benzene-1,4-dicarbaldehyde **2**, azide-dendron **1-D1**, and triphenylphosphine and the appearance of triphenylphosphine oxide and new spot were observed from TLC analysis. The resultant imine product was identified by ¹H-NMR spectroscopy which showed the characteristic imine peak at 8.36 ppm (Ar-CH=N-). This process can be achieved by the conversion of the azide into an imonophosphorane (the Staudinger reaction) followed by *in-situ* aza-Wittig reaction with aldehyde. The reduction of the imine intermediate with NaBH₄ in MeOH gave the desired



Scheme 1. Synthetic strategies of dendrimers by *in-situ* Staudinger/aza-Wittig reactions followed by the reduction of imine intermediates. Reagents and conditions: (a) PPh₃, toluene, reflux, (b) NaBH₄, MeOH, rt.

secondary amine product.

With this basic result, we began our study by establishing the validity of the chemistry in the synthesis of dendrimers. The reaction of benzene-1,4-dicarbaldehyde **2** and 2 equiv of azide-dendron **1-D1** in the presence of PPh₃ (2.2 equiv) in toluene (0.1 M) for 24 h under reflux followed by reduction with NaBH₄ afforded the desired product **3-G1** in yield of 96%. The dendrimer **3-G1** was purified by column chromatography and the structure of dendrimer was confirmed by ¹H and ¹³C NMR spectroscopy, IR spectroscopy, and FAB mass spectra. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. Reactions of the benzene-1,4-dicarbaldehyde **2** with dendron **1-D2** and **1-D3** afforded the dendrimers **3-G2** and **3-G3** in yields of 97 and 94%, respectively, which were separated by column chromatography. In case of **1-D4**, the dendrimer **3-G4** was obtained in 92% yield. This comparative efficiency of the new click methodology is emphasized by the synthesis of the dendrimers with the tailed 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.

All dendrimers were confirmed by ¹H and ¹³C NMR spectroscopy.⁹ From their ¹H NMR spectra (CD₂Cl₂), the peaks of the benzene protons of core and the secondary amine protons in dendrimers **3-Gm** were found at 7.19 and 1.63 ppm for **3-G1**, 7.16 and 1.47 ppm for **3-G2**, 7.15 and 1.44 ppm for **3-G3**, and 7.12 and 1.41 ppm for **3-G4**, respectively. As the dendrimer generation increased, the peaks of the benzene protons of core and the secondary amine protons showed up-field shift which may be influenced by the dendritic microenvironment effect. The IR spectra show the disappearance of the aldehyde peak and the azide peak 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 (PDI = 1.01-1.02).

In summary, the convergent synthesis of dendrimers has been described by using Staudinger/aza-Wittig reactions. Fréchet-type dendrons **1-Dm** containing azide moiety at their focal point were allowed to react with commercial benzene-1,4-dicarbaldehyde central linker **2** to provide first through fourth generation dendrimers **3-Gm**. Selection of appropriately functionalized azides, aldehydes, and dendrons will likely lead to the synthesis of new nanoscopic materials.

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by the Korean Government(MOEHRD) (KRF-2006-311-C00432).

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- Spectral data for dendrimers (**3-Gm**). **3-G1**. A white solid; m.p. 72-74 °C, 99% yield; IR 3001, 2936, 2835, 1597, 1462, 1432, 1346 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 1.63 (s, 2H), 3.62 (s, 4H), 3.65 (s, 12H + 4H), 6.22 (t, *J* = 2.0 Hz, 2H), 6.40 (d, *J* = 2.0 Hz, 4H), 7.19 (s, 4H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 53.3, 53.7, 55.8, 99.3, 106.4, 128.7, 139.7, 143.6, 161.5; MS (FAB): *m/z* 437.15 [M⁺ + H]; HRMS (FAB) Calcd for C₂₈H₃₂N₂O₄: 436.2362. Found: 437.2438 [M⁺ + H]. PDI: 1.01. **3-G2**. A white solid; m.p. 60-62 °C, 96% yield; IR 3001, 2936, 2839, 1597, 1459, 1431, 1323 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 1.47 (s, 2H), 3.62 (s, 4H), 3.63 (s, 4H), 3.65 (s, 24H), 4.85 (s, 8H), 6.28 (m, 4H), 6.36 (m, 2H), 6.45 (d, *J* = 1.0 Hz, 8H), 6.49 (m, 4H), 7.16 (s, 4H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 53.4, 53.7, 55.9, 70.5, 100.2, 101.1, 105.8, 107.6, 128.7, 139.8, 140.1, 143.9, 160.5, 161.6; MS (FAB): *m/z* 981.3 [M⁺ + H]; HRMS (FAB) Calcd for C₅₈H₆₄N₂O₁₂: 980.4459. Found: 981.4534 [M⁺ + H]. PDI: 1.01. **3-G3**. A white solid; m.p. 56-58 °C, 96% yield; IR 3001, 2936, 2839, 1597, 1458, 1431, 1373 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 1.44 (s, 2H), 3.61 (s, 4H), 3.64 (s, 48H + 4H), 4.84 (s, 24H), 6.27 (m, 8H), 6.35 (m, 2H), 6.43 (m, 20H), 6.48 (m, 4H), 6.55 (m, 8H), 7.15 (s, 4H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 53.4, 53.7, 55.9, 70.4, 70.6, 100.3, 101.1, 102.0, 105.8, 106.9, 107.6, 128.7, 139.8, 139.9, 140.3, 143.9, 160.5, 160.6, 161.6; MS (MALDI): Calcd for C₁₂₂H₁₂₈N₂O₂₈: 2068.8654. Found: 2069.8203 [M⁺ + H]. PDI: 1.01. **3-G4**. A colorless oil; 92% yield; IR 3001, 2939, 2839, 1597, 1458, 1431, 1373 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 1.41 (s, 2H), 3.57 (s, 4H), 3.58 (s, 4H), 3.61 (s, 96H), 4.81 (s, 56H), 6.25 (m, 16H), 6.36 (m, 2H), 6.39 (m, 12H), 6.41 (m, 32H), 6.47 (m, 4H), 6.52 (m, 24H), 7.12 (s, 4H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 53.4, 53.7, 55.8, 70.40, 70.48, 70.54, 100.3, 101.1, 102.0, 102.1, 105.8, 106.9, 107.6, 128.7, 139.8, 139.9, 140.0, 140.3, 144.0, 160.5, 160.6, 161.6; MS (MALDI): Calcd for C₂₅₀H₂₅₆N₂O₆₀: 4245.7042. Found: 4246.6340 [M⁺ + H]; 4249.7056 [M⁺ + H + Na]. PDI: 1.02. FAB and MALDI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu or Daejeon and POSTECH.