

Staudinger/Aza-Wittig 반응에 의한 삼발이 핵을 갖는 Fréchet-type 덴드리머의 합성

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Synthesis of Fréchet-type Dendrimers with Tripodal Core via Staudinger/Aza-Wittig Reactions

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초록: 덴드리머의 중심에 삼발이 핵을 갖는 덴드리머의 합성을 위한 효율적인 연결 방법이 개발되었다. 합성전략은 알데히드 덴드론과 아자이드기를 갖는 삼발이 핵 사이의 반응을 톨루엔 용매와 triphenylphosphine 존재하에서 진행하는 새로운 클릭화학(Staudinger/aza-Wittig 반응)을 이용하였다. 덴드리머의 삼발이 핵으로 작용할 수 있는 단위체인 1,3,5-tris-(3-azido-propoxy)-benzene을 합성하였고, 이 화합물의 아자이드기는 덴드리머의 형성에 이용되었다. 1,3,5-Tris-(3-azido-propoxy)-benzene을 이용하여 알데히드 덴드론과 Staudinger/aza-Wittig 반응을 통해 덴드리머를 합성하였으며, 모든 덴드리머는 높은 수득률로 얻어졌다.

Abstract: Efficient stitching methods for the synthesis of tripodal Fréchet-type dendrimers containing secondary amine as a connector were elaborated. The synthetic strategy involved Staudinger/aza-Wittig reactions (new click reaction) between tripodal tris(azides) and aldehyde-dendrons in toluene in the presence of triphenylphosphine and followed by the reduction of imine intermediates. The tripodal core (1,3,5-tris-(3-azido-propoxy)-benzene) was chosen to serve as the azide functionalities for dendrimer growth. 1,3,5-Tris-(3-azido-propoxy)-benzene was stitched with the aldehyde-functionalized Fréchet-type dendrons via Staudinger/aza-Wittig reactions leading to the formation of the corresponding Fréchet-type dendrimers in high yields.

Keywords: Staudinger/aza-Wittig reaction, aldehyde, azide, dendrimer, tripodal.

Introduction

Dendrimers represent a novel type of polymeric material that has generated much interest in diverse areas due to their unique structure and properties, and have served as functional objects in nanotechnology and nanoscience.^{1,2} Dendrimers are highly branched macromolecules, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies.³ Generally, the reactions employed are high yielding without any side reactions. This then allows one to obtain defined and uniform structures. Well known processes, such as the Michael reaction, Williamson ether synthesis, amidations

and reductions have been used extensively in pioneering work by Vögtle, Tomalia, Fréchet and Newkome.⁴⁻⁶ Recent investigation of the click chemistry, the Staudinger/aza-Wittig reaction between an organic azide and an aldehyde, has attracted attention which has found many applications in organic chemistry,^{7,8} supramolecular chemistry,⁹ and materials science.¹⁰ Azides have proven to be useful as a kind of protecting group and precursor of amine compound in chemical synthesis.¹¹ Azide is easily accessible to prepare from the corresponding halide.^{11,12} In addition, azides are among the most stable 1,3-dipoles and generally can be stored for indefinite time without significant decomposition. There are few reports to synthesize the tripodal dendritic materials using click chemistry with dendronized azide.¹³⁻¹⁵ In continuation with our research on the synthesis of dendrimers via click chemistry using azide deriv-

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atives, we have developed the fusion and stitching methods for the synthesis of dendrimers *via* Staudinger/aza-Wittig reactions (new click reaction) between azide and aldehyde.¹⁶⁻¹⁸ We are still intrigued to apply this methodology for the convergent synthesis of dendrimers. The poly(benzyl ether) dendrons, now frequently referred to as Fréchet-type dendrons, was selected because they are relatively readily accessed and exhibit the chemical stability associated with ether linkages.¹⁹⁻²⁸ Here we present the convergent synthesis of tripodal Fréchet-type dendrimers by trimerization of aldehyde-dendrons *via* Staudinger/aza-Wittig reactions using tripodal core, 1,3,5-tris-(3-azido-propoxy)-benzene.

Experimental

¹H NMR spectra were recorded on a 400 or 500 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; d of d, doublet of a doublet; m, multiplet; br, broad. ¹³C NMR spectra were proton decoupled and recorded on a 100 or 125 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. FAB mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu. Flash chromatography was performed with 37-75 μ m silica gel. Analytical thin layer chromatography was performed on silica plates with F₂₅₄ indicator and the visualization was accomplished by UV lamp or using an iodine chamber.

Synthesis of 1,3,5-Tris-(3-Azido-propoxy)-Benzene 1. A mixture of benzene-1,3,5-triol (0.22 g, 1.33 mmol) and 1-azido-3-iodo-propane (0.98 g, 4.66 mmol) in DMF (13 mL) in the presence of potassium carbonate (0.64 g, 4.66 mmol) was stirred for 24 h at 50 °C. The resulting solution was extracted with methylene chloride (50 mL $\times$ 4). The organic phase was dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography (EtOAc/hexane=1:4) to afford the desired product **1** (0.45 g, 90%). A yellowish oil; IR : 2939, 2878, 2099, 1597, 1462, 1265, 1165, 1065 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 2.03 (quin, *J* = 6.3 Hz, 6H), 3.50 (t, *J* = 6.5 Hz, 6H), 4.01 (t, *J* = 5.8 Hz, 6H), 6.08 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 28.8, 48.3, 64.7, 94.3, 160.6; MS (FAB): *m/z* 376.05 [M⁺+H]; HRMS (FAB): Calcd for C₁₅H₂₁N₉O₃: 375.1767. Found: 376.1844 [M⁺+H].

General Procedure for the Preparation of Dendrimers

3-Gm by Reaction between 1,3,5-Tris-(3-Azido-propoxy)-Benzene 1 and Aldehyde-dendrons 2-Dm. A solution of 1,3,5-tris-(3-azido-propoxy)-benzene **1** (0.14 mmol) and aldehyde-dendron **2-Dm** (0.46 mmol) in toluene (1.4 mL) in the presence of triphenylphosphine (0.46 mmol) was stirred under reflux. After 24 h, the reaction solution was diluted with MeOH (2 mL) and subsequently added NaBH₄ (0.46 mmol). Then the reaction was stirred overnight at room temperature. After evaporation, the residue was partitioned in CH₂Cl₂ and saturated Na₂CO₃ aqueous solution and extracted two to three times with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, and filtered and the filtrate was concentrated. The crude product was purified by flash chromatography to afford the dendrimer **3-Gm**.

Compound 3-G1. *R*_f = 0.3 (EA/CH₂Cl₂ = 2:1); A yellowish oil; 95% yield; IR : 3333, 2997, 2936, 2835, 1597, 1462, 1431, 1204, 1157, 1065 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.78 (br, 3H), 1.96 (t, *J* = 6.0 Hz, 6H), 2.81 (t, *J* = 6.5 Hz, 6H), 3.75 (s, 6H), 3.77 (s, 18H), 3.99 (t, *J* = 5.5 Hz, 6H), 6.05 (s, 3H), 6.35 (s, 3H), 6.49 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ = 29.7, 46.3, 54.1, 55.3, 66.4, 94.1, 99.1, 105.9, 142.8, 160.8, 160.9; MS (FAB): *m/z* 748.2 [M⁺+H]; HRMS (FAB): Calcd for C₄₂H₅₇N₉O₉: 747.4095. Found: 747.4041 [M⁺], 748.4174 [M⁺+H]. PDI: 1.01.

Compound 3-G2. *R*_f = 0.1 (EA/CH₂Cl₂ = 2:1); A yellowish oil; 92% yield; IR : 3352, 2997, 2935, 2839, 1597, 1463, 1431, 1204, 1153, 1053 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.68 (br, 3H), 1.92 (t, *J* = 5.8 Hz, 6H), 2.76 (t, *J* = 6.3 Hz, 6H), 3.73 (s, 6H), 3.78 (s, 36H), 3.96 (t, *J* = 5.0 Hz, 6H), 4.95 (s, 12H), 6.04 (s, 3H), 6.40 (s, 6H), 6.50 (s, 3H), 6.57-6.58 (m, 18H); ¹³C NMR (125 MHz, CDCl₃): δ = 29.7, 46.3, 54.0, 55.3, 66.4, 70.0, 94.0, 99.9, 100.8, 105.2, 107.1, 139.4, 143.0, 160.0, 160.8, 161.0; MS (FAB): *m/z* 1564.2 [M⁺+H]; HRMS (FAB): Calcd for C₉₀H₁₀₅N₃O₂₁: 1563.7241. Found: 1563.7250 [M⁺], 1564.7313 [M⁺+H]. PDI: 1.01.

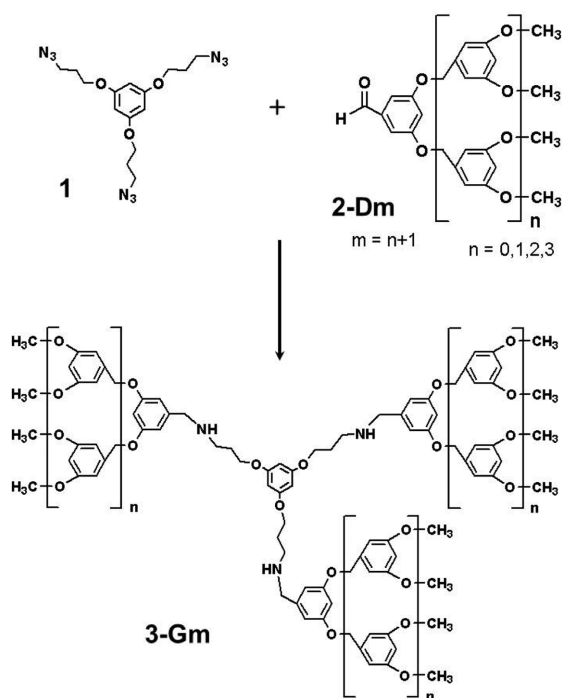
Compound 3-G3. *R*_f = 0.2 (MeOH/CH₂Cl₂ = 2:1); A yellowish oil; 89% yield; IR : 3410, 3001, 2936, 2839, 1597, 1458, 1431, 1204, 1153, 1053 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.76 (br, 3H), 1.91 (t, *J* = 6.0 Hz, 6H), 2.76 (t, *J* = 6.2 Hz, 6H), 3.76 (m, 78H), 3.94 (t, *J* = 4.4 Hz, 6H), 4.91 (s, 12H), 4.94 (s, 24H), 6.04 (s, 3H), 6.39 (t, *J* = 2.2 Hz, 12H), 6.48 (t, *J* = 2.0 Hz, 3H), 6.53-6.57 (m, 36H), 6.65 (d, *J* = 2.0 Hz, 12H); ¹³C NMR (100 MHz, CDCl₃): δ = 29.7, 46.3, 54.0, 55.3, 66.3, 70.0, 94.0, 99.9, 100.5, 101.5, 105.2, 106.4, 107.1, 139.1, 139.9, 143.0, 160.0, 160.7, 160.9, 161.0; MS (MALDI): Calcd for C₁₈₆H₂₀₁N₃O₄₅: 3196.3532. Found: 3196.9298 [M⁺],

3219.9316 [$M^+ + Na$]. PDI: 1.01.

Compound 3-G4. $R_f = 0.1$ (MeOH/ $CH_2Cl_2 = 5:1$); A yellowish oil; 85% yield; IR : 3410, 3001, 2935, 2839, 1597, 1458, 1431, 1204, 1153, 1053 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.77$ (br, 3H), 1.90 (t, $J = 5.6$ Hz, 6H), 2.75 (t, $J = 6.0$ Hz, 6H), 3.76 (m, 150H), 3.92 (t, $J = 4.8$ Hz, 6H), 4.91 (s, 36H), 4.93 (s, 48H), 6.03 (s, 3H), 6.38 (t, $J = 2.2$ Hz, 24H), 6.47 (t, $J = 2.4$ Hz, 3H), 6.53-6.55 (m, 72H), 6.64 (m, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.6, 46.2, 53.9, 55.3, 66.3, 69.9, 70.0, 93.9, 99.9, 100.4, 101.5, 101.6, 105.2, 106.4, 107.1, 139.1, 139.2, 139.8, 143.0, 160.0, 160.6, 160.9, 161.0$; MS (MALDI): Calcd for $C_{378}H_{393}N_3O_{93}$: 6461.6115. Found: 6461.8174 [M^+]. PDI: 1.02.

Results and Discussion

Staudinger/aza-Wittig reactions are a powerful tool in organic synthetic strategies directed towards the construction of nitrogen-containing heterocycles.²⁹⁻³² To the best of our knowledge, there is no report to synthesize tripodal dendrimers using Staudinger/aza-Wittig reactions. The synthetic strategy for the Fréchet-type dendrimers **3-Gm** utilized a convergent method using the tripodal tris(azides) **1** and the Fréchet-type



Scheme 1. Synthetic strategies of tripodal dendrimers **3-Gm**. Reagents and conditions: (a) PPh_3 , toluene, reflux; (b) $NaBH_4$, MeOH, rt.

aldehyde-dendrons **2-Dm** (Scheme 1). For the effective synthesis of the Fréchet-type dendron aldehydes, we have designed and utilized 3,5-dihydroxybenzaldehyde as an aldehyde focal point functionalized unit for the efficient synthesis of aldehyde-functionalized Fréchet-type dendrons. The Fréchet-type aldehyde-dendrons **2-Dm** ($m = 1, 2, 3$, and 4: generation of dendron) were prepared according to the reported procedure.¹⁷ The 1,3,5-tris-(3-azido-propoxy)-benzene **1** was chosen to present azide functionalities available for dendrimer growth *via* new click reaction with the dendrons.

To test the effectiveness of *in-situ* Staudinger/aza-Wittig reactions of tripodal tris(azides) **1** and aldehyde-dendrons **2-Dm**, we have reacted **1** with **2-D1** in toluene in the presence of triphenylphosphine and followed by the reduction of imine intermediates. From the investigation using compounds (**1** and **2-D1**), 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 1,3,5-tris-(3-azido-propoxy)-benzene **1**, **2-D1**, and triphenylphosphine and the appearance of triphenylphosphine oxide and new spot were observed from TLC analysis. The resultant imine product, which is achieved by the conversion of the azide into an imonophosphorane (the Staudinger reaction) followed by *in-situ* aza-Wittig reaction with aldehyde, was identified by 1H NMR spectroscopy which showed the characteristic imine peak around 8.25 ppm ($Ar-CH=N-$). The reduction of the imine intermediate with $NaBH_4$ in MeOH gave the desired secondary amine product. With this basic result, we began our study by establishing the validity of the chemistry in the synthesis of tripodal dendrimers. The reaction of 1,3,5-tris-(3-azido-propoxy)-benzene **1** and 3 equiv of aldehyde-dendron **2-D1** in the presence of PPh_3 (3.3 equiv) in toluene (0.1 M) for 24 h under reflux followed by reduction with $NaBH_4$ afforded the desired product **3-G1** in yield of 95%. The dendrimer **3-G1** was purified by column chromatography and the structure of dendrimer was confirmed by 1H and ^{13}C 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 1,3,5-tris-(3-azido-propoxy)-benzene **1** with dendron **2-D2**, **2-D3**, and **2-D3** afforded the dendrimers **3-G2**, **3-G3**, and **3-G4** in yields of 92%, 89%, and 85%, respectively, which were separated by column chromatography. 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.

All tripodal dendrimers **3-Gm** were confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB or MALDI mass spectra. From their ^1H NMR spectra (CDCl_3), the peaks of the benzene protons of tripodal core and the secondary amine protons in dendrimers **3-Gm** were found at 6.05 and 1.78 ppm for **3-G1**, 6.04 and 1.68 ppm for **3-G2**, 6.04 and 1.76 ppm for **3-G3**, and 6.03 and 1.77 ppm for **3-G4**, respectively (Figure 1). As the dendrimer generation increased, the peaks of the benzene protons of core showed up-field shift which may be influenced by the dendritic microenvironment effect.³³⁻³⁵

The IR spectra show the disappearance of the aldehyde peak (2808, 2727, and 1701 cm^{-1}) and the azide peak (2099 cm^{-1}) in the final dendrimer (Figure 2). Analysis of the dendrimers by mass spectrometry as well as by gel permeation chromatog-

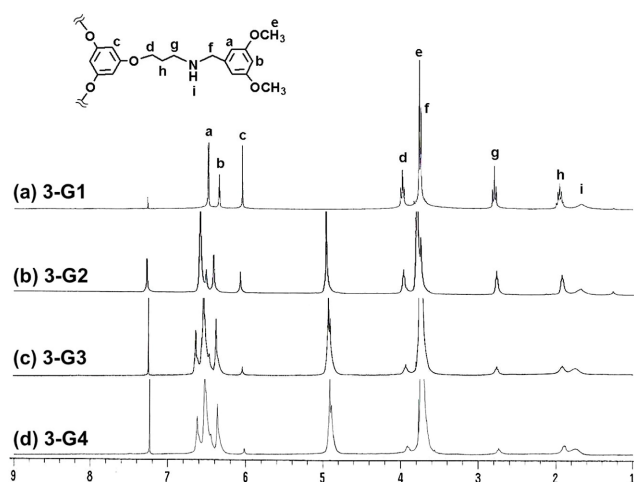


Figure 1. ^1H NMR spectra for (a) **3-G1**; (b) **3-G2**; (c) **3-G3**; (d) **3-G4**.

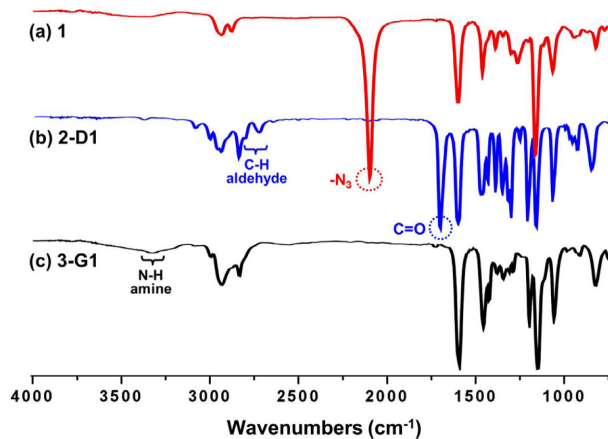


Figure 2. FTIR spectra for (a) **1**; (b) **2-D1**; (c) **3-G1**.

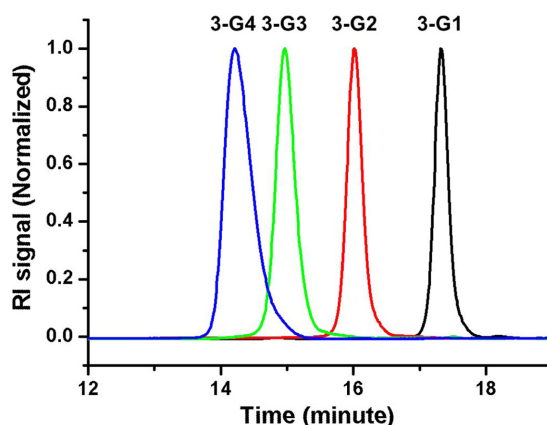


Figure 3. GPC diagrams of dendrimers **3-Gm** obtained from THF eluent.

raphy (GPC) provides no signs of products with defects that would arise from incomplete coupling (Figure 3). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values ($\text{PDI} = 1.01\text{--}1.02$).

Conclusions

We have demonstrated general, fast, and efficient stitching methods for the synthesis of Fréchet-type dendrimers with tripodal core. The stitching method was based on the trimerization reactions (Staudinger/aza-Wittig reactions) between tripodal tris(azides) and aldehyde-dendrons. The tripodal core (1,3,5-tris-(3-azido-propoxy)-benzene), was chosen to serve as the azide functionalities for dendrimer growth, was stitched together with the aldehyde-functionalized Fréchet-type dendrons in a convergent strategy to lead to the formation of the corresponding Fréchet-type dendrimers in high yields. This method may provide an insight into designing various functional tripodal dendrimers. We are currently working towards the synthesis of fluorophore-encapsulated dendrimers using this strategy for various applications.

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