Synthesis of [3]-Rotaxane Dendrimers by Host-mediated Click Chemistry

Seung Choul Han,‡ Jinhwan Yoon,† Jinho Oh,§,* and Jae Wook Lee†,‡,*

‡Department of Chemistry and †Department of Medical Bioscience, Dong-A University, Busan 604-714, Korea
*E-mail: jlee@donga.ac.kr
†Department of Chemistry and Biology, Korea Science Academy of KAIST, Busanjin-gu, Busan 614-822, Korea
*E-mail: jinhooh@kaist.ac.kr

Received August 8, 2011, Accepted August 24, 2011

Key Words: Click reaction, Cucurbit[6]uril, Dendrimer, Rotaxane

The 1,3-dipolar cycloaddition between azides and alkynes first reported by Huisgen et al. has attracted much attention due to the synthetic importance of five-membered [1,2,3]-triazole heterocycles. Since the traditional method working only at elevated temperatures produces a mixture of 1,4- and 1,5-disubstituted triazoles as a product, many research efforts have been devoted to overcoming the regioselectivity problem. Among them, a Cu(I)-catalyzed Huisgen [2 + 3] dipolar cycloaddition is currently regarded as the most efficient method that was developed by Sharpless and Torno, and now is known as click chemistry. This reaction has many advantages: very high yields, mild and simple reaction conditions, oxygen and water tolerance, and easy isolation of product. In addition, it is highly chemoselective, affording 1,4-regiospecific 1,2,3-triazole even in the presence of various functional groups. This reaction has been also applied successfully to the synthesis of dendrimers.1,7

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. Concurrently with this, another fascinating development in chemistry has been the efficient synthesis of rotaxane dendrimers containing rotaxane-like mechanical bonds in dendritic components, which have also attracted considerable attention not only due to their aesthetic appeal but also their potential applications. We have developed novel fusion and stitching methods for the synthesis of various dendrimers by the click chemistry between alkyne and azide. Here, we add a new method, a host-mediated 1,3-dipolar cycloaddition reaction between alkyne and azide for the synthesis of rotaxane dendrimers. The used host is cucurbit[6]uril (CB[6]) that can accelerate azide-alkyne cycloadditions by stabilizing an activated complex in its cavity. In more detail, we report the synthesis of [3]-rotaxane dendrimers (4-Gm) using cucurbit[6]uril as a host.

Experimental Section

General. 1H NMR and 13C NMR spectra were recorded on 300 and 500 MHz NMR spectrometers. ESI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daejeon.

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).

Preparation of N,N'-Dipropargyl-p-xylylenediammonium dichloride. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product precipitated as hydrochloric salts (0.99 g, 93%).
protons showed up-field shifts. This observation clearly supports that the phenylene moiety is located outside CB[6] whereas the propargylic groups are located inside CB[6]. The parent ion peak at 1103.7 [M+2]/2 in the ESI-MS spectrum also suggests the formation of [3]-pseudorotaxane between 1 and CB[6]. Thus, these analyses confirm that the ligand 1 forms a dumbbell-shaped [3]-pseudorotaxane, 2 with two CB[6] molecules.

When 2 (1 equiv.) was reacted with 2 equivalents of the azide-functionalized PAMAM dendrons 3-D1 or 3-D2 in water (0.05 M) at ambient temperature, precipitates were obtained respectively by slow addition of EtOH to the reaction mixtures. The measured 1H-NMR spectra indicated that the products suffered from a partial hydrolysis of the methyl ester groups. Therefore, the coupling reaction between 2 and 3-D1 was conducted again in 5% HCl solution (0.05 M) for 14 h at ambient temperature to produce the rotaxane dendrimer 4-G1 as precipitate in yield of 96% after adding EtOH and THF. The 1H NMR spectrum of the product indicated that the triazole moiety is located inside CB[6]; the triazole proton in 4-G1 was observed at 6.48 ppm, and shifted up-field compared with those of free triazoles (ca. 7.50 ppm). Indeed, the ion peaks in the ESI-MS spectrum supported the successful formation of the [3]-rotaxane dendrimer.

Given the first generation dendrimer, we applied repeatedly the host-mediated 1,3-dipolar cycloaddition reaction to get higher-generation dendrimers. The reaction of 2 and 2 equiv. of the azide-functionalized PAMAM dendrons 3-D2 in 5% HCl solution (0.05 M) for 48 h at ambient temperature gave the desired product 4-G2 in yield of 96%. In contrast, a same reaction with the third-generation dendrons 3-D3 was not finished over 1 week. Therefore, the reaction temperature was increased to 60 °C. The reaction was completed within 24 h, and the product 4-G3 was obtained in a high yield, 96%.

In the case of 3-D4, the dendrimer 4-G4 could not be obtained in a satisfactory yield. As the generation increases, the repulsion between host and dendron will affect the reaction more significantly. Therefore, the azide group in 3-D4 may have decreased accessibility to 2 compared to that in 3-D3. The 1H NMR signals of the phenylene, triazole, methylene protons adjacent to the carbon of triazole, and core benzylic protons in dendrimers 4-Gm were observed at 7.96, 6.48, 4.60, and 4.46 ppm for 4-G1, 7.92, 6.44, 4.56, and 4.42 ppm for 4-G2, 7.92, 6.46, 4.58, and 4.44 ppm for 4-G3, respectively (Figure 2). The proton signals for the terminal alkyne of 4-Gm were not shown at 2.06 ppm in the spectra of 4-Gm. Indeed, the ESI mass spectrometry confirmed the formation of those rotaxane dendrimers.

In summary, we have demonstrated the formation of [3]rotaxane dendrimers having [3]rotaxane unit at core via host-mediated click chemistry which is based on the cucurbit[6]uril mediated 1,3-dipolar cycloaddition reaction between alkylene and azide. The [3]-pseudorotaxane, which is derived by N,N’-diproparyl-p-xylylenediammonium dichloride with 2 equiv of cucurbit[6]uril, reacted with the azide-functionalized PAMAM dendrons to provide efficiently the rotaxane dendrimers. Because of the high yields and lack of byproducts provided by the host-mediated 1,3-dipolar cycloaddition reaction between alkylene and azide for stitching together dendrons and [3]-pseudorotaxane as core unit, the various rotaxane materials could be constructed easily and shown the characteristic behaviors.

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

References and Notes

4. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B.


