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Efficient synthesis of immolative carbamate dendrimer with olefinic periphery

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Abstract—An efficient synthetic strategy for immolative carbamate dendrons and dendrimers is described that requires no protection/deprotection in the convergent growth step. 1,3-Diamino-2-propanol was used as AB_2 building block and 4-nitrophenyl chloroformate as carbamate forming reagent. The method was demonstrated with a G3-dendron. A combination of convergent and divergent growth method was used to couple G2-dendrons to a G2-core or G3-dendrons to a tetrahedral G1-core with amine functional groups to form a spherical carbamate dendrimer (G4) possessing an olefinic periphery. © 2007 Elsevier Ltd. All rights reserved.

Because of their highly regulated topology (mostly spherical or disk shaped) and high densities of interior functional groups and end groups, dendrimers have been explored for many applications such as artificial enzymes and drug-delivery agents,¹ catalysts,² scaffold for metal catalysts,³ liquid crystals and organic light-emitting diodes,⁴ sensors,⁵ and magnetic resonance imaging (MRI) contrast agents.⁶ The structures and compositions of the dendrimers are designed for specific applications.7 Thus, preservation of the structural features during use is important. However, there are examples where destruction of the dendrimer is desirable. For example, molecular imprinting inside a dendrimer is achieved by cleavage of the template core from the cross-linked shell,⁸ and self-immolative dendrons are attractive candidates for drug-delivery.⁹ Such examples suggest that a nano-scale dendrimer (2-10 nm), which has properties that include immolative linkages of building blocks, possibilities for shell cross-linking, easily tunable peripheral end groups, and a functional core, offers possible new applications including temporary scaffold or transfer agent. However, most common dendrimers

are designed for high structural stability, including Fréchet's polyether and Tomalia's poly(amidoamine).

The carbamate linkage $(R_1-NHCOO-R_2)$ is ideal for immolative dendrimers as it can be readily cleaved by a selective chemical treatment¹⁰ or thermolysis,¹¹ but is stable under common synthesis conditions. There are reports of dendron or dendrimer synthesis using carbamate linkages formed by reaction between alcohols and isocyanates¹² or diphenylphosphorylazide coupling with carboxylic acids at elevated temperatures.¹³ Here, we report a convenient synthetic strategy for a spherical carbamate dendrimer of 4th generation (G4) in which 4nitrophenyl (PNP) chloroformate was used as the carbamate-forming reagent and 1,3-diamino-2-propanol as the AB₂ branching unit. The hydroxyl group of the AB₂ branching unit reacts with **PNP** chloroformate to form a carbonate intermediate, which reacts selectively with the amine groups of 1,3-diamino-2-propanol. Thus, in the convergent growth sequence, hydroxyl protection is unnecessary. Although PNP chloroformate^{9b,c,14} or carbonyl diimidazole¹⁵ can be used to form carbamate linkages and both can be handled without special precautions, we opted to use the former reagent because of its higher reactivity. An olefinic periphery was designed to permit easy modification of surface properties.

As an illustration to synthesize a symmetrical, spherical dendrimer, we used a tetrahedral core prepared by esterification between pentaerythritol and Boc-Glycine

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(**Boc-Gly-OH**). A convergent approach was employed for dendron growth up to 3rd generation (G3). A full G4-dendrimer was formed by reacting G3-dendrons with a G1-core, or G2-dendrons with a G2-core, that is, by using a combination of divergent and convergent methods. Because of steric crowding, the yield from G3-dendrons coupling to a G1-core was lower than that from G2-dendrons to a G2-core.

Scheme 1 shows the convergent synthetic route for carbamate dendrons up to G3. 2-Methyl-3-buten-2-ol was condensed with PNP chloroformate to generate 1 in 95% yield. Subsequent reaction between 1 and 1,3-diamino-2-propanol (2:1 molar ratio) gave G1-dendron (G1D, 2, 93% yield). The selective reaction of 2-nitrophenyl carbonate intermediate with amines was advantageous for multi-generation growth by eliminating the need for protection of the alcohol functionality in the AB₂ branching unit. Activating the hydroxyl group of G1D with PNP chloroformate followed by reaction with the linker (1,3-diamino-2-propanol) produced the G2 carbamate dendron (G2D, 3, 85% yield). Repeating the same reactions yielded G3 carbamate dendron (G3D, 4) in 75% yield. These results suggest that extending the growth to higher generation dendrons can be readily accomplished.

To synthesize a G4-dendrimer by coupling G3-dendrons to a G1-core, we designed a tetrahedral core, **Core-Boc** (5, Scheme 2). Pentaerythritol was coupled to **Boc-Gly-OH** by esterification, using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC) and 4-di(methylamino)pyridine (DMAP) as coupling agents¹⁶ to afford 5 (95%) as a white solid. For the alternative method of coupling G2-dendrons to a G2-core, a **Core-G2D-Boc** (7) was synthesized by coupling 4 equiv of PNP-activated, Boc-protected linker **PNPC-LK-Boc** (6) (Scheme 2) to 1 equiv of Boc-deprotected **Core-Boc** (5). Finally,

the G4-carbamate dendrimers were successfully prepared by using the same reaction steps as growing carbamate dendrons (Scheme 3). The hydroxyl group of a dendron was activated with PNP chloroformate to give PNPC-dendron (PNPC-G2D or PNPC-G3D), which was then coupled to the core amines after Boc-deprotection with TFA. We found that coupling of PNPC-G2D (8) to Core-G2D-Boc (7) (G2-dendrons to G2-core) gave a higher yield (72%) than coupling of PNPC-G3D to Core-Boc (5) (G3-dendrons to G1-core). Reaction (c) in Scheme 3, between 7 and 8, was found to be complete in 4 days at room temperature, much slower than the same reaction between small molecules due to steric hindrance, as is usually the case for coupling large dendrons to small cores.⁸ The pure G4-dendrimer (9) was obtained after two series of flash chromatography using large-pore (15 nm) silica gel. Excess PNPC-G2D was removed in the first series, and the complete dendrimer (8/8 product) was separated from small amounts of incomplete dendrimers (mainly 7/8 and 6/8) in the second series (see Supplementary data, Fig. S3). The complete dendrimer was synthesized in gram scale.

All the dendrons and dendrimers were white solids readily soluble in a variety of solvents such as dichloromethane, chloroform, alcohols, ethyl acetate, and toluene. Their chemical structures were confirmed with ¹H, ¹³C NMR, and MALDI-TOF mass spectroscopy. As expected, the ¹H NMR spectra of the G1–G3-dendrons and the G4-dendrimer (Fig. 1) are quite similar, except that the peaks broaden for higher generations, especially for the dendrimer. Therefore, careful integration of each peak was required to differentiate the generations. For example, the integral ratio of $-CH_2$ – (at 3.2–3.5 ppm) to $-CH=CH_2$ peaks (at 5.0–5.2 ppm) increased from 1.0 to 1.5 to 1.75 for G1, G2, and G3-dendrons, respectively. The chemical shifts of the ¹³C carboxyl peaks -(C=O)– of the carbamate groups at 156–157 ppm



Scheme 1. Synthesis of carbamate dendrons. Reagents and conditions: (a) CH_2Cl_2 , DMAP, pyridine, rt, 3–5 h; (b) CH_2Cl_2 , DMF, Et_3N , rt, overnight.



Scheme 2. Synthesis of cores and intermediates. Reagents and conditions: (a) DMF, CH₂Cl₂, DMAP, EDC, rt, overnight; (b) CH₂Cl₂, TFA, rt, 2 h; (c) DMF, DIPEA, CH₂Cl₂, TEA, rt, 5 h; (d) *t*-BuOH/MeOH, rt, overnight; (e) CH₂Cl₂, DMAP, pyridine, rt, 3 h; (f) CH₂Cl₂, DMAP, pyridine, rt, 5 h.



Scheme 3. Synthesis of G4-carbamate dendrimer. Reagents and conditions: CH₂Cl₂/TFA, DMF, DIPEA, rt, 3-4 days.

(Fig. S2, Supplementary data) were slightly different for the different generations, resulting in one (δ 157.1), two (δ 156.7 and 156.3), and three (δ 156.8, 156.6, and 156.4) peaks for **G1D**, **G2D** and **G3D**, respectively. The chemical shifts for the carbons at CH₂–(*CO*–)–CH₂ (δ **G1D** 71.1, **G2D** 72.7 and 69.5, **G3D** 72.7, 72.0, and 69.6) and *C*H₂–(*CO*–)–*C*H₂ (δ **G1D** 43.7, **G2D** 44.1 and 40.5, **G3D** 44.3, 40.9, and 40.7) also varied among the generations (Fig. S1, Supplementary data). The ¹H NMR peaks of G4-dendrimer were broad, but all the protons could be detected and the peaks could be assigned. However, in its ¹³C NMR spectrum, the carbon atoms with small populations near the core were beyond detection.

Additional structural confirmation was obtained with MALDI-TOF mass spectroscopy. The mass spectrum of a purified G4-dendrimer (Fig. 2) exhibited a peak at $[(M+Na)^+ = 7222.7]$, close to the theoretical mass of 7226.7. In addition, there were other intense peaks at



Figure 1. ¹H NMR spectra of carbamate dendrons and dendrimer.

7155 and 7087, which could be assigned to G4-dendrimers lacking one and two surface tertiary alkyl allyl groups (mass of $C_5H_8 = 68.0$), respectively, consequence of fragmentation during analysis. The FTIR spectrum of a G4-dendrimer showed intense characteristic bands for $-(C=O)-(v \ 1701)$, $-(N-H)-(v \ 3343)$, and $-(CH=CH_2)(v \ 2981, \ 1519)$ (Supplementary data, Fig. S4). The approximate size of G4-dendrimer was measured by dynamic light scattering (DLS) to be 4.3 nm in diameter, consistent with the simulated molecular structure (highly symmetrical and spherical shape, inset, Fig. 2) obtained by semi-empirical equilibrium geometry calculation (AM1).

Degradation of the carbamate linkages of G2D, as a model for the G4-dendrimer, was demonstrated by both base hydrolysis and reaction with trimethylsilyl iodide (TMSI)/methanol. Base hydrolysis was accomplished with 1.5 M KOH in CD₃OD/D₂O at rt for 3 days. TMSI treatment at 40 °C for 16 h followed with methanol treatment at rt for 3 h resulted in breaking of the four carbamates with tertiary alkoxy groups. Increasing the temperature to 80 °C and reacting for an additional 2 days with TMSI and subsequent treatment with methanol at 50 °C overnight cleaved most of the remaining carbamate bonds.

In summary, we have reported an efficient scheme for growing dendrons containing immolative carbamate linkages with high yields without employing protection and deprotection. The dendrons so obtained were coupled to an amine core to form a dendrimer. The tertiary alkyl allyl end groups of the dendrons and dendrimer can be functionalized to generate surface functional groups or be subjected to metathesis or hydrosilylation with alkoxysilanes or chlorosilanes for shell cross-linking if desired. This versatile dendrimer and its synthetic scheme should find applications in many areas.

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Supplementary data

Detailed experimental procedures for the synthesis of carbamate dendrons and dendrimers, and the related analysis methods and results are available online. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet 2007.05.034.

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Figure 2. MALDI-TOF mass spectrum of carbamate dendrimer of 4th generation. Inset: molecular structure, obtained by semi-empirical equilibrium geometry calculation (AM1), showing highly symmetrical and spherical shape.

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