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A divergent synthesis of new aliphatic poly(ester-amine) dendrimers bearing peripheral hydroxyl or acrylate groups

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Abstract—A novel class of aliphatic poly(ester-amine) dendrimers, bearing hydroxyl or acrylate peripheral groups, was designed and synthesized via a divergent strategy using readily available piperazine, diethanolamine and acryloyl chloride as the monomeric building blocks.

Dendrimers are highly ordered, globular monodisperse macromolecules composed of branched repeat units emanating from a central core.[1] As a result of their structural precision, globular shape and high functionality, dendrimers are currently being synthesized and investigated for applications in catalysis,[2] molecular encapsulation,[3] light harvesting[4] and drug delivery.[5] However, the synthesis of dendrimers often involves multiple steps of protection/deprotection and complicated purification, that limits their widespread use. In previous work, only methacrylate-terminated dendrimers have been synthesized by modification of amino functional poly(propyleneimine) dendrimers through a Michael reaction.[6] Here we report the development of an efficient and convenient divergent approach for the synthesis of aliphatic poly(ester-amine) dendrimers using readily available diethanolamine and acryloyl chloride as monomeric building blocks. The hydroxyl and acrylate peripheral groups could be easily further derivatized for different purposes. This divergent synthesis produced not only water-soluble hydroxyl-terminated dendrimers but also acrylate-terminated dendrimers for the first time. Using this approach, a third generation **G3-(OH)$_{16}$** dendrimer bearing 16 hydroxyl end groups and a third generation **G3-(acrylate)$_{16}$** bearing 16 acrylate end groups were obtained. In each step, only a small excess ($\leq$15%) of reagent was required to achieve quantitative growth.

The synthesis is shown in Scheme 1. Piperazine was acylated using 2 equiv. of acryloyl chloride in the presence of 2 equiv. of Et_3N to produce **GO-(acrylate)$_2$**, **1**, which was purified by column chromatography (70% yield). A Michael reaction between diethanolamine and the acrylate end groups on **GO-(acrylate)$_2$** was readily accomplished using only 1.05 equiv. of diethanolamine in ethanol to produce **G1-(OH)$_4$**, **2**, in 85% yield after purification by precipitation from acetone. Then, **G1-(OH)$_4$** was acylated with 4.2 equiv. acryloyl chloride in the presence of 4.2 equiv. of Et_3N to produce **G1-(acrylate)$_4$**, **3**, in 79% yield after column chromatography. The **G2-(OH)$_8$**, **4**, dendrimer was prepared by reaction of 4.4 equiv. of diethanolamine with **G1-(acrylate)$_4$** in ethanol. The residual diethanolamine was removed by precipitation of **4** from cold acetone (82% yield). Likewise, **G2-(acrylate)$_8$**, **5**, was obtained in 62% yield through esterification of **4** and **G3-(OH)$_{16}$**, **6**, was obtained in 80% yield by Michael addition of **5** with 9.2 equiv. of diethanolamine in THF. Reiteration of the esterification with **6** produced **G3-(acrylate)$_{16}$** dendrimer, **7** (48% yield). The structures were identified through ESI-MS, NMR and IR spectroscopy.[7]

A typical procedure is described as follows for the preparation of compounds **5** and **6**: A solution of acryloyl chloride (2.7 g, 29.9 mmol) in 10 mL CH_2Cl_2 was added dropwise to solution of **G2-(OH)$_8$** (3.7 g, 3.6 mmol) and Et_3N (3.2 g, 31.7 mmol) in 60 mL CH_2Cl_2 at −5°C over 1 h. The reaction mixture was stirred overnight at room temperature, then, Et_3N·HCl was filtered off. The filtrate was diluted with 100 mL CH_2Cl_2 and extracted with 2×50 mL $NaHCO_3$ (10%) and 1×50 mL brine. The organic phase was dried over $MgSO_4$, filtered and distilled to give the crude product.

Keywords: synthesis; poly(ester-amine); dendrimer.

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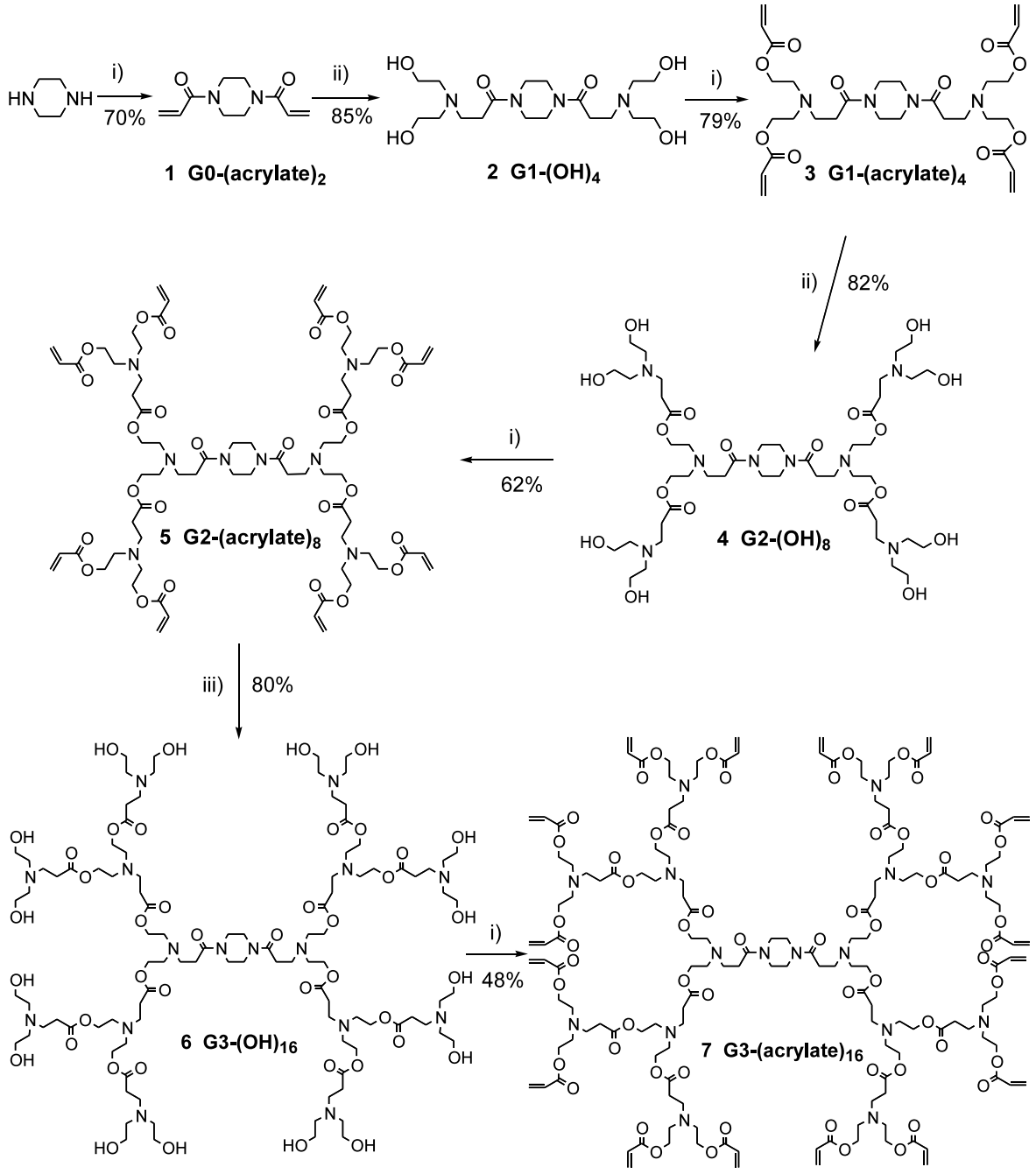

Scheme 1. Divergent synthesis of poly(ester-amine) dendrimers. *Reagents and conditions*: (i) acryloyl chloride, CH_2Cl_2, Et_3N, −5°C, 1 h, room temperature, 12 h; (ii) diethanolamine, ethanol, room temperature, 20 h; (iii) diethanolamine, THF, 20 days.

After purification by silica gel column chromatography (methanol:CH_2Cl_2 = 3:97–10:90), 3.2 g of dendrimer **5** was obtained in 62% yield as a pale-yellow oil. Dendrimer **5** (3.2 g, 2.2 mmol) and diethanolamine (2.1 g, 20.0 mmol) were mixed in 50 mL THF at 0°C. The reaction mixture was stirred at room temperature for 20 days. THF was then removed by distillation under reduced pressure, the crude product was washed with 3×10 mL cold acetone to afford dendrimer **6** (4.2 g, 80% yield) as a yellow oil.

In conclusion, an efficient divergent procedure for synthesizing novel aliphatic poly(ester-amine) dendrimers bearing hydroxyl or acrylate peripheral groups has been described, which may be easily modified for various applications. This divergent synthesis used readily available monomers and required only small excesses of reagents to achieve quantitative growth. The synthesis of high generation dendrimers is in progress.

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7. Selected characterization data of the third generation dendrimers. **G3-(OH)$_{16}$**, **6**: IR 3392, 2951, 2833, 1728(s), 1624(s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (t, 24H, -CO_2CH_2-, $J=6.2$ Hz), 3.78 (bs, 16H, -OH), 3.64–3.58 (m, 8H, -NCH_2CH_2N-, piperazine), 3.60 (t, 32H, -$\underline{CH_2}$OH, $J=5.5$ Hz), 2.91–2.87 (m, 12H, O=$CCH_2\underline{CH_2}N$-, $J=6.9$ Hz), 2.84 (t, 16H, O=$CCH_2\underline{CH_2}N$-, $J=6.9$ Hz), 2.78 (t, 24H, -$N\underline{CH_2}CH_2OC$=O, $J=6.2$ Hz), 2.63 (t, 32H, -$N\underline{CH_2}CH_2OH$, $J=5.5$ Hz), 2.51 (t, 20H, O=CCH_2-, $J=6.9$ Hz), 2.46 (t, 8H, O=CCH_2-, $J=6.9$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.06, 172.22, 62.70, 62.44, 60.49, 59.51, 59.10, 56.33, 55.82, 52.75, 50.83, 50.44, 49.81, 32.90, 32.77, 31.30; ESI-MS: calcd for $(M+H)^+$: 2315.7. Found: m/z $(M+H)^+$: 2315.6. **G3-(acrylate)$_{16}$**, **7**: IR 2958, 2835, 1724(s), 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (q, 16H, =CH, $J=17.5$ Hz, $J'=1.0$ Hz), 6.12 (q, 16H, O=CCH=, $J=17.5$ Hz, $J'=10.5$ Hz), 5.84 (q, 16H, =CH, $J=10.5$ Hz, $J'=1.0$ Hz), 4.21 (t, 32H, CH_2=CHCOO$\underline{CH_2}$-, $J=6.0$ Hz), 4.10 (t, 24H, -$COOCH_2$-, $J=6.0$ Hz), 3.65–3.49 (q, 8H, -NCH_2CH_2N-, piperazine), 2.91 (m, 28H, O=$CCH_2\underline{CH_2}N$-, $J=7.0$ Hz), 2.85 (m, 32H, CH_2=CHCOOC$H_2\underline{CH_2}N$-, $J=6.0$ Hz), 2.77 (t, 24H, -$N\underline{CH_2}CH_2OC$=O, $J=6.0$ Hz), 2.47 (t, 28H, O=CCH_2-, $J=7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.87, 165.77, 130.60 (-CH=CH_2), 128.24 (-CH=CH_2), 62.47, 62.28, 52.53, 50.28, 32.92, 31.15, 30.14; ESI-MS: calcd for $(M+H)^+$: 3180.5. Found: m/z $(M+H)^+$: 3183.0.