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RESEARCH ARTICLE

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Synthesis of dendritic polyamide with protected amino functional groups in the periphery

Abstract A homologous series of first- to third-generation dendritic polyamides **2a**, **3,** and **5** with tris(aminoethyl) amine (TREA) as the core and the protected amino functional groups at the periphery were synthesized *via* active ester route from "Schlüter" type dendron **1a**. Their structures were characterized by ^{1}H-NMR and mass spectra. Based on the efficient synthesis of the first generation dendrimer **2a** (yield 75%), the synthesis of second-generation dendrimer **3** was found to be more efficient *via* the convergent method (yield 69%), while the mixed strategy was applied efficiently for the synthesis of the higher generation dendrimer **5** (yield 37%). The overall yield for the third generation dendrimer **5** from Schlüter dendron is 12%.

Keywords dendrimer, convergent, divergent, Schlüter dendron

Dendrimers are treelike mono-dispersed macromolecules of spherical shape [1–4]. They are perfectly cascade-branched, highly defined units, characterized by a combination of high-group functionalities and a compact molecular structure with a precise generation number. The structural precision of dendrimers has motivated numerous studies aimed at different applications, such as, catalysis [5, 6], molecular recognition [7], and electro-optical materials [8–10]. Many different architectures have been used for dendrimer construction, including polyester, polyether, polypeptide, and polyamide. Dendrimers are normally synthesized *via* convergent route or divergent route from the branching unit, *i.e.*, dendron, but most dendrimers synthesized so far have no achievable functional group in the periphery, which hinders their modification and easy applications.

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The present paper describes the synthesis of a new type of polyamide dendrimer (1st to 3rd generation) based on Schlüter dendron with tris (aminoethyl) amine (TREA) as the core via different strategies, in order to develop an efficient synthesis route for a new type of dendrimer with an amino functional group in the periphery.

1 Experimental

Compounds **1a** [11], **1b** [11], **1c** [13], **1d** [13], **4a** [13], **4b** [14], and **4c** [14] were synthesized according to literature methods. All chemical reagents were purchased from Acros or Alfa Aesar, and used without further purification. N_2 (99.9993%) from Praxair China (Beijing), Silica gel (200–300 mesh) from Qingdao Ocean Chemical Works, and THF was dried over sodium. NMR was recorded on a Buker DPX-400, ESI Mass spectrum was carried out on a Q-Tof Micro™ High Resolution Mass Spectrometer (Waters Micromass Corp.), and MALDI-TOF was measured on a Kratos MALDI 3 Mass Spectrometer.

1.1 Tri-{[3,5-bis-(3-*tert*-butoxycarbonylamino-propyl) benzoylamino]- ethyl} amine (**2a**)

TREA (0.23 g, 1.57 mmol) in methanol (5 mL) was slowly dropped at –20°C to a solution of compound **1c** (3.03 g, 5.68 mmol), and TEA (1.91 g, 18.9 mmol) in 30 mL of CH_2Cl_2, and the mixture was stirred for 16 h. TLC was used to follow the reaction. After completion, it was washed with brine，then the organic phase was dried over $MgSO_4$. Chromatographic separation (ethyl acetate/petroleum ether, 5:1) gave a colorless product of the first generation dendrimer **2a (**1.65 g, 75%). ^{1}H-NMR ($CDCl_3$): δ = 1.43 (s, 54H, *tert*-Butyl), 1.71 (m, 12H, C$\underline{H}_2$), 2.52 (t, 12H, C$\underline{H}_2$Ph), 2.77 (t, 6H, C$\underline{H}_2$N), 3.01 (m, 12H, C$\underline{H}_2$NH), 3.53 (m, 6H, C$\underline{H}_2$NH), 4.87 (br, 6H, N$\underline{H}$), 7.04 (s, 3H, $\underline{Ph}$), 7.50 (s, 6H, $\underline{Ph}$), 7.66 (br, 3H, N$\underline{H}$). ESI-MS, *m/z* (%): 1401.9012 (25)

$[M+H]^+$, 1423.8702 (100) $[M+Na]^+$, 1439.8558 (10) $[M+K]^+$.

1.2 Tri-{[3,5-bis-(3-amino-propyl)benzoylamino]-ethyl} amine × 6 HCl (**2b**)

HCl (36%, 1.3 g, 12.8 mmol) was added at 0°C into **2a** (0.57 g, 0.41 mmol) in 100 mL of THF, and the mixture was stirred for 5 h. Evaporation of all solvent yielded compound **2b** (0.40 g, 96.4%). ^{1}H-NMR (CD_3OD): δ = 2.01 (m, 12H, C$\underline{H_2}$), 2.73 (t, 12H, C$\underline{H_2}$Ph), 2.73 (m, 12H, C$\underline{H_2}$NH), 3.71 (t, 6H, C$\underline{H_2}$N), 3.87 (m, 6H, C$\underline{H_2}$NH), 7.36 (s, 3H, $\underline{Ph}$), 7.59 (s, 6H, $\underline{Ph}$).

1.3 Tri-{[3,5-Bis-{3-[3,5-bis-(3-*tert*-butoxycarbonylamino-propyl)-benzonylamino]-propyl}benzoylamino]-ethyl}amine (**3**)

Divergent route:
Solution of compound **2b** (0.4 g, 0.39 mmol) in 7 mL of methanol was dropped at –20°C into the mixture of compound **1c** (1.60 g, 3.0 mmol) and TEA (1.34 g, 13.2 mmol) in 30 mL of CH_2Cl_2, and stirred for 16 h, then washed with brine. The organic phase was dried over $MgSO_4$. Chromatographic separation (CH_2Cl_2/methanol, 15:1) gave a colorless product of the second generation dendrimer **3 (**0.69 g, 50.9%).
Convergent route:
TREA (0.1 g, 0.68 mmol) in 5 mL of methanol was dropped at –20°C into the mixture of compound **4c** (3.16 g, 2.70 mmol) and TEA (1.79 g, 17.7 mmol) in 30 mL of CH_2Cl_2, and stirred for 16 h, then washed with brine. Chromatographic separation (CH_2Cl_2/methanol, 15:1) gave a colorless product of the second generation dendrimer **3 (**1.56 g, 69%). ^{1}H-NMR ($CDCl_3$): δ = 1.44 (s, 108H, *tert*-Butyl), 1.78 (m, 36H, C$\underline{H_2}$), 2.48 (t, 12H, C$\underline{H_2}$Ph), 2.56 (t, 24H, C$\underline{H_2}$Ph), 2.75 (t, 6H, C$\underline{H_2}$N), 3.02 (m, 24H, C$\underline{H_2}$NH), 3.24 (m, 12H, C$\underline{H_2}$N), 3.50 (m, 6H, C$\underline{H_2}$N), 4.94 (br, 12H, N$\underline{H}$), 6.94 (s, 3H, $\underline{Ph}$), 7.06 (s, 6H, $\underline{Ph}$), 7.42 (s, 6H, $\underline{Ph}$), 7.49 (s, 12H, $\underline{Ph}$), 7.51 (br, 6H, N$\underline{H}$), 7.82 (br, 3H, N$\underline{H}$). MS (MALDI-TOF), *m/z* (%): 3333.2 (100%) $[M+Na]^+$.

1.4 Tri-{[3,5-bis-{3-[3,5-bis(3-{3,5-bis-(3- tert-butoxycarbonylamino-propyl)-benzonylamino}propyl)benzonylamino] propyl benzoylamino}-ethyl]amine (**5**)

TEA (0.55 g, 5.4 mmol) was added into the solution of compound **4c** (1.0 g, 0.854 mmol) in 12 mL mixed solvents of CH_2Cl_2 and CH_3OH (5:1). Then compound **2b** (0.1 g, 0.098 mmol) in 2 mL of methanol was added into the mixture at –15°C, and stirred for 12 h, then washed with brine. Chromatographic separation (CH_2Cl_2/methanol, 15:1) gave a colorless product of the third generation dendrimer **5 (**0.26 g, 37%). ^{1}H-NMR ($CDCl_3$): δ = 1.40 (s, 216H, *tert*-Butyl), 1.71 (m, 48H, C$\underline{H_2}$), 1.81 (m, 24H, C$\underline{H_2}$), 1.91 (m, 12H, C$\underline{H_2}$), 2.33 (m, 12H, C$\underline{H_2}$Ph), 2.52 (m, 72H, C$\underline{H_2}$Ph), 2.64 (m, 6H, C$\underline{H_2}$N), 3.01 (m, 48H, C$\underline{H_2}$NH), 3.20 (m, 12H, C$\underline{H_2}$NH), 3.29 (m, 24H, C$\underline{H_2}$NH), 3.44 (m, 6H, C$\underline{H_2}$NH), 5.03 (br, 24H, N$\underline{H}$), 6.88 (s, 3H, $\underline{Ph}$), 7.01 (s, 6H, $\underline{Ph}$), 7.04 (s, 12H, $\underline{Ph}$), 7.38 (s, 6H, $\underline{Ph}$), 7.46 (s, 36H, $\underline{Ph}$), 7.59 (br, 12H, N$\underline{H}$), 7.83 (br, 6H, N$\underline{H}$), 7.96 (br, 3H, N$\underline{H}$). MS (MALDI-TOF), *m/z* (%): 7095.5 (40%) $[M+Na]^+$.

2 Results and discussion

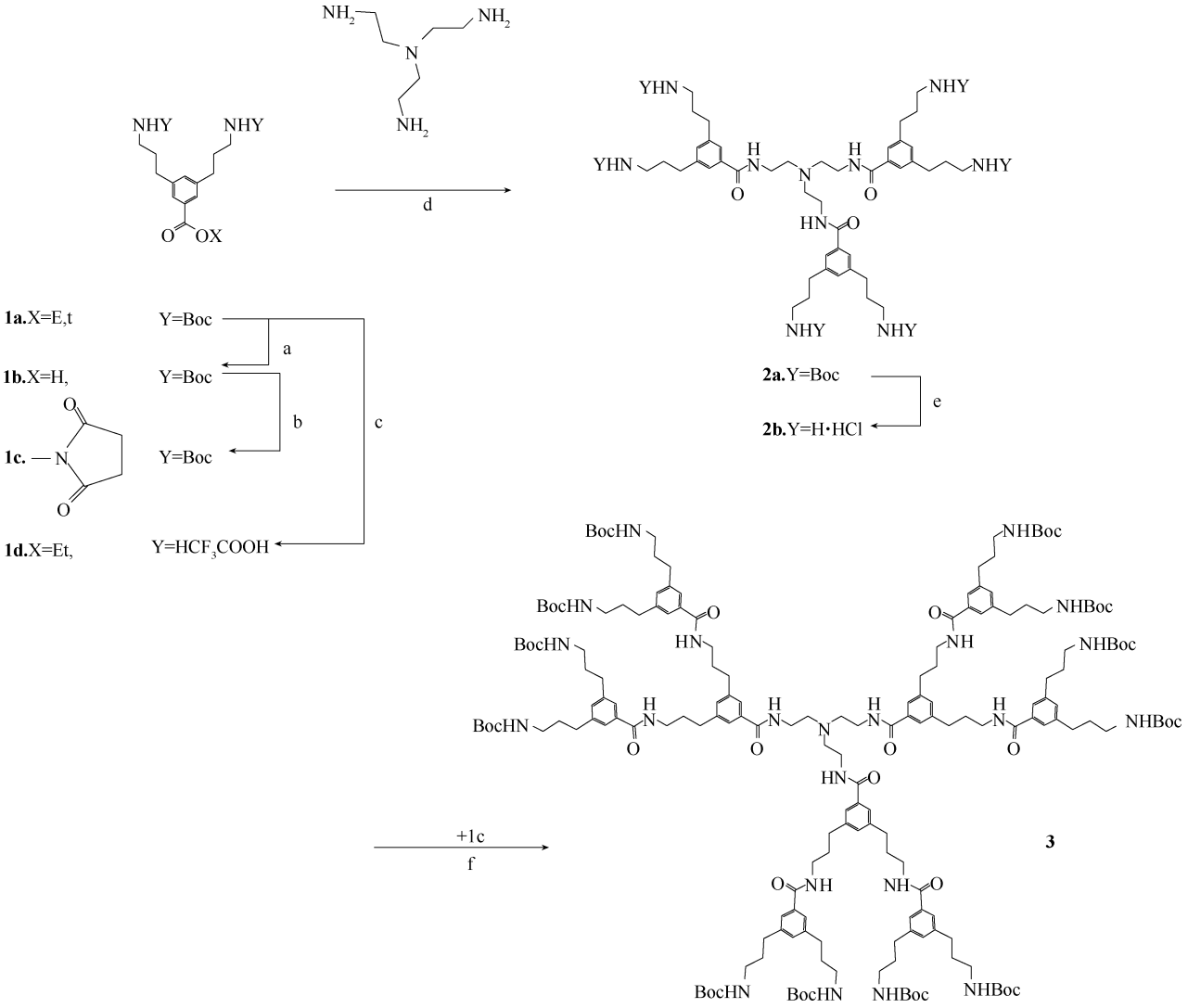
The dendrimer aimed for this present work is based on Schlüter dendron via amide coupling. There are three different amide coupling procedures reported in literature, i.e., (1) high vacuum route [15]; (2) carbodiimide route [16]; and (3) active ester route [13]. Among these routes, routes (2) and (3) are normally the efficient ways for the synthesis of compounds with complicated structures. Here we applied the active ester route to synthesize the aimed dendrimer based on the amide coupling procedures developed from our former work.

2.1 The first generation dendrimer (**2a**)

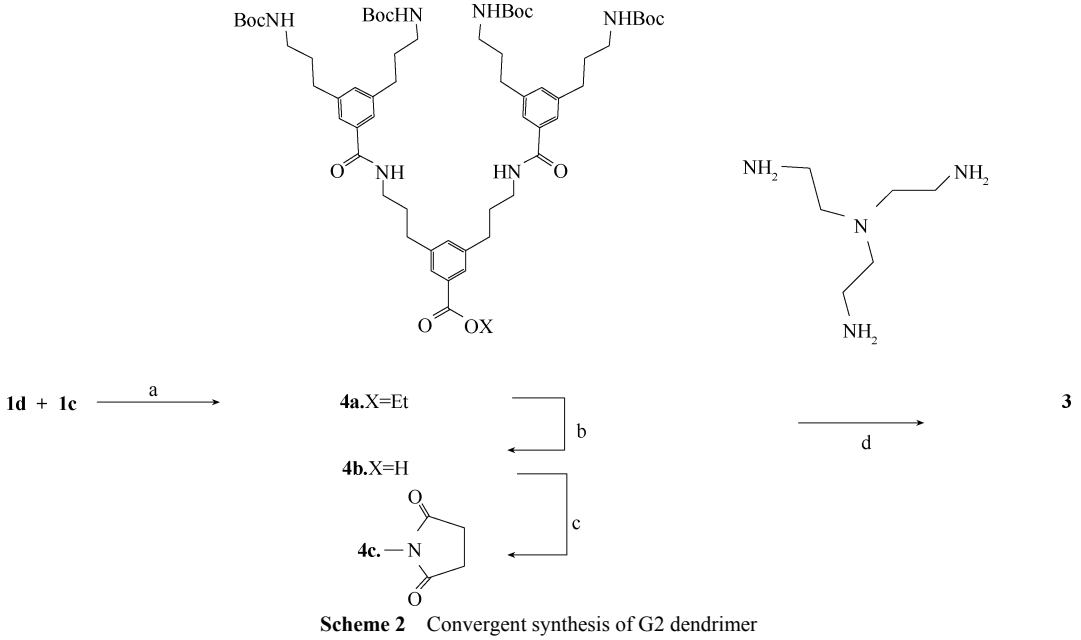
The first generation (G1) dendrimer (**2a**) was synthesized via divergent route as shown in Scheme 1. First of all, hydrolysis of dendron **1a** formed the acid (**1b)**, which was then converted into the active ester **(1c)**, then **1c** and TREA were condensed into the targeted dendrimer **2a** with high yield (75%).

2.2 The second generation dendrimer (**3**)

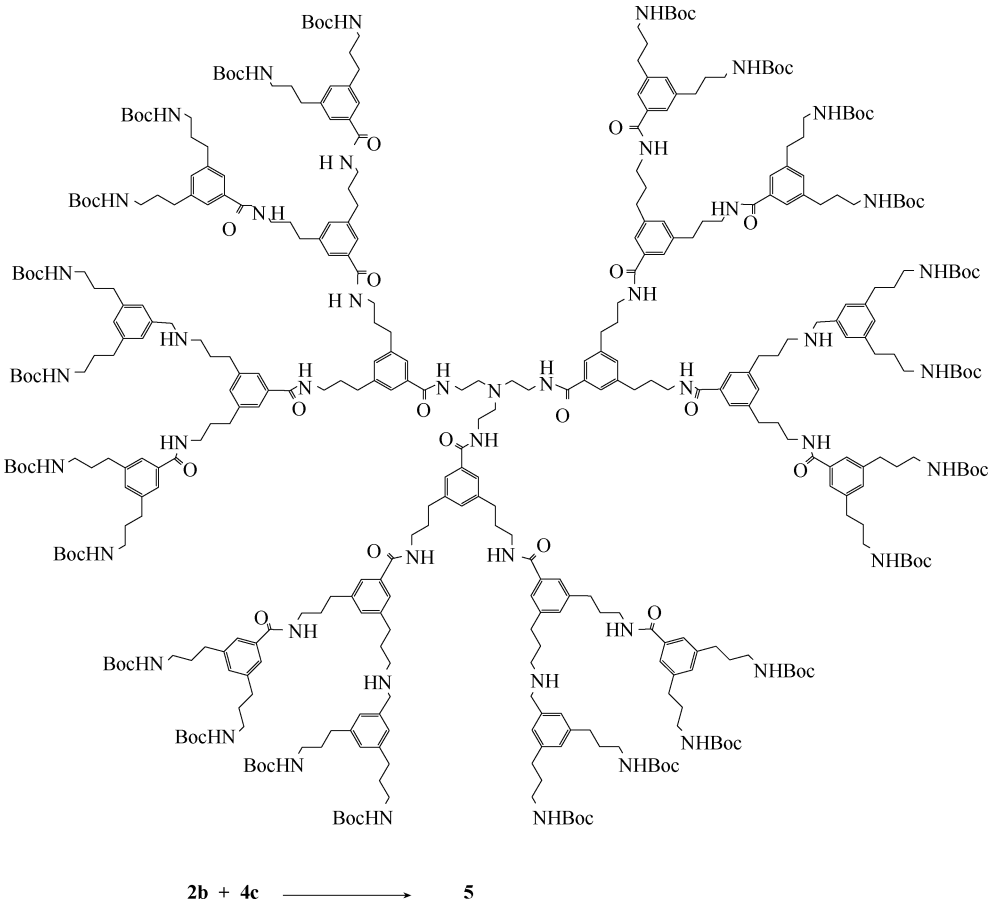
First, the divergent route was also tried to synthesize the second generation (G2) dendrimer **3** as shown in Scheme 1. The amine **2b**, a de-protection product of the G1 dendrimer **2a**, reacted with the active ester **1c** to form the G2 dendrimer **3**. But this route turned out to be an unsatisfactory route because of the low yield (maximal 51%) and also the difficulties in the purification step. This is probably due to the six coupling sites in a single compound, which may lead to low reactivity for all sites at the same time or some side reactions. Therefore, convergent route is adopted to overcome this problem. The detailed route is shown in Scheme 2. First de-protection of **1a** with CF_3CO_2H gave **1d**, then **1d** reacted with active ester **1c** to form the G2 dendron **4a** (as shown in Scheme 2), which was then hydrolyzed into acid, then transformed into G2 active ester **4c** by the same method as G1 active ester. This active ester then reacted with the core TREA to form the G2 dendrimer with yield 69%, which is much efficient than the divergent route.



Scheme 1 Divergent synthesis of G1 and G2 dendrimers



Scheme 2 Convergent synthesis of G2 dendrimer



Scheme 3 Mixed route for the syntheses of G3 dendrimer

2.3 The third generation dendrimer (**5**)

Bear in mind that the same difficulty should happen in the G3 dendrimer synthesis *via* divergent route as described in the case of G2 because the reaction sites in a single core molecule will increase into 12. But with the convergent route, the steric demand of the dendron during the amide coupling should also lead to a problem. Therefore, a mixed route was adopted for this purpose. First de-protection of G1 dendrimer gave the amine **2b**, then **2b** reacted with G2 active ester **4c** to directly form G3 dendrimer **5** with yield 37%, as shown in Scheme 3. The advantage of this route is that amide coupling sites in the single molecule are reduced into 6, compared to 12 in the divergent case, and also the steric demand of the dendron is much less than that in the convergent case. So, the mixed route is an efficient way in the synthesis of G3 dendrimer.

3 Conclusion

The G1 to G3 dendrimers with amino functional groups in the periphery based on Schlüter dendron and TREA core were efficiently synthesized *via* divergent, convergent and mixed routes with yields of 75%, 69%, and 37%, respectively. The structures of the dendrimers were verified by ^{1}H-NMR and mass spectra measurements. The amino function groups in the periphery of this kind of dendrimers will make them attractive in different application areas.

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