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Facile Synthesis of Amine-Terminated Aromatic Polyamide Dendrimers via a Divergent Method

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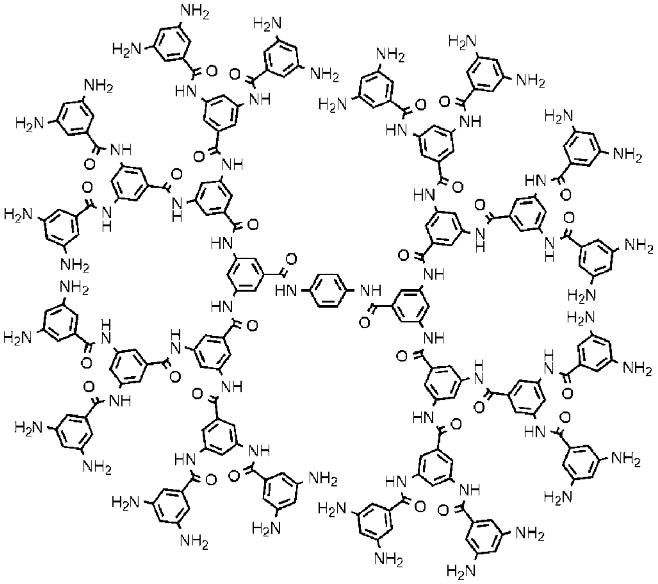
ABSTRACT



A novel, rapid, inexpensive, and highly efficient divergent approach for the synthesis of a 32-amine-terminated G4 polyamide dendrimer has been developed. Each generation dendrimer was successfully obtained by the condensation of the preceding generation dendrimer with the building block and the deprotection with hydrazine in one pot. All the dendrimers were easily purified by precipitation in alkaline water, and the purity was confirmed by NMR, MALDI-TOF mass spectra, and elemental analysis.

Dendrimers are hyperbranched three-dimensional macromolecules possessing a regular treelike array of branch units. The possibility of effectively modifying the properties of dendritic molecules by the introduction of reactive functional groups at the core, peripheral surface, branching unit, or multiple sites within the dendrimer leads to a variety of applications in areas such as molecular light harvesting,[1] catalysts,[2] liquid crystals,[3] molecular encapsulation,[4] and drug delivery systems.[5]

However, the synthetic procedures used for their preparation detract from their widespread use. Dendrimers are generally formed by means of divergent[6] or convergent[7] methods that involve reiterative growth strategies. A stepwise process is necessary for both these methods: attaching one generation to the preceding one, purifying, followed by changing the functional groups for the next-stage reaction.

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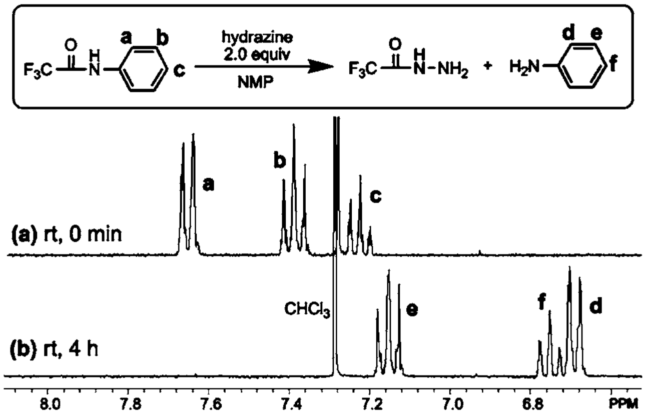
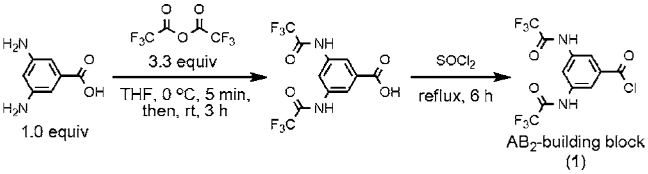


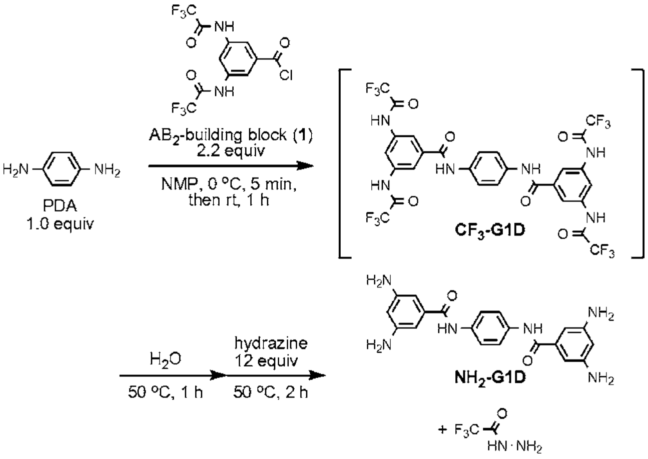
Figure 1. Expanded ^{1}H NMR spectra of reaction solutions.

Several methods such as double-stage growth,[8] double-exponential growth,[9] hypermonomers,[10] and orthogonal coupling strategies[11] have reported a decrease in the time required for these lengthy syntheses by reducing the number of steps.[12] These approaches, however, still require multiple steps to achieve the synthesis of high-generation dendrimers. A one-pot multiple-addition convergent synthesis of polycarbonate dendrimers was recently reported in which the second-generation dendrimer was prepared by the sequential activation of an alcohol with 1,1-carbonyl diimidazole and an AB_2 triol.[13] We demonstrated the rapid synthesis of a perfectly branched third-generation (G3) polyamide dendrimer using a convergent method without repetitive protection−deprotection procedures.[14] This technique utilizes a two-step method that consists of the activation of carboxylic acids and condensation with an unprotected AB_2 building block having diamine moieties using the activating agent diphenyl(2,3-dihydro-2-thioxo-3-benzoxazolyl)-phosphonate (DBOP)[15] and later using a more versatile activating reagent thionyl chloride.[16] Recently, we have also reported the facile synthesis of Fréchet-type aryl ether dendrimers using thionyl chloride by using the same concept.[17] However, these two-step methods are limited to only the convergent approach because of the difficulties in the complete activation of end groups at the dendrimer periphery and the quantitative condensation of the resulting active intermediates with AB_2 building blocks without side reactions such as the hydrolysis of active intermediates, which would result in the formation of defects, in a divergent approach.

Scheme 1. Synthesis of AB_2 Building Block **1**



Scheme 2. Synthesis of G1 Dendrimer



Nevertheless, the divergent approach has several advantages such as the simplicity of the purification process and accessibility in large-scale industrial synthesis; this is demonstrated by the fact that most commercially available dendrimers are currently prepared using the divergent method. Although several synthetic methods have been

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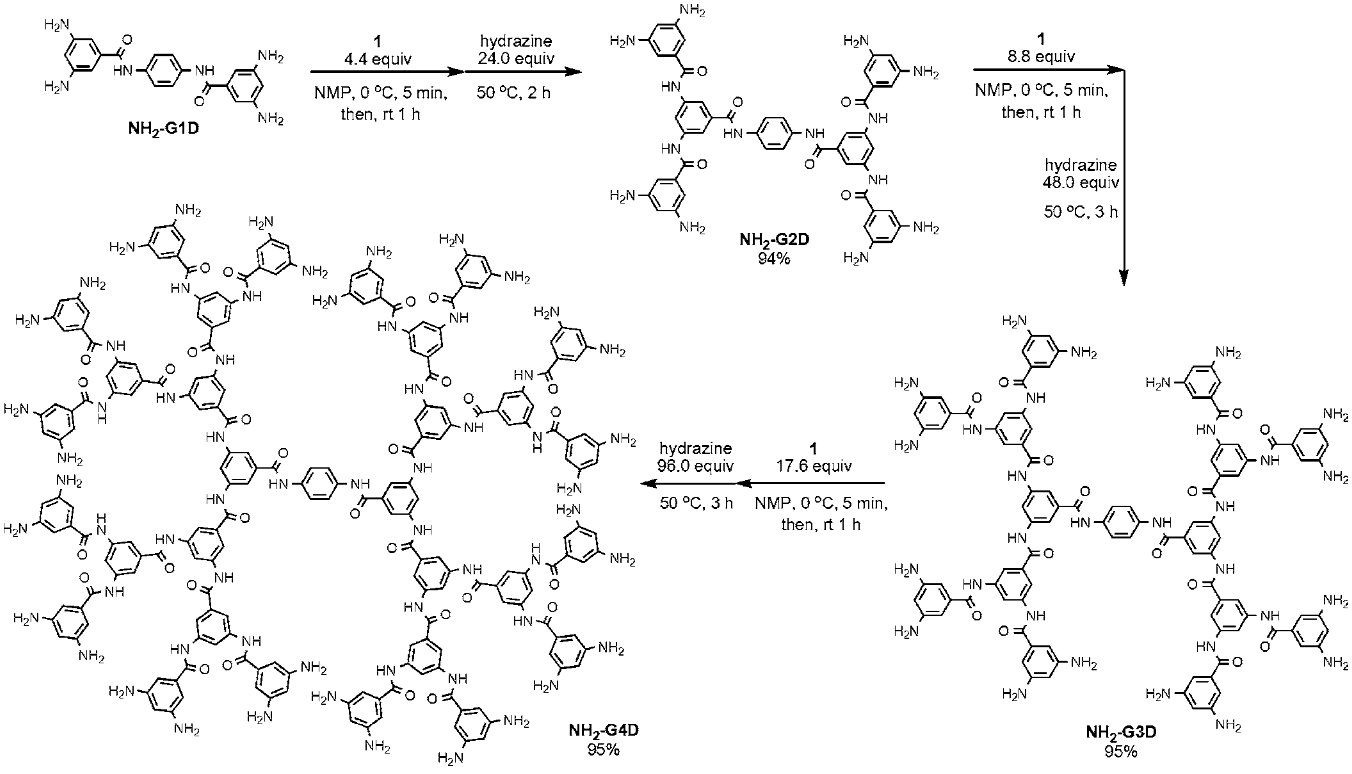
Scheme 3. Synthesis of Polyamide Dendrimers



developed to prepare entirely aromatic polyamide dendrimers,[18] the divergent method is only applied to smaller generation dendrimers.[18d,e] Moreover, to prepare each generation dendrimer, these methods require two-step reactions: the condensation of benzoyl chloride derivatives with amino groups at the periphery of the preceding generation dendrimer and the reduction of all the nitro groups at the periphery into amino groups with long reaction times.

Here, we have developed a two-step method for the facile synthesis of amine-terminated aromatic polyamide dendrimers using 3,5-bis(trifluoroacetamido)benzoyl chloride as an AB$_2$ building block via a divergent approach in which the condensation and deprotection reactions are carried out rapidly in one pot. Furthermore, the purification of every generation dendrimer only requires precipitation in alkaline water.

The protecting group of amines should fill at least three requirements. First, it has to be stable under acidic conditions, which result from the condensation reaction of acid chlorides with amines. Second, the intermediates, protecting group terminated dendrimers, have good solubility in a reaction solvent. Third, it must be selectively deprotected while maintaining the amide bonds of the dendrimer backbone. Therefore, we selected a trifluoroacetyl group due to its high stability toward an acid, good affinity to common organic solvents, and outstanding ability as a leaving group. It was found that trifluoroacetanilide was completely converted into aniline without producing any byproducts during the transamidation reaction with 2 equiv of hydrazine in *N*-methyl-2-pyrrolidone (NMP) at room temperature for 4 h, as shown in Figure 1.[19] On the contrary, benzanilide—a model compound of the dendrimer backbone—failed to react with hydrazine even at 80 °C for 1 day.

Consequently, we synthesized 3,5-bis(trifluoroacetamido)-benzoyl chloride **1** as a novel AB$_2$ building block (Scheme 1). 3,5-Diaminobenzoic acid was first reacted with excess amounts of trifluoroacetic anhydride in tetrahydrofuran, followed by the addition of water to produce 3,5-bis-(trifluoroacetamido)benzoic acid in 94% yield. Chlorination was then conducted in thionyl chloride under reflux conditions. The AB$_2$ building block **1** was recrystallized twice from tetrachloroethane followed by chloroform in 55% yield and was characterized by IR and ^{1}H NMR spectroscopy and elemental analysis.

The G1 dendrimer was prepared using *p*-phenylenediamine (PDA) as a core molecule in one pot (Scheme 2). Further, 1.1 equiv of AB$_2$ building block **1** was added to each amino group in a solution of PDA in NMP at 0 °C and stirred for 1 h at room temperature to yield the trifluoroacetyl-terminated G1 dendrimer (CF$_3$-G1D) in situ. After achieving

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[19] For deprotection using hydrazine, see: (a) Dzvinchuk, I. B.; Lozinskii, M. O. *Chem. Heterocycl. Compd.* **2005**, *41*, 845. (b) Luo, J.; Smith, M. D.; Lantrip, D. A.; Wang, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 10004.

complete condensation, the acid chloride of the unreacted AB_2 building block was hydrolyzed with a small amount of water at 50 °C for 1 h to avoid undesired reactions of the acid chloride with hydrazine. Then, 5.5 equiv of hydrazine was added to **1** to form the amine-terminated G1 dendrimer (NH_2-G1D) by a transamidation reaction at 50 °C for 2 h. Because the byproducts in the resulting final solution are only trifluoroacetyl hydrazide, 3,5-diaminobenzoic acid, HCl, and hydrazine, NH_2-G1D can be purified simply by precipitation in $NaHCO_{3aq}$ in quantitative yield. The formation and isolation of NH_2-G1D were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis.

The synthetic route for the 32-amine-terminated G4 polyamide dendrimer is shown in Scheme 3. NH_2-G2D, NH_2-G3D, and NH_2-G4D were synthesized using a protocol similar to that described above, that is, condensation of the preceding generation dendrimer with the AB_2 building block **1**, followed by the deprotection of the trifluoroacetylamide group in CF_3-G*n*D in one pot. The deprotection reaction was completely achieved at 50 °C within 3 h even in the case of NH_2-G4D synthesis. Interestingly, although the reaction time of transamidation with hydrazine was prolonged by 1 day, no changes were observed in every generation dendrimer, suggesting that the excess hydrazine was inert to all the dendrimers under those conditions. The yields of NH_2-G2D, NH_2-G3D, and NH_2-G4D after precipitation in alkaline water were 94, 95, and 95%, respectively. The structures of all the dendrimers were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis. Although the MALDI-TOF MS measurement of NH_2-G2D provided a clear spectrum and indicated its formation and isolation, NH_2-G3D and NH_2-G4D could not be analyzed by the MALDI-TOF MS spectrum probably because of strong intermolecular interactions of terminated amines and dendrimers. To reduce the interactions, we isolated the intermediates, CF_3-G3D and CF_3-G4D, without using any purification processes except precipitation in alkaline water. Thus, we could obtain clear charts of them on MALDI-TOF MS spectrometry. Because the spectrum of CF_3-G4D exhibits a desired single signal at 7228.3 as shown in Figure 2, we believe that the corresponding NH_2-G4D was isolated in high purity as well as was CF_3-G4D. Further, the GPC traces of all the amine-terminated dendrimers were unimodal and had narrow distributions (see Supporting Information).

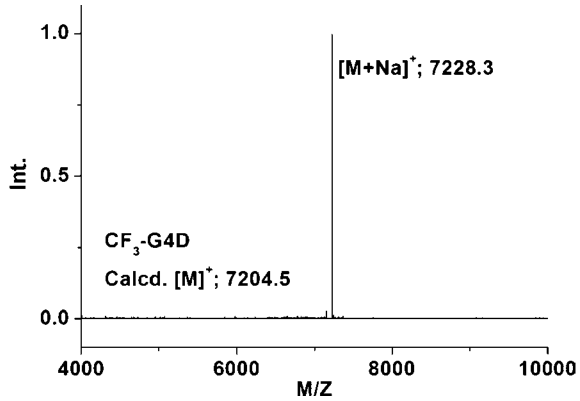

Figure 2. MALDI-TOF MS spectrum of CF_3-G4D.

In summary, we have developed a facile synthetic method for amine-terminated aromatic polyamide dendrimers via the divergent approach. In this method, the trifluoroacetyl group was employed as a protecting group for the AB_2 building block, which enabled a reduction in the deprotection reaction time of amines using a transamidation reaction with hydrazine as well as the performance of the condensation and deprotection reaction in one pot. Furthermore, the purification of each generation dendrimer is performed by precipitation in alkaline water. The simplicity and experimental ease of this novel divergent method for the generation of polyamide dendrimers makes it extremely attractive for the preparation of dendrimers for use in both laboratories and industry.

Supporting Information Available: Full synthetic details, spectral data of products, ^{1}H NMR, ^{13}C NMR, MALDI-TOF MS spectra, and GPC charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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