Rapid Synthesis of Dendrimers by an Orthogonal Coupling Strategy

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Dendrimers are polymers that radiate out from a central core, with the number of branch points on a given arm increasing exponentially from the core to the periphery.1 Because of their novel properties, dendrimers have found many uses, including as unimolecular micelles,2 novel amphiphiles,3 complexation agents,4 and MRI contrast agents.5 These and other applications will benefit from more efficient methods of dendrimer preparation because the iterative synthetic approaches to even small dendrimers are multistep. In particular, both the divergent approach developed by Tomañila6 and Newkome7 and the convergent method of Fréchet8 minimally require a deprotection or activation step in addition to the coupling step that adds each new generation. Several successful attempts to shorten these synthetic sequences were reported,9–11 however, these approaches still require (de)protection or activation chemistry.

Several years ago, Baranay and Merrifield12 defined an orthogonal system as “a set of completely independent classes of protection groups, such that each class can be removed in any order and in the presence of all other classes.” Orthogonal protecting group strategies have found widespread use in peptide chemistry, and recently Ogawa13 used two independent (orthogonal) glycosylation reactions to accelerate the synthesis of oligosaccharides. We now describe a rapid synthesis of dendrimers using an orthogonal coupling strategy wherein each synthetic step adds a generation to the existing dendrimer.14

In the orthogonal approach the protection or activation steps are eliminated by sequential use of two different building blocks in two orthogonal coupling reactions. The current study uses AB2 monomer units 1 and 2 which contain two pairs of complementary coupling functionality. These monomer units were designed to couple by the Mitsunobu esterification reaction16 or by the Sonogashira reaction of a terminal acetylene with an aryl iodide.17 The latter reaction has been used extensively by Moore in the preparation of phenylacetylene dendrimers and other nanostructures.18 It was anticipated that both pairs of functional groups and their resulting coupling products would be inert to the conditions of the other coupling reaction, orthogonality that would allow 1 and 2 to be employed consecutively in either order.


Scheme 1a

*a Reaction conditions: (a) PPh3, diethyl azodicarboxylate (DEAD), THF; (b) Pd(PPh3)2Cl2, Cul, or Pd2(dba)3, Cul, PPh3, Et3N, PhCH3.
The application of this orthogonal coupling strategy to the synthesis of a first-generation dendron is outlined in Scheme 1. (4-tert-Butylphenoxy)ethanol (3) was coupled to 1 under Mitsunobu conditions to give first-generation dendron 4 in 80% yield. At the focal point of dendron 4 is an iodide group, which coupled to 2 using the Sonogashira reaction to form second-generation dendron 5 in 82% yield. The alcohol group at the focal point of this dendron was set to react with diacid 8 to produce third-generation dendron 6 in 85% yield. In a final iteration, 6 coupled to 2 to produce fourth-generation dendron 7 in 78% yield. By alternate use of 1 and 2 in their respective orthogonal reactions, the fourth-generation dendron 7 was synthesized in four steps.

To further increase the efficiency of this strategy, the orthogonal coupling method was merged with Fréchet’s branched-monomer approach. New “branched monomers” 8 and 9, already at the second-generation stage, were used for this purpose. These compounds contain the same functionality as do 1 and 2 but are expanded by an ether linkage and have four peripheral reaction sites. Compound 8 was obtained in four steps from 1 (Scheme 2). The desired monomer 9 was prepared in two steps by conversion of 2 to the corresponding bromide which was coupled to 11.

Scheme 3 illustrates the synthesis of a sixth-generation dendron from 8 and 9 using the orthogonal coupling approach. Tetraesterification of alcohol 3 with tetraacid 8 under Mitsunobu conditions afforded second-generation iodide 12 in 84% yield. Coupling of this iodide with tetraacetylene 9 under Sonogashira conditions afforded fourth-generation dendron 13 in 66% yield. Alcohol 13, an analog of 7, was used to synthesize higher generation dendrimers. Thus, esterification of 13 with diacid 1, trimesic acid, and tetraacid 8 under Mitsunobu conditions afforded the corresponding dendron 14 (G5I), dendrimer 15 ((G4I)3), and dendron 16 (G6I) in 80%, 46%, and 62% yield, respectively. The yields of these coupling reactions are based on relatively low conversions of 13 to 14 (46%), 15 (41%), and 16 (22%), which likely reflects the congestion at the focal point. Thus, from 8 and 9, the synthesis of sixth-generation dendron 16 required only three steps and two chromatographic separations.

All the dendrimers were characterized by standard spectroscopic methods and by size-exclusion chromatography (SEC) with differential refractometer index (DRI) and dual-angle laser light scattering (LLS) detectors. The molecular weights were determined directly by LLS and from their retention times using polystyrene standards. Although the latter method underestimated the molecular weight of high-generation (>4) dendrimers because of their compactness, results from the laser light scattering technique were in good agreement with the theoretical values. The dendrimers were also characterized by mass spectrometry using matrix-assisted laser desorption ionization (MALDI). In the MALDI spectra, the major peaks often appeared 23 or 39 mass units higher than the corresponding molecular ions, presumably representing sodium or potassium ion adducts.

In comparison to the most efficient dendrimer syntheses available, the orthogonal coupling approach halves the number of steps needed by obviating (de)protection or activation steps. Each synthetic step adds at least one generation to the dendrimer. As a case in point, sixth-generation dendron 16, with molecular formula C1292H1369IO242 and a molecular weight of 20,896 g mol⁻¹, was synthesized in just three steps from 8 and 9. There is nothing special about the reactions and subunits in Schemes 1 and 2; they were chosen simply to demonstrate the orthogonal coupling strategy, an approach that should be broadly applicable to dendrimer synthesis using any series of orthogonal coupling reactions.

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Supporting Information Available: Spectral and chromatographic data for 4–7 and 12–16 (48 pages). Ordering information is given on any current masthead page.

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