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Dendrimers Terminated with Dichlorotriazine Groups Provide a Route to Compositional Diversity

Subrata Patra,[†] Brittany Kozura,[†] Adela Y.-T. Huang,[‡] Alan E. Enciso,[†] Xiankai Sun,[§] Jer-Tsong Hsieh,[∥] Chai-Lin Kao,[‡] Hui-Ting Chen,[⊥] and Eric E. Simanek*,[†]

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129, United States, Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan, Department of Radiology, University of Texas Southwestern Medical Center, Dallas, Texas 75390, United States, Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas 75390, United States, and Department of Fragrance and Cosmetic Science, Kaohsiung Medical University, Kaohsiung, Taiwan

e.simanek@tcu.edu

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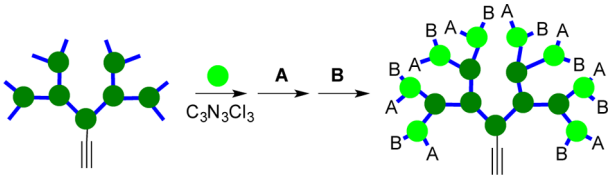
ABSTRACT



Triazine dendrimers terminated with either four or eight dichlorotriazines can be prepared in high yields by reacting an amine-terminated dendrimer with cyanuric chloride. These materials exist as white powders and are stable to storage at room temperature. Sequential nucleophilic aromatic substitution with two different amine nucleophiles yields compounds that display the desired compositional diversity. Reaction conditions for the substitution were developed using a model dichlorotriazine with amine nucleophiles at −20, 0, and 25 °C. Selective substitution is favored at lower temperatures and with more nucleophilic amine groups.

The generation of compositional diversity on the periphery of dendrimers is a long-standing goal of the community.[1] The easiest route to this end is to apply substoichiometric derivatization of dendrimers bearing a common reactive surface group such as an amine.[2] While this strategy benefits from a low synthetic burden, the result is a diversity of products that can present challenges to the characterization. Methods for characterizing such mixtures, however, are becoming increasingly refined.[3] Using convergent synthetic approaches,[4] dendrimers with

[†] Department of Chemistry, Texas Christian University.
[‡] Department of Medicinal and Applied Chemistry, Kaohsiung Medical University.
[§] Department of Radiology, University of Texas Southwestern Medical Center.
[∥] Department of Urology, University of Texas Southwestern Medical Center.
[⊥] Department of Fragrance and Cosmetic Science, Kaohsiung Medical University.

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specific compositional diversity can be obtained across a variety of platforms including aryl[5] and aliphatic[6] ethers, PAMAM,[7] and triazines[8] by carrying the diversity-generating groups through the entire synthesis. Here, the synthetic burden is substantially increased and the versatility can be limited by the initial choice of the diversity elements. Oftentimes, these products are derived from the dimerization of dendrons displaying two different surface chemistries[6a] including those relying on selective click chemistry.[7] Recently, Rudick reported that a three-component Passerini coupling reaction has been efficiently utilized to generate triblock dendrimers of low generations from dendrons functionalized at the focus.[9] Still, the diversity elements are carried through the convergent synthesis. Divergent strategies to dendrimers offer compelling advantages over convergent routes. Divergent routes provide access to larger dendrimers and benefit from mole conservation. That is, multimerizations do not reduce the number of moles of product theoretically available, and instead, mass is added throughout the synthesis. Generating diversity using this strategy is challenging and can introduce additional synthetic burden (vide infra). Mixed approaches, as representative of recent work of Weck, have yielded structurally diverse platforms.[10]

Our interest in triazine dendrimers is fueled, in part, by the ease at which stepwise substitution of trichlorotriazine occurs with amine nucleophiles.[11] By controlling the reaction temperature, trisubstituted triazines can be readily accessed in good yields, purity, and at large scale.[12] We have invested significant energies in understanding the relative reactivity of amine nucleophiles for triazines[13] and used these methods to generate a range of dendrimer targets.[11] Early efforts to generate compositional diversity to make a dendrimer with a unique site on the periphery[8a] or to install different orthogonal protecting groups both relied on a convergent synthetic strategy.[8b] Thayumanavan has generated similarly diverse targets using arylethers.[5c–e]

We have achieved diversity by reacting poly(amine) dendrimers with functionalized mono-[14] or dichlorotriazine groups.[15] Although these methods have been applied during divergent syntheses of low generation dendrimers, these still require the separate synthesis of the diversity-generating mono- or dichlorotriazine. Accordingly, we have historically avoided the synthesis of large libraries of compounds. Our explorations of small libraries have focused on either stoichiometric functionalization of peripheral amines[16] or the laborious substitution of internal linking amine groups[17] in order to execute the desired structure–property relationship studies.

Triazines have been used for small molecule libraries.[18] Extrapolating to dendrimers, however, requires two challenges to be overcome. First, a reactive dendrimer in the form of a poly(dichlorotriazine) must be prepared and established as a stable and viable intermediate. Second, conditions for the selective, stepwise functionlization of these molecules must be developed. Here, we report that both challenges have been met.

We describe a strategy wherein amine-terminated dendrimers are reacted with cyanuric chloride to yield poly (dichlorotriazine) targets. These intermediates are subjected to stepwise substitution of the triazine rings with two different nucleophiles to yield targets that display these nucleophiles in a 1:1 ratio. Accordingly, this chemistry represents the first step necessary to efficiently prepare libraries from the wealth of commercially available amine nucleophiles.

We find that the desired poly(dichlorotriazine) targets are readily accessible. Dendrimers **1** and **2** display either 4 or 8 dichlorotriazines on the surface, respectively (Figure 1). Both compounds are white powders that can be stored for months at rt.

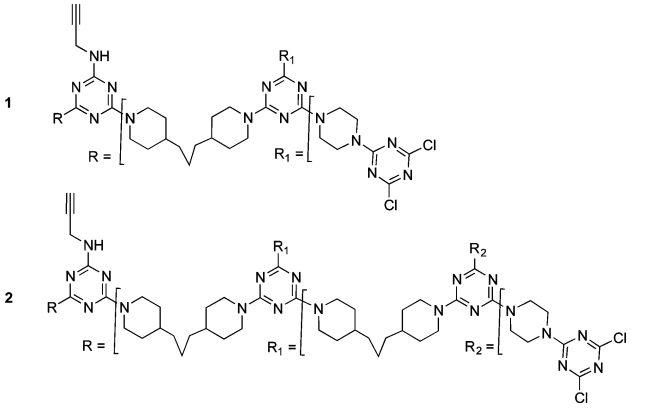

Figure 1. Targets.

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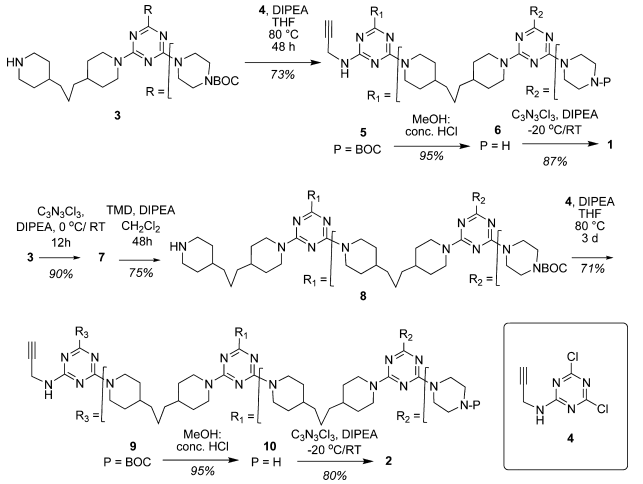
The synthesis starts with the preparation of monomer **3** which presents two BOC-protected piperazine groups and a trismethylene dipiperidine amine (Scheme 1).[19] Cyclic secondary amines were chosen for both their high reactivity during nucleophilic aromatic substitution of the triazine ring and the perceived solubility advantages deriving from a lack of H-bond donating groups. The reaction of **3** with a dichlorotriazine displaying an alkyne group (reagent **4**, Scheme 1) yields **5**. Upon deprotection with 2:1 methanol: conc. HCl, the penultimate intermediate **6** is obtained. Dendrimer **1** is realized by reacting **6** with 12 equiv of cyanuric chloride—a 3-fold excess—in tetrahydrofuran at −20 °C for 4 h. Evidence for the formation of crosslinked sideproducts is not observed by mass spectrometry or NMR spectroscopy. Intramolecular cross-links to yield a monochlorotriazine should present a mass defect equivalent to $C_3N_3Cl_3$. Intermolecular cross-links will yield species with higher molecular weights.

Similarly, the synthesis of dendrimer **2** commences with the reaction of **3** with 0.5 equiv of cyanuric chloride to yield **7**. In a subsequent reaction, the linking diamine was added to provide **8**. The reaction of **8** with reagent **4** yields **9**. Deprotection of **9** provides **10**, which is reacted with cyanuric chloride under similar conditions to provide **2**.

Dendrimers **1** and **2** and most intermediates are isolated by conventional silica gel chromatography and characterized by NMR spectroscopy and mass spectrometry. All of these intermediates are stable at room temperature.

Scheme 1. Synthesis of Poly(dichlorotriazine) Dendrimers **1** and **2**[a]

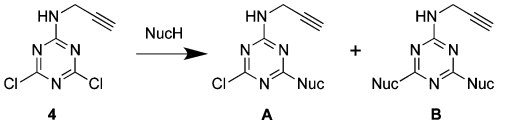


[a] TMD is trismethylene dipiperidine.

To evaluate conditions for achieving selective substitution of these dendrimers, **4** was used as a model.[20] Using 1 equiv of an amine nucleophile, the ratio of desired single substitution A and undesired double substitution B could be assessed as a function of temperature upon isolating the product of the reaction (Scheme 2). The reactions were executed for 4 h at the prescribed temperatures using 1 equiv of diisopropylethylamine at 0.03 M **4** in a 2:1 tetrahydrofuran/dichloromethane mixture. The solvent mixture was required due to solubility challenges encountered with the methyl ester of proline (entry 8 in Table 1).

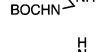
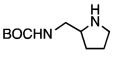
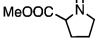
Table 1 summarizes the results of these experiments. The amines in this table are organized from least reactive to most reactive as would be predicted from our earlier studies.[11] This reactivity prediction excludes steric effects deriving from substituents on the carbon adjacent to the nucleophilic nitrogen (entries 6–8). These encumbered amines clearly react more sluggishly than their unsubstituted analogues. The impact that steric encumberance has on five-membered rings over six-membered rings is pronounced as the former do not react completely in the time provided.

Scheme 2. Reaction of Alkyne Dichlorotriazine with Nucleophile



Many lessons emerge from these studies. First, as the observed nucleophilicity of the amine increases, selectivity also increases. Second, the ratio of A:B is maximized at low temperature. Third, steric congestion near the nucleophilic nitrogen has pronounced effects on the rate and selectivity of the reaction. Methanol is unreactive under these conditions.

Table 1. Product Distribution Reported As the Ratio of Monosubstituted/Disubstituted at Three Temperatures after 4 h of Reaction

		Temperature					Temperature		
#	NucH	25 °C	0 °C	-20 °C	#	NucH	25 °C	0 °C	-20 °C
1	$BuNH_2$	89:11	93:7	98:2	5		92:8	96:4	>99:1
2	$PhCH_2NH_2$	91:9	95:2	98:2	6		93:7	96:4	98:2
3		90:10	96:4	99:1	7		64:24[a]	77:10[a]	82:5[a]
4	 R=$CH_2CH_2OCH_2CH_2OH$	83:17	86:14	94:6	8		53:32[a]	50:28[a]	48:26[a]

[a] Remainder isolated as unreacted **4**.

With these results in hand, we pursued selective substitution of dendrimers **1** and **2**. The HEEP

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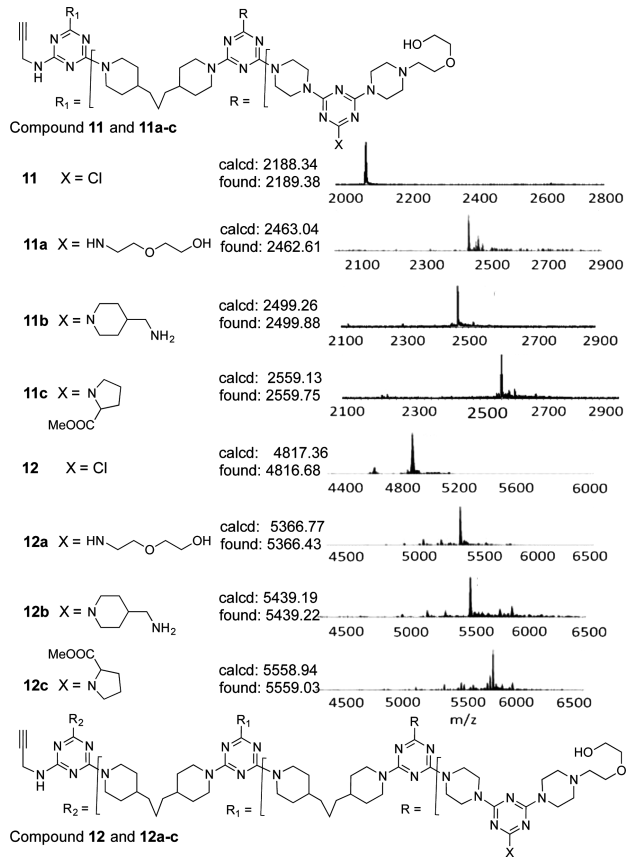

Figure 2. ESI mass spectrograms of dendrimer derivatives.

(1-[2-[2-hydroxyethoxy)ethyl]-piperazine) group was installed as a common surface group, as the amine conveys solubility and the PEG-like tail is hypothesized to reduce the cytotoxicity of the cation should these molecules ever be assessed in cell culture. These benefits outweighed factors associated with the poorer selectivity observed for this species than the hydrophobic alternatives. Using identical reaction conditions to the model studies, compounds **11** and **12** were obtained. These intermediates could be isolated by silica gel chromatography in 85% and 79% yields, respectively. These yields exceed what would be expected based on the model studies (0.94^4 = 78%; 0.94^8 = 61%) reflecting higher selectivity under the conditions employed, or an inability to detect side reactions including oversubstitution.

Figure 2 shows the derivatives of **11** and **12** (identified **a**–**c**) that were prepared using aminoethoxyethanol, 4-aminomethylpiperidine and proline methylester as nucleophiles. The reaction progress can be monitored by mass spectrometry, and the major species that were identified corresponds to the desired target. These traces appear in Figure 2. Data derived from mass spectrometry are compiled and include the calculated (calcd) and observed (found) ions.

Not surprisingly, evidence for the incomplete reaction of **11** and **12** with the proline methyl ester to yield **11c** and **12c** is seen in the mass spectrum in the crude samples.

In summary, the poly(dichlorotriazine) dendrimers are viable synthetic targets that exist as stable, white powders. These molecules react with commercially available amine nucleophiles to yield diversity in well-defined ratios. While demonstrated on triazine dendrimer platforms, this strategy should be applicable to most amine terminated dendrimers. These results open the possibility for the preparation of larger libraries of dendrimers for more detailed structure–activity relationship studies.

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Supporting Information Available. Information includes details of synthesis, ^{1}H and ^{13}C NMR spectra, and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.