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# Chemoselective Building Blocks for Dendrimers from Relative Reactivity Data

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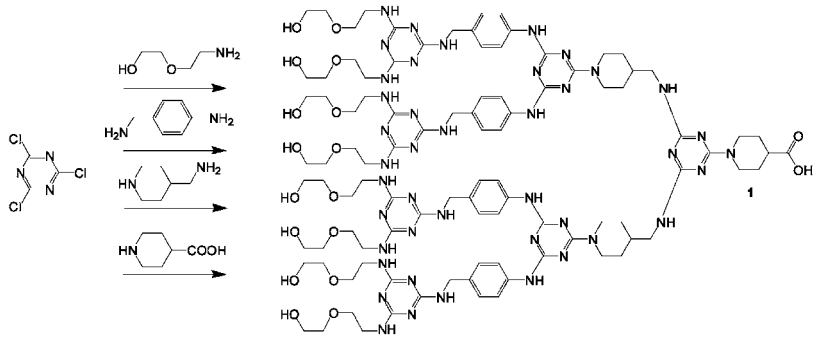
## ABSTRACT



**Competition reactions for the substitution of monochlorotriazines with different amines provide relative reactivity data that can be used to identify new groups for the chemoselective syntheses of dendrimers based on melamine. Target 1 is prepared using a one-pot per generation strategy without protecting group manipulations or functional group interconversions.**

Our efforts in the synthesis of dendrimers based on melamine, triazines interconnected with diamines, aim to reduce many of the synthetic challenges to compositional diversity to the trivial.[1] The ease with which compositional diversity can be introduced into dendrimers depends greatly on the nature of the dendritic building blocks.[2] Diversity in dendritic homopolymers is usually limited to the choice of core or peripheral groups.[3] Modification of the surface is usually stoichiometric or statistical, although examples of dendrimers with specific, substoichiometric numbers of surface modifications have been described.[1,4−7] Generating diversity in the interior usually involves either structural modifications to the monomer that preserve the general synthetic route[7,8] or the use of multimonomer systems.[9] With efficient access to compositional diversity, dendrimers may find greater utility. Strategies that (i) reduce the number of synthetic manipulations, (ii) proceed in high yields, and (iii) proceed in high atom economy further this opportunity.

The synthesis of dendrimers based on melamine relies on iterative reactions of cyanuric chloride and diamine linkers. The stepwise substitution of the triazine ring (equation 1) provides an efficient one-pot strategy for the preparation of

(1) Zhang, W.; Nowlan, D. T., III; Thomson, L. M.; Lackowski, W. M.; Simanek, E. E. *J. Am. Chem. Soc.* **2001**, *123*, 8914−8922.
(2) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819−3867.
(3) (a) Diederich, F.; Felber, B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4778−4781. (b) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74−91.
(4) Hawker, C. J.; Fréchet, J. M. J. *Macromol.* **1990**, *23*, 4726−4729.
(5) Kawaguchi, T.; Moore, J. S. *Polym. Prepr.* **1994**, *35*, 872−873.
(6) Vutukuri, D. R.; Sivanandan, K.; Thayumanavan, S. *Chem. Commun.* **2003**, *6*, 796−797.
(7) For the incorporation of reactive halides: Bo, Z.; Schäfer, A.; Franke, P.; Schlüter, A. D. *Org. Lett.* **2000**, *2*, 1645−1648.
(8) For varying stereochemistry of the monomer: Seebach, D.; Rheiner, P. B.; Greiveldinger, G.; Butz, T.; Sellner, H. *Curr. Top. Chem.* **1998**, *197*, 125−164.
(9) For biodegradable dendrimers on diacids and poly(ols)s: (a) Schmalenberg, K. E.; Frauchiger, L.; Nikhouy-Albers, L.; Uhrich, K. E. *Biomacromolecules* **2001**, *2*, 851−855. (b) Carnahan, M. A.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2001**, *123*, 2905−2906.

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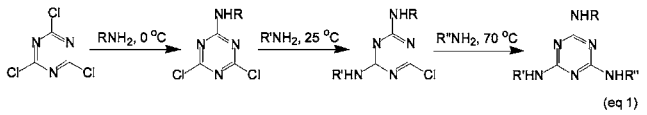
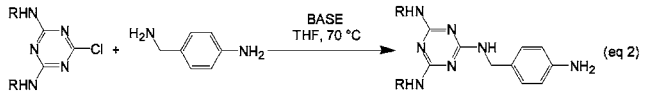
a dendron with two different surface groups (R and R′) and a diamine linking group (R″) using the convergent approach.[2]




Utilizing diamines comprising amines of significantly different reactivity affords chemoselective routes to these targets and obviates the need for protecting groups. For example, the benzylic amine of *p*-aminobenzylamine (*p*ABA) preferentially reacts with monochlorotriazines (equation 2) to yield an aniline that can be elaborated into higher generations of dendrimers. Here, we report the relative reactivities of amines (and other functional groups) for monochlorotriazines. These values are useful for the identification of linking, surface, and focal groups for the chemoselective synthesis of dendrimers based on melamine.




The reactivity map resulting from competition reactions between amine nucleophilies **A**−**H** for monochlorotriazine **2** is shown in Figure 1. The reactivity difference between consecutive amines appears over the "$>$" sign. The strategy employed is based on Ley's technique for evaluating the relative reactivity of glycosyl donors present in excess for a common acceptor by evaluating the end product distribution.[10] These reactions were conducted with 3 equiv of three different amines chosen from **A**−**H** and 1 equiv of the **2** over a range of temperatures (Supporting Information). Our choice of three amines instead of two made the effort more efficient and provided additional internal checks of consistency. The final reactivity map was obtained by determining the relative product ratios from $^1$H NMR after disappearance of **2**. These values are consistent multiplicatively across the range within experimental error. The chemical shift of the protons α to the amine generally appear downfield from those

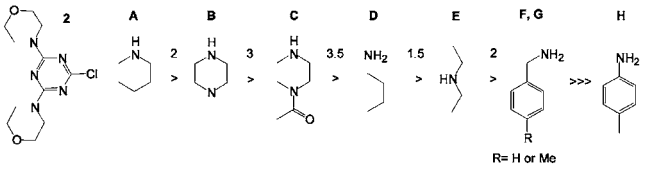


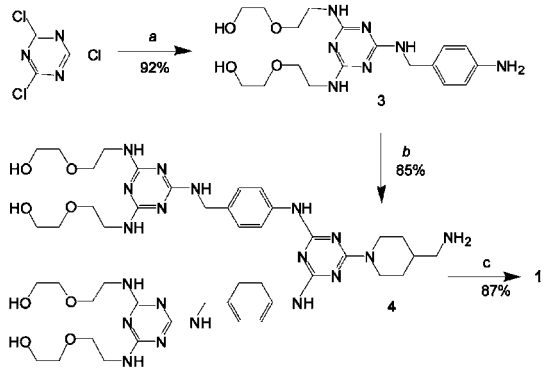

**Figure 1.** Relative reactivity map for the substitution of monochlorotriazines. The reactivity difference between consecutive amines appears over the "$>$" sign.

(10) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkins Trans. 1* **1998**, 51.

in the free amine. Alcohols (including phenols) and carboxylic acids are unreactive under the reaction conditions.

To keep the number of side-products to a minimum during a dendrimer synthesis, we favor a minimum reactivity difference of ≥20 for the two amines of a diamine linker. Target **1** (Scheme 1) illustrates this strategy using four

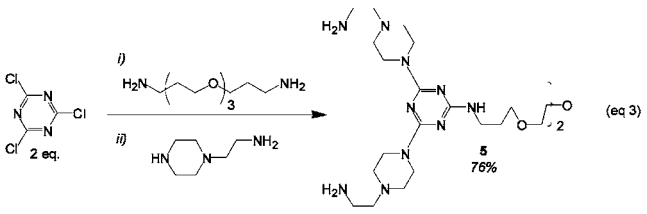
**Scheme 1.** G3 Dendron Synthesis[a]




[a] Reagents and conditions: (a) $HO(CH_2)_2O(CH_2)_2NH_2$, Hünig's base, THF, 0 °C to rt; then *p*-ABA, 70 °C. (b) $C_3N_3Cl_3$, Hünig's base, 1:1 THF:MeOH, 0 °C to rt; then AMP, rt. (c) $C_3N_3Cl_3$, Hünig's base, 1:1 THF:MeOH, 0 °C to rt; then INP, 1% $NH_4OH$, 50 °C.

chemoselective building blocks, an amino alcohol, *p*-ABA, aminomethylpiperidine (AMP), and isonipecotic acid (INP). The target was obtained in three pots in 68% overall yield. The progress of the reactions is readily monitored by TLC because of the marked differences in polarity between starting amine, intermediate monochlorotriazine, and final amine products. Some features worthy of note are (i) a hydroxyl periphery that is left unprotected throughout the synthesis and (ii) interiors of *p*ABA and AMP that exploit the significant differences in reactivity of the constituent amine groups and proceed without a trace of the undesired isomers. The order of incorporation of these groups has been interchanged (AMP first, then *p*ABA, not shown) without any significant deviation in yield or purification strategy. Active esters (NHS) of **1** have been prepared and isolated. The dendron can be condensed with a diamine to afford dendrimer using a peptide coupling reagent.

The differential reactivity map appears to hold for dichlorotriazines as well. For example, core **5** can be prepared in one pot through the selective reaction of a diamine and aminoethylpiperazine (AEP, eq 3). The selective addition of the secondary amine over the primary amine is evident in



the $^{1}H$ and $^{13}C$ NMR spectra. Both spectra show a distinct downfield shift of the protons and carbons α to the secondary amine, while the signals corresponding to the resonances α to the primary amine remain the same as AEP. This core can be condensed with a dendron bearing an INP group at the focus.

In conclusion, diamines with differences in reactivity of ≥20 provide useful building blocks for the preparation of dendrimers based on melamine. AMP has emerged as the linking diamine of choice for reactivity and stability issues.

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**Supporting Information Available:** Synthetic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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