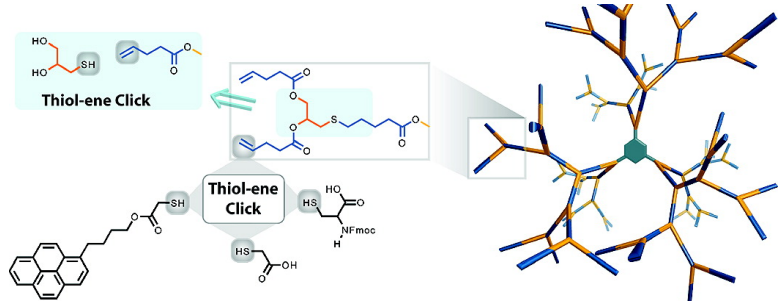
Communication

Robust, Efficient, and Orthogonal Synthesis of Dendrimers via Thiol-ene "Click" Chemistry

Kato L. Killops, Luis M. Campos, and Craig J. Hawker

J. Am. Chem. Soc., **2008**, 130 (15), 5062-5064 • DOI: 10.1021/ja8006325 • Publication Date (Web): 20 March 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 12 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 03/20/2008

Robust, Efficient, and Orthogonal Synthesis of Dendrimers via Thiol-ene "Click" Chemistry

Kato L. Killops, Luis M. Campos, and Craig J. Hawker*

Department of Chemistry and Biochemistry, Department of Materials, and Materials Research Laboratory, University of California, Santa Barbara, California 93106

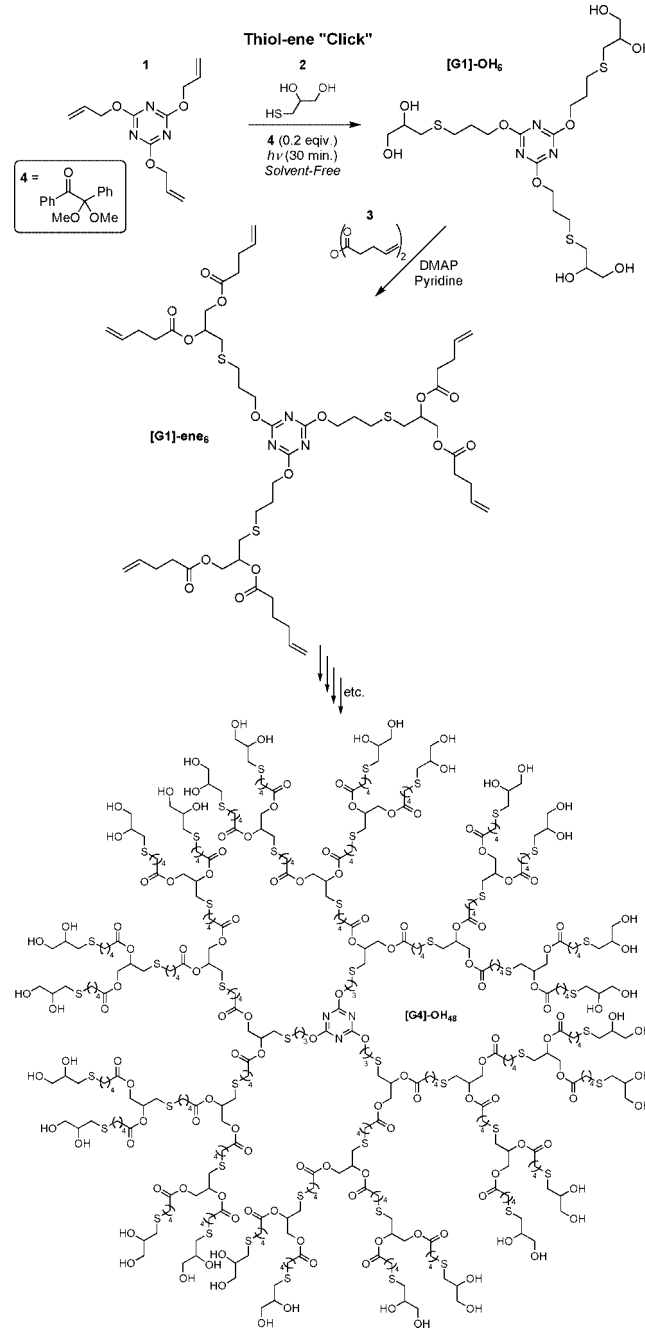
Received February 6, 2008; E-mail: hawker@mrl.ucsb.edu

The continued success of dendrimers[1,2] in applications ranging from medicine to nanoengineering[3,4] imposes a challenge to develop practical syntheses of these highly branched macromolecules. In turn, this challenge has focused attention on the much greater need to elaborate highly efficient and orthogonal reactions, such as "click" chemistry,[5] for the preparation of functional materials.[6] Underlying both of these synthetic goals is the additional desire to develop scalable reactions that fall within the philosophical realm of green chemistry.[7]

When considering the synthesis of dendritic macromolecules, both the divergent[8,9] and convergent[10] strategies offer advantages and disadvantages with the traditional divergent approach being particularly challenging from a synthetic viewpoint. At each step, the number of functional groups rapidly increases, and efficient reactions are therefore required to accurately build a well-defined structure without using large excesses of reagents. The classical example of using dendrimers as test vehicles for the development of robust and efficient synthetic tools is the Cu(I)-mediated Huisgen 1,3-dipolar cycloaddition reaction of azides and acetylenes. Tremendous success has been achieved with this example of click chemistry[5,11,12] and it has been employed for the synthesis of block copolymers, cross-linked materials, and dendrimers.[6,13–16] However, its limitations include the need for a metal catalyst, an inability to photochemically control the reaction or to conduct the reaction in the absence of solvent. To further develop this fundamentally important aspect of polymer synthesis, the discovery and exploitation of additional robust, efficient, and orthogonal click reactions is highly desirable.

The appeal of click chemistry is a result of the modular nature of the reaction coupled with synthetically powerful characteristics such as: regioselectivity, quantitative yields, nonchromatographic purification, use of benign solvents (e.g., water), and mild reaction conditions.[5] In this context, thiol-ene chemistry has many of the attributes of click chemistry and has been used to fabricate a multitude of thin-film systems[17–19] with outstanding efficiency and most importantly, in the presence of oxygen. More recently, the synthetic potential of thiol-ene chemistry has been exploited for the modification of the backbone of poly(oxazolines) and poly(butadiene) with an array of thiols[20] and to build glycodendrons.[21] These promising results suggest a much greater role for thiol-ene chemistry as a new click reaction, which is compatible with water and oxygen and can be performed in the absence of solvent and under photochemical initiation. To fully probe the efficiency of this process, this Communication describes the synthesis of fourth-generation dendrimers using thiol-ene chemistry to construct both the backbone as well as functionalize the chain ends. The overall synthetic strategy is highlighted in Scheme 1, starting from the tris-alkene core 2,4,6-triallyloxy-1,3,5-triazine **1**. The AB_2-monomer, 1-thioglycerol **2**, was appropriately chosen for its thiol functionality, two readily functionalizable hydroxy groups, and its miscibility with **1**.

Scheme 1



10.1021/ja8006325 CCC: $40.75

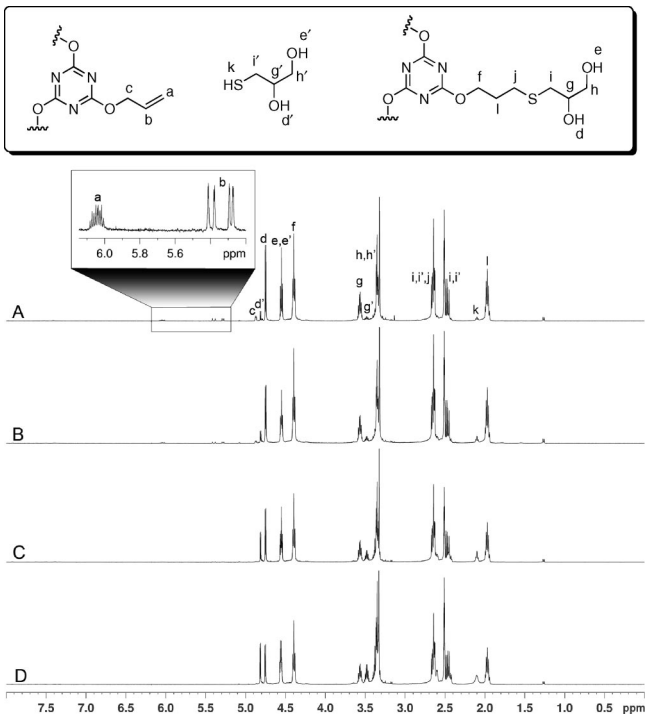


Figure 1. ^{1}H NMR spectra of the crude reaction mixtures after photolysis of **1**, photoinitiator, and (A) 1.0 equiv (95% conversion), (B) 1.2 equiv (98% conversion), (C) 1.5 equiv (quantitative), and (D) 2.0 equiv (quantitative), of compound **2**.

The solvent-free reaction between **1** and **2**, in the presence of trace amounts of the photoinitiator 2,2-dimethoxy-2-phenylacetophenone **4**, was carried out at room temperature, without deoxygenation, by irradiation with a hand-held UV-lamp (λ_{ex} = 365 nm) for 30 min. The thiol-ene reaction was optimized by varying the thiol/alkene ratio from 1:1, 1.2:1, 1.5:1, to 2:1 to determine the minimum number of equivalents of **2** required to drive the reaction to completion. The ^{1}H NMR spectra of the crude reaction mixtures are shown in Figure 1 and analysis of the peaks in the region between 5.2 to 6.2 ppm, corresponding to the alkene protons at the periphery, clearly shows that at a 1:1 ratio small peaks due to unreacted double bonds are observed (see insert). However these disappear at a ratio above 1.2:1 and a quantitative reaction is obtained when 1.5 and 2 equiv of the AB_2 monomer, **2**, were used. The thiol-ene reaction between **1** and **2** therefore yields the first-generation, hexa-hydroxy dendrimer [G1]-OH_6 in quantitative yield and subsequent esterification of [G1]-OH_6 with 4-pentenoic anhydride **3**, furnishes the ene-functional dendrimer [G1]-ene_6. Of particular note is that even at higher generations, only 1.5 equivalents of **2** per alkene and a 30-min irradiation time was required for quantitative functionalization. After repetition of this stepwise procedure, the fourth generation dendrimer, [G4]-OH_{48}, is obtained with unprecedented efficiency. In addition, the ability to perform all of the thiol-ene generation growth steps under bulk conditions and at room temperature in the presence of oxygen allows for a robust, environmentally benign process that is scaleable.

The efficient nature of thiol-ene chemistry and the lack of byproducts also allow all [G*n*]-OH_x dendrimers to be purified by simple precipitation into diethyl ether and were obtained in 90+% recovered yields as viscous liquids. Characterization of the purified products was aided by the symmetrical dendritic framework with the monodisperse nature of each generation being demonstrated by a combination of gel-permeation chromatography (GPC) and

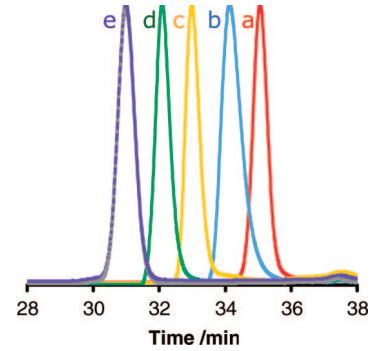


Figure 2. GPC traces of the products: (a) [G1]-ene_6, (b) [G2]-OH_{12}, (c) [G3]-OH_{24}, (d) [G4]-OH_{48}, and (e) [G4]-ene_{48}.

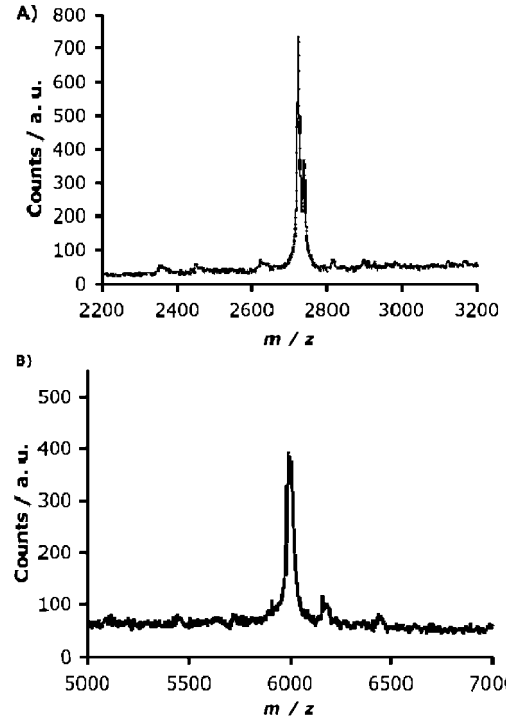
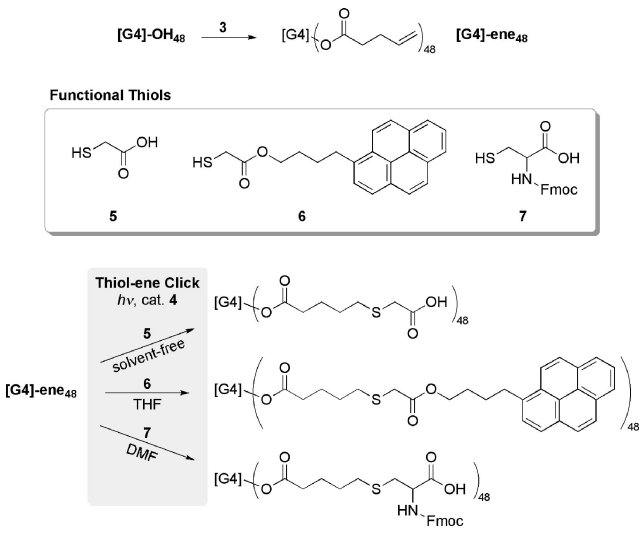


Figure 3. MALDI-TOF spectra of (A) [G2]-ene_{12} ($M + Na^+$ and $M + K^+$) and (B) [G3]-ene_{24} ($M + Na^+$ and $M + K^+$).

MALDI-TOF mass spectrometry. The GPC traces indicate that both the hydroxyl and alkene-terminated dendrimers are monodisperse with the expected increase in molecular size as the generation number is increased from 1 to 4 (Figure 2a−d). Interestingly, the change in chain-end functional groups can also be readily observed by GPC and even for the fourth generation hydroxy-terminated dendrimer, nearly complete baseline separation is observed on conversion of the 48 hydroxy groups to 48 alkene units (Figure 2d and 2e).

Given that the divergent growth strategy can dramatically amplify imperfections and structural defects in dendritic macromolecules, it was critical to examine molecular integrity by mass spectrometry. In all cases a strong signal for molecular ion is observed at the expected molecular weight with only minor contamination from defect structures (see Figure 3). For example, the [G3]-ene_{24} primarily shows molecular ions at 5990 and 6006, which correspond with the Na^+ and K^+ adducts and is in excellent agreement with the calculated value of 5966 (Figure 3B). This is in direct contrast to other divergent materials such as PAMAM dendrimers which are characterized by defect structures and a range

Scheme 2



of molecular species with only minor contributions from the expected molecular ion.[22] The high degree of structural fidelity resulting from the thiol-ene reaction was also confirmed by ^{1}H and ^{13}C NMR spectroscopy, which further supported the high level of purity and structural perfection for these systems.

The orthogonality and efficiency of the thiol-ene chemistry used in construction of the dendritic backbone strongly suggests that this chemistry can also be employed for functionalization of the numerous chain ends. To demonstrate this concept, the [G4]-ene$_{48}$ dendrimer was coupled with a diverse set of functional units using a second thiol-ene reaction. As noted by Frey and co-workers,[23] this terminal functionalization is greatly aided by the wide availability of monofunctional thiols with thioglycolic acid **5**, 4-(pyren-1-yl)butyl 2-mercaptoacetate **6**, and 9-fluorenylmethoxycarbonyl cysteine **7** being examined (Scheme 2).

For liquid precursors such as **5**, the high degree of tolerance for impurities allows similar room temperature, bulk reaction conditions to be used for functionalization of the chain ends as were used to construct the dendrimer backbone. Quantitative reaction of the terminal groups with 3.0 equiv of **5** was observed by ^{1}H NMR and found to occur within 30 min under atmospheric conditions. The resulting carboxylic acid functionalized dendrimer was soluble in *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), and water, in direct contrast to the starting material. While it is desirable to perform the functionalization chemistry in the absence of solvent, solid starting materials, such as **6** and **7**, can be used by performing the thiol-ene reactions in minimal solvent, the nature of which can be varied widely. In both cases, functionalization of the periphery resulted in essentially quantitative conversion, although an increase in the amount of initiator, from 2 mol % to 10 mol % (per alkene), was required for these reactions. As expected, the nature of the chain end groups had a dramatic effect on the physical properties of the dendrimer with compounds **8**, **9**, and **10** exhibiting glass transitions at −39, −8, and −3 °C, respectively. This is in contrast to the glass transition temperature (T_g) of the starting fourth generation dendrimers [G4]-OH$_{48}$ (−36 °C) and [G4]-ene$_{48}$ (−57 °C).

Using the divergent approach to dendritic macromolecules as an ardent test of the synthetic capabilities of thiol-ene chemistry, we have presented the facile and efficient synthesis of poly(thioether) dendrimers using thiol-ene addition reactions for construction of both the dendritic backbone as well as functionalization of the chain ends. Conducting the thiol-ene reactions in the absence of solvent under benign reaction conditions and without the use of any metal catalysts allows for an environmentally friendly process to be developed, further enhancing the attractive nature of this process.[24] The robust, efficient, and orthogonal nature of thiol-ene chemistry therefore shows great potential as a versatile synthetic tool for the fabrication of a wide variety of well-defined functional macromolecules and strongly suggests its addition to the list of reactions that fulfill the requirements of click chemistry.

Acknowledgment. Financial support from the NSF (Grant CHE-0514031 and the MRSEC Program DMR-0520415 (MRL-UCSB) is greatly acknowledged. We also thank Dr. B. W. Messmore for the synthesis of compound **6**. K.L.K. thanks the DOD for a Science Mathematics and Research for Transformation Fellowship.

Supporting Information Available: Synthetic procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Tomalia, D. A.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2719–2728.
(2) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819–3868.
(3) Helms, B.; Meijer, E. W. *Science* **2006**, *313*, 929–930.
(4) Almutairi, A.; Guillaudeu, S. J.; Berezin, M. Y.; Achilefu, S.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2008**, *130*, 444–445.
(5) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
(6) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928–3932.
(7) Horvath, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2167–2168.
(8) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J. (Tokyo, Jpn.)* **1985**, *17*, 117–132.
(9) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003–2004.
(10) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
(11) (a) Lutz, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025. (b) Binder, W. H.; Sachenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15–54.
(12) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197–2208.
(13) (a) Ornelas, C.; Ruiz Aranzaes, J.; Cloutet, E.; Alves, S.; Astruc, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 872–877. (b) Gondi, S. R.; Vogt, A. P.; Sumerlin, B. S. *Macromolecules* **2007**, *40*, 474–481.
(14) (a) Antoni, P.; Nystrom, D.; Hawker, C. J.; Hult, A.; Malkoch, M. *Chem. Commun.* **2007**, 2249–2251. (b) Urbani, C. N.; Bell, C. A.; Whittaker, M. R.; Monteiro, M. J. *Macromolecules* **2008**, *41*, 1057–1060.
(15) Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38*, 5436–5443.
(16) (a) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663–3678. (b) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, (46), 5775–5777. (c) Liu, Y.; Díaz, D. D.; Accurso, A. A.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A Polym. Chem.* **2007**, *45*, 5182–5189. (d) Vestberg, R.; Malkoch, M.; Kade, M.; Wu, P.; Fokin, V. V.; Sharpless, K. B.; Drockenmuller, E.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 2835–2846.
(17) Hoyle, C. E.; Lee, T. Y.; Roper, T. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 5301–5338.
(18) Rydholm, A. E.; Bowman, C. N.; Anseth, K. S. *Biomaterials* **2005**, *26*, 4495–4506.
(19) Hagberg, E. C.; Malkoch, M.; Ling, Y.; Hawker, C. J.; Carter, K. R. *Nano Lett.* **2007**, *7*, 233–237.
(20) (a) Gress, A.; Volkel, A.; Schlaad, H. *Macromolecules* **2007**, *40*, 7928–7933. (b) David, R. L. A.; Kornfield, J. A. *Macromolecules* **2008**, *41*, 1151–1161.
(21) Heidecke, C. D.; Lindhorst, T. K. *Chem. Eur. J.* **2007**, *13*, 9056–9067.
(22) Hummelen, J. C.; Dongen, J. L. J. V.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1489–1493.
(23) Lorenz, K.; Frey, H.; Stuhn, B.; Mulhaupt, R. *Macromolecules* **1997**, *30*, 6860–6868.
(24) Anastas, P.; Horvath, I. T. *Chem. Rev.* **2007**, *107*, 2169–2173.

JA8006325