

APPLICATIONS OF THIOL – ENE COUPLING

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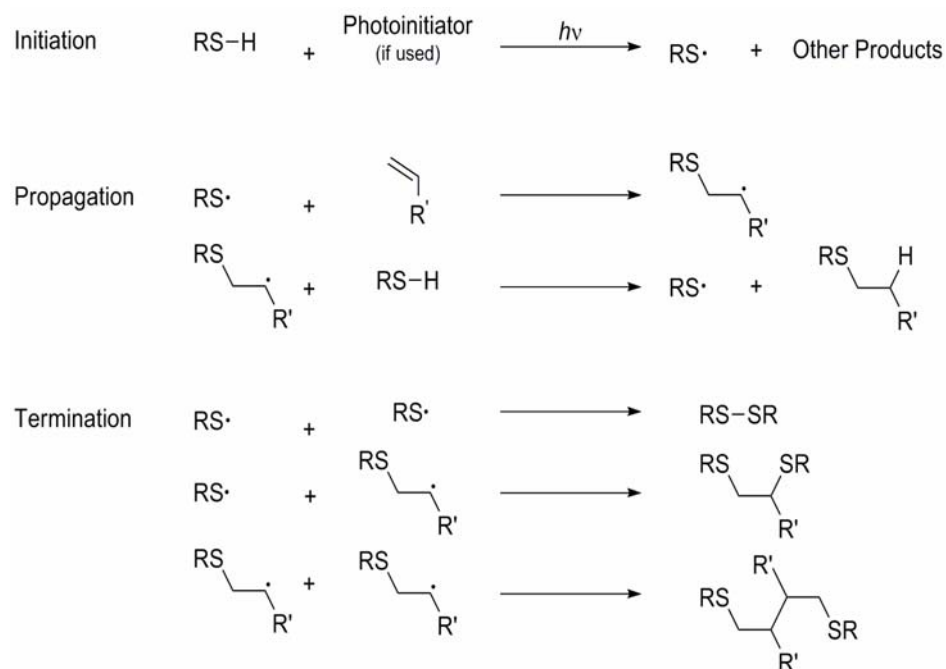
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INTRODUCTION

The crosslinking of unsaturated polymers through the addition of elemental sulfur was discovered in 1839 by Goodyear.¹ This process later became known as vulcanization, and it is used extensively in the tire industry to this day. The addition of thiols to olefins was shown by Posner in 1905.² Applications of the thiol-ene reaction are also far ranging, in both polymer and synthetic chemistry. Whereas the early work on thiol-ene coupling in polymer chemistry focused on the determination of the mechanism of addition, optimization of conditions, creation of cross-linked polymer composites, and the development of initiator-free reaction conditions,³ more recent research has focused on the use of thiol-ene reactions in selective functionalization and modification of molecular structures.⁴ One recent application is the functionalization of silicon surfaces. Depending on the polymer system used, several surface characteristics can be tailored, including adhesion, corrosion, friction resistance, and biocompatibility.⁵ A second application includes functionalization of polymer side chains using thiol-ene coupling conditions.⁶ This allows for the creation of “biohybrids” or

“molecular chimeras” comprised of synthetic polymer backbones with biologically inspired side chains.⁷ Additionally, thiol-ene coupling has been used in both the formation and modification of dendritic structures. This presentation will discuss the history of the thiol-ene reaction as well as some recent materials applications that harness this environmentally friendly chemistry.

Scheme 1. General thiol-ene coupling reaction mechanism



Background

In 1938 it was shown that the addition of thiols to alkenes proceeds via a free-radical chain mechanism (Scheme 1).⁸ Initiation occurs by radical formation upon UV excitation of a photoinitiator or the thiol itself. The resulting sulfenyl radical subsequently adds to the unsaturated alkene substrate in an anti-Markovnikov fashion to form a new carbon radical. In a second propagation step, the secondary radical that results then reacts with another thiol molecule to give the thioester product and a new sulfenyl radical, which propagates to continue the radical cycle. A variety of termination pathways are possible through recombination of sulfenyl or carbon radicals.

The thiol-ene reaction occurs predominately with anti-Markovnikov regioselectivity. This selectivity has been explained by the enhanced stability of the intermediate carbon radical upon addition to the less substituted alkene carbon.⁹ This reaction typically requires a photoinitiator such as benzophenone (BP) or dimethoxyphenyl acetophenone (DMPA).³ In many systems, the use of a photoinitiator has several disadvantages. Upon long term exposure to sunlight, the photoinitiators generally degrade to produce an observable yellowing effect in otherwise clear polymer films formed through thiol-ene polymerizations.

In an effort to avoid the disadvantages of photoinitiators, an alternative method of initiation has been developed. Cramer and coworkers showed that it was possible to initiate the radical chain through the use of an ultraviolet light source – specifically 254 nm - to promote the homolysis of the sulfur-hydrogen bond.¹⁰ However, this alternative method of initiation often proceeds more slowly than does initiation through the use of a photoinitiator, which results from lower rates of radical formation.

The thiol-ene coupling reaction can be described as a “click” reaction.⁴ According to the original definition forwarded by Sharpless and co-workers, “click” reactions are “modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods and be stereospecific (but not necessarily enantioselective).”¹¹ Several aspects of the thiol-ene coupling reaction fit this definition. For example, thiol-ene coupling reactions can be controlled with light, there is no need for an external catalyst, addition is regioselective, reaction conditions are compatible with water and oxygen, they are very atom efficient, they typically give quantitative yields, and they are tolerant of a wide variety of functional groups. However, despite the advantages that fit the “click” definition, there are potential limitations of this type of chemistry, which include its lack of

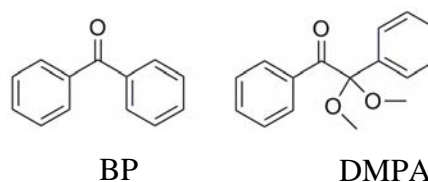


Figure 1. Commonly used photoinitiators

stereospecificity, the formation of unwanted disulfide byproducts through radical recombination, and the reversibility of the radical sulfenyl addition until proton radical abstraction (propagation step 2).⁴

As a result of the advantageous properties of thiol-ene coupling and the usefulness of thiol-enes in materials applications, the thiol-ene reaction has been used to produce a variety of polymers with interesting physical characteristics. This review will highlight and describe some of these systems.

MATERIAL SYSTEMS USING THIOL-ENE COUPLING

Functionalization of Polymer Chains

The functionalization of alkene-containing polymer side chains can lead to interesting morphologies and modification of the physical properties of the polymer. It has been suggested that combining synthetic polymers with biologically inspired functional groups could lead to “biohybrids” that could have potential in biomedicine.⁷ In this case, a synthetic polymer with alkene side chains could be modified using thiol-functionalized proteins, sugars, or other biological structures.

The thiol-ene addition to 1,2-polybutadiene (PDB) (Scheme 2) was first reported by Serniuk and coworkers in 1948 through the addition of aliphatic thiols to PBD.⁶ More recently, it has been demonstrated that PBD block

copolymers can be functionalized using a variety of thiol-containing small molecules, including amines, carboxylates, phosphonates, and alcohols.^{12,13} This reaction has thus allowed for the facile preparation of polymers that could not be easily synthesized using conventional methods. Active amino acids, sugars, and cholesterol moieties have also been introduced using this method (Figure 2).^{14,15} Although photoinitiators were initially used for the modification of these polymers, more recently these transformations have been improved to avoid the use of photoinitiators, relying instead upon the use of UV or even sunlight to directly activate the thiol.¹⁵

Scheme 2. Thiol-ene coupling to 1,2-polybutadiene

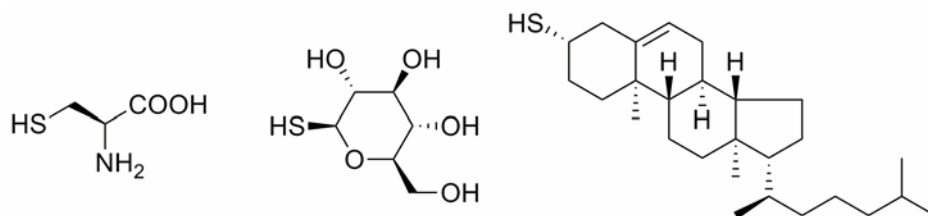
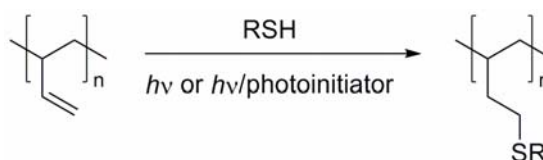
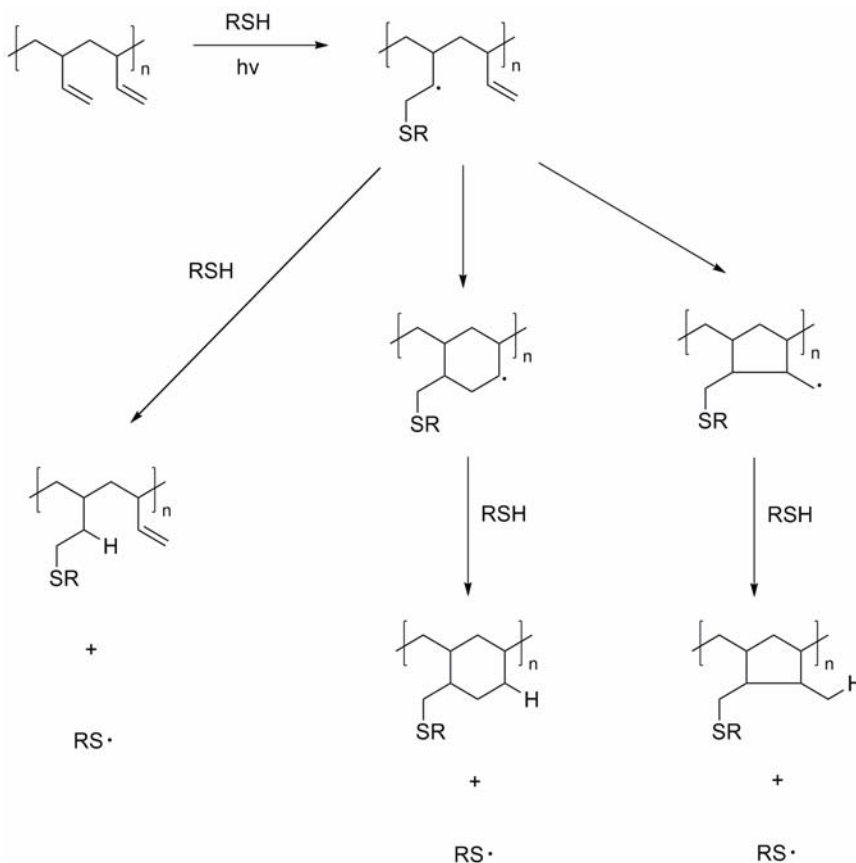


Figure 2. Representative thiols used in functionalization of 1,2-Polybutadiene

David and coworkers showed how the addition of thiols to PBD can be accomplished using a protected thiol precursor.¹⁶ The use of acetyl or benzoyl

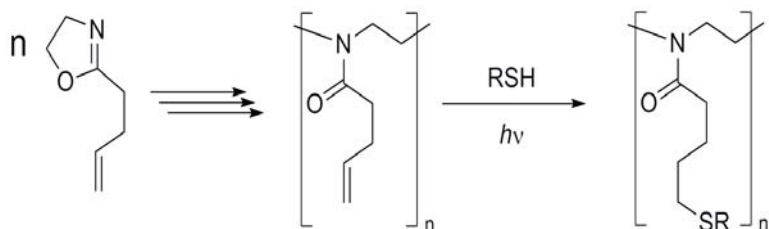
thioesters as precursors allowed for facile deprotection and addition to the polymer in a two step process without direct isolation of the thiol intermediate. This approach circumvents possible degradation of the thiol precursors upon long-term storage, since thioesters are generally less amenable to oxidation than thiols. Additionally, these thiol ester intermediates are often easier to prepare than their thiol counterparts. Lastly, volatile thiols generally have a characteristic stench, so it is advantageous to avoid isolation before addition to the substrate.

Scheme 3. Possible pathways for competing cyclization reactions



One disadvantage of introducing thiol-ene grafted side chains into PB is the competing formation of rings as a result of intramolecular reactions, as shown in Scheme 3. These competing reactions result in the formation of both five- and six-membered rings on the backbone of the polymer chain in addition to the desired thiol grafted sidechains. As a result of this undesired side reaction, a maximum of only 80% thio-ester functionalization is possible, even when a large excess of thiol is used.¹²

Scheme 4. Synthesis and modification of poly[2-(3-butenyl)-2-oxazoline]



Intramolecular cyclization can be avoided by increasing the distance between the intermediate radical and neighboring double bond so that ring formation is less favored. This approach was achieved using an alternative polymer, poly[2-(3-butenyl)-2-oxazoline],

which was formed through a controlled living cationic isomerization polymerization.¹⁷ By changing the structure of the polymer backbone, the authors obtained essentially complete conversion of the double bonds to thioether-linked side groups (Scheme 4). This ultimately resulted in a more uniform morphology and avoided the formation of unwanted cyclic units.

Surface Patterning and Functionalization Through Thiol-ene Polymerization

New methods in surface functionalization are also possible using thiol-ene photopolymers grafted on thiol-functionalized silicon surfaces.¹⁸ Surface-based polymerizations can have important implications on such material properties such as biocompatibility, corrosion resistance, and friction coefficients.⁵ The resulting ultrathin films display different properties than the original surface. Depending on the monomers used, either a linear polymer or crosslinked polymer film is formed on the surface of the silicon. The use of diene and dithiol monomers results in linear polymers, whereas the use of tri- or tetra-substituted enes and thiols results in

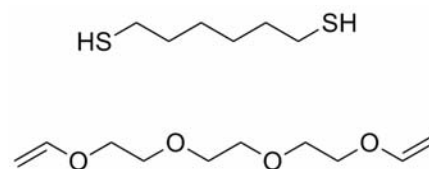


Figure 3. 1,6-hexanedithiol and triethylene glycol divinyl ether

crosslinked polymer networks.³ Prior to polymerization, the surface of the silicon was functionalized with a thiol-terminated self assembled monolayer (SAM) to provide sites for polymer attachment.¹⁸

Using this method of surface polymerization and functionalization, Harant and coworkers were able to form ultra-thin films resulting from the copolymerization of 1,6-hexanedithiol and triethylene glycol divinyl ether (Figure 3) that ranged from 0.1 nm to 9.6 nm in thickness. Surface thickness was adjusted by either limiting the monomer conversion (monitored through in-situ

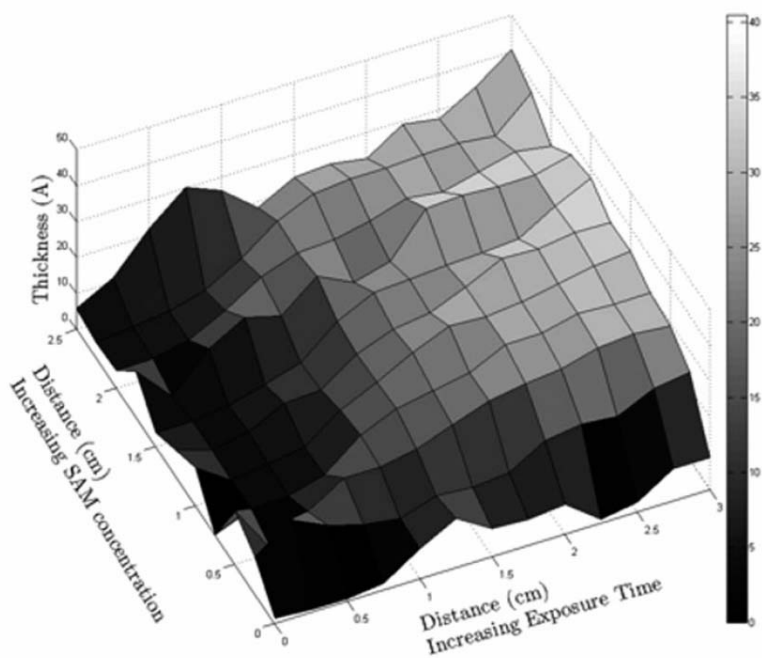


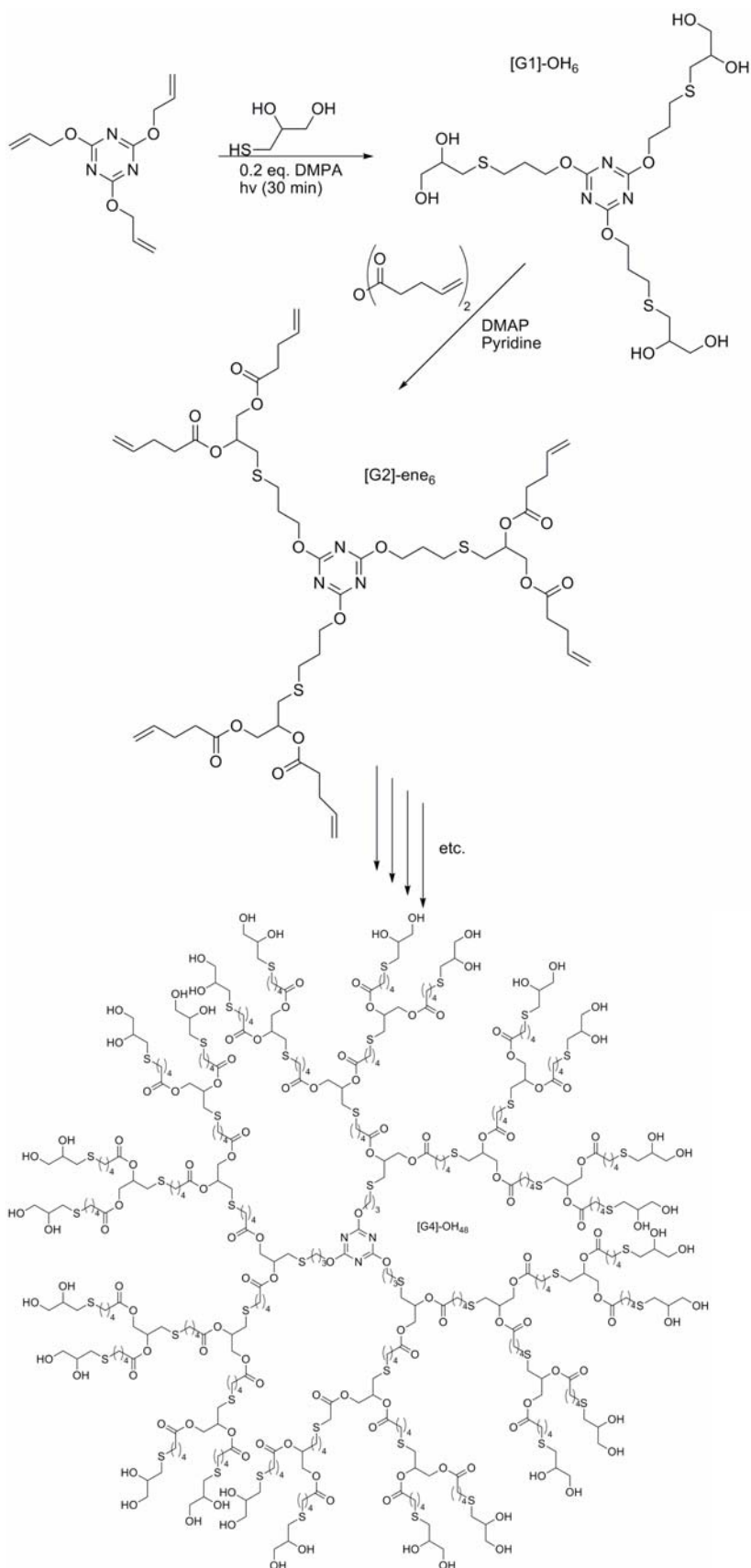
Figure 4. Bi-directional surface gradient obtained through thiol-ene polymerization techniques

IR spectroscopy) or by controlling the alkene to thiol ratio.¹⁸

In an extension of this work, Khire and coworkers showed that the unique properties of the thiol-ene coupling reaction could be used to form bi-directional surface gradients with varying thickness.¹⁹ The authors used two methods to control the surface thickness. First, they systematically increased the density of the surface-bound thiol across the sample surface to increase the amount of polymer binding sites present. Second, they increased the UV-exposure time across the surface of the sample, which increased the amount of polymerization that occurred. Using these techniques, a two-dimensional gradient of varying thickness is formed. Figure 4 shows the gradient as measured by ellipsometry.

By employing a slightly different method, Jonkheim and coworkers showed that a monolayer of olefin-functionalized proteins could be selectively bound to a thiol-functionalized surface on silicon oxide.²⁰ Instead of forming a polymer film on the surface of the silicon, an array of proteins is tethered using the thiol-ene reaction to the functionalized

Scheme 5. Synthesis of 4th generation Hawker dendrimer

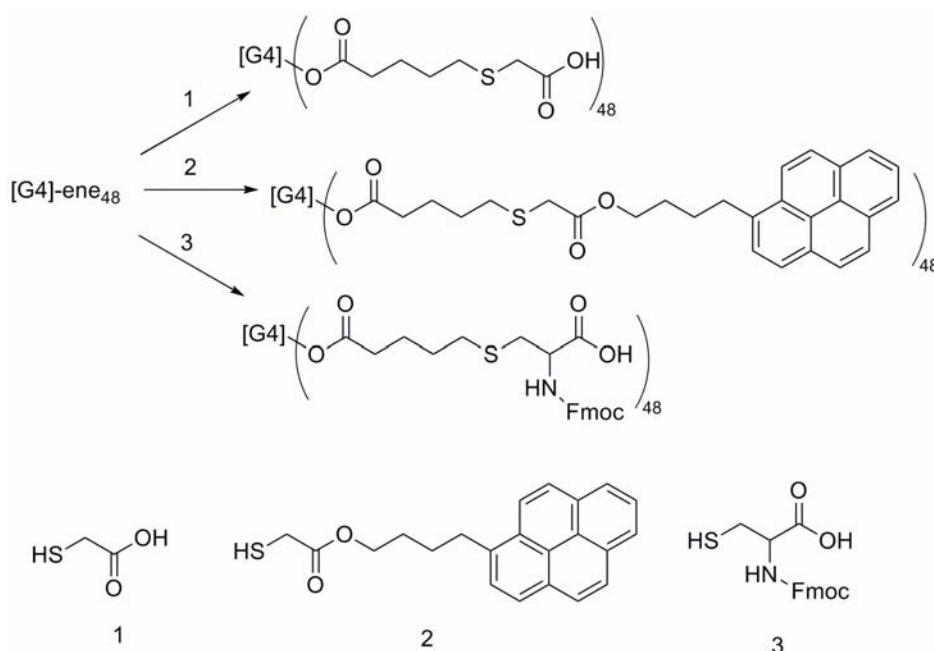


silicon surface. Furthermore, the site and extent of functionalization is controlled through the use of a photomask and by varying the UV-light exposure time. Using this method, micro-size patterns and lateral gradients can be formed through the selective modification of surface functional groups. One advantage of site-specific immobilization (and consequently control over protein orientation) is that, unlike nonspecific absorption, it generates homogeneous surface coverage and protein configuration. Making use of this type of protein immobilization, arrays of proteins may be created on solid chips for assay studies or testing purposes.²⁰

Formation of Thiol-ene Dendrimers

Dendrimer formation is a facile way to build up a core framework for later functionalization of a supramolecular molecule. Thiol-ene coupling can be utilized in dendrimer formation. Nilsson and coworkers reported the variation of first generation dendritic cores on the properties of crosslinked thiol-ene polymers.²¹ More recently, Hawker and coworkers have shown that up

Scheme 6. Functionalization of 4th generation Hawker dendrimer



to fourth generation dendrimers can be synthesized in a divergent fashion starting from a 2,4,5-triallyloxy - 1,3,5-triazine core, which underwent a thiol-ene reaction with 1-thioglycerol to give the hexahydroxy dendrimer. The hexahydroxy dendrimer was then esterified using 4-pentenoic anhydride to give the corresponding hexa-functionalized alkene dendrimer. This process was iterated to give the 4th generation dendrimer seen in Scheme 5.²² Following generation growth and alkene introduction, the periphery could be modified through the functionalization of the chain ends using thiol-ene coupling to introduce additional functional units to the periphery, as shown in Scheme 6. Although the usefulness of these dendrimers has not yet been shown, they nevertheless illustrated that

repetitive functionalization through thiol-ene coupling is possible and proceeds with high fidelity, as well as allowing further functionalization at later stages.

CONCLUSIONS

Thiol-ene couplings have been used in chemical reactions for decades, but it was not until recently that chemists have taken advantage of its synthetic utility to produce potentially useful materials. Thiol-ene coupling reactions display many characteristics of click reactions and are an extremely facile way to link two molecular structures in a regio-selective manner. Additionally, this reaction is a relatively easy method for generating unique polymers and dendrimers. The synthetic utility of this reaction has been exploited in the fields of surface chemistry, dendrimer formation, and post-polymerization functionalization of polymers. Although historically this reaction was not often used in materials chemistry beyond the formation of crosslinked polymer composites, in recent years it has become a valuable tool in performing “click” type reactions for polymer modification.

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