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Sequential Phosphine-Catalyzed, Nucleophilic Thiol−Ene/Radical-Mediated Thiol−Yne Reactions and the Facile Orthogonal Synthesis of Polyfunctional Materials

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The thiol−ene reaction has recently attracted significant attention in the materials arena,[1] as it displays many of the attributes of click chemistry.[2] Hawker and co-workers[3] have highlighted its application in dendrimer synthesis, while Chan et al.[4] have described a macromolecular version in convergent star synthesis. Dove and co-workers[5] described its use in preparing functional biodegradable polylactides, and Schlaad and co-workers[6] utilized it to modify side chains of poly[2-(3-butenyl)-2-oxazoline], while Rissing and Son[7] detailed the synthesis of branched organosilanes with a range of functional thiols. Importantly, it should be noted that the thiol−ene reaction proceeds under a variety of experimental conditions, including acid/base catalysis,[8] nucleophilic catalysis,[9] radical mediation (most commonly under photochemical conditions),[1] and via a solvent-promoted process.[10] The real strength of the thiol−ene reaction is the broad range of ene substrates that readily undergo hydrothiolation, including activated and nonactivated species.[1]

The reaction between a thiol and an yne has been widely studied.[11] As with the thiol−ene reaction, the thiol−yne reaction proceeds rapidly under a variety of experimental conditions, selectively yielding the mono- or bis-addition products. While the thiol−yne reaction is well-documented in the fields of organic[12] and organometallic[13] chemistry, it has been essentially overlooked in the polymer/materials area, with very few examples detailing its application appearing in the literature. However, recent reports have appeared from Fairbanks et al.[14] and Chan et al.[15] The latter described the straightforward synthesis of high-refractive-index materials derived from the radical-mediated reaction of alkylthiols and simple diynes. It is important to note that the radical thiol−yne reaction possesses characteristics virtually identical to those of the radical thiol−ene reaction. However, the reaction of 2 equiv of thiol with the alkyne is itself a two-step process. The first step involves the addition of thiol to the C≡C bond to yield an intermediate vinyl thioether that subsequently undergoes a second, formally thiol−ene, reaction with additional thiol, yielding the 1,2 double-addition species as the sole product in quantitative yield.[16]

We highlight here the first example of *sequential* thiol−ene/thiol−yne reactions that proceed in an orthogonal fashion, as a means of preparing highly functional materials under facile conditions (i.e., at ambient temperature and humidity under an air atmosphere). We specifically take advantage of the extremely rapid and quantitative reaction of a thiol with an activated ene under *nucleophile-initiated* conditions (a thiol-Michael reaction), employing dimethylphenylphosphine (Me_2PPh) as the initiator, in conjunction with the *radical-mediated* thiol−yne reaction, which proceeds rapidly to yield the 1,2-addition product exclusively[16] and quantitatively.

Initially, a model reaction was examined to determine the general reaction kinetics and to establish the feasibility of the proposed sequential approach to a range of multifunctional materials. The 1:1 reaction of the mercaptoethylester **1** with propargyl acrylate (**2**) at ambient temperature under bulk conditions in the presence of $\sim 2 \times 10^{-3}$ M Me_2PPh resulted in the rapid, *selective* addition of the thiol group across the activated ene to yield the propargyl thioether diester **3** in 100% yield (Figure 1A). Even at such a low concentration of Me_2PPh, the reaction reached ~90% conversion within ~2.5 min and was complete after ~17 min. Increasing the concentration of Me_2PPh significantly enhanced the rate to the extent that the reaction was complete in less than 1 min. The impressive rate of these phosphine-mediated reactions is attributed to the *anionic chain mechanism* (Scheme 1), in which the powerful nucleophile Me_2PPh is employed to generate a strong enolate base. Gimbert et al.[17] previously proposed such a mechanism for phosphine-mediated Michael addition reactions, and Stewart et al.[18] highlighted the same mechanism for the phosphine-catalyzed oxa-Michael addition of water and alcohols to activated enes. However, this is the first time it has been proposed for the nucleophilic thiol-Michael reaction. It should be highlighted that a key feature of this combination of reagents, namely, the low pK_a of the thiol coupled with the high reactivity of the thiolate anion toward conjugate addition, enables this reaction to be performed with 100% efficiency even in the presence of other protic species such as water.

Subsequently, the terminal propargyl group in **3** was reacted with 2 equiv of thiolglycerol (**4**) in the presence of 2 wt % α,α-dimethoxy-α-phenylacetophenone at 365 nm under a normal air atmosphere at ambient temperature and humidity. The thiol−yne reaction can be readily followed using real-time FTIR (RT-FTIR) spectroscopy (Figure 1B) by recording the disappearance of the peak at 2127 cm^{-1} associated with the yne and that at 2570 cm^{-1} associated with the thiol. Under these experimental conditions, >90% conversion was observed within ~1.5 min, and *complete* consumption of both functional species occurred within ~10 min, yielding the tetraol **5** quantitatively. The structure of product **5** was confirmed unambiguously via ^1H and ^{13}C NMR spectroscopy. Figure 1C shows the ^1H NMR spectrum of **5**, with peak assignments.

After this demonstration of the feasibility of conducting sequential thiol−ene/thiol−yne reactions in an orthogonal manner, the methodology was applied to the synthesis of a series of polyfunctional structures employing a range of functional thiols, including examples recently highlighted by Hawker et al.,[19] to demonstrate the broad utility of the thiol−yne reaction and also the sequential thiol−ene/thiol−yne process. Specifically, in addition to **4**, we examined mercaptosuccinic acid (**6**), a secondary thiol; captopril (**7**), an angiotensin converting enzyme (ACE) inhibitor; 3-(trimethoxysilyl)propanethiol (**8**); the 3-mercaptopropyl polyhedral oligomeric silsesquioxane (POSS) **9**; adamantane-1-thiol (**10**), a tertiary thiol; 3-mercaptopropionic acid (**11**); and 6-mercaptohexanol (**12**) (Figure 2).

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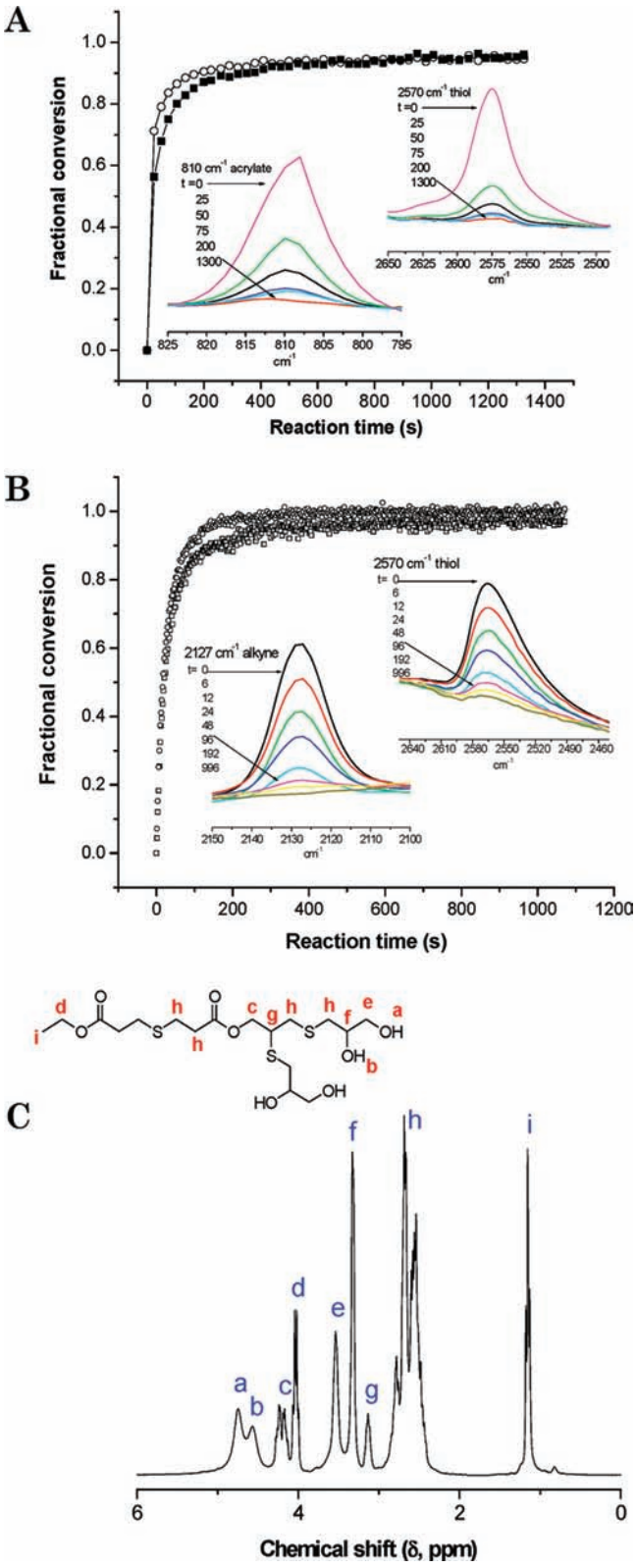
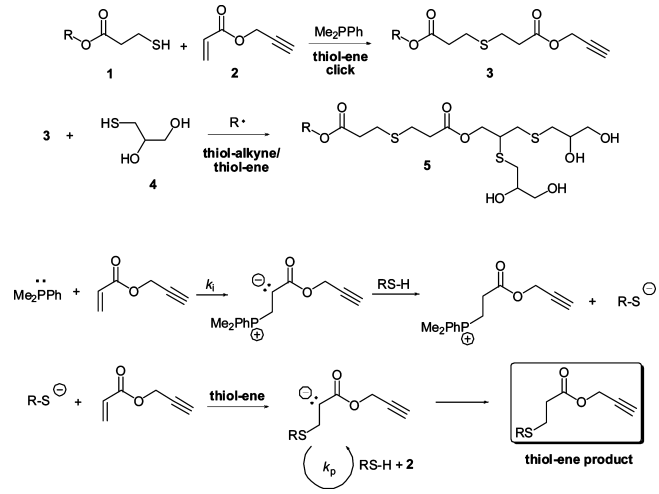


Figure 1. (A) RT-FTIR monitoring of the reaction between **1** (R = CH_2CH_3) and **2**: (○) thiol peak area at 2570 cm^{-1}, and (■) acrylate peak area at 810 cm^{-1}. (B) RT-FTIR monitoring of the photochemical reaction between **3** (R = CH_2CH_3) and **4**: (□) thiol peak area at 2570 cm^{-1} and (○) yne peak height at 2127 cm^{-1}. (C) ^1H NMR spectrum recorded in d_6-DMSO, with relevant peak assignments, confirming the structure of **5** (R = CH_2CH_3).

The synthetic approach was identical to that highlighted above, except that the tetrathiol pentaerithrytol tetra(3-mercaptopropionate)

Scheme 1. Sequential Thiol−Ene/Thiol−Yne Reactions[a] and the Proposed Anionic Chain Mechanism for the Me_2PPh-Initiated Thiol−Ene Reaction to an Activated Ene



[a] (i) Dimethylphenylphosphine (Me_2PPh) (~2×10^{-3} M), **1** (1 equiv), **2** (1 equiv); (ii) **3** (1 equiv), **4** (2 equiv), 2 wt % α,α-dimethoxy-α-phenylacetophenone, 365 nm (reaction rate depends on sample thickness).

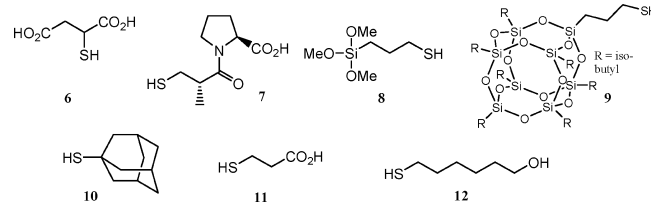
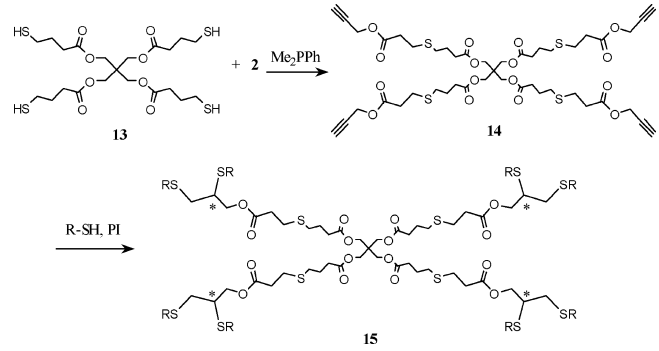


Figure 2. Chemical structures of commercially available functional thiols employed for the synthesis of polyfunctional materials.

(**13**) was used in place of **1** in the initial thiol−ene reaction with **2** (Scheme 2). Where possible, the reactions were conducted neat,

Scheme 2. Synthesis of Multifunctional Thioethers via Sequential Thiol−Ene/Thiol−Yne Reactions (Generated Stereocenters Denoted by *)



but in the case of **6**, **7**, **9**, and **10**, solvents were required (see the Supporting Information).

In all instances, the resulting multifunctional materials required no cleanup or were easily purified by simple washing/extraction. The products were characterized by a combination of NMR spectroscopy and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). For example, Figure 3 shows the MALDI-TOF MS trace for the 16-functional polyol obtained from reaction of **14** with R−SH = **4**. With the assumption of quantitative reaction for both the thiol−ene and thiol−yne reactions, which is reasonable given the results for the

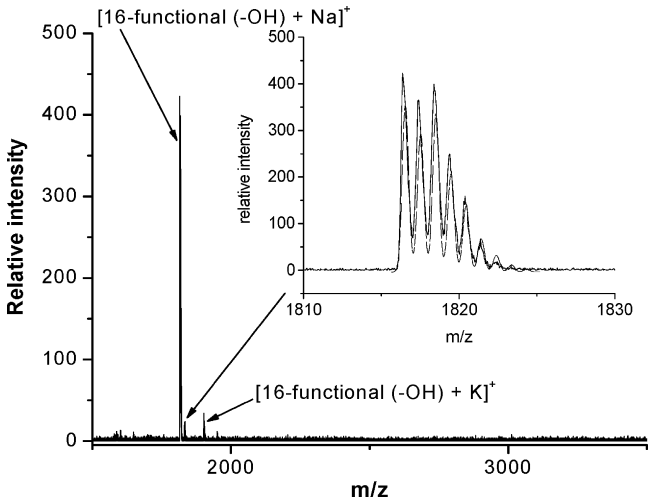


Figure 3. MALDI-TOF MS trace of the 16-functional polyol derived from the thiol−yne reaction of **4** with **14** under photochemical conditions.

model reaction, the resulting 16-functional polyol would have an expected molecular mass of 1794.4 Da. The MALDI-TOF MS trace indicates a primary peak at $m/z = 1816.4$ that is due to the Na^+-cationized 16-functional polyol, i.e., [16-functional polyol + $Na]^+$. The Figure 3 inset shows the measured (black line), and calculated (gray line) isotopic distributions associated with [16-functional polyol + $Na]^+$. These agree perfectly with each other and further serve to confirm the quantitative nature of these sequential thiol-based click reactions. (It should be noted that it is also possible to observe a lower-molecular-weight peak due to products derived from the trithiol impurity in **14**.) Additional MALDI-TOF MS plots and isotopic splitting patterns are given in the Supporting Information.

Table 1 summarizes the experimentally determined molecular masses, with the major *m/z* peak listed along with the theoretical

Table 1. Summary of Measured Molecular Masses of the Thioether-Based Polyfunctional Products

	theoretical molecular mass (Da)		
target molecule	H^+	Na^+	major MALDI-TOF MS peak (*m/z*)
16-alcohol (**4** +**14**)	1794.4	**1817.4**	1816
16-acid (**6** + **14**)	**2130.4**	2153.3	2128.5
8-alcohol (**12** + **14**)	2003.1	**2026.0**	2025
8-acid (**11** + **14**)	1778.3	**1801.3**	1799
8-captopril (**7** +**14**)	**2667.4**	2690.4	2666.5
8-silane (**8** +**14**)	2499.9	**2522.9**	2519

molecular masses of the H^+- and Na^+-cationized products calculated by assuming that quantitative conversion was obtained, from the reactions of **14** with **4**, **6**−**8**, **11**, and **12**. In all instances, the major observed MALDI-TOF MS peak corresponds to either the H^+- or Na^+-cationized species. The agreement between the theoretical molecular masses based on quantitative conversion for the thiol−ene/thiol−yne sequence and the experimentally determined values is excellent, generally within 1−2 Da. Such agreement further highlights the broad utility and quantitative nature of these sequential thiol-based reactions.

Unfortunately, the products derived from the reactions of **14** with **9** and **10** could not be successfully analyzed by MALDI-TOF MS. However, FTIR spectroscopic monitoring of these reactions indicated complete consumption of both the thiol and yne components, consistent with the results of the reactions of the other thiols with **14**.

In summary, we have presented the first examples of *sequential* thiol−ene/thiol−yne reactions for the facile synthesis of polyfunctional materials using a range of commercially available thiols, including examples having potential biomedical significance. We have highlighted the radical-mediated thiol−yne reaction and demonstrated its versatility in advanced materials synthesis. In view of the combination of yield, orthogonality, and rate, it is expected that the phosphine-mediated thiol−ene reaction, the radical-mediated thiol−yne reaction, and the tandem thiol−ene/thiol−yne sequence will be employed in a plethora of applications ranging across the chemical, materials, optical, electronic, and biomolecular fields.

Supporting Information Available: Full experimental details, MALDI-TOF MS isotopic distributions, and NMR/FTIR data for the reactions of **9** and **10** with **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hoyle, C. E.; Lee, T. Y.; Roper, T. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 5301.
(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
(3) Killops, K. L.; Campos, L. M.; Hawker, C. J. *J. Am. Chem. Soc.* **2008**, *130*, 5062.
(4) Chan, J. W.; Yu, B.; Hoyle, C. E.; Lowe, A. B. *Chem. Commun.* **2008**, 4959.
(5) Pounder, R. J.; Stanford, M. J.; Brooks, P.; Richards, S. P.; Dove, A. P. *Chem. Commun.* **2008**, 5158.
(6) Gress, A.; Völkel, A.; Schlaad, H. *Macromolecules* **2007**, *40*, 7928.
(7) Rissing, C.; Son, D. Y. *Organometallics* **2008**, *27*, 5394.
(8) Li, M.; De, P.; Gondi, S. R.; Sumerlin, B. S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5093.
(9) Sanui, K.; Ogata, N. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1727.
(10) Tolstyka, Z. P.; Kopping, J. T.; Maynard, H. D. *Macromolecules* **2008**, *41*, 599.
(11) Rutledge, T. F. *Acetylenes and Allenes*: Reinhold Book Corporation: New York, 1969.
(12) See, for example: Yadav, J. S.; Subba Reddy, B. V.; Raju, A.; Ravindar, K.; Baishya, G. *Chem. Lett.* **2007**, *36*, 1474.
(13) See, for example: Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108.
(14) Fairbanks, B. D.; Scott, T. F.; Kloxin, C. J.; Anseth, K. S.; Bowman, C. N. *Macromolecules* **2009**, *42*, 211.
(15) Chan, J. W.; Zhou, H.; Hoyle, C. W.; Lowe, A. B. *Chem. Mater.* **2008**, *21*, DOI: 10.1021/cm803262p.
(16) Sauer, J. C. *J. Am. Chem. Soc.* **1957**, *79*, 5314.
(17) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598.
(18) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.
(19) Campos, L. M.; Killops, K. L.; Sakai, R.; Paulusse, J. M. J.; Damiron, D.; Drockenmuller, E.; Messmore, B. W.; Hawker, C. J. *Macromolecules* **2008**, *41*, 7063.

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