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Thiol-ene reactions of 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT): facile access to functional tripodal thioethers

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ABSTRACT

Efficient syntheses of tripodal thioethers have been achieved by ionic thiol-ene reactions of 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) with a variety of commercially available thiols. The reactions are complete within minutes and give the products in high yields (63–96%) and high purity without a complex workup. The thiol-ene reactions tolerate a wide range of functionality, including hydroxy, amino, carboxylate, and trimethoxylsilyl groups. The amino acid cysteine is also an excellent substrate for this reaction.

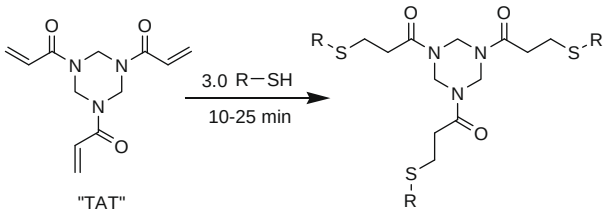
1. Introduction

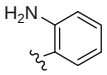
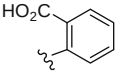
The thiol-ene reaction is an excellent synthetic tool for the creation of sulfur–carbon bonds.[1] Due to the high yields of products, lack of byproducts, and tolerance of air and water, the thiol-ene reaction is rapidly gaining acceptance as a 'click' reaction.[2–6] Although the thiol-ene reaction has been known for many years,[7,8] it is only recently that more research groups have exploited its versatility. The groups of Hoyle[3,9–12] and Bowman,[13–18] for example, have extensively utilized the thiol-ene reaction in polymer and materials chemistry.

The thiol-ene reaction proceeds by either a free-radical or ionic mechanism. Free-radical reactions typically involve AIBN or UV irradiation to generate the thiyl radicals necessary for the reaction to occur.[1] Ionic thiol-ene reactions generally occur in the presence of a base such as an amine, and are limited to compounds possessing electron-deficient unsaturation, for example, α,β-unsaturated carbonyl compounds.[10,15,17,19–25] Thus, the ionic thiol-ene reaction can essentially be viewed as a Michael-type addition reaction.

On the basis of our interest in organosilicon dendrimers,[26,27] we recently reported the synthesis of various functionalized organosilicon thioethers via free-radical thiol-ene reactions of tetravinylsilane.[28] As part of another line of investigation concerning multidentate N- and S-containing ligands,[29–34] we identified 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) as a potentially useful starting material for the synthesis of tripodal thioether compounds, which are of value as chelating ligands[35–47] and in nanoparticle assembly.[48–52] TAT is an inexpensive, stable, and symmetrical compound that possesses three electron-deficient olefin groups. Herein, we describe the facile synthesis of a series of functionalized tripodal thioethers from ionic thiol-ene reactions of TAT.

The basic reaction scheme and the compounds synthesized are shown in Scheme 1. Reaction conditions and product yields are reported in Table 1. As described below, the reaction conditions varied somewhat depending on the starting thiol. However, some features were common to all of the reactions. In all cases, it was not necessary to use more than an exact stoichiometric equivalent of the thiol for the reaction to reach completion. The progress of the reactions could be noted by observing the TAT in the reaction mixture. TAT was relatively insoluble in the solvent systems we utilized, but disappearance of the TAT would occur within several



1, R = -CH_2CH_2OH
2, R = -$CH_2CH(OH)CH_2(OH)$
3, R = -$CH_2CO_2CH_3$
4, R = -$CH_2CH_2CH_2Si(OCH_3)_3$
5, R = -$CH_2CH_2NH_2$
6, R = 
7, R = -$CH_2CH_2CO_2H$
8, R = 
9, R = -$CH_2CH(NH_2)CO_2H$

Scheme 1. Thiol-ene synthesis of **1**–**9**.

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Table 1
Product yields and reaction conditions (all reactions conducted at room temperature)

Product	Reaction conditions	Yield (%)
1	MeOH, cat. *n*-$PrNH_2$	92
2	MeOH, cat. *n*-$PrNH_2$	96
3	MeOH/$CHCl_3$, cat. *n*-$PrNH_2$	94
4	MeOH, cat. *n*-$PrNH_2$	93
5	MeOH	95
6	MeOH/$CHCl_3$	82
7	MeOH, $KHCO_3$	63
8	MeOH, $KHCO_3$	90
9	MeOH/H_2O	88

minutes of the start of the reactions. Most reactions were complete *within 10 min*. After the reactions were complete, the solutions were gravity filtered and all volatiles were removed under reduced pressure to give the products in high yields, typically not requiring further purification. All products were characterized by 1D and 2D NMR spectroscopy, and elemental analysis.

For the synthesis of compounds **1**–**4**, the appropriate thiol was added to a stirred suspension of TAT (1.0 g) in 10 mL of methanol. A single drop of *n*-propylamine (10 mg) was then added and the reaction was worked up as described above to give **1**–**4** in high yields and excellent purity. Alcohol derivatives **1** and **2** were obtained as a crystalline and hard, transparent solid, respectively. Both compounds are somewhat hygroscopic and are best stored in a dessicator. For the synthesis of **3**, a second liquid layer formed during the reaction at the bottom of the vessel. ^{1}H NMR experiments indicated that this layer was primarily **3**. In order to obtain higher yields of **3**, a small amount of chloroform was added to create a uniform solution and then the reaction was worked up in the normal manner to give **3** as an oil. The synthesis of **4** was straightforward and gave the product as a clear, colorless viscous oil. This oil proved to be unstable; on standing it slowly hardened to a clear insoluble solid. Since we made no effort to dry the methanol or exclude moisture during the reaction, we speculate that the combination of trace moisture and residual amine catalyst causes **4** to undergo a sol–gel crosslinking process.[53]

Compounds **5** and **6** were synthesized in the same way as **1**–**4**, except no amine catalyst was added. The starting thiols, cysteamine and *o*-aminothiophenol, both contain amino groups and thus 'self-catalyze' their own reactions. For the synthesis of **6**, chloroform was added to the reaction mixture after 10 min in order to dissolve the crude product oil that precipitated out of solution. Compounds **5** and **6** were isolated as yellow solids. It should be noted that in neither case was addition of the amino groups to TAT observed.

The standard amine-catalyzed thiol-ene reaction conditions were ineffective for the syntheses of **7** and **8**, presumably because the added amine was protonated by the carboxyl groups in the thiols. For these thiols, the carboxyl groups were deprotonated by heating methanol solutions of the thiols in the presence of potassium bicarbonate. TAT was then added to the resulting clear solutions at room temperature. Under these conditions, the thiol-ene reactions occurred spontaneously *without amine catalysis* to give the potassium salts in quantitative yield. The free acids could be obtained by acidifying aqueous solutions of the salt products. Although compound **8** precipitated as a white solid on acidification and was easily isolable, compound **7** separated as an oil. On cooling, the oil crystallized to give pure **7** as a colorless crystalline solid in 63% yield. We attribute the relatively low yield of **7** to incomplete crystallization of the oil from the aqueous medium. Some of the crystals of **7** were large, colorless blocks which were suitable for X-ray structural analysis (Fig. 1).[54] The triazine ring exists in the chair conformation with the three 'arms' pointing out toward the same side of the ring to create a bowl-like cavity. Due to a combination of intra- and intermolecular hydrogen bonding, the extended structure consists of a linear chain of dimeric capsules in which triazine rings constitute the ends of the capsules (see Supplementary data for diagram).

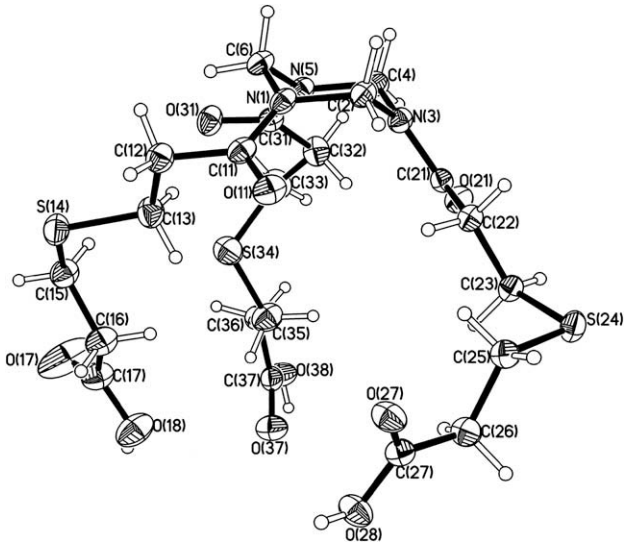

Figure 1. ORTEP plot of **7** (50% ellipsoids).

Compound **9** is the product of the thiol-ene reaction of TAT with the amino acid DL-cysteine, which is known to add to double bonds through the thiol group.[55–58] In our experiments, we found it necessary to use a methanol/water solvent system to aid in the solubility of the cysteine. In this case, the thiol-ene reaction proceeded without amine catalysis to give **9** as a white solid after workup.

The attractive features of this general synthetic scheme are numerous. Firstly, the starting thiols are commercially available and inexpensive and allow a wide range of functionalization to be present in the final products. Secondly, there is no need to exclude air or moisture from the reaction mixtures; all reactions can be carried out in open vessels on the benchtop. Thirdly, the reaction times are extremely short. Finally, product yields are high and, as mentioned above, little if any workup is necessary.

In conclusion, we have synthesized a series of highly functionalized thioethers from thiol-ene reactions of commercially available thiols with 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT). We are currently investigating the application of these compounds as dendrimer cores and as metal chelating agents.

2. Experimental

2.1. Synthesis of 1,1′,1″-(1,3,5-triazinane-1,3,5-triyl)tris(3-(2-hydroxyethylthio)propan-1-one) (1)

The synthesis of **1** is representative of the general synthetic procedure. Certain products required slightly modified procedures which are detailed in the Supplementary data. A 100-mL round-bottomed flask was charged with 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) (1.0 g, 4.0 mmol), methanol (10 mL), and a magnetic stirring bar. To this stirred suspension was added 2-mercaptoethanol (0.94 g, 12 mmol) and a single drop of *n*-propylamine (10 mg). The suspension of TAT disappeared within several minutes, leaving a clear solution. After a total of 10 min stirring, the solution was filtered through a fluted filter paper and all volatiles were removed under reduced pressure to give **1** as a white solid (1.8 g, 92%). Mp 49–52 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72 (t, $HOCH_2CH_2$–, 6H, ^3J = 6.6 Hz), 2.82 (t, –$SCH_2CH_2C(O)$–, 6H, ^3J = 6.0 Hz), 2.86

(t, –CH_2C(O)–, 6H, ^3J = 6.0 Hz), 3.73 (t, HOC$H_2$$CH_2$–, 6H, ^3J = 6.0 Hz), 5.30 (s, –C(O)NH_2N–, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.7 (–$CH_2$$CH_2$C(O)–), 33.4 (–$CH_2$C(O)–), 35.5 (HOC$H_2$$CH_2$S–), 56.4 (–N$CH_2$N–), 61.2 (HO$CH_2$$CH_2$S–), 171 (–C(O)–). Calcd for $C_{18}H_{33}O_6N_3S_3$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.64; H, 6.81; N, 8.43.

Acknowledgments

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Supplementary data

Complete experimental and characterization details for all compounds reported; ^{1}H and ^{13}C NMR spectra of **1**–**9**; extended crystal structural diagram of **7** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.094.

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54. Compound **7**: $C_{21}H_{33}N_3O_9S_3$, FW 567.68, space group $P\bar{2}$, a = 10.1945(8), b = 11.8087(9), c = 12.6371(10) Å, α = 64.895(1)°, β = 82.421(1)°, γ = 71.751(1)°, V = 1308.30(18) Å^3, Z = 2, D = 1.441 Mg/m^3, μ = 0.338 mm^{-1}. R_1 [$I > 2\sigma(I)$] = 0.045, and wR_2 [all data] = 0.130. Crystallographic data (excluding structure factors) for compound **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 708858. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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