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Facile and efficient synthesis of star-shaped oligomers from a triazine core

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ABSTRACT

A facile and efficient synthetic approach to tripodal star-shaped oligomers is described. Several generations of hydroxyl-terminated tripodal star-shaped oligomers were prepared in high yield from 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) as a core by alternating amine-catalyzed thiol-ene and acrylate esterification reactions. The compounds were fully characterized by 1D and 2D NMR spectroscopy, ESI-MS, and elemental analysis. The combination of thioether groups and hydrogen bonding moieties suggests that these products can be used as metal chelating ligands.

Branched molecules such as dendrimers and hyperbranched polymers possess unique architectural, structural, and functional features which make them interesting for applications that range from medicine[1–4] to nanoengineering.[5–7] Star-shaped oligomers and polymers, while less branched, are of interest in biomedicine and pharmaceutics.[8,9] In particular, star-shaped oligomers with hydroxyl groups have been used as essential starting building blocks in the synthesis of well-defined star polymers for drug delivery systems.[10]

The thiol-ene reaction is emerging as an attractive click process[11] since it is highly efficient, orthogonal to a wide range of functional groups, and compatible with water and oxygen. Although the term 'thiol-ene' has traditionally been used to describe the free-radical addition of thiols to alkenes and alkynes, more researchers are using the term to also describe the 1,4-conjugate addition of thiols to electron-deficient alkenes.[12–15] Recently, thiol-ene reactions have been used for the formation of well-defined branched compounds and dendrimers.[16–18] In another recent report, star polymers from RAFT-prepared poly(*N*,*N*-diethylacrylamide) were synthesized convergently in which a phosphine-catalyzed thiol-ene reaction was utilized in the final coupling step.[13] In our laboratory, we have sought to use an amine-catalyzed thiol-ene reaction[12] as a key iterative step in the synthesis of star oligomers or polymers.

Herein we describe a facile and efficient divergent synthesis of a series of star-shaped oligomers from 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) as a central core. The divergent approach we chose is readily accomplished by alternating amine-catalyzed thiol-ene and acrylate esterification reactions. The newly synthesized star-shaped oligomers can be used as metal chelating ligands[19,20] or as precursors for more complex molecular architectures.[21]

The synthesis of the star-shaped oligomers is shown in Scheme 1. The first generation star-shaped oligomer (**1-OH**) was synthesized in 96% yield by the amine-catalyzed thiol-ene reaction of TAT (**1**) and 3 equiv of 2-mercaptoethanol in the presence of a catalytic amount of *n*-propylamine in methanol.[22] **1-OH** was directly esterified using 3 equiv of acryloyl chloride (based on –OH groups) and K_2CO_3 (3 equiv) in refluxing acetone overnight to produce **1-Acr**, which was purified by simple filtration through a short silica gel column (45 mm high, 4:6 EtOAc/hexane, then 100% EtOAc, 98% yield). The excess of acryloyl chloride prevented the formation of unidentifiable byproducts, and efficient and rapid stirring was also important for high yields of pure product. The larger star oligomers were synthesized by repeating the previous two steps.

The hydroxyl-terminated star oligomers were obtained in analytical purity by simple filtration through silica gel (1:1 acetone/hexane, then 100% acetone). The acrylate-terminated oligomers were purified as described above for **1-Acr** (4:6 EtOAc/hexane, then 100% EtOAc). Product yields are listed in Table 1. All the oligomers were isolated as thick, pale yellow oils (except **1-OH**,[22] which is a white solid), and they dissolve in most common organic solvents. Oligomer structures were determined by 1D (^{1}H and ^{13}C) and 2D (COSY, HETCOR, and HMBC) NMR spectroscopy, ESI-MS, and elemental analysis.[23] In the high-resolution electrospray ionization (ESI) mass spectra, the ions of the hydroxyl-terminated oligomers (**2-OH**, **3-OH**, and **4-OH**), were observed as $[M+Na]^+$ and $[M+H]^+$ and they correlated very well with the calculated molecular masses, thereby supporting the proposed structures (Table 2). The acrylate-terminated star oligomers were not analyzed due to the inherent reactivity of the acrylate groups which limited their stability under ambient conditions; thus, their characterization was limited to NMR spectroscopy.

A general procedure for amine-catalyzed thiol-ene and esterification steps is described as follows for the preparation of compounds **1-Acr** and **2-OH**: A 250-mL round-bottomed single-necked flask equipped with a magnetic stir bar was charged with

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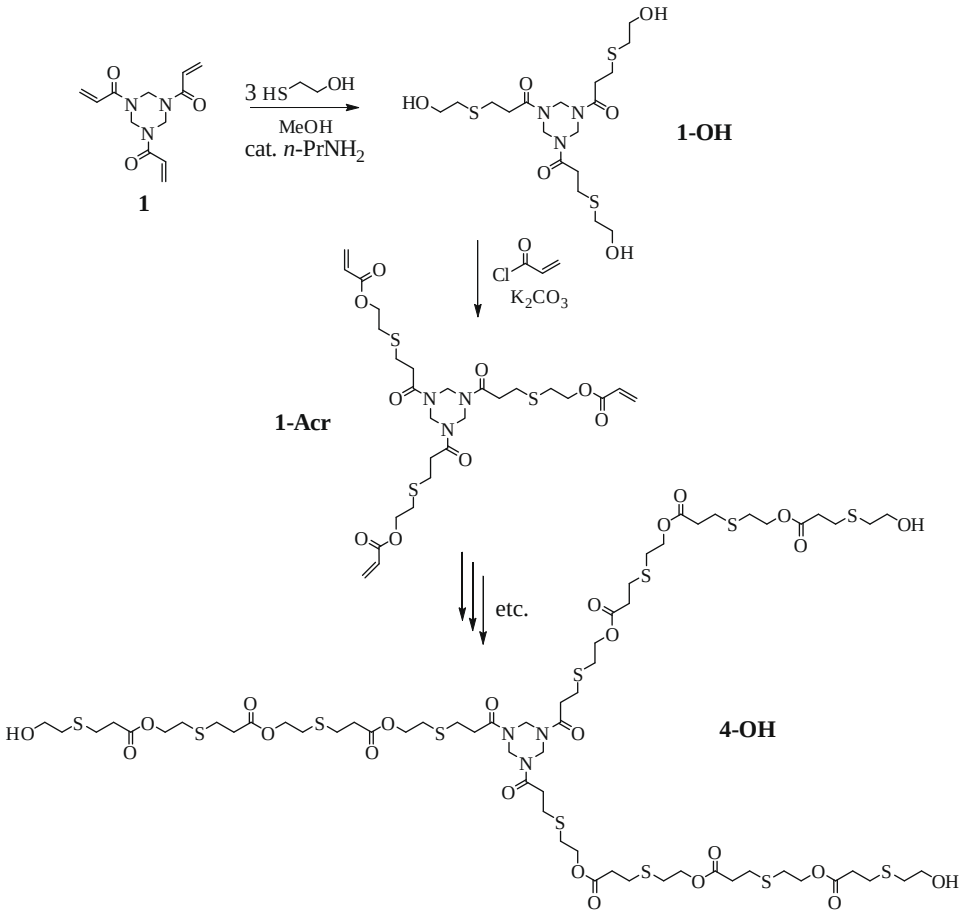

Scheme 1. Divergent synthesis of star-shaped thioether oligomers.

Table 1
Product yields

Compound	Yield[a]
1-OH	96
1-Acr	98
2-OH	79
2-Acr	88
3-OH	88
3-Acr	78
4-OH	89

[a] Yield after silica gel filtration (except for **1-OH**).[22]

Table 2
HRMS(ESI) data for the hydroxyl-terminated star polymers

Compound	$[M+Na]^+$ *m/z* (calcd)	$[M+Na]^+$ *m/z* (found)
2-OH	902.2165	902.2156
3-OH	1298.2900	1298.2894
4-OH	1672.3809	1672.3812

1-OH[22] (2.0 g, 4.2 mmol) and K_2CO_3 (5.1 g, 37 mmol) in 100 mL of acetone. To this rapidly stirred mixture, acryloyl chloride (3.0 mL, 37 mmol) was added slowly by syringe. The mixture was refluxed with rapid stirring overnight. After filtration, the solvent was evaporated to yield the crude product. The crude product was dissolved in a minimum amount of chloroform, and then it was added to the top of a dry silica gel pad. Washing the column with EtOAc/hexane (6:4) and then with 100% EtOAc gave **1-Acr** as a clear thick oil in 98% yield (2.6 g) after removal of volatiles. A 100-mL round-bottomed single-necked flask equipped with a magnetic stir bar was charged with **1-Acr** (2.6 g, 4.0 mmol) and 2-mercaptoethanol (0.93 g, 12 mmol) in 20 mL of methanol. A catalytic amount of *n*-propylamine (1 drop) was added to the mixture at room temperature. The solution was stirred for 10 min at room temperature. After filtration, the solvent was evaporated and the crude product was purified by filtration through a short column of silica gel with acetone/hexane (1:1) and then with 100% acetone to give **2-OH** as clear thick oil in 79% yield (2.8 g).

The amine-catalyzed thiol-ene and acrylate esterification reactions described herein have many advantages for the synthesis of star oligomers. Firstly, the starting materials are commercially available and inexpensive. For the hydroxyl-terminated oligomers, the reaction times are extremely short, and all reactions can be performed in open vessels because of the insensitivity of the thiol-ene reactions to air and moisture. Lastly, the product yields are high and the purifications are extremely simple, even for the acrylate-terminated oligomers.

In conclusion, we have synthesized a series of star-shaped oligomers from 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT) by alternating amine-catalyzed thiol-ene and acrylate esterification reactions. The reaction steps are highly efficient, high yielding, and reproducible, and give star-shaped oligomers containing repeated thioether moieties. We expect star polymers larger than those described here to be easily attainable by simple repetition of the two steps.

Acknowledgments

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Supplementary data

Supplementary data (MALDI-TOF and ESI Q-TOF mass spectral data for **4-OH**, and discussion of results) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.132.

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23. *Characterization data of tripodal star-shaped oligomers*. **1-OH**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.67 (t, 6H, CH_2CH_2OH, ^3J = 6.6 Hz), 2.77 (t, 6H, CH_2CH_2S, ^3J = 6.0 Hz), 2.81 (t, 6H, CH_2CH_2S, ^3J = 6.0 Hz), 3.69 (t, 6H, CH_2OH, ^3J = 6.0 Hz), 5.27 (s, 6H, NCH_2N). ^{13}C NMR: δ 26.8 (CH_2CH_2S), 33.4 ($COCH_2$), 35.3 (CH_2CH_2OH), 56.3 (NCH_2N), 61.2 (CH_2OH), 171.1 (CO). Anal. Calcd for $C_{18}H_{33}N_3O_6S_3$: C, 44.70; H, 6.88. Found: C, 44.64; H, 6.81. **1-Acr**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.80 (t, 6H, SCH_2CH_2O), 2.84 (s, 12H, CH_2CH_2S), 4.29 (t, 6H, CH_2O), 5.28 (s, 6H, NCH_2N), 5.84 (dd, 3H, CHCH*H*, ^2J = 1.2 Hz, ^3J = 10.3 Hz), 6.11 (m, 3H, $CHCH_2$), 6.41 (dd, 3H, CH*CH*H, ^2J = 1.2 Hz, ^3J = 17.2 Hz). ^{13}C NMR: δ 27.2 (CH_2CH_2S), 30.9 (CH_2CH_2O), 33.4 ($COCH_2$), 56.2 (NCHN), 63.6 (CH_2OH), 128.2 ($CHCH_2$), 131.3 ($CHCH_2$), 166.0 (OCO), 171.1 (NCO). **2-OH**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (t, 6H, $OCOCH_2CH_2S$, ^3J = 7.2 Hz), 2.73 (t, 6H, CH_2CH_2OH, ^3J = 6.0 Hz), 2.75–2.84 (m, 24H), 3.74 (t, 6H, CH_2OH, ^3J = 6.0 Hz), 4.26 (t, 6H, SCH_2CH_2O, ^3J = 6.9 Hz), 5.28 (s, 6H, NCH_2N). ^{13}C NMR: δ 26.7 ($OCOCH_2CH_2S$), 27.1 ($COCH_2CH_2S$), 30.8 (SCH_2CH_2O), 33.3 ($COCH_2$), 34.8 ($OCOCH_2$), 35.1 (CH_2CH_2OH), 56.3 (NCHN), 60.8 (CH_2OH), 63.9 (CH_2OCO), 170.7 (NCO), 171.8 (CO). Anal. Calcd for $C_{33}H_{57}N_3O_{12}S_6$: C, 45.03; H, 6.53. Found: C, 45.10; H, 6.60. HRMS (ESI): calcd for $[M+Na]^+$ *m/z* 902.2165, found *m/z* 902.2156. **2-Acr**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63 (t, 6H, $OCOCH_2CH_2S$), 2.73–2.85 (m, 30H), 4.24 (t, 6H, $N–CH_2O$), 4.30 (t, 6H, CH_2OCOVi), 5.28 (s, 6H, NCH_2N), 5.84 (dd, 3H, CHCH*H*, ^2J = 1.2 Hz, ^3J = 10.3 Hz), 6.11 (m, 3H, $CHCH_2$), 6.41 (dd, 3H, CH*CH*H, ^2J = 1.2 Hz, ^3J = 17.2 Hz). ^{13}C NMR: δ 27.2 ($NCOCH_2CH_2S$), 27.3 (CH_2CH_2S), 30.6 (CH_2CH_2OCOVi), 30.9 (CH_2CH_2O), 33.4 ($NCOCH_2$), 34.8 (CH_2CH_2S), 56.2 (NCHN), 63.6 (6C, CH_2O), 128.1 ($CHCH_2$), 131.3 ($CHCH_2$), 166.0 (OCOVi), 170.7 (NCO), 171.6 (CO). **3-OH**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (t, 12H, SCH_2CH_2O, ^3J = 7.2 Hz), 2.70 (t, 6H, CH_2CH_2OH, ^3J = 6.0 Hz), 2.72–2.82 (m, 36H), 3.75 (t, 6H, CH_2OH, ^3J = 6.0 Hz), 4.25 (t, 12H, SCH_2CH_2O, ^3J = 6.6 Hz), 5.26 (s, 6H, NCH_2N). ^{13}C NMR: δ 26.8 ($CH_2SCH_2CH_2OH$), 27.2 ($COCH_2CH_2S$), 30.6 ($SCH_2CH_2O–OH$), 30.9 ($N–SCH_2CH_2O$), 33.3 ($NCOCH_2$), 34.8 ($OCOCH_2$), 35.1 (CH_2CH_2OH), 56.3 (NCHN), 60.8 (CH_2OH), 63.7 (CH_2OCO), 63.8 (CH_2OCO), 170.7 (NCO), 171.6 (CO), 171.8 (CO). Anal. Calcd for $C_{48}H_{81}N_3O_{18}S_9$: C, 45.15; H, 6.39. Found: C, 45.19; H, 6.29. HRMS (ESI): Calcd for $[M+Na]^+$ *m/z* 1298.2900, found *m/z* 1298.2894. **3-Acr**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (t, 12H, $OCOCH_2CH_2S$), 2.70–2.90 (m, 42H), 4.25 (t, 12H, $N–CH_2O$), 4.31 (t, 6H, CH_2OCOVi), 5.29 (s, 6H, NCH_2N), 5.84 (dd, 3H, CHCH*H*, ^2J = 1.2 Hz, ^3J = 10.3 Hz), 6.11 (m, 3H, $CHCH_2$), 6.41 (dd, 3H, CH*CH*H, ^2J = 1.2 Hz, ^3J = 17.2 Hz). ^{13}C NMR: δ 27.2 ($NCOCH_2CH_2S$), 27.3 (CH_2CH_2S), 30.6 (CH_2CH_2O), 30.9 ($N–CH_2CH_2O$), 33.4 ($NCOCH_2$), 34.8 (CH_2CH_2S), 56.2 (NCHN), 63.6 (CH_2O), 128.2 ($CHCH_2$), 131.4 ($CHCH_2$), 166.0 (OCOVi), 170.7 (NCO), 171.6 (CO). **4-OH**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.59 (t, 18H, SCH_2CH_2O, ^3J = 7.2 Hz), 2.68–2.82 (m, 54H), 3.70 (t, 6H, CH_2OH, ^3J = 6.0 Hz), 4.21 (t, 18H, SCH_2CH_2O, ^3J = 5.7 Hz), 5.25 (s, 6H, NCH_2N). ^{13}C NMR: δ 26.6 ($CH_2SCH_2CH_2OH$), 27.0 ($COCH_2CH_2S$), 30.4 ($SCH_2CH_2O–OH$), 30.7 (SCH_2CH_2O), 30.8 ($N–SCH_2CH_2O$), 33.2 ($NCOCH_2$), 34.6 ($OCOCH_2$), 34.7 ($OCOCH_2$), 35.0 (CH_2CH_2OH), 56.0 (NCHN), 60.7 (CH_2OH), 63.6 (CH_2OCO), 170.5 (NCO), 171.4 (CO), 171.6 (CO). Anal. Calcd for $C_{63}H_{105}N_3O_{24}S_{12}$: C, 45.22; H, 6.32. Found: C, 45.53; H, 6.35. HRMS (ESI): calcd for $[M+H]^+$ *m/z* 1672.3809, found *m/z* 1672.3812.