Convergent synthesis of 3-arm star polymers from RAFT-prepared poly(*N*,*N*-diethylacrylamide) *via* a thiol–ene click reaction†

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A novel convergent route to 3-arm star polymers is described that takes advantage of RAFT-synthesized homopolymers serving as masked macromolecular terminal thiol-containing materials capable of undergoing thiol–ene click reactions.

Historically, the thiol–ene reaction has been studied primarily as a means of preparing well-defined films or near-perfect networks.[1] Using highly efficient primary or secondary amine-catalyzed nucleophilic addition reactions,[2] thiols have also been used to synthesize a variety of new highly reactive chemical systems for use in producing new polymers.[3] Recently, the thiol–ene reaction has begun to attract researchers in alternative areas of materials synthesis. For example, Gress *et al.*[4] described the application of the radical-mediated thiol–ene reaction in the functionalization of poly[2-(3-butenyl)-2-oxazoline], and Hawker *et al.*[5] detailed the synthesis of well-defined thioether dendrimers employing thiol–ene chemistry as a key building step and made a strong case for the inclusion of the thiol–ene reaction in the list of established "click" chemistries. Qiu and Winnik[6] demonstrated the ability to reduce trithiocarbonate end groups on homopolymers of *N*-isopropylacrylamide (PNIPAM), prepared *via* RAFT, in the presence of butylamine and triscarboxyethyl phosphine, to yield the corresponding thiol-terminated homopolymers that were subsequently shown to undergo thiol–Michael (thiol–ene) addition to both *n*-butyl acrylate and 2-hydroxyethyl acrylate yielding the corresponding thioether–ester end-functionalized materials. A similar study was reported by Lima *et al.*[7] Also, Qiu *et al.*[8] described the synthesis of cyclic PNIPAMs, ultimately *via* the Cu-catalyzed alkyne–azide reaction, from RAFT prepared precursors with a key step being a macromolecular thiol–ene reaction between a reduced thiocarbonylthio end-group and propargyl acrylate. Scales *et al.*[9] reacted a thiol-terminated PNIPAM, prepared by RAFT with a trithiocarbonate-based chain transfer agent, that was subsequently reacted with a pyrene maleimide as a means of preparing fluorescently labeled materials and, most recently, Li *et al.*[10] reported the NEt_3-mediated thiol–ene reaction of RAFT prepared PNIPAM with bis-maleimides that were subsequently used in additional post-polymerization modification reactions.

Star (co)polymers are the simplest examples of branched polymers, with all arms extending from a single branching point.[11] Such materials can be made using one of three approaches: the arm first (convergent) approach; the multifunctional initiator (divergent) approach; or *via* microgel formation with a multifunctional monomer. Each method has its associated advantages/disadvantages including the often long reaction times and residual arm-polymer for convergent syntheses, the need for uniform reactivity at the initiating sites for divergent syntheses, and poor control of the number of arms in the case of the microgel approach.[12] While star polymers have been prepared *via* a large number of techniques, the use of click chemistry has also recently attracted attention as a means of preparing such materials as well as more complex structures such as dendrimers.[13]

Herein, preliminary observations regarding a facile, rapid, convenient one-pot convergent route to star polymers by a macromolecular thiol–ene reaction involving a RAFT[14]-synthesized precursor is described. It should be noted that organocatalytic couplings *via* the thiol–ene reaction compare favourably to the Cu(I) mediated alkyne–azide reaction, including the use of readily available starting materials and catalysts. Additionally, from a rate perspective, the thiol–ene reaction is extremely rapid (often quantitative reaction is observed within a period of ***seconds*** at ambient temperature) compared with extended reaction times, and elevated temperatures occasionally required for the catalyzed alkyne–azide reaction.[15] Key to the approach described here is the use of a RAFT-prepared polymer since (co)polymers synthesized by this technique bear thiocarbonylthio end groups that can be reduced to thiol functional species under facile conditions.[14a] The general synthetic approach to star polymers is shown in Scheme 1. It should be noted that while RAFT has been employed in both convergent[16] and divergent[17] star syntheses this has typically been accomplished using multifunctional RAFT agents and/or the microgel approach. However, an alternative approach was recently described by Inglis *et al.* in which a convergent synthesis of star polymers was described *via* a hetero-Diels–Alder reaction.[18] However, convergent star synthesis from RAFT-prepared precursors has not been described by the method detailed herein.

A homopolymer of *N*,*N*-diethylacrylamide (DEAm), **1**, was prepared under standard RAFT conditions employing 1-cyano-1-methylethyl dithiobenzoate, **2**, as the RAFT agent in conjunction with AIBN in DMF at 70 °C with a target molecular mass of 4500 at quantitative conversion. The polyDEAm (PDEAm) homopolymer was characterized by size exclusion chromatography (SEC), MALDI-TOF mass spectrometry (MALDI-TOF MS), and ^{1}H NMR spectroscopy. Fig. 1 shows the characterization data for the PDEAm

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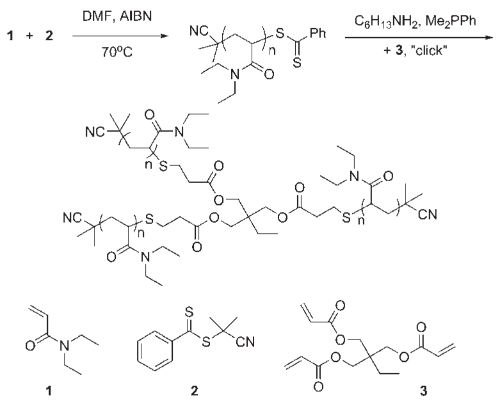

Scheme 1 General outline for the preparation of the target 3-arm star polymers and structures of the monomer, RAFT chain transfer agent, and coupling agent used in these studies.

homopolymer. SEC, calibrated with narrow molecular mass poly(methyl methacrylate) standards, indicated an M_n of 2900 and a polydispersity index (M_w/M_n) of 1.18, whereas the absolute molecular mass as determined by end-group analysis was determined to be 4400, Fig. 1A. This latter value is in excellent agreement with the value of *ca*. 4000 measured by MALDI-TOF MS, Fig. 1B. Shown inset in Fig. 1B is an expanded region of the same MALDI spectrum between 3000 and 4000 amu, showing the difference in mass between the major peaks of 127.25 amu, which is essentially identical to the molecular mass of the DEAm monomer (127.10 amu).

With the well-defined DEAm homopolymer in-hand we next examined the convergent synthesis of star polymers *via* a macromolecular thiol–ene click reaction. Importantly, the thiol–ene reaction proceeds rapidly under nucleophilic catalysis with primary and secondary amines.[3a,6,19] However, we have recently found that dimethylphenylphosphine (DMPP) is an extremely potent catalyst for such thiol–ene reactions. Indeed, it is known that phosphines are good catalysts for the addition of alcohols to electron deficient enes.[20] Also, primary and secondary amines are convenient, and efficient, reducing agents for the thiocarbonylthio end-groups.[14] As such, it was anticipated that simple mixing of PDEAm with trimethyolpropane triacrylate (TMPTA, **3**), a primary or secondary amine, and DMPP would result in the sequential reduction of the thiocarbonylthio end-group of PDEAm to a thiol functional group followed by thiol–Michael addition to yield the target star polymers. Since the reaction involves a macromolecular secondary thiol, the primary amine–phosphine combination, as opposed to only amine, was employed. It should be pointed out that the amine–phosphine combination is also beneficial since the phosphine serves a second, important role and eliminates the formation of the polymeric disulfide species that can form after end-group reduction, and which can readily occur in the presence of only amines, Fig. 2. Clearly the reduction of the thiocarbonylthio end-group of PDEAm in the absence of DMPP under a normal air atmosphere results in the formation of some dimeric disulfide species whereas such disulfide is completely absent when the reduction is performed in the presence of DMPP (see MALDI-TOF MS trace shown inset).

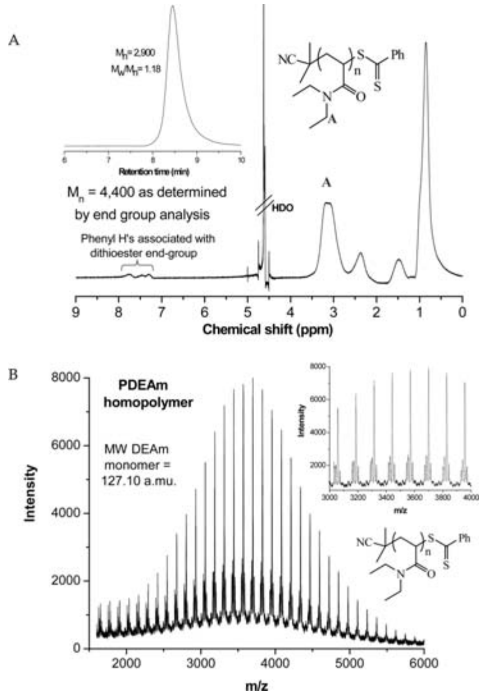

Fig. 1 (A) ^{1}H NMR spectrum of the PDEAm homopolymer, recorded in D_2O, showing the phenyl protons of the dithioester end-group with the SEC trace (RI signal) and measured M_n and M_w/M_n shown inset, and (B) MALDI-TOF MS trace of the same homopolymer with an expansion between 3000 and 4000 amu shown inset.

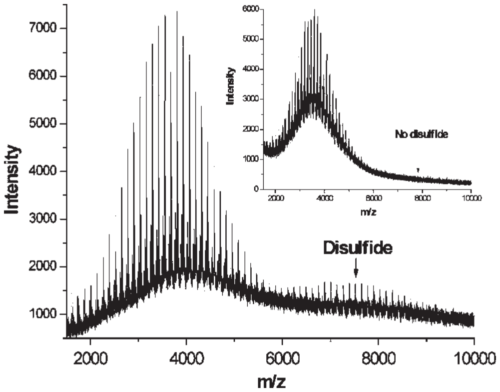

Fig. 2 MALDI-TOF MS traces of the PDEAm homopolymer with –SC(=S)–Ph end-groups reduced in the presence (inset) and absence of DMPP at RT under a normal air atmosphere.

For such a macromolecular thiol–ene reaction to be accurately described as a click reaction it must be both fast and essentially quantitative. To this end, reactions with the PDEAm were analyzed by FT-IR spectroscopy with an emphasis on the consumption of acrylate, followed by examining the disappearance of the band at 810 cm^{-1} associated with the C–H bend in C=C–H. This has previously been demonstrated to be an effective procedure for quantifying the rates of thiol–acrylate reactions *via* real-time FT-IR spectroscopy.[1,3] We found that the signal associated with the C–H bend at 810 cm^{-1} was completely absent after only 5 min of reaction, verifying the rapid nature of the reaction (data not shown). Considering the macromolecular/convergent nature of the reaction such a fast reaction is impressive, although entirely consistent with the thiol–ene reaction in general. The disappearance of the vinylic Hs was also monitored by ^{1}H NMR spectroscopy. Fig. 3A1 shows the ^{1}H NMR spectrum (recorded on a 500 MHz instrument) plotted between 6.5 and 5.5 ppm for a mixture of PDEAm and TMPTA, and clearly demonstrates the presence of the resonances associated with the vinylic hydrogens in TMPTA. Fig. 3A2 shows the same region, for the same sample in which the NMR tube was removed, DMPP and hexylamine added, the NMR tube reinserted, locked and a spectrum recorded (requiring approximately 5–10 min). Consistent with the results noted above from the FT-IR measurements, the double bonds of the TMPTA are completely consumed within minutes in the presence of DMPP and hexylamine.

While the FT-IR and ^{1}H NMR results indicate the successful formation of the 3-arm star polymer, it was also confirmed *via* a combination of ^{13}C NMR spectroscopy, SEC (data not shown) and MALDI-TOF MS. All techniques indicated, qualitatively, the successful formation of the target 3-arm star polymer. For example, Fig. 3B shows the MALDI-TOF MS spectrum, plotted between 8000 and 15 000 amu for the products resulting from the reaction of a PDEAm homopolymer with the TMPTA–$C_6H_{13}NH_2$–DMPP combination at a molar ratio of –SH : ene of 1.5 : 1 (to favour star formation). This spectrum was recorded 12 h after the reaction was completed. In this instance, the parent PDEAm homopolymer had a measured M_n of 3700 amu as determined by MALDI-TOF MS. The primary distribution shown in Fig. 3B is centered about 11 100 amu, which is in excellent agreement with the anticipated molar mass of *ca.* 11 400 amu expected for the 3-arm star product, thus confirming successful formation. We also verified that the ene was consumed ***only*** in the presence of thiol functional groups and that consumption did ***not*** proceed *via* a free radical pathway (data not shown).

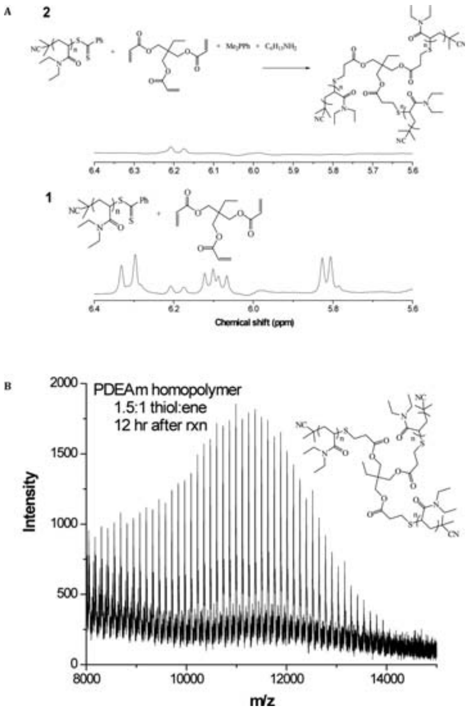

Fig. 3 (A) ^{1}H NMR spectrum, plotted between 6.5 and 5.5 ppm, demonstrating the disappearance of vinylic hydrogens in a PDEAm (0.028 M), TMPTA (0.0166 M), DMPP (0.11 M), hexylamine (0.35 M) reaction, in 0.5 g of THF, and (B) MALDI-TOF MS spectrum of the products from the same reaction recorded 12 h after completion of reaction.

Herein is described a facile, rapid (as determined by FT-IR and NMR spectroscopic analysis), one-pot application of a macromolecular thiol–ene click reaction for the convergent synthesis of star polymers. Key to this approach is the use of RAFT-prepared polymers with thiocarbonylthio end-groups that can be readily reduced by mild reagents, such as primary amines, to the corresponding thiol. Reduction with hexylamine in the presence of DMPP and TMPTA results in 3-arm star formation *via* a macromolecular thiol–ene click reaction as verified by a combination of NMR spectroscopy, GPC, and MALDI-TOF MS. Further details will be reported in a future manuscript.

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