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Desulfurization–bromination: direct chain-end modification of RAFT polymers†

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We report a simple and efficient transformation of thiol and thiocarbonylthio functional groups to bromides using stable and commercially available brominating reagents. This procedure allows for the quantitative conversion of a range of small molecule thiols (including primary, secondary and tertiary) to the corresponding bromides under mild conditions, as well as the facile chain-end modification of polystyrene (PS) homopolymers and block copolymers prepared by reversible addition–fragmentation chain transfer (RAFT) polymerization. Specifically, the direct chain-end bromination of PS prepared by RAFT was achieved, where the introduced terminal bromide remained active for subsequent modification or chain-extension using classical atom transfer radical polymerization (ATRP). This transformation sets the foundation for bridging RAFT and ATRP, two of the most widely used controlled radical polymerization (CRP) strategies, and enables the preparation of chain-end functionalized block copolymers not directly accessible using a single CRP technique.

Introduction

The combination of controlled radical polymerizations (CRPs) with post-polymerization modification reactions has had a significant impact on the applications of synthetic polymers.[1–5] Chain-end functionalized polymers have been utilized in, for example, surface/particle ligation,[6] self-assembly,[7] molecular labelling,[8] and bioconjugation.[9] Three main strategies exist for the incorporation of specific end groups into polymers: (1) the use of functional initiators, (2) specific termination reactions, or (3) through the post-polymerization modification of residual reactive functional groups.[10] Post-polymerization modification is often the preferred method, enabling the preparation of a range of materials with different chain-ends from a common polymer precursor. When combined with CRPs, these approaches can be used to prepare a diverse range of polymers with control over molar mass, dispersity (*Đ*) and molecular architecture, while also incorporating reactive chemical functionality for further modification.[11–15]

As a widely utilized CRP technique, reversible addition–fragmentation chain transfer (RAFT) relies on the presence of a chain transfer agent (CTA) that acts to reversibly cap the propagating radical during polymerization.[14,16] The key features of RAFT polymerization are its broad monomer scope, metal-free conditions and overall ease of use. Moreover, the recent development of photoinduced-electron transfer RAFT (PET-RAFT) processes offers numerous advantages over conventional thermally-initiated polymerizations, including milder polymerization conditions and spatiotemporal control of polymer chain growth.[17–21]

Despite the versatility of RAFT polymerizations, the sulfur-based CTAs that facilitate radical propagation often endow the resulting materials with adverse properties, including off-white color, odor and chain-end instability.[22,23] As such, a number of methods for the removal of the CTA have been reported. For example, both radical-induced reduction and thermolysis have been widely utilized to yield polymers with inert chain-ends.[22–24] More recently, several mild and quantitative light-mediated approaches have been developed for the quantitative transformation of the CTA into a hydrogen chain-end.[25–27] For further modification of RAFT polymers, the majority of chain-end functionalization strategies have focused on the use of the CTA as a masked thiol.[28,29] In the presence of excess nucleophiles, including amines,[23,24] azides[30] and hydrazine,[31] the CTA can be reduced to a thiol chain-end suitable for further reaction. In particular, thiol-Michael addition

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has been commonly reported for the introduction of a range of chain-end groups.[32,33]

Although considerable progress has been made towards post-polymerization modification of RAFT polymers, the range of quantitative and efficient functional group transformations available still lags significantly behind that of atom transfer radical polymerization (ATRP).[10] This is predominantly a result of the synthetic versatility enabled by halide substitution reactions.[12,13] The conversion of RAFT chain-ends to the corresponding bromides would therefore expand the scope of possible chain-end modifications of RAFT polymers, while also allowing conversion between RAFT and ATRP processes.[34–38]

Herein, we report the development of a facile and quantitative procedure for the conversion of thiol functional groups into the corresponding bromide derivatives using commercially available reagents. Significantly, this procedure allows for the transformation of trithiocarbonate-terminated polystyrene (PS) homopolymers and block copolymers to the corresponding bromide-terminated derivatives. The chemical integrity of the newly installed bromide chain-end was further supported by successful chain-end modification and chain extension using traditional ATRP.

Results and discussion

Chain-end reactivity of functionalized macromolecules has been a long-standing focus in synthetic polymer chemistry. In addressing this challenge, our group has recently reported a metal-free photochemical desulfurization of RAFT chain-ends.[26] Under visible-light irradiation, the reaction proceeded *via* a two-step process – nucleophilic cleavage of the CTA followed by radical desulfurization – to afford a hydrogen-terminated polymer. With the aim of expanding RAFT desulfurization chemistry, we investigated the development of a two-step protocol to remove the CTA chain-end while subsequently introducing a synthetically versatile bromide at the terminus of polymers prepared by RAFT. Specifically, this route relies on conventional aminolysis of the CTA, followed by subsequent desulfurization–bromination of the thiol to afford a bromide-terminated polymer (Fig. 1).

While aminolysis of RAFT polymers has been demonstrated in the literature,[23,24,39] the concept of transforming the thiol chain-end to a bromide has not been previously reported. Inspired by the non-quantitative bromination of cysteine residues[40] and other small molecule thiols[41] using a combination of triphenylphosphine (PPh_3) and *N*-bromosuccinimide (NBS), we envisioned an improved protocol for the conversion of thiols to bromides. The conversion of alcohols, thiols and selenols to halides has also been reported using a complex of triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone, where the halides were introduced as ammonium or quaternary ammonium salts.[42] Key to our strategy is the use of commercially available triphenylphosphine dibromide (PPh_3Br_2) as a single-component reagent for this desulfurization–bromination. This reagent is effective for the conversion of alcohols to bromides (Appel reaction)[43] and has been reported in the patent literature for the conversion of thiols to halides at elevated temperatures.[44]

To test the viability of this reagent, 1-dodecanethiol was initially chosen as a model compound and treated with five equivalents of PPh_3Br_2 in dichloromethane (DCM) at room temperature (RT) (Fig. 2). Remarkably, analysis of the crude mixture by ^{1}H NMR spectroscopy revealed complete disappearance of resonances for the starting material and clear downfield shifts of the proximal methylene peaks from 2.5 (●) to 3.4 (▼) ppm and from 1.6 (★) to 1.85 (◆) ppm (Fig. 2). These new resonances were consistent with the quantitative formation (>95%) of 1-bromododecane (Fig. 2).[45]

The facile conversion of 1-dodecanethiol to 1-bromododecane using PPh_3Br_2 inspired an exploration of the substrate scope of the reaction. In particular, we focused on secondary and tertiary thiols with the aim of utilizing this procedure for the chain-end modification of RAFT-derived polymers. Following application of the aforementioned reaction conditions (5 equivalents of PPh_3Br_2 in DCM at RT) to a variety of alkyl thiols, including primary alkyl, benzyl, secondary benzyl, and tertiary alkyl thiols (Table 1, entries 1–4), ^{1}H NMR characterization revealed near quantitative conversion (>95%) to the corresponding alkyl bromides in each case (Table 1, entries 1–4; Fig. S1–S5†). For the most sterically hindered, tertiary 1-adamantanethiol, full conversion of the starting material to 1-bromoadamantane was achieved after addition of equimolar triethylamine to the reaction to neutralize HBr that was formed at slightly elevated temperatures (40 °C) (Table 1, entry 4;

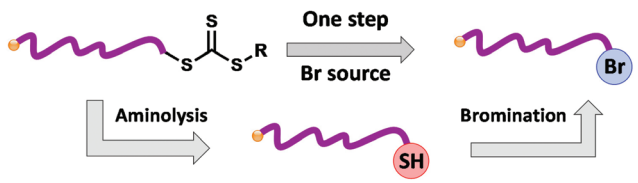


Fig. 1 Schematic representation of the one and two step routes for the conversion of trithiocarbonate and thiol-functionalized polymers and small molecules to the corresponding bromide derivatives.

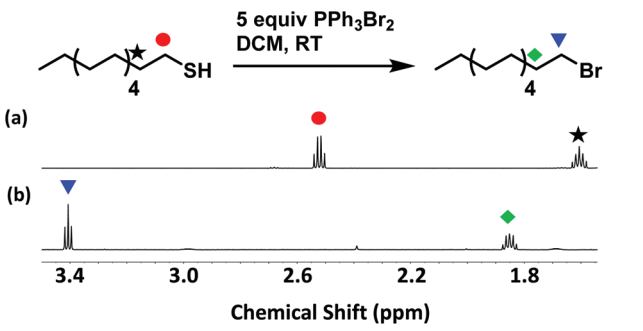
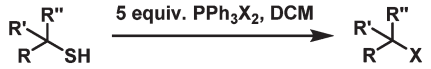
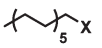
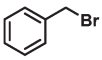
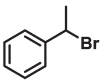
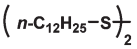


Fig. 2 Desulfurization–bromination of 1-dodecanethiol using PPh_3Br_2 and corresponding ^{1}H NMR spectra of diagnostic proton signals (a) before and (b) after reaction.

Table 1 Desulfurization–halogenation of small molecule thiols using PPh_3X_2 (X = Br, Cl, and I)



Entry	Product	Halide (X)	Temperature	Conversion
1		Br, Cl[b]	RT	>95%
2		Br	RT	>95%
3[a]		Br	RT	>95%
4[b]		Br, Cl	40 °C	>95%
5[b]		I	RT	>95%

[a] PPh_3 and Br_2 were added separately. [b] TEA (5 equiv.) was added.

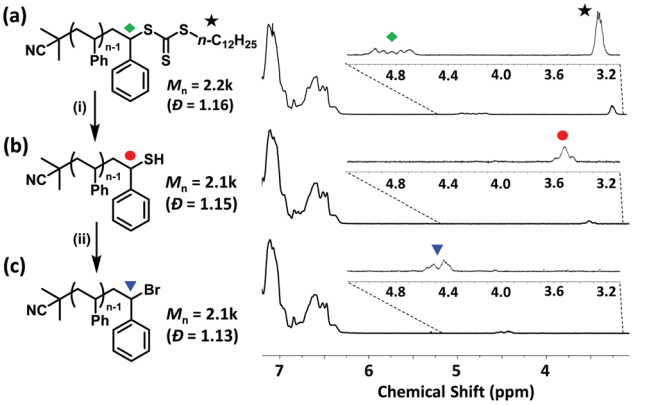


Fig. 3 Stepwise transformation of (a) PS-CTA to (b) PS-SH to (c) PS-Br and corresponding ^{1}H NMR spectra. (i) n-$C_6H_{13}NH_2$, P(n-Bu)$_3$, THF, RT, overnight. (ii) PPh_3, Br_2, DCM, RT, 2 h.

Fig. S5†). Overall, these results illustrate the efficient and quantitative conversion of a range of small molecule thiols to the corresponding bromides using PPh_3Br_2 that should be applicable to a variety of substrates.

Owing to the simplicity of PPh_3Br_2 as a brominating reagent, we envisaged that commercially available PPh_3Cl_2 would yield the corresponding chloride. In an analogous manner to PPh_3Br_2, 1-dodecanethiol and 1-adamantanethiol were treated with PPh_3Cl_2 in DCM at RT, affording the desired chlorinated products, 1-chlorododecane and 1-chloroadamantane, in near quantitative yields (Table 1, entries 1 and 4; Fig. S2 and S5†). Interestingly, when commercially available PPh_3I_2 was used for the desulfurization–iodination of 1-dodecanethiol, only quantitative conversion to the disulfide product was observed, as evidenced by ^{1}H NMR analysis (Table 1, entry 5; Fig. S6†). While PPh_3I_2 did not yield the expected iodinated product, the ability to quantitatively produce disulfide bonds from free thiols using a single reagent may be of general interest for a variety of applications.[46,47] Overall, the success of these small molecule reactions exemplifies the broad applicability of commercially available PPh_3X_2 (X = Cl or Br) for facile chlorination and bromination.

Having successfully demonstrated desulfurization–bromination on a range of small molecule thiols, we sought to expand this transformation as a viable chain-end modification strategy for RAFT polymers. PS was selected as a model polymer due to the distinct ^{1}H NMR peak resonances for the chain-end CH-unit when functionalized with different groups.[26] Bromination of PS-CTA would also represent the first example for the conversion of a RAFT derived polymer to an ATRP active polymer. PS-CTA (M_n = 2.2 kg mol^{-1}, $Đ$ = 1.16) was prepared by thermally-initiated RAFT polymerization using 2-cyano-2-propyl dodecyl trithiocarbonate as the CTA.[39] Analysis by ^{1}H NMR displayed a broad diagnostic signal around 4.8 ppm (◆), consistent with literature values for the benzylic proton adjacent to the CTA, and a signal at 3.2 ppm (★) matching reported values for the α-methylene protons of the dodecyl chain (Fig. 3a).[39] Following this, PS-CTA was subjected to conventional aminolysis conditions, n-hexylamine and tributylphosphine (P(n-Bu)$_3$) in tetrahydrofuran (THF) at RT, to give PS-SH (Fig. 3b).[39] ^{1}H NMR of the resulting PS-SH confirmed the disappearance of the resonances corresponding to the CTA and the concomitant appearance of a broad peak at 3.5 ppm (●), identified as the benzylic proton adjacent to the thiol chain end (Fig. 3b).[39] Importantly, size-exclusion chromatography (SEC) analysis of the resulting PS-SH showed a unimodal distribution with a similar dispersity ($Đ$ = 1.15) to the starting PS-CTA ($Đ$ = 1.16) (Fig. S7†).

Following the preparation of PS-SH, desulfurization–bromination was attempted using identical conditions to the small molecule reactions. Initial conversion of PS-SH to PS-Br using PPh_3Br_2 afforded a mixture of products, with three different chain-end resonances observed by ^{1}H NMR at 6.1, 4.5 (▼), and 3.5 (●) ppm, corresponding to PS-alkene,[48] PS-Br, and the starting material, PS-SH, respectively (Fig. S8†). Optimization of the reaction conditions to reduce the elimination side product by varying the equivalents of Br_2 showed that separately adding PPh_3 and Br_2 with a molar equivalent ratio of 2 : 10, significantly increased the bromination rate and suppressed formation of the undesired PS-alkene (Fig. 3c and S9†). Indeed, ^{1}H NMR showed the appearance of a broad signal at 4.5 ppm (PS-Br) and the complete absence of the undesired peaks at 6.1 (PS-alkene) and 3.5 ppm (PS-SH) under these conditions (Fig. 3c and S9†). Moreover, SEC analysis of the resulting polymer (M_n = 2.1k, $Đ$ = 1.13) showed negligible difference to that observed for the starting PS-SH (M_n = 2.1k, $Đ$ = 1.15) (Fig. S7†), confirming the absence of any deleterious side reactions.

After demonstrating the conversion of PS-CTA to PS-Br through a PS-SH intermediate, we focused our attention on developing a one-pot transformation of PS-CTA to PS-Br (Fig. 4a). We hypothesized that combining both aminolysis and desulfurization–bromination conditions would enable the

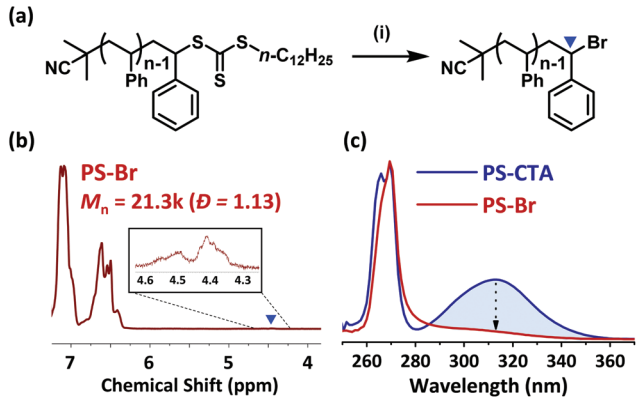


Fig. 4 (a) Direct conversion of PS-CTA to PS-Br, (i) NBS, PPh_3Br_2, DCM, RT, 1 h. (b) ^{1}H NMR of high MW PS-Br. (c) $CHCl_3$ SEC-UV traces at 310 nm for high MW PS-CTA and PS-Br.

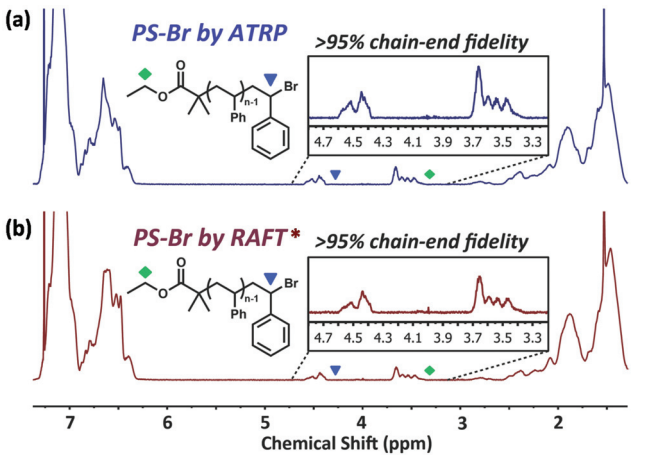


Fig. 5 Comparison of chain-end fidelity of PS-Br (a) prepared directly by ATRP and (b) prepared by RAFT polymerization followed by CTA-bromination reaction (RAFT*). ^{1}H NMR spectroscopy showed over 95% end-group fidelity in both cases.

selective *in situ* generation of PS-SH, followed by rapid desulfurization–bromination. To investigate this possibility, PS-CTA was dissolved in DCM and allowed to stir at RT overnight in the presence of *n*-hexylamine, PPh_3 and Br_2 (Fig. S10†). Analysis of the ^{1}H NMR spectrum of the resulting polymer matched the desired PS-Br product, suggesting a viable one-pot conversion of a RAFT derived, CTA-functionalized PS to a bromide-functionalized PS-Br (Fig. S10†). Interestingly, it was also observed that the addition of commercially available PPh_3Br_2 and NBS (without addition of amine) resulted in the direct and quantitative formation of PS-Br from PS-CTA in a single step (Fig. 4 and S10†). This method was also successfully applied to higher molecular weight PS-CTA (M_n = 21.3 kg mol^{-1}, $Đ$ = 1.13; Fig. 4b) with ^{1}H NMR analysis verifying the emergence of the expected chain-end resonance for PS-Br (Fig. 4b) and SEC-UV confirming near quantitative loss of the absorption signal at 310 nm attributed to the trithiocarbonate chain-end (Fig. 4c).

A key requirement for all polymer chain-end functionalization reactions is high chain-end fidelity. To critically assess the functionality and utility of PS-Br prepared by RAFT/bromination, we first compared its chain-end fidelity to that for PS-Br directly derived from classical ATRP using one of the most widely utilized ATRP initiators, ethyl α-bromoisobutyrate (EBiB). Following successful synthesis of a CTA analogue of EBiB (Fig. S11†), polymerization of styrene under thermally-initiated RAFT conditions (Fig. S12†)[39] afforded PS-CTA with good molecular weight control (M_n = 2.3 kg mol^{-1}, $Đ$ = 1.14). Treatment of the resulting PS-CTA with the optimized one-step bromination conditions using a combination of NBS and PPh_3Br_2 in DCM for one hour afforded PS-Br (Fig. S12†), which showed negligible differences to PS-Br prepared by conventional Cu-mediated ATRP (Fig. 5). Specifically, the peak resonances for chain-end termini in the ATRP and RAFT/bromination cases overlay and integrate to the expected values (Fig. 5). As a result, this approach to bromide-functionalized PS derivatives represents the first method to prepare well-defined PS-Br *via* an entirely metal-free process, with implications for applications where trace metal contamination could be detrimental to overall materials performance.

A wide range of functional group transformations are available for bromide-terminated polymers obtained by ATRP.[10] To demonstrate the synthetic versatility of PS-Br obtained *via* RAFT, the bromide chain-end was reacted with excess sodium azide to furnish the azide-terminated polymer (Fig. 6a). Analysis by ^{1}H NMR indicated complete disappearance of

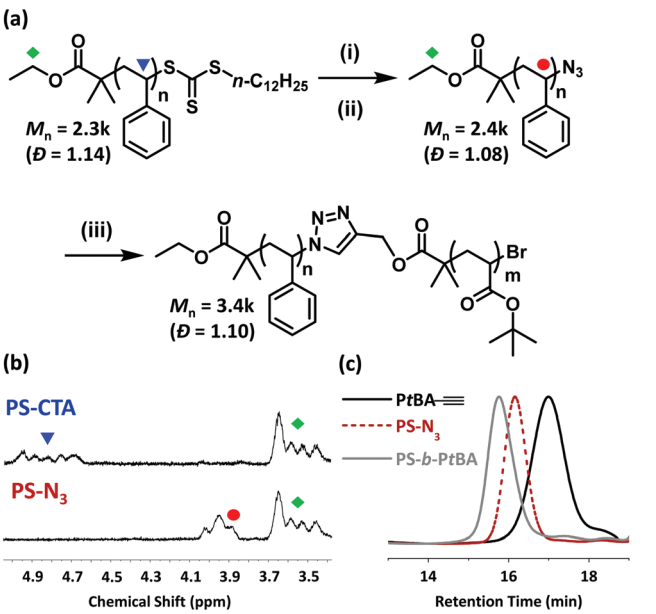


Fig. 6 (a) Chemical scheme for chain-end modification of PS-CTA to PS-N_3 *via* PS-Br (top). Click reaction between PS-N_3 and P*t*BA-alkyne (bottom). (i) NBS, PPh_3Br_2, DCM, RT, (ii) NaN_3, DMF, RT, (iii) P*t*BA (M_n = 0.9k, $Đ$ = 1.20), CuBr, PMDETA, THF, 50 °C. (b) ^{1}H NMR spectra for PS-CTA and PS-N_3. (c) $CHCl_3$ SEC-RI traces of P*t*BA, PS-N_3, and PS-*b*-P*t*BA.

peaks at 4.5 ppm corresponding to PS-Br and the emergence of new peaks at 3.9 ppm corresponding to the protons adjacent to the azide in PS-N_3, suggestive of quantitative conversion to the desired end group (Fig. 6b).[49] To further confirm the formation of PS-N_3, Cu-catalyzed "Click" chemistry was performed with alkyne-terminated poly(*tert*-butyl acrylate) (P*t*BA) to afford the diblock copolymer (Fig. 6 and S13†). Characterization by SEC verified the expected molar mass increase (Fig. 6c) and also confirmed successful attachment of P*t*BA to yield PS-*b*-P*t*BA. As a final showcase of the utility of the newly incorporated bromide chain-end, we demonstrated the chain-extension of PS-Br with styrene using Cu-catalyzed ATRP (Fig. S14†), highlighting the potential of this method to achieve sequential RAFT and ATRP polymerizations.

A particular advantage of this RAFT/bromination protocol lies in its ability to access bromide-terminated polymers that are inaccessible by classical ATRP. By taking advantage of RAFT to synthesize an initial starting block which is difficult to prepare by ATRP, followed by transformation of the CTA to a bromide, well-defined chain-end functionalized polymeric materials can be accessed that are unattainable *via* a single CRP method. To demonstrate this concept, poly(*N*,*N*-dimethylacrylamide) (PDMA),[26] a polymer that is difficult to obtain using ATRP due to poor chain-end fidelity, often attributed to the coordination of Cu to the amide functionality of the monomer,[50–52] was prepared by RAFT polymerization. Through subsequent chain-extension with styrene, PDMA-*b*-PS with a trithiocarbonate end group was obtained (Fig. 7a and S15†).[53] The resulting diblock copolymer was treated with our optimized bromination protocol (Fig. 7). Analysis by SEC showed negligible change in the molar mass or $Đ$ of the polymer during bromination (RI trace, Fig. 7b) and confirmed the disappearance of the CTA chain-end (UV-vis trace, Fig. 7c). Furthermore, ^{1}H NMR confirmed the incorporation of the bromide chain-end and the formation of the desired PDMA-*b*-PS-Br (Fig. S16†), leveraging the distinct advantages of both RAFT and ATRP. Although a variety of different polymer types (*e.g.*, PDMA and P*t*BA) were found to be compatible with chain-end bromination, these reaction conditions are currently limited to polymers where the CTA is adjacent to a PS end group. The adaptation of this chain-end modification approach for CTAs adjacent to other polymer types is currently ongoing.

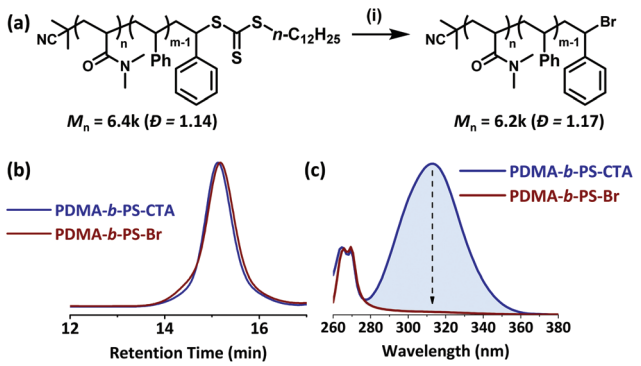


Fig. 7 (a) Chemical scheme of chain-end bromination of PDMA-*b*-PS-CTA prepared by RAFT polymerization, (i) NBS, PPh_3Br_2, DCM, RT. $CHCl_3$ SEC (b) RI traces and (c) UV response at 14.5 min of PDMA-*b*-PS-CTA and PDMA-*b*-PS-Br. M_n and $Đ$ values were measured by $CHCl_3$ SEC calibrated using PS standards.

Conclusions

In summary, we have developed an efficient protocol for the quantitative transformation of thiol functional groups to chlorides and bromides using inexpensive, commercially available and easy to handle reagents. This method was adapted for the one-step conversion of a CTA-derived chain-end to a bromide in PS homopolymers and block copolymers. Importantly, negligible differences were observed when PS-Br prepared by classical ATRP was compared to PS-Br prepared by RAFT with subsequent conversion of the CTA chain-end to a bromide. The reactivity of the bromide chain-end was demonstrated by performing chain-extension using classical ATRP conditions, or through post-polymerization modification. For the latter, the bromide was converted to an azide chain-end for subsequent "click" coupling with an alkyne-functionalized polymer, affording the corresponding diblock copolymer, PS-*b*-P*t*BA. Significantly, this bromination procedure enables the synthesis of PDMA-*b*-PS with a bromide chain-end, an example of a diblock copolymer composition not directly accessible using a single CRP technique. This direct CTA to bromide chain-end transformation sets the foundation for bridging RAFT and ATRP, two of the most widely used controlled radical polymerization strategies.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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