Facile one pot synthesis of a range of reversible addition–fragmentation chain transfer (RAFT) agents†

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The application of a universal synthetic strategy for the high yielding and facile synthesis of a wide range of functional RAFT agents including trithiocarbonates, xanthates and dithiocarbamates is described.

There is great current interest in the synthesis of well-defined and functional polymers using controlled radical polymerisation (CRP) techniques and the advances in these techniques have enabled access to a wide range of functional materials for a diverse range of applications. In particular over the last decade there has been significant interest in reversible addition–fragmentation chain transfer polymerisation (RAFT), and macromolecular design *via* the interchange of xanthates (MADIX) techniques.[1] RAFT/MADIX have recently been proven to be perhaps the most versatile of the CRP techniques given their tolerance to functionality and their ability to polymerise in a controlled manner a wide range of monomers, with access to a range of architectures.[2] RAFT polymerisation is mediated by a chain transfer agent or CTA of which there are at least 4 main classes depending on the substituent next to the C=S functionality; dithioesters, trithiocarbonates, xanthates and dithiocarbamates. This range of CTAs with different Z groups (where Z activates the C=S towards radical addition and stabilises the intermediate radical formed) allows for good control over the majority of monomers; however a key consideration is the correct choice of CTA agent.

One apparent disadvantage of RAFT is the often difficult or hazardous materials required for the synthesis of the CTAs. Thus, the development of novel routes towards the facile synthesis of active and effective CRP initiators has received significant interest in recent years. Most notably, Perrier and Rannard introduced an elegant strategy for the synthesis of a wide range of CTAs using 1,1′-thiocarbonyl diimidazole, which avoids the use of toxic and hazardous CS_2.[3] These reactions were performed under anhydrous and anaerobic experimental conditions, often with multistep purification procedures and in all CTA syntheses thiols were required as reagents. In this communication we report a universal and facile one pot strategy for the high yielding synthesis of a wide range of RAFT agents, including the preparation of 3 classes of CTAs, in excellent yields (Scheme 1). A key advantage of this methodology is that the reactions can be performed in air, with readily available starting materials, can be isolated in high yields (>70%) after column chromatography and can be utilised for the synthesis of functional and tertiary CTA agents.

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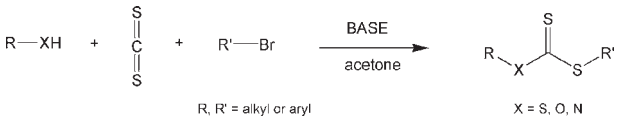
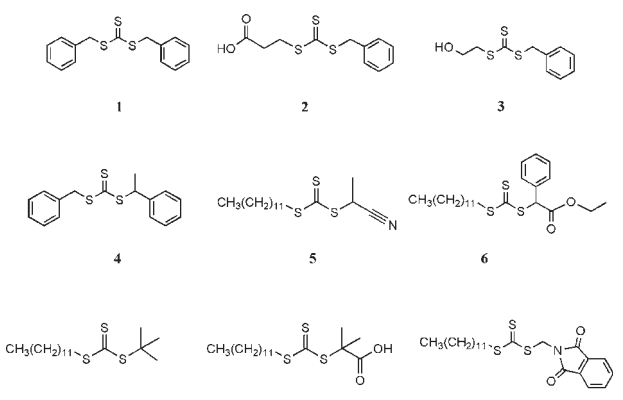


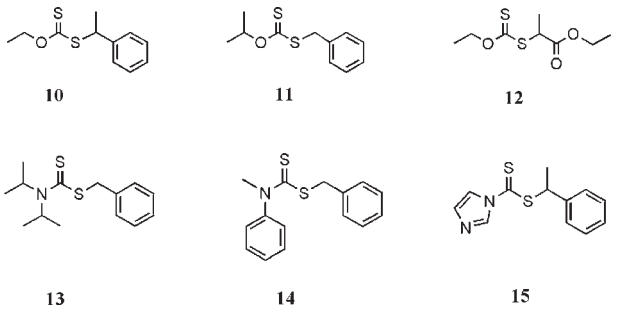
Scheme 1 General strategy for the synthesis of a range of CTAs for application in RAFT.

Our initial interest in this area was in the report by Li and coworkers that 1-(alkyldithiocarbonyl)imidazoles could be synthesised in a mild and efficient procedure using CS_2, a non-nucleophilic base, an alkylating agent and imidazole.[4] In this report they described the synthesis of a range of novel dithiocarbamates using this mild chemistry. We were keen to explore further the scope of this reaction by expanding the synthetic procedure to enable the synthesis of other classes of RAFT agent including trithiocarbonates and xanthates. This would allow for a novel, universal and mild synthetic procedure for the high yielding synthesis of a diverse range of RAFT agents.

Using this approach a range of trithiocarbonates, xanthates and dithiocarbamates (Schemes 2 and 3) were synthesised in a single step at room temperature in air, in excellent yields (**1–4** were isolated in greater than 90% yield).‡ For example, the synthesis of trithiocarbonate **1**, which is a commonly used RAFT agent for the polymerisation of styrene and acrylate monomers, with K_3PO_4 as a base, is almost quantitative in only 30 min (see ESI†). The synthesis of this RAFT agent has been reported previously, however using this methodology, **1** can be synthesised in very high yield (96% and after purification by column chromatography). This single step methodology is also applicable for the synthesis of unsymmetrical trithiocarbonates, primary and secondary, alkyl and aryl, R and Z substituents (**1–4**) to allow for tailoring the CTAs' activity. The synthesis of CTAs **5** and **6** was lower yielding (>70%) perhaps due to less reactive alkyl thiol, which resulted in incomplete conversion. Of further interest is the



Scheme 2 Synthesis of a range of trithiocarbonates, **1–9**.



Scheme 3 Synthesis of xanthates (**10–12**) and dithiocarbamates (**13–15**).

synthesis of trithiocarbonates which contain tertiary R groups (**7** and **8**), which can be challenging using existing radical induced decomposition methods but are of interest given their ability to homopolymerise methacrylic monomers in a controlled manner. Using this strategy we were able to synthesise **7** after column chromatography in excellent yield (93%) as a bright yellow oil. Interestingly no byproducts such as disulfides were observed in these reactions despite the reactions being run without the exclusion of oxygen. Overall, the synthesis of a range of trithiocarbonates is fast and effective using this route with facile work up producing CTAs in high yield.

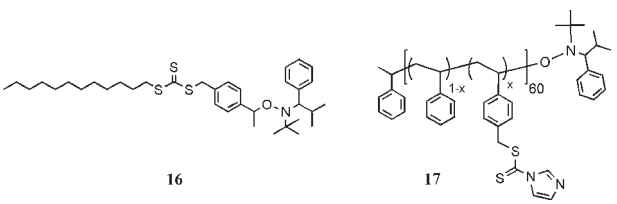
Also of interest is the synthesis of functional RAFT agents especially those which contain alcohol, amine or carboxylic acid functionality to enable or facilitate post-polymerisation coupling or further functionalisation of the polymers. We thus investigated the synthesis of alcohol and carboxylic acid functionalised RAFT agents (**2** and **3**) using simple commercial thiols and the chemistry described in Scheme 1. These functional RAFT agents were isolated following filtration and reduction to dryness in quantitative yield—this demonstrates an important aspect of our strategy which enables us to selectively react quantitatively at one chemical functionality to allow for the synthesis of functionalised RAFT agents. Such functional RAFT agents have found application in the synthesis of more complex architectures and as initiating sites for orthogonal polymerisation strategies.[5] For the synthesis of an amine functionalised RAFT agent, established phthalimide protection chemistries were utilised given the incompatibility of the RAFT agent with the nucleophilic amine. This enabled access to RAFT agent **9** from *N*-bromomethylphthalimide in a moderate 59% yield; this however does not compare favourably with the report of yields $>90\%$ for related CTAs which indicates that this method may not be suitable for the synthesis of phthalimide CTAs.[6]

We were especially interested in the synthesis of *S*-dodecyl-*S*′-(α,α'-dimethyl-α''-acetic acid) trithiocarbonate, (DDMAT), a commonly used RAFT agent which has been demonstrated to mediate the polymerisation of acrylic acid, acrylates, acrylamides, styrenes and vinyl ketones.[7] The reported literature procedure for the synthesis of this RAFT agent requires stringent anaerobic conditions and has been reported in 63% yield.[7h] Using our methodology we have been able to synthesise this RAFT agent, **8**, in one pot, in air, overnight in 83% yield, after chromatography. This represents a significant advance from the reported procedure and allows facile access to this high interest CTA *via* simple chemistry and using commercially available starting materials.

We also explored the application of this methodology for the synthesis of xanthate and dithiocarbamate CTA agents given their application in the polymerisation of more reactive monomers such as vinyl acetate (VAc), *N*-vinylcarbazole (NVC) and vinyl propionates, *via* a MADIX process.[8] The controlled polymerisation of vinyl acetate is difficult to achieve given the highly reactive nature of the monomer radical which reacts with activated bonds such as C=S to form a relatively stable radical which does not readily fragment. Thus, of the classes of RAFT CTAs only xanthates and dithiocarbamates which contain an electron withdrawing Z group allow for the controlled polymerisation of more reactive monomers such as vinyl acetate. Hence, the synthesis of these classes of CTA agents are of great current interest. Using the universal chemistry herein we were also able to synthesise a wide range of xanthates (Scheme 3) in excellent yields in a single step by changing the solvent to the alcohol and using Cs_2CO_3 as a base. This included the xanthate **11**, in 97% yield, and also other interesting RAFT/MADIX active derivatives (**10** and **12** in yields $>70\%$). This represents a significant advance in the synthesis of these xanthate CTAs and allows for greater access to a range of novel RAFT/MADIX agents.

This chemistry was also extended to include the synthesis of dithiocarbamates, which are of increasing interest along with trithiocarbonates given their yellow colour which does not affect the final product polymer characteristics as much as dithioesters which have a bright red-orange colour. There have been previous reports of the application of one pot strategies for the synthesis of dithiocarbamates, however the focus was not on their application as polymerisation CTAs.[9] The synthesis of a range of dithiocarbamates was explored including those containing heterocyclic and secondary amines (**13–15**) (Scheme 3). All of these CTAs reported were isolated in greater than 60% yield following chromatography. One advantage of this method for the synthesis of xanthates and dithiocarbamates compared to other strategies is that volatile and malodorous thiols are not required.

To further highlight and explore the scope of this mild reaction we investigated this chemistry as a post-functionalisation strategy for both small molecules and polymers. Given the versatility in this method we can utilise a primary thiol or halogenomethyl groups as reactive units to enable modification with reactive CTA functionality. To explore this we initially investigated the post-functionalisation of a chloro-functionalised NMP initiator (2,2,5-trimethyl-3-(1-(4′-chloromethyl)phenylethoxy)-4-phenyl-3-azahexane) which has been reported by Hawker for the controlled polymerisation of styrenes and acrylates.[10] Using the chemistry outlined above for the trithiocarbamates we were able to prepare a dual functionalised RAFT–NMP initiator species (**16**) in *ca.* 87% yield (Scheme 4). Initiator **16** is of significant interest given its ability to polymerise methacrylates through the RAFT



Scheme 4 Novel dual functional initiator species, **16** and post-polymerisation functionalised polymer, **17**.

functionality but not though the NMP functionality—hence potentially allowing access to an orthogonally reactive CRP initiator. Further work is exploring the application of this novel NMP–RAFT initiator and in particular in the one pot preparation of block copolymers.

We have also applied this chemistry as a strategy for the post-functionalisation and grafting of polymers. For example, a poly(styrene-*co*-chloromethylstyrene) (M_n^{NMR} = 10 600, M_w/M_n = 1.13, with 12.1% functional monomer incorporation) was prepared using reported NMP procedures (120 °C, bulk, 100 equiv.) and 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-aza-hexane as an initiator.[10] This polymer was isolated and then modified to incorporate a RAFT initiator through the reactive chloro functionality in the side chain (evidence of complete conversion, by halide analysis and also shift of the methylene signal in the ^{1}H NMR spectrum from δ 4.5 to 4.7). This RAFT macro initiator, **17**, (M_n^{NMR} = 11 700, M_w/M_n = 1.15) was then utilised to polymerise *tert*-butyl acrylate (*t*BuA) (60 °C, dioxane, 100 equiv., 0.1 equiv. AIBN) to afford a diblock graft copolymer (M_n^{NMR} = 28 300, M_w/M_n = 1.23). This highlights the scope of this chemistry to enable access to novel block and graft copolymers, which are perhaps inaccessible using conventional strategies, *via* a post-polymerisation CTA functionalisation and subsequent polymerisation strategy.

All the CTAs in this work have been characterised fully by ^{1}H, ^{13}C NMR spectroscopy, IR, MS and elemental analysis (see ESI†). A selection of the CTAs were also utilised in RAFT/MADIX polymerisations to highlight their purity and effectiveness in mediating the controlled polymerisation of a wide range of monomers (Table 1 and ESI†). In particular CTA **1a** which was isolated directly from the reaction mixture (after filtration and removal of solvent) was utilised in the polymerisation of styrene and compared to results for the purified initiator **1**. Table 1 highlights that in the synthesis of dithiocarbonate CTA **1a** no purification of the reaction mixture is required before utilisation as CTA for the polymerisation of styrene, given the high yield of the reaction.

Overall this chemistry has been demonstrated to be both versatile and efficient for the synthesis of novel and previously reported RAFT agents. This methodology can be readily tailored to allow for the high yielding synthesis of dithiocarbamates, xanthates and trithiocarbonate CTAs. The significant advantage of this strategy over existing methods is the wide range of CTAs accessible *via* mild reaction conditions and without difficult purification procedures. Current work is exploring this method for the synthesis of novel polymer architectures and functional materials. It is proposed that the universal nature of this chemistry allows for access to a wider range of RAFT/MADIX agents using facile, efficient and high yielding strategies.

Table 1 Polymers formed by RAFT/MADIX polymerisations using CTAs synthesised in this study

CTA	Monomer	Time/ h	$M_{n,th}$/ g mol^{-1}	$M_{n,GPC}$/ g mol^{-1}	M_w/M_n	Conversion (%)
1a	*t*BuA	24	25 400	24 000	1.18	>99
1	*t*BuA	24	25 400	24 500	1.18	>99
2	Styrene	22.5	8000	7300	1.18	77
3	Styrene[a]	40	7200	7300	1.13	69
8	MMA	2.75	29 200	39 300	1.30	>99
11	VAc	13	8900	8700	1.43	>99
10	NVC[a]	22.5	9100	5700	1.32	46
6	*t*BuA	21.5	12 600	13 100	1.17	97
9	*t*BuA	21.5	12 800	13 600	1.12	98
16	*t*BuA	4	12 300	12 400	1.08	97

[a] Polymerisation run in 1 : 1 monomer : dioxane.

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Notes and references

‡ *Typical experimental procedure*. To a round bottomed flask, equipped with a stirrer bar, was added thiol, solvent and base. The mixture was allowed to stir and the CS_2 added and then the alkyl halide. The reaction was then monitored by TLC (with reaction times ranging from 1 min to 13 h. The reaction mixture was filtered and solvent removed under vacuum to afford a yellow oil/solid which was purified by column chromatography.

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