Pergamon

Tetrahedron Letters 43 (2002) 6811–6814

TETRAHEDRON LETTERS

Multiarm organic compounds for use as reversible chain-transfer agents in living radical polymerizations

Roshan T. A. Mayadunne,* Graeme Moad and Ezio Rizzardo

Cooperative Research Center for Polymers, CSIRO Molecular Science, Bag 10, Clayton South, Victoria 3169, Australia

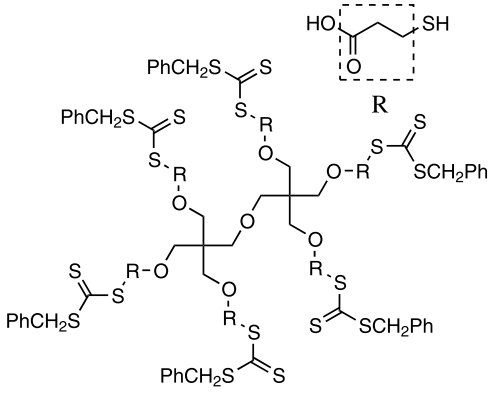
Received 24 April 2002; accepted 19 July 2002

Abstract—Generic approaches to the synthesis of multi-thiocarbonyl thio compounds are described. A multi-hydroxy core was condensed with either α-bromophenyl acetic acid or 2-mercaptopropanoic acid in the presence of *p*-toluenesulfonic acid catalyst to afford the corresponding esters in quantitative yield. Treatment of the bromo esters with sodium methyl trithiocarbonate or the thiols with carbon disulfide, benzyl bromide and triethylamine then affords two series of trithiocarbonates. The process is exemplified by application to mono, di- or tri-pentaerythritol. These multi-thiocarbonyl thio compounds have application as chain-transfer agents in reversible addition fragmentation chain-transfer (RAFT) polymerization as precursors to star polymers.

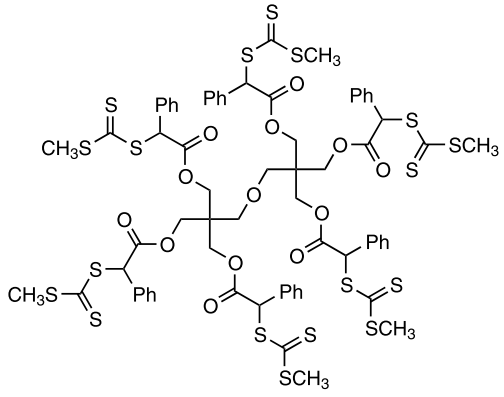
Star polymers see increasingly widespread application as, for example, rheology control agents, dispersants, toughening agents, thermoplastic elastomers, membranes, and drug delivery systems.[1] As a consequence, efficient methods of construction of these multi-armed polymers and their precursors are highly sought after.

Radical polymerization with reversible addition fragmentation chain-transfer (RAFT polymerization) is the latest addition to the polymer chemist's armoury of techniques[2] for the preparation of polymers with precisely controlled molecular weight, narrow molecular weight distribution and designed architecture. Thiocarbonyl thio compounds such as dithioesters, dithiocarbamates and trithiocarbonates are the preferred reagents for RAFT polymerization.[3–8]

The synthesis of star polymers by RAFT polymerization requires an efficient synthesis of multi thiocarbonyl thio compounds for use as RAFT agents. Previously[5,8] we and others[9] have accessed these structures via commercially available multi-thiols or multi-halides. However, only a limited range of compounds is available by these routes.



1



2

* Corresponding author. Tel.: +61 3 9545 8138; fax: +61 3 9545 2446; e-mail: roshan.mayadunne@molsci.csiro.au

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)01497-1

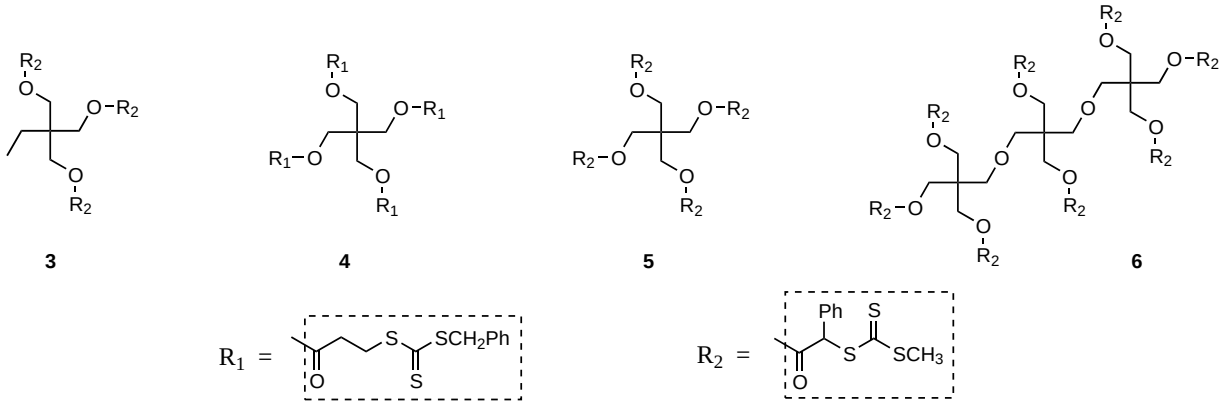


Table 1.

Compound	Number of arms	% Yield (first step)	% Overall yield[a]
1	Six (type 1)	Quantitative	86
2	Six (type 2)	>95	58
3	Three (type 2)	Quantitative	73
4	Four (type 2)	>97	73
5	Four (type 1)	>96	76
6	Eight (type 2)	Quantitative	87

[a] Isolated yield based on the hydroxy functional cores and are unoptimized.

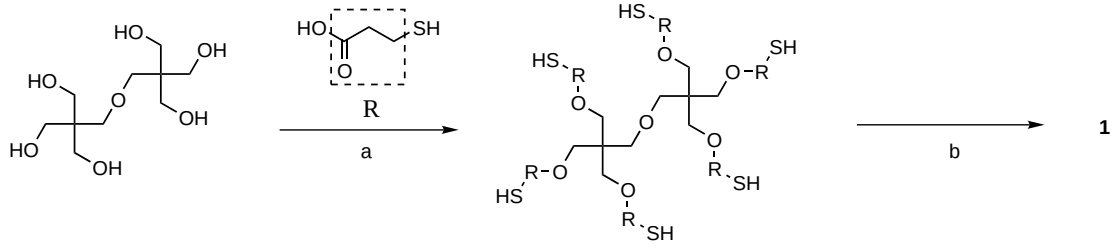
This paper reports the preparation of multi arm trithiocarbonate RAFT agents (e.g. **1** and **2**) in high yield from inexpensive commercially available precursors. The method developed involves classical condensation chemistry in which hydroxy functionalized cores are condensed with carboxylic acids in the presence of an acid catalyst. To our knowledge this approach has not previously been applied to the preparation of star polymer precursors and is far more efficient than previously reported routes.[10,11] The use of the RAFT agents **1**–**6** in the preparation of star polymers will be detailed in a forthcoming paper.

The two series of trithiocarbonate RAFT agents prepared in this work differ in that compounds such as **2** possess a free radical leaving group (substituted benzyl) between the core and a thiocarbonyl thio group (type 2: see Table 1). In compounds such as **1**, the free radical leaving group (benzyl) is separated from the core by a thiocarbonylthio group (type 1: see Table 1). Note that methyl and primary alkyl are poor free radical leaving groups. This difference in structure determines whether the polymer chains formed during RAFT polymerization grow attached to or separate from the core.[5]

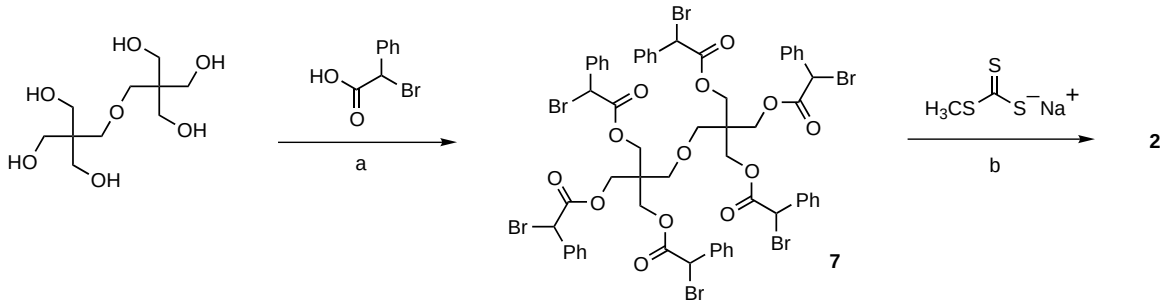
The challenge in preparing such multifunctional molecules lies with developing reactions that proceed in quantitative yield and produce no by-products. Whereas incomplete reaction or side reactions in the case of a monofunctional compound will give residual starting materials or a by-product to be removed, in the case of multifunctional compounds, such process lead to molecules with incomplete functionality. For example, in the case of an 8-armed product, a yield of 95% for an individual functionalization step would mean that <70% of the product would contain the requisite number of arms. Purification of mixtures of cores with differing levels of functionality is extremely difficult and the process then becomes unviable.

The classical condensation reaction is preferred over methods making use of coupling agents (e.g. DCC) or acid halide/anhydrides as it requires less stringent reaction conditions and is more readily taken to complete conversion. Inexpensive reagents and the ease with which the process can be carried out also offer tangible commercial advantages. We envisage the present route might be readily adapted to prepare precursors for other forms of controlled radical polymerization. In atom-transfer radical polymerization (ATRP) multihalo compounds are used as cores (compound **7** might be used to initiate ATRP directly). These have been prepared from multi-hydroxy compounds by reaction with appropriate acid bromides[10] or anhydrides[11] as reagents. Only low yields were reported.

The six arm trithiocarbonate **1** and its variant **5** were synthesized[12] by condensing the appropriate core (penta-



Scheme 1. *Reagents and conditions*: (a) *p*-TsOH, toluene, 110°C, 6 h; (b) CS_2, Et_3N, $PhCH_2Br$, rt, THF.[12]



Scheme 2. *Reagents and conditions*: (a) *p*-TsOH, toluene, 110°C, 6 h; (b) EtOAc, rt.[13]

erythritol and dipentaerythritol for the four and six arms, respectively) with 2-mercaptopropanoic acid in the presence of *p*-toluenesulfonic acid as a catalyst (Scheme 1). The reaction was carried out in toluene at reflux with Dean–Stark water separation. The intermediate tetra- or hexamercapto derivatives were obtained in near quantitative yield. These mercapto derivatives were converted to the desired multi-trithiocarbonate derivatives by treatment with carbon disulfide, triethylamine and benzyl bromide.

Multi arm chain-transfer agents **2**, **3**, **4**, and **6** were prepared[13] similarly (Scheme 2). α-Bromophenylacetic acid was condensed with the appropriate core to form tri, tetra, hexa, and octa bromo derivatives in high isolated yield (see Table 1). The purified bromo derivatives were subsequently treated with freshly prepared sodium methyl trithiocarbonate[14] (prepared from sodium methyl thiolate and carbon disulfide) in ethyl acetate to afford the macromolecule **2** and the variants **3**, **4**, and **6** as yellow oils.

Non-esterified arms, if any, in the reaction products are clearly distinguishable in the ^{1}H NMR spectra. The methylene groups α to the hydroxy groups of the starting cores appear at δ 3.45. Complete disappearance of this signal from the NMR spectrum of the crude mixtures and the appearance of a sharp singlet at δ 4.20, integrating to the expected number of protons was observed in each case confirming the completeness of the reaction.

Final proof of the completeness of the reaction comes from analysis of the star polymers prepared using type 1 as RAFT agents (e.g. **1** and **5**). The arms of these star polymers can be cleaved at the core (trithiocarbonate link) to result in linear polymer (the arms). The fact that the polydispersity of the resulting polymer remained similar to that of the starting material (consistent propagation at each arm) and the molecular weight was equal to the molecular weight of the original star polymer divided by the number of arms confirms that each arm of the RAFT agent was composed of a thiocarbonyl thio group.

In conclusion, organic molecules having three, four, six and eight arms, each functionalized with a trithiocarbonate moiety have been synthesized for use as chain-transfer agents in RAFT polymerization. These products are obtained in high yields using convenient reaction conditions and inexpensive commercially available substrates and reagents. The present route is readily adapted to the synthesis of initiators for other controlled radical polymerization methods, e.g. ATRP.

The use of these multi arm RAFT agents in the preparation of star polymers will be the subject of a forthcoming paper.

References

1. (a) Mishra, M. K.; Kobayashi, S. *Star and Hyperbranched Polymers*; Marcel Dekker: New York, 1999; (b) Mishra, M. K.; Shirodkar, S. M.; Jung, A. K. PCT Int. Appl. WO96-US753 19960122; (c) Bennett, S. L.; Jiang, Y.; Gruskin, E. A.; Connolly, K. M. Eur. Pat. Appl. EP693294 A2 19960124, EP 95-111520 19950721; *Chem. Abstr.* **1996**, *124*, 242385; (d) Hoxmeier, R. J.; Spence, B. A.; Southwick, J. G. US 5461116 A 19951024; *Chem. Abstr.* **1996**, *124*, 58780; (e) Spinelli, H. J. Eur. Pat. Appl. EP420686 A2 19910403.
2. Matyjaszewski, K. Comparison and classification of controlled/living radical polymerization. In *Controlled Radical Polymerization*; Matyjaszewski, K., Ed.; ACS Publishing: Washington, DC, 2000, ACS Symposium Series #768, pp. 2–26.
3. (a) Le, T. P.; Moad, G.; Rizzardo, E.; Thang, S. H. PCT Int. Appl. WO9801478 A1 980115; *Chem. Abstr.* **1998**, *128*, 115390; (b) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559–5562.
4. Chiefari, J.; Mayadunne, R. T. A.; Moad, G.; Rizzardo, E.; Thang, S. H. PCT Int. Appl. WO 31144; *Chem. Abstr.* **1999**, *131*, 45250.
5. Rizzardo, E.; Chiefari, J.; Mayadunne, R. T. A.; Moad, G.; Thang, S. H. Synthesis of defined polymers by reversible addition—fragmentation chain-transfer: the RAFT process. In *Controlled Radical Polymerization*; Matyjaszewski, K., Ed.; ACS Publishing: Washington, DC, 2000, ACS Symposium Series #768, pp. 278–296.
6. Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Chong, Y. K.; Moad, G.; Thang, S. H. *Macromolecules* **1999**, *32*, 6977–6980.
7. Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Krstina, J.; Moad, G.; Postma, A.; Thang, S. H. *Macromolecules* **2000**, *33*, 243–245.

8. Moad, G.; Chiefari, J.; Chong, Y. K.; Krstina, J.; Mayadunne, R. T. A.; Postma, A.; Rizzardo, E.; Thang, S. H. *Polymer Int*. **2000**, *49*, 993–1001.
9. Stenzel-Rosenbaum, M.; Davis, T. P.; Chen, V.; Fane, A. G. *J. Pol. Sci., Part A* **2001**, *39*, 2777–2783.
10. Matyjaszewski, K.; Miller, P. J.; Pyun, J.; Kickelbick, G.; Diamanti, S. *Macromolecules* **1999**, *32*, 6526–6535.
11. Ohno, K.; Wong, B.; Haddleton, D. M. *J. Polym. Sci., Part A* **2001**, *39*, 2206–2214.
12. Preparation of dipentaerythritolhexakis(3-(*S*-benzyltrithiocarbonyl) propionate) (**1**): Dipentaerythritol (1.27 g, 5 mmol), 2-mercaptopropanoic acid (4.78 g, 45 mmol) in the presence of a catalytic amount of *p*-toluene sulfonic acid (~100 mg) was heated to reflux in toluene until the theoretical amount of water was collected (overnight). The reaction mixture was poured into 100 mL of saturated $NaHCO_3$, extracted with 3×100 mL $CHCl_3$. The solution of combined extracts was washed with 10% HCl, saturated NaCl solution and dried with $MgSO_4$. The solids were filtered from the heterogeneous mixture and the solvent evaporated. The product was used in the next step without purification. Triethylamine (6.06 g in 20 mL) in $CHCl_3$ was added to a stirred solution of the hexamercapto derivative (3.91 g, 5 mmol), and carbon disulfide (4.56 g, 60 mmol) in $CHCl_3$ (20 mL) at room temperature. The solution was allowed to stir for 1 h before benzyl bromide (5.64 g, 33 mmol) was added. The mixture was stirred for 2 h, poured into a cold solution of aqueous 10% HCl, and extracted three times with ethyl acetate (3×50 mL) to afford a thick yellow oil. The crude product was purified by column chromatography using 30% ethyl acetate in petroleum spirits to afford the six arm chain-transfer agent (7.63 g) in 86% yield. ^{1}H NMR δ 2.8 (12H), 3.4 (4H), 3.6 (12H), 4.2 (12H), 4.6 (12H), 7.3 (30H). ^{13}C NMR δ 9.4, 31.2, 33.0, 41.5, 45.9, 62.6, 127.8, 128.7, 129.3, 134.7, 170.8, 223.4.
13. Preparation of dipentaerythritolhexakis(phenyl-*S*-methyl trithiocarbonyl methanoate) (**2**): Dipentaerythritol (1.27 g, 5 mmol), α-bromophenyl acetic acid (9.68 g, 45 mmol) and *p*-toluenesulfonic acid (200 mg) in toluene (50 mL) were heated to reflux for 16 h. The water formed was collected using a Dean–Stark apparatus fitted to the round bottom flask. Toluene was removed from the reaction mixture under reduced pressure and the residue purified by column chromatography (20% ethyl acetate in petroleum spirits) to obtain the hexabromo product in 95% yield. The bromo derivative (4.6 g) in 5 mL of ethyl acetate was added to freshly prepared sodium methyl trithiocarbonate (45 mmol) in 10 mL of ethyl acetate at room temperature. The solution was allowed to stir for 4 h and quenched with satd NaCl (25 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL), the combine organic layer washed with 10% HCl (50 mL), dried with $MgSO_4$, filtered and the solvent removed. The residue was purified by column chromatography using 0.1% ethyl acetate in benzene to afford the six arm trithiocarbonate chain-transfer agent (2.86 g) in 61% yield. ^{1}H NMR δ 2.7 (18H), 3.0 (4H), 3.9 (12H), 5.8 (6H), 7.4 (30H). ^{13}C NMR δ 20.4, 43.5, 58.0, 63.3, 69.0, 96.1, 128.8, 129.1, 129.2, 132.9, 168.0, 222.0.
14. Preparation of sodium methyl trithiocarbonate: Carbon disulfide (9.1 g, 0.12 mol) in diethyl ether (100 mL) was added dropwise over 30 min to a suspension of sodium methane thiolate (7 g, 0.1 mol) in diethyl ether (300 mL) at room temperature. The solution was stirred for 2 h and used in the above reactions. Alternatively, to isolate the title compound, the solvent was removed and the residue extracted three times with ethyl acetate to afford the product (13.4 g, 92%). The crude product was sufficiently pure (by ^{1}H NMR) to be used without further purification.