Triazole-Based Leaving Group for RAFT-Mediated Polymerization Synthesized via the Cu-Mediated Huisgen 1,3-Dipolar Cycloaddition Reaction

Niels Akeroyd,[†] Rueben Pfukwa,[†] and Bert Klumperman*[,†,‡]

Department of Chemistry and Polymer Science University of Stellenbosch, Private Bag X1, Matieland 7602, South Africa, and Laboratory of Polymer Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands

Received December 23, 2008; Revised Manuscript Received February 9, 2009

ABSTRACT: A new RAFT agent leaving group based on a triazole moiety is introduced. The triazole moiety plays an active role in the stabilization of the intermediate radical, comparable to the phenyl group in a benzyl leaving group. The newly developed leaving group allows easy conjugation to a large variety of substrates where the triazole linking group is hydrolytically stable. Good control is reported in the polymerizations of vinyl acetate, *N*-vinylpyrrolidone, *n*-butyl acrylate, and styrene. The versatility of the method is exemplified by linking the triazole to a phenyl and to an oligosaccharide substrate. Overall, this new RAFT agent leaving group is a useful addition to the limited set of leaving groups reported in literature.

Introduction

The field of polymer science is currently at a level where many desired functionalities can be designed and built into macromolecular architectures. The controlled polymerization of vinyl monomers is often combined with a variety of additional chemical transformations.[1] This leads to all sorts of possibilities toward the synthesis of polymer brushes, chain-end-functional polymers, block copolymers, and so on. In a fairly large number of cases, reversible addition−fragmentation chain transfer (RAFT)-mediated polymerization[2] is used to conduct the controlled polymerization of vinyl monomers. To link the vinyl polymer to a substrate, esterification via the leaving group of the RAFT agent is used in the overriding number of cases.[3] This induces a hydrolyzable link, which is not always desirable.

Here we report the use of a new RAFT agent leaving group that possesses all of the desired properties of a leaving group and is easily linked to a variety of substrates. These substrates may be small organic molecules, polymers, or naturally occurring compounds such as proteins, (poly)saccharides, and so on. In addition, the link to those substrates is aromatic in nature and is therefore extremely stable. The general synthetic approach is depicted in Scheme 1. In brief, the precursor of the RAFT agent is synthesized via the addition of propargyl bromide to the potassium salt of the thiocarbonyl thio compound of choice. The alkyne is subsequently reacted in a Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition ("click chemistry")[4,5] with any azide functional substrate to create the leaving group. Because of the aromaticity of the triazole ring, the 4-methyl-1,2,3-triazole leaving group shows great similarity to the benzyl leaving group and is expected to be an appropriate leaving group for a variety of monomers. In some cases, additional stabilization of the leaving group radical is required. In those cases, an additional methyl substituent can be introduced by using 3-bromo-1-butyne instead of propargyl bromide. In a sense, the current study is related to the work of Thibault et al., who recently published the synthesis of a triazole-based vinyl monomer.[6] In their publication, they explain the effect of the aromatic character of the triazole motif on the reactivity of the vinyl monomer.

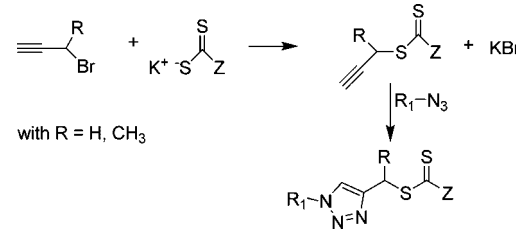
Experimental Section

Warning: Working with organic azides is potentially dangerous.[7] There has never been an incident in our laboratories while working with them, but care is needed.

Materials. Acetic anhydride, butanethiol, diethyl ether, DMF, ethyl acetate, HCl 32%, magnesium sulfate anhydrous, pentane, potassium hydroxide, pyridine, sodium nitrite, and THF were obtained from Merck (Saarchem, Wadeville, Gauteng, South Africa). Boron trifluoride diethyl etherate, sodium ascorbate, sodium azide, phosphorus tribromide, and sodium chloride were obtained from Aldrich (Sigma-Aldrich Chemie, Steinheim, Germany). Potassium ethyl xanthogenate, 80% propargyl bromide solution in toluene, phenylhydrazine, and silica gel 60 were obtained from Fluka (Sigma-Aldrich Chemie, Steinheim, Germany). Azo bis(isobutyronitrile) (AIBN) and carbon disulphide were obtained from Riedel-De Haën (Sigma-Aldrich Chemie, Steinheim, Germany). *n*-Butyl acrylate, methyl methacrylate, and styrene were obtained from Plascon Research Centre, University of Stellenbosch (purity 99% from ^{1}H NMR). Cavasol W7 M (Cyclodextrin) was obtained from Wacker Chemie AG, Burghausen Germany. All chemicals were used as received unless stated otherwise.

Characterization. NMR spectra were recorded on a Varian VXR 400 apparatus. All samples were prepared in $CDCl_3$ (Cambridge Isotope Laboratories). The SEC setup consisted of a Waters Alliance apparatus, a two-column set (Polymer Laboratories mixed C), and a dual wavelength UV detector (Waters, 2487) and a differential refractive−index detector (DRI) (Waters, 2414) in series. The injection volume was 100 μL, and the solvent was THF at a flow rate of 1.0 mL·min^{-1}. Data acquisition and processing were performed with Waters Breeze software. The calculated molar masses were based on a calibration curve for polystyrene standards (molar mass range: 650 to (1.5 × 10^6) g·mol^{-1}) of narrow

Scheme 1. General Synthetic Strategy for the Synthesis of RAFT Agents



* Corresponding author. E-mail: bklump@sun.ac.za.
† University of Stellenbosch.
‡ Eindhoven University of Technology.

10.1021/ma802846g CCC: $40.75
Published on Web 03/20/2009

polydispersity (Polymer Laboratories). SEC with DMF as a solvent was performed on the same system using Polymer Laboratories mixed D columns and DMF with 0.02 M LiCl as eluent at 0.7 mL/min and PMMA standards (molar mass range: 850 to (3.5×10^5)). ESI-MS was carried out on a Waters micromass Q-TOF Ultima API mass spectrometer with the following settings: sample introduction: 0.3 mL/min Waters Alliance 2690; injection: 10 μL; source: ESI+; MS settings: capillary voltage: 3.5 kV, cone voltage: 15, RF1: 40, source: 100 °C, desolvation temp: 400 °C, desolvation gas: 500 L/h, cone gas: 50 L/h.

Synthesis of 3-Bromobut-1-yne. 3-Butyne-2-ol (10 g, 0.143 mol) was placed in a 50 mL three-necked round-bottomed flask and cooled in an ice bath. Phosphorus tribromide (14.16 g, 0.052 mol) was added dropwise at 0 °C. After complete addition, the reaction was stirred at 0 °C for 2 h and at room temperature for 1 h. The mixture was poured in 100 mL of distilled water. The product was extracted three times with 50 mL of pentane, dried with anhydrous magnesium sulfate, filtered, and concentrated. The product was filtered over silica using pentane as an eluent. (Note: the product has a low boiling point. It is not possible to evaporate solvents with boiling points higher than 50 °C without losing the product. Use only pentane, not hexane or petroleum ether, as a replacement.) The obtained pentane fraction was concentrated, and the product was obtained as a colorless oil (yield: 12.5 g, 67%). ^{1}H NMR (δ): 1.91 CH_3 (d, $J = 7.04$, 3H), 2.62 CH (d, $J = 2.05$, 1H), 4.57 C*H*$-CH_3$ (dq, $J = 7.04$, 1H). ^{13}C NMR (δ): 22.54 CH_3, 34.36 *C*H$-CH_3$, 74.21 CH, 83.85 C.

Synthesis of Potassium Butyl Carbonotrithioate. Potassium hydroxide pellets were crushed in a mortar until a fine powder was obtained. Potassium hydroxide (6.70 g, 0.119 mol) and 150 mL of diethyl ether were placed in a three-necked round-bottomed flask. The suspension was stirred while being cooled in an ice bath. Butanethiol (9.00 g, 9.90×10^{-2} mol) in 50 mL of diethyl ether was added dropwise, and after complete addition, the reaction mixture was stirred for 1 h at 0 °C. (Note: Take extreme care when working with butanethiol.) Carbon disulphide (8.07 g, 0.106 mol) in 50 mL of diethyl ether was added dropwise (the suspension turns bright yellow upon the addition of a few drops) after complete addition, the ice bath was removed, and the reaction was stirred at room temperature for 2 h. The reaction mixture was poured in 500 mL of distilled water. (From this step on, working with the product is tricky. Everything the product touched has to stay in the fumehood because of the smell. Use two pairs of gloves to avoid getting the smell on your hands.) Extract the product to the water layer. The ether should be colorless after one or two extractions. The water was extracted three times with 150 mL of ethyl acetate. The product was dried with anhydrous magnesium sulfate, filtered, and concentrated. The product was obtained as yellow crystals. The crystals were dissolved in 100 mL of acetone, and the salts were filtered off and washed with some more acetone. The acetone was evaporated, and the product was obtained as yellow crystals (yield 17.9 g, 84%).

Synthesis of *O*-Ethyl *S*-Prop-2-ynyl Carbonodithioate. Potassium ethyl xanthogenate (1 g, 6×10^{-3} mol), propargyl bromide 80% solution in toluene (1.02 g, 7.00×10^{-3} mol), and THF (10 mL) were placed in a 25 mL round-bottomed flask covered in aluminum foil. The reaction mixture was stirred overnight at room temperature. A white precipitate was formed (KBr). This was filtered off, and the reaction mixture was diluted with 100 mL of water. The product was extracted with diethyl ether (3×50 mL). The ether layer was dried with anhydrous magnesium sulfate and concentrated. The product was purified using silica column chromatography with pentane as eluent. The product was dried overnight under vacuum and obtained as a pale-yellow oil (yield 0.81 g, 81% yield). ^{1}H NMR (δ): 1.41 CH_3 (t, $J = 7.26$, 3H), 2.21 CH (t, $J = 2.70$, 1H), 3.84 CH_2S (d, $J = 2.70$, 2H), 4.66 CH_2O (q, $J = 7.05$, 2H). ^{13}C NMR (δ): 13.64 CH_3, 24.26 CH_2S, 70.3 CH_2O, 71.55 CH, 77.62 C, 211.94 C=S.

Synthesis of Butyl Prop-2-ynyl Carbonotrithioate. Synthesis and purification were carried out as described for *O*-ethyl *S*-prop-2-ynyl carbonodithioate. The product was obtained as a bright-yellow oil in 79% yield. (The product is light-sensitive and can be kept in the freezer for only a limited amount of time.) ^{1}H NMR (δ): 0.94 CH_3 (t, $J = 7.36$, 3H), 1.44 CH_2-CH_3 (m, 2 H), 1.69 C$H_2-CH_2-CH_3$ (m, 2H), 2.24 CH (t, $J = 2.69$, 1H), 3.38 CH_2-CH_2-S (t $J = 7.40$, 2H), 4.11 C$-CH_2-$S (d, $J = 2.69$, 2H). ^{13}C NMR (δ): 13.54 CH_3, 21.99 *C*H_2-CH_3, 25.08 C$-CH_2-$S, 29.89 *C*H_2-CH_2-S, 36.89 CH_2-CH_2-S, 72.14 CH, 77.12 C, 221.62 C=S.

Synthesis of But-3-yn-2-yl Butyl Carbonotrithioate. Synthesis and purification were carried out as described for *O*-ethyl *S*-prop-2-ynyl carbonodithioate. The product was obtained as a bright-yellow oil in a 68% yield. (The product is light-sensitive and can be kept in the freezer for only a limited amount of time.) ^{1}H NMR (δ): 0.94 *C*H_3-CH_2, (t, $J = 7.34$, 3H), 1.44 CH_2-CH_3 (m, 2H), 1.63 *C*H_3-CH (d, $J = 7.34$, 3H), 1.69 C$H_2-CH_2-CH_3$ (m, 2H), 2.34 CH (t, $J = 2.64$, 1H), 3.37 S$-CH_2$ (t, $J = 7.63$, 2H), 4.90 S$-$C*H*$-CH_3$ (dq, $J = 7.04$, 1H). ^{13}C NMR (δ): 13.89 *C*H_3-CH_2, 21.42 *C*H_2-CH_3, 22.34 *C*H_3-CH, 30.24 *C*H_2-CH_2-S, 31.55 CH_2-S, 35.95 S$-$*C*H$-CH_3$, 71.98 CH, 82.77 C, 221.86 C=S.

Synthesis of Phenylazide. HCl 32% (6 mL) and water (20 mL) were placed in a 50 mL three-necked round-bottomed flask. The solution was cooled to 0 °C. Phenylhydrazine (3 mL, 3×10^{-2} mol) was added dropwise while the temperature was kept at 0−5 °C. Sodium nitrite solution (2.5 g, 3.6×10^{-2} mol in 3 mL of water) was added dropwise, and the temperature was kept at 0−5 °C. After the addition was completed, the mixture was stirred for 30 min at 0 °C. Water was added, and the product was extracted with diethyl ether (3×20 mL), dried with anhydrous magnesium sulfate, and concentrated. The product was purified by filtration over silica using pentane as the eluent. (A yellow band was collected, and an orange/brown band stayed behind.) The obtained solution was concentrated, and phenyl azide was obtained (yield: 2.8 g, 85%).

Synthesis of *O*-Ethyl *S*-[(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-methyl] Carbonodithioate (1). Phenylazide (0.27 g, 2.0×10^{-3} mol), *O*-ethyl *S*-prop-2-ynyl carbonodithioate (0.34 g, 2.0×10^{-3} mol), copper(II) sulfate·$5H_2O$ (0.05 g, 2×10^{-4} mol), sodium ascorbate (0.106 g, 5×10^{-4} mol), and 1 mL of DMF were mixed in a 25 mL round-bottomed flask and stirred overnight at RT. The product was purified by column chromatography. At first, pentane was used as an eluent to remove the impurities. After all of the impurities where removed (checked by TLC), the product was eluted using diethyl ether as eluent. The solvent was removed on a rotary evaporator, and the product was dried overnight under reduced pressure. *O*-Ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (**1**) was obtained as a yellow oil (yield: 0.42 g, 72%; purity: >95% (^{1}H NMR)). ^{1}H NMR (δ): 1.41, CH_3 (t, $J = 7.05$, 3H), 4.56 CH_2-S (d, $J = 0.42$, 2H), 4.66 O$-CH_2$, (q, $J = 7.05$, 2H), 7.40−7.45, para (m, 1H), 7.48−7.55, meta (m, 2H), 7.69−7.73, ortho (m, 2H), 8.02, CH triazole (s, 1H). ^{13}C NMR (δ): 13.8, CH_3, 30.72 CH_2-S, 70.45 O$-CH_2$, 120.48 ortho, 120.60, CH triazole, 128.78 para, 129.72 meta, 136.90 C phenyl, 144.1 C triazole, 213.68 C=S. ESI mass spectrometry: $M^{+1} = 280$ ($M = 279$).

Synthesis of Butyl(1-phenyl-1*H*-1,2,3-triazol-4-yl) Methyl Carbonotrithioate (2). Synthesis and purification were carried out as described for *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (**1**). The product was obtained as yellow crystals in 89% yield (purity: >95% (^{1}H NMR)). ^{1}H NMR (δ): 0.94 CH_3 (t, $J = 7.34$, 3H), 1.44 CH_2-CH_3 (sextet, $J = 7.34$, 2H), 1.70 C$H_2-CH_2-CH_3$ (pentet, $J = 7.34$, 2H), 3.39 S$-CH_2-CH_2$ (t, $J = 7.34$, 2H), 4.81 CH_2-S (s, 2H), 7.40−7.56 para and meta (m, 3H), 7.68−7.74 ortho (m, 2H), 7.97 CH triazole (s, 1H). ^{13}C NMR (δ): 13.81 CH_3, 22.29, *C*H_2-CH_3, 30.19 *C*$H_2-CH_2-CH_3$, 31.34 *C*H_2-S, 37.22, S$-$*C*H_2-CH_2, 120.80 ortho, 121.10 CH triazole, 129.05 para, 129.96 meta, 137.15 C phenyl, 143.89 C triazole, 223.67 C=S. ESI mass spectrometry: $M^{+1} = 324$ ($M = 323$).

Synthesis of Butyl(1-phenyl-*1H*-1,2,3-triazol-4-yl) Ethan-1-yl Carbonotrithioate (3). Synthesis and purification were carried out as described for *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)-methyl] carbonodithioate (**1**). The product was obtained as yellow crystals in 76% yield (purity: >95% (^{1}H NMR)). ^{1}H NMR (δ): 0.94

CH_3-CH_2 (t, J =7.34, 3H), 1.41 CH_2-CH_3 (m, 2H), 1.67 $CH_2-CH_2-CH_3$ (m, 2H), 1.90 CH_3-CH (d, J = 7.19, 3H), 3.36 $S-CH_2$ (t, J = 7.48, 2H), 5.57 CH−S (m, 1H), 7.38−7.55 para and meta (m, 3H), 7.68−7.75 ortho (m, 2H), 7.94 CH triazole (s, 1H). ^{13}C NMR (δ): 13.55 CH_3-CH_2, 19.72 CH_3-CH, 22.02 CH_2-CH_3, 29.93 $CH_2-CH_2-CH_3$, 36.58 $S-CH_2$, 41.21 CH−S, 119.66 ortho, 120.48 CH triazole, 128.71 para, 129.66 meta, 136.90 C phenyl, 148.48 C triazole, 222.73 C=S. ESI mass spectrometry: M^{+1} = 338 (M = 337).

Polymerization Experiments. Poly(vinyl acetate) was polymerized via RAFT using *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (**1**) ($M_{n,target}$ = 10 000 Da). Vinyl acetate (10 mL, 9.3 g, 0.108 mol), *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (0.246 g, 8.8×10^{-4} mol), and AIBN (0.031 g, 1.9×10^{-4} mol) were added to a Schlenk flask and degassed by six freeze−pump−thaw cycles. The polymerization was run for 10 h at 70 °C. A yellow viscous liquid was obtained; the polymer was precipitated from diethyl ether.

All of the polymerizations where carried out following the same protocol. The RAFT agent, monomer, and precipitation medium were changed as indicated. A RAFT-agent-to-initiator ratio of 5/1 was used. (Only for NVP, a ratio of 3/1 was used.)

Synthesis of *O*-Substituted Maltoheptaose. The synthesis was carried out as reported by Haddleton et al.[8] Briefly, 10 g of (partially methylated) cyclodextrin was acetylated using pyridine, acetic anhydride, and DMAP. NMR showed full acetylation of the hydroxyl groups of the partially methylated cyclodextrin. Yield: 11.04 g, 72%.

Acetylated cyclodextrin (5 g) was ring-opened using sulfuric acid and acetic anhydride. The product was purified via column chromatography using ethyl acetate/pentane 3/1 as the eluent. *O*-Acetyl maltoheptaose was obtained (yield: 4.87 g, 94%).

Synthesis of O-Substituted 1-*O*-2-Azido Ethyl Maltoheptaoside. The method of Sun et al.[9] was used. Briefly, 4.87 g of O-substituted maltoheptaose was stirred with 2-azido ethanol in dichloromethane at 0 °C. BF_3ET_2O was added dropwise. The mixture was first stirred for 1 h at 0 °C and then at room temperature overnight. Yield: 1.2 g, 19%.

Synthesis of O-Substituted *O*-Ethyl *S*-[1-(1-*O*-Maltoheptaoside)-1*H*-1,2,3 Triazole-4-yl] Dithiocarbonate (RAFT Agent 4). We mixed 1.2 g (5.59×10^{-4} mol) of O-substituted 1-*O*-2-azido ethyl maltoheptaoside (0.51 g, 2.29×10^{-3} mol), *O*-ethyl *S*-prop-2-ynyl carbonodithioate, copper sulfate·$5H_2O$ (0.014 g), sodium ascorbate (0.022 g, 1.12×10^{-4} mol), HMTETA (0.014 g, 6.15×10^{-5} mol), and 10 mL of THF at room temperature for 24 h. The product was purified using column chromatography with pentane/ethyl acetate 1/1 as the eluent. Yield: 0.38 g, 30%. ^{1}H NMR (δ) shows all of the sugar peaks, the $O-CH_2$ peak at 4.60, and the triazole peak at 7.60. ^{13}C NMR (δ): 12 CH_3, 128 CH triazole, 147 C triazole, 215 C=S. (CH_2-O was hidden by sugar peaks.)

Degradation Experiments. Polybutyl acrylate (50 mg) synthesized using RAFT agent **2** was dissolved in THF (2 mL). Water (1 mL) containing HCl or NaOH in different concentrations was added. The solutions where stirred at room temperature for 24 h. The polymer was precipitated from ice-cold methanol and dried in vacuo overnight. The polymer was redissolved in $CDCl_3$ and analyzed with ^{1}H NMR to confirm the presence of the phenyl end group.

Results and Discussion

Xanthate RAFT agents are known to control vinyl acetate (VAc) polymerizations.[10] *O*-Ethyl *S*-(1-phenyl-1-*H*-1,2,3-triazol-4-yl) methyl carbonodithioate (**1**) was synthesized by click chemistry from a propargyl xanthate RAFT agent precursor and phenyl azide. It was subsequently used as a RAFT agent for the polymerization of VAc.

The polymerization of VAc with RAFT agent **1** at 70 °C yielded an adequately controlled polymer. After 9 h, the conversion was 38%. The agreement between experimental and theoretical M_n was very good, and the PDI varied between 1.20 and 1.28. (See Figure 2.) The overlay of the size exclusion chromatography (SEC) curves from samples taken from the polymerization shows a clear shift toward lower elution volumes (not shown). This clearly shows that the (1-substituted-1-*H*-1,2,3-triazol-4-yl) methyl is a good leaving group for the RAFT-mediated polymerization of VAc. *N*-vinylpyrrolidone (NVP) was also polymerized using RAFT agent **1**. RAFT agent **1** shows good control over the polymerization with the experimental M_n corresponding well with the theoretical M_n and a PDI of 1.16. (See Table 1.)

Trithiocarbonates have been used in RAFT polymerizations for a variety of monomers.[11] Butyl(1-phenyl-1-*H*-1,2,3,-triazol-4-yl) methyl carbonotrithioate (**2**) was synthesized from butyl propargyl trithiocarbonate and the appropriate azide. It was subsequently used as a RAFT agent in the polymerization of styrene (STY) and butyl acrylate (nBA). RAFT agent **2** shows good control over the polymerization of nBA, the theoretical and experimental M_n correspond well, and the PDI is 1.11. (See

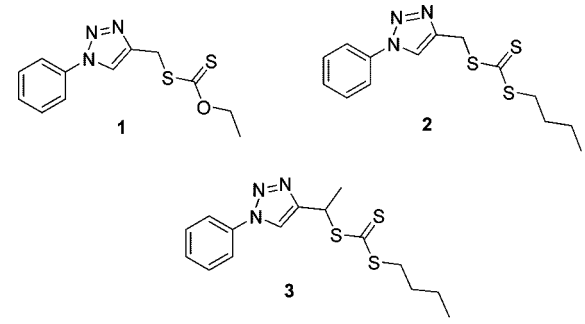


Figure 1. Structures of *O*-ethyl *S*-(1-phenyl-1-*H*-1,2,3-triazol-4-yl) methyl carbonodithioate (**1**), butyl(1-phenyl-1-*H*-1,2,3-triazol-4-yl) methyl carbonotrithioate (**2**), and butyl(1-phenyl-1-*H*-1,2,3-triazol-4-yl) ethan-1-yl carbonotrithioate (**3**).

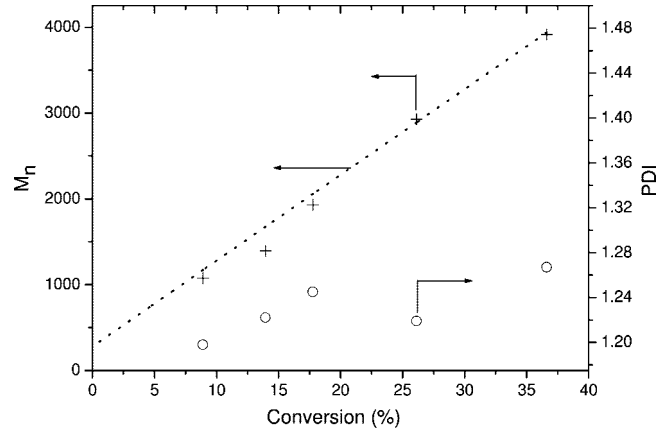


Figure 2. M_n and PDI versus conversion for the *O*-ethyl *S*-(1-phenyl-1-*H*-1,2,3-triazol-4-yl) methyl carbonodithioate (**1**)-mediated polymerization of VAc at 70 °C.

Table 1. SEC Results of Different Polymers Synthesized Using RAFT Agent 1, 2, and 3[a]

monomer	RAFT agent	$M_{n,theor}$ (Da)	$M_{n,exptl}$ (Da)[b]	PDI	conv (%)
VAc[c]	1	3940	3920	1.26	37
NVP[d]	1	4500	5400	1.16	45
STY[c]	2	8060	6990	1.43	53
STY[c]	3	7580	7120	1.14	54
nBA[c]	2	10 000	12 000	1.11	66
nBA[c]	3	800	1200	1.10	8

[a] Polymerizations were conducted for 10 h at 70 °C. [b] $M_{n,exptl}$ values are reported relative to the PSTY and PMMA standards, respectively. [c] SEC done on mixed C columns at 30 °C with THF (BHT-stabilized) flow rate of 1.0 mL/min using polystyrene standards. [d] SEC done on mixed D columns at 30 °C with DMF 0.020 M LiCl flow rate of 0.7 mL/min using PMMA standards.

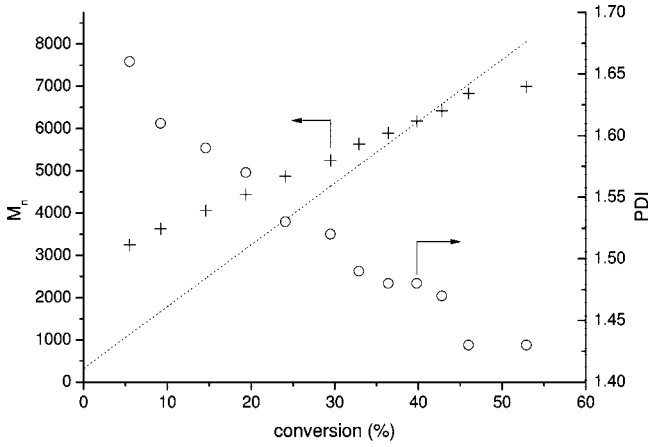


Figure 3. M_n and PDI versus conversion for the butyl(1-phenyl-1-*H*-1,2,3,-triazol-4-yl) methyl carbonotrithioate (**2**)-mediated polymerization of STY at 70 °C.

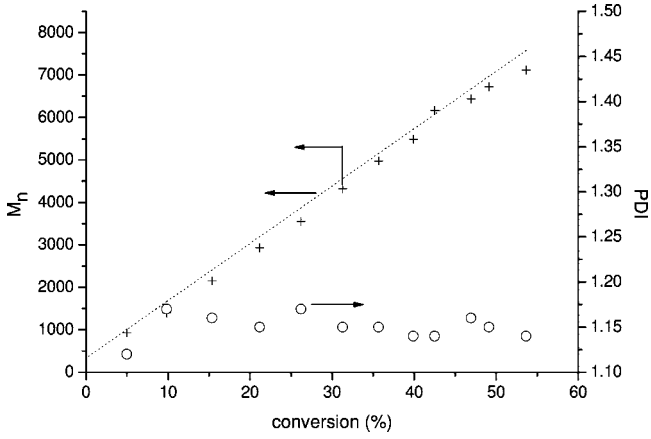


Figure 4. M_n and PDI versus conversion for the butyl(1-phenyl-1-*H*-1,2,3-triazol-4-yl)ethan-1-yl carbonotrithioate (**3**)-mediated polymerization of STY at 70 °C.

Table 2. Degradation Study Results Using Polybutyl Acrylate Polymerized with RAFT Agent 2

sample treated with	M_n (kDa)
before degradation	12.0
1 M NaOH	12.0
0.1 M NaOH	12.1
1 M HCl	12.0
0.1 M HCl	12.2

Table 1.) For the STY polymerization, the difference between experimental and theoretical M_n versus conversion values can be explained by a phenomenon called "hybrid behavior".[12] This behavior is caused by the slow conversion of the RAFT agent into polymer chains and the concomitant growth of the already initiated chains. The (1-substituted-1-*H*-1,2,3-triazol-4-yl) methyl leaving group is not the most favorable leaving group for STY polymerizations. However, trithiocarbonate **2** still shows control over the molecular weight distribution of polystyrene. At 55% conversion (12 h), the PDI has decreased to a value of 1.4, where the reaction was stopped because of high viscosity. (See Figure 3.)

The relatively poor control by the (1-substituted-1-*H*-1,2,3-triazol-4-yl)methyl leaving group is attributed to its slow fragmentation relative to the polystyrene macroradical. To improve this situation, a trithiocarbonate with the 1-substituted-1-*H*-1,2,3-triazol-4-yl)ethan-1-yl leaving group was synthesized (**3**).

Styrene was polymerized in bulk at 70 °C. As shown in Figure 4, this leaving group shows excellent control over the polymerization. As expected, the polymerization of methyl methacrylate (MMA) was not adequately controlled by RAFT agents **2** or **3** (results not shown). By analogy to the cumyl leaving group, a RAFT agent with a second methyl substituent on the α carbon of RAFT agent **3** is expected to control the polymerization of MMA.

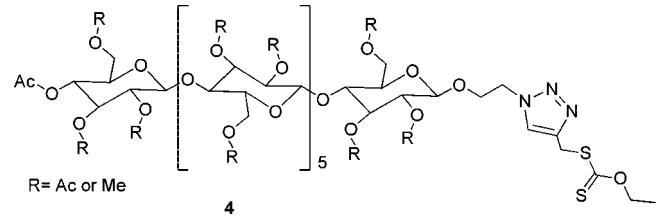


Figure 5. Structure of O-substituted *O*-ethyl *S*-[1-(1-*O*-maltoheptaoside)-1*H*-1,2,3 triazole-4-yl] dithiocarbonate (RAFT agent **4**).

The use of click chemistry in conjunction with RAFT-mediated polymerization has been reported several times before. In most cases, the triazole moiety is linked via an ester to the RAFT agent.[13,14] This is the first time that the triazole moiety fulfills the role of stabilizing the leaving group radical.

To analyze the stability of the triazole linker, we performed a degradation study. Polybutyl acrylate (50 mg) synthesized using RAFT agent **2** was dissolved in THF (2 mL). Water (1 mL) containing HCl or NaOH in different concentrations was added. The solutions were stirred at room temperature for 24 h. The polymer was analyzed with ^{1}H NMR to confirm the presence of the phenyl end group. Table 2 shows the results of the degradation studies.

M_n was calculated using the phenyl para and meta signal at 7.4 ppm and the *n*-butyl acrylate CH_3 at 0.9 ppm. Loss of the phenyl end group would lead to an overestimation of the molar mass because it would induce an apparent reduction in the number of chains. The absence of any change in molar mass is clear evidence of the anticipated stability of the triazole link.

An O-substituted maltoheptaose was prepared by a method based on that reported by Haddelton et al.[8] The substitution was partially methyl and partially acetyl because of the partial methylation of the starting material. The resulting sugar was azide-functionalized using the method by Sun et al.[9] to obtain the O-substituted 1-*O*-2-azido ethyl maltoheptaoside. This azide was reacted with *O*-ethyl S-prop-2-ynyl carbonodithioate to yield O-substituted *O*-ethyl *S*-[1-(1-*O*-maltoheptaoside)-1*H*-1,2,3 triazole-4-yl] dithiocarbonate RAFT agent **4** (Figure 5).

RAFT agent **4** was used for the polymerization of NVP. SEC measurements against PMMA standards reveal an $M_{n,exptl}$ of 6.6 kDa and a PDI of 1.16 at 36% monomer conversion ($M_{n,theor}$ = 12.4 kDa). The large discrepancy between $M_{n,exptl}$ and $M_{n,theor}$ is due to the difference in hydrodynamic volume between PMMA and the sugar−PVP block copolymer. Molar mass calculated from ^{1}H NMR shows that $M_{n,NMR}$ = 14.2 kDa, which is in satisfactory agreement with $M_{n,theor}$.

Conclusions

The (1,2,3-triazol-4-yl)methyl leaving group shows great potential in RAFT polymerization. Because of the straightforward synthesis and the availability of starting materials, it can be easily implemented for the conversion of, for example, bromides and primary amines into RAFT agents. Especially in the polymerization of VAc, NVP, and nBA, the (1-substituted-1-*H*-1,2,3-triazol-4-yl) methyl leaving group showed good control over the molecular weight and PDI. For STY, the (1-substituted-1-*H*-1,2,3-triazole-4-yl) ethan-1-yl leaving group is needed. Overall, we present here a new, versatile, and easy route for the synthesis of RAFT agents. The full scope of this class of RAFT agents is currently under investigation in our labora-

tories. We are looking at various substrates, including polymeric ones, for the click chemistry with our propargyl functional RAFT agent precursors.

Acknowledgment. We thank Gareth Bayley for SEC, Elsa Malherbe and Jean M. McKenzie for NMR, and Marietjie Stander for ESI-MS. DPI is thanked for funding. B.K. acknowledges support by the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation.

References and Notes

(1) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200–1205.
(2) Chiefari, J.; Chong, Y. K. B.; 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.
(3) Perrier, S.; Takolpuckdee, P.; Westwood, J.; Lewis, D. M. *Macromolecules* **2004**, *37*, 2709–2717.
(4) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
(5) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
(6) Thibault, R. J.; Takizawa, K.; Lowenheilm, P.; Helms, B.; Mynar, J. L.; Frechet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 12084–12085.
(7) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240.
(8) Haddleton, D. M.; Ohno, K. *Biomacromolecules* **2000**, *1*, 152–156.
(9) Sun, X.-L.; Grande, D.; Baskaran, S.; Hanson, S. R.; Chaikof, E. L. *Biomacromolecules* **2002**, *3*, 1065–1070.
(10) Stenzel, M. H.; Davis, T. P.; Barner-Kowollik, C. *Chem. Commun.* **2004**, 1546–1547.
(11) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Krstina, J.; Moad, G.; Postma, A.; Thang, S. H. *Macromolecules* **2000**, *33*, 243–245.
(12) Barner-Kowollik, C.; Quinn, J. F.; Nguyen, U. L.; Heuts, J. P. A.; Davis, T. P. *Macromolecules* **2001**, *34*, 7849–7857.
(13) Bernard, J.; Save, M.; Arathoon, B.; Charleux, B. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 2845–2857.
(14) Gondi, S. R.; Vogt, A. P.; Sumerlin, B. S. *Macromolecules* **2007**, *40*, 474–481.

MA802846G