Polymer xxx (2015) 1–7

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Debromination of ATRP-made Wang soluble polymer supports

Laurence Oswald, Thanh Tam Trinh, Delphine Chan-Seng, Jean-François Lutz*

Precision Macromolecular Chemistry, Institut Charles Sadron, UPR-22 CNRS, 23 rue du Loess, 67034 Strasbourg, France

ARTICLE INFO

Article history:
Received 26 January 2015
Received in revised form
24 February 2015
Accepted 28 February 2015
Available online xxx

Dedicated to Prof. Krzysztof 'Kris' Matyjaszewski in honor of his 65th birthday.

Keywords:
Soluble polymer supports
Controlled radical polymerization
Atom transfer radical polymerization

ABSTRACT

This article describes two convenient methods for removing the ω-terminal bromine atom of well-defined soluble polymer supports prepared by atom transfer radical polymerization (ATRP). The targeted soluble supports are linear polystyrene chains that contain an acid-labile p-alkoxybenzyl ester linker (i.e. Wang linker) at their α-chain end. These polymers are synthesized by ATRP using a fluorenylmethoxycarbonyl (Fmoc)-protected amino functional ATRP initiator, namely 3-(Fmoc-amino)propyl 2-bromoisobutyrate. After polymerization and before Wang functionalization, the bromine-atom of the ATRP-made soluble supports was removed. Two different debromination approaches were considered. The first one consists in reducing the terminal alkyl bromide in the presence of a trialkyltin hydride. This method can be applied directly in the ATRP medium at the end of the polymerization or can be performed on a purified polymer sample. The latter conditions were found to be more suitable. It was also observed that the use of tributyltin hydride in the absence of additional radical initiator led to the best results. Indeed, well-defined polymer supports with controlled chain-length, molecular weight distribution and fully dehalogenated chain-ends were obtained. The second dehalogenation approach consisted in removing the terminal bromide by nucleophilic substitution with sodium azide. Afterwards, the formed terminal azide group was reacted with 1-pentyne by copper-catalyzed azide-alkyne 1, 3-dipolar Huisgen cycloaddition. This method was also found to be valid for preparing bromine-free polystyrene supports. After ω-chain-end debromination, Fmoc-deprotection was performed on the α-chain-end and the resulting amine function was reacted with 4-(hydroxymethyl)phenoxyacetic acid. Further esterification of the Wang linker is also possible.

1. Introduction

Soluble polymer supports are an interesting alternative to traditional crosslinked polymer resins for polymer-supported catalysis and synthesis [1,2]. Such supports are linear, branched or dendritic macromolecules, to which are covalently attached catalysts or reagents. They can be solubilized in a liquid medium and used for homogeneous chemistry. After reaction, the polymer support is precipitated in a non-solvent, filtered and can be potentially re-used. Thus, this method elegantly combines the efficacy of solution chemistry and the handiness of solid-phase chemistry. As reviewed by Janda and coworkers [1,2], soluble polymer supports have been widely used in supported catalysis, organic chemistry and iterative oligomer synthesis. In the latter case, they have been successfully used for peptide [3], oligosaccharide [4] and oligonucleotide [5] synthesis [1]. More recently, soluble polymer supports have been used by our group [6] and others [7,8] to prepare non-natural sequence-defined polymers [9–11].

Soluble polymer supports can be hydrophilic or solvophilic and can be prepared by a variety of polymerization methods. However, many supports that have been described in the literature exhibit ill-defined molecular structures, i.e. broad molecular distributions and uncontrolled architectures. The current state-of-the-art in polymer synthesis allows undoubtedly preparation of better-defined polymers. For instance, controlled radical polymerization methods such as nitroxide mediated polymerization (NMP) [12], atom transfer radical polymerization (ATRP) [13,14] and reversible addition–-fragmentation chain-transfer (RAFT) [15] polymerization allow synthesis of tailor-made polymers with controlled chain-length, molecular weight distribution, topology [16–19], microstructure [20–24] and chain-ends [25]. Janda and coworkers have reported the NMP synthesis of well-defined block and graft soluble supports [26]. Our group has also described the ATRP synthesis of

* Corresponding author.
E-mail address: jflutz@unistra.fr (J.-F. Lutz).

http://dx.doi.org/10.1016/j.polymer.2015.02.057
0032-3861/

polystyrene soluble supports containing acid-labile Wang [6,27] and Rink [28] linkers. These polymers are typically prepared using functional ATRP initiators that are eventually modified after polymerization. It was shown that these supports made by ATRP are very useful for peptide synthesis [29], peptide PEGylation [30] and also for the synthesis of non-natural sequence-encoded polymers [6]. However, due to the ATRP mechanism [31,32], these polystyrene supports possess a bromine atom at the ω-chain-end. In our previous studies [6,29], this halogen moiety was kept on the support and was not found to promote noticeable side reactions in iterative synthesis. Yet, in some other syntheses, e.g. in iterative approaches involving radical reactions, the presence of a bromine atom might be a source of problems. Thus, the debromination of ATRP-made Wang soluble supports was studied in the present work. In particular, two different routes were studied to remove bromine atoms from the ω-chain-end of the supports. The first approach was inspired by the work of Coessens and Matyjaszewski on polymer dehalogenation using trialkyltin hydride [33]. It was shown in the 1960's by Kuivila and coworkers that organotin hydride lead to the reduction of alkyl halide via a radical mechanism [34–36]. This reaction is very useful for the debromination of ATRP polymers and was therefore tested in the present work. In the second approach, the bromine atom was removed by nucleophilic substitution with sodium azide [37,38]. The formed reactive azide function was afterwards quenched by copper-catalyzed azide-alkyne Huisgen cycloaddition [38–40]. The validity of these two methods was studied on model Wang polystyrene supports. Size exclusion chromatography as well as ^{1}H and ^{13}C NMR were used to characterize the polymers before and after debromination.

2. Experimental part

2.1. Materials

Copper(I) bromide (CuBr, 98%, Sigma–Aldrich), 4,4'-di-*n*-nonyl-2,2'-bipyridine (dNbipy, 97%, Alfa Aesar), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), tributyltin hydride (97%, Aldrich), piperidine (99%, Alfa Aesar), *N*,*N*′-dicyclohexylcarbodiimide (DCC, 99%, Alfa Aesar), *N*-hydroxysuccinimide (NHS, 98%, Aldrich), 4-(hydroxymethyl)phenoxyacetic acid (HMPA, 98%, Aldrich), sodium azide (99%, Alfa Aesar), 1-pentyne (99%, Alfa Aesar), benzene (99%, Sigma–Aldrich), methanol (99.9%, Carlo Erba), tetrahydrofuran (THF, 99.5%, stabilized with BHT, Carlo Erba), *N*,*N*-dimethylformamide (DMF, 99.8%, Sigma–Aldrich), and dichloromethane (DCM, ≥99.9%, stabilized with amylene, Sigma Aldrich) were used as received. Styrene (S, Sigma–Aldrich, 99%) was distilled over CaH_2 (90–95%) under reduced pressure and stored under an argon atmosphere at −25 °C. CuBr was purified by stirring in acetic acid overnight, washing with ethanol, and drying under vacuum at RT. Anhydrous THF was obtained using a dry solvent station GT S100. 3-(Fmoc-amino)propyl 2-bromoisobutyrate was prepared as reported previously [29].

2.2. Example of in-situ debromination performed after ATRP using trialkyltin hydride

Copper(I) bromide (50 mg, 0.35 mmol, 1 eq.), dNbipy (0.28 g, 0.70 mmol, 2 eq.) and 3-(Fmoc-amino)propyl 2-bromoisobutyrate (155 mg, 0.35 mmol, 1 eq.) were placed in a round bottom flask equipped with a magnetic stirrer and sealed with a rubber septum. The mixture was degassed and purged with dry argon for 5 min. Then, degassed styrene (1.60 mL, 13.9 mmol, 40 eq.) was added using a degassed syringe and the flask was placed in an oil bath thermostated at 110 °C for 120 min. An aliquot was then taken in order to measure styrene conversion by NMR. Degassed benzene (1.5 mL) followed by tributyltin hydride (0.28 mL, 1.04 mmol, 3 eq.) were added using a degassed syringe and the flask was placed in an oil bath thermostated at 85 °C for 60 min. An aliquot was taken just after the addition of tributyltin hydride and another after 60 min. The polymer was then dissolved in THF (3 mL) and precipitated in cold methanol (150 mL) one time. The precipitate was collected by filtration, washed with methanol and dried under vacuum at RT overnight. The formed polymer was recovered as a white solid in 59% yield (0.92 g). The polymer was characterized by SEC in THF (M_n = 3000 g mol^{-1}, M_w/M_n = 1.09), ^{1}H and ^{13}C NMR.

2.3. General conditions for the ATRP synthesis of polystyrene **P1** and **P2**

Copper(I) bromide (1 eq.), dNbipy (2 eq.) and initiator 3-(Fmoc-amino)propyl 2-bromoisobutyrate (1 eq.) were placed in a round bottom flask equipped with a magnetic stirrer and sealed with a rubber septum. The mixture was degassed and purged with dry argon for 20 min. Then, degassed styrene (n eq.) was added using a degassed syringe and the flask was placed in an oil bath thermostated at 110 °C. During the polymerization, aliquots were withdrawn for ^{1}H NMR analysis to follow the conversion. In the case of **P1**, the reaction was stopped at moderate styrene conversion in order to avoid bimolecular termination and HBr elimination [32]. The formed polymers were then dissolved in THF and precipitated in cold methanol one or two times. The precipitate was collected by filtration, washed with methanol and dried under vacuum at RT overnight. The polymers were recovered as white solid powders and were characterized by SEC, ^{1}H and ^{13}C NMR (Table 1).

2.4. Post-polymerization debromination using tributyltin hydride

Polystyrene (Entry **P1** in Table 1, 8 g, 1.56 mmol, 1 eq.) was placed in a round bottom flask equipped with a magnetic stirrer and sealed with a rubber septum. The mixture was degassed and purged with dry argon for 20 min. Then, degassed benzene (25 mL) followed by tributyltin hydride (1.26 mL, 4.68 mmol, 3 eq.) were added using a degassed syringe and the flask was placed in an oil bath thermostated at 85 °C for 60 min. The polymer was then dissolved in $CHCl_3$ (5 mL) and precipitated in cold methanol (800 mL) one time. The precipitate was collected by filtration, washed with methanol and dried under vacuum at RT overnight. The modified polymer **P1**′ was recovered as a white solid in 96% yield (7.60 g) and was characterized by SEC in THF (M_n = 5100 g mol^{-1}, M_w/M_n = 1.11), ^{1}H and ^{13}C NMR.

2.5. Post-polymerization debromination using sodium azide

Polystyrene (Entry **P2** in Table 1, 0.5 g, 0.08 mmol, 1 eq.) was dissolved in 8 mL of DMF. Sodium azide (0.01 g, 0.16 mmol, 2 eq.) was added to the reaction flask. The reaction mixture was stirred overnight at RT. The reaction mixture was filtered and then

Table 1
Experimental conditions and molecular characterization of the ATRP polymers.

	M/I/CuBr/dNbipy[a]	*Conv.*$_S$[b]	DP_n	M_n th[c] [g mol^{-1}]	M_n[d] [g mol^{-1}]	M_w/M_n[d]
P1	90/1/1/2	0.52	47	5320	5100	1.11
P2	60/1/1/2	0.80	48	5445	5900	1.08

[a] The acronym I stands for initiator.
[b] Calculated from ^{1}H NMR spectra in $CDCl_3$.
[c] M_nth = M_I + M_S·conv.$_S$[S]/[I] where M_I and M_S are the molecular weights of initiator and styrene, respectively.
[d] Measured by SEC in THF.

Please cite this article in press as: Oswald L, et al., Debromination of ATRP-made Wang soluble polymer supports, Polymer (2015), http://dx.doi.org/10.1016/j.polymer.2015.02.057