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Practical Synthesis of Alkoxyamine Initiators for Living Radical Polymerization

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Abstract: Various alkoxyamine initiators for nitroxide mediated radical polymerization (NMRP) were prepared in high yields by a simple substitution reaction of nitroxide anions with benzyl bromide. The required nitroxide anions were easily generated by treating either nitroxide free radicals or hydroxy amine with an alkali metal such as sodium or potassium in THF. This method is both practical and efficient, since the ionic conditions prevent other side reactions from occurring, such as the self-coupling or oligomerization reactions that are observed in the case of radical trapping conditions. To demonstrate the utility of the resulting alkoxyamine initiators, *end-* and *telechelic*-alkoxyamine PEG macroinitiators derived from the alkoxyamines were synthesized by a simple chemical modification, and used for the preparation of PEG-*b*-PS and PS-*b*-PEG-*b*-PS block copolymers by NMRP.

Keywords: nitroxide mediated radical polymerization (NMRP), alkoxyamine initiator, polystyrene-*b*-poly(ethylene oxide) block copolymer.

Introduction

Since the seminal 'controlled living radical polymerization' protocols such as atom transfer radical polymerization (ATRP),[1] nitroxide mediated radical polymerization (NMRP),[2] and reversible addition-fragmentation chain transfer polymerization (RAFT)[3] were discovered, polymer chemistry has observed a renaissance expanding its area to nano-,[4] electronic,[5] and bio-[6] materials. These numerous applications of the controlled radical polymerization to such wide areas are mainly attributed to its mild reaction conditions and broad functional group tolerance compared to other living polymerization techniques known as conventional anionic and cationic polymerizations.

Among these, NMRP has unique advantages such as the well-understood polymerization mechanism, better impurity control, and versatile polymer architecture control over the other two methods. However, relatively complicate and difficult preparation methods for the necessary alkoxyamine initiators have limited its utility. The most representative styrenic initiators developed for NMRP are shown in Figure 1. The main synthetic pathways for these alkoxyamine derivatives involved either coupling of the stable nitroxide radicals with organometallic reagents[2b,7] or capture of the carbon-centered free radicals by stable nitroxide radicals.[8] Some other unique methodologies such as Meisenheimer rearrangement of allyl *N*-oxide,[9] use of $Mn(OAc)_3$ as an electron-transfer reagent,[10] and double trapping of carbon-centered radical with nitroso compound[11] are also reported. However, these methods are limited to certain specific initiators and require the use of expensive and/or sophisticated reagents. In addition, the radical trapping methods suffer from low yields mainly arising from the self-coupling of the radical species and oligomerization.

From this respect, we have been in search of a more practical and convenient method and found that reduction of the stable alkoxy-amine radical with alkali metal and the subsequent reaction with benzylic bromide provide the alkoxyamine initiators in high yields. Although alkylation at the oxygen of a bulky dialkyl nitroxide by generating anion and the subsequent alkylation with alkyl halide is a known procedure,[12] this method has not been scrutinized for access to the popular nitroxide initiators **1**-**3**[13] shown in Fig-

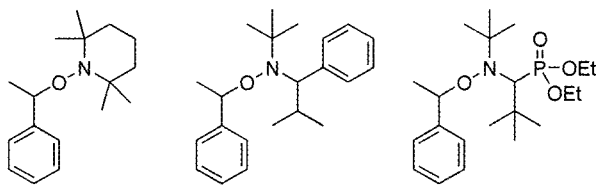

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Figure 1. Representative NMRP initiators.

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ure 1.

Here we report that the nucleophilic substitution of alkyl bromide with nitroxy anions generated by treatment of the stable nitroxy radicals with alkali metal provides an easy access to the corresponding nitroxide initiators and demonstrate the utility of the initiators by preparing polyethylene glycol-*b*-polystyrene (PEG-*b*-PS) block copolymers.

Experimental

General. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to tetramethylsilane peak (δ 0.00) or solvent peak (δ 7.27 for $CDCl_3$ in ^{1}H NMR, δ 77.2 for $CDCl_3$ in ^{13}C NMR). Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. Tandem gas chromatography/low resolution mass spectroscopy (GC/LRMS) using electron impact (EI) ionization were obtained with a Agilent 6890 series gas chromatography and a 5973N mass selective detector at 70 eV. THF and ethyl ether were distilled from sodium benzophenone ketyl. Dry methylene chloride was distilled from calcium hydride. *N,N*-dimethylformamide (DMF) was dried over 4 Å molecular sieves. 2,2,6,6-Tetramethyl-4-piperidinyloxy, free radical (TEMPO, free radical), mono-methoxy PEG (5,000 g/mol) and PEG (10,000 g/mol) were purchased from Aldrich. 2-Bromo-2-ethanol was prepared from styrene oxide by the known procedure in the literature.[14] All other chemicals were used as received otherwise specified.

Polymer Characterization. Polymer molecular weights were estimated using a Sykam GmbH GPC system equipped with a Sykam S1122 HPLC pump, a S5200 autosampler, a S3580 differential RI and a S3210 UV/VIS detectors, and three Jordi Gel DVB GPC columns (500 Å, 1,000 Å, 10,000 Å, 300 mm × 7.8 mm). The UV detector was set at 256 nm and $CHCl_3$ was used as an eluent at flow rate 1 mL/min. Seven standard polystyrenes (Polymer Laboratories) were used for the calibration: 0.580, 1.65, 3.79, 9.92, 30.3, 60.5, and 52.3 × 10^3 g/mol. GPC samples were prepared by dissolving 3 mg of polymer in 2 mL of $CHCl_3$ and 100 μL of the solution was injected for each run.

2,2,6,6-Tetramethyl-1-(1-phenylethoxy)-piperidine (1). Sodium metal (18 mg, 0.77 mmol) was added to a solution of TEMPO (100 mg, 0.65 mmol) in dry THF (5 mL) under an argon blanket and the resulting mixture was stirred at room temperature until it became a homogeneous solution (~4 h). To the red solution was added (1-bromoethyl)benzene (118 mg, 0.64 mmol) via a syringe. The orange color of the solution turned to light yellow after the addition. After stirring the reaction mixture for 3 h at room temperature, the reaction was quenched by adding water (~2 mL). The mixture was extracted with CH_2Cl_2 (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a colorless oil. The resulting crude product was purified by flash column chromatography using hexanes/EtOAc (20:1) to yield alkoxyamine **1** (110 mg, 72%): R_f=0.56 (hexanes:EtOAc =20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 5H), 4.78 (q, J=6.5 Hz, 1 H), 1.49 (br m, 2H), 1.48 (d, J=6.5 Hz, 3H), 1.37 (br m, 2H), 1.29 (br s, 3H), 1.28 (br m, 2H), 1.17 (br s, 3H), 1.02 (br s, 3 H), 0.66 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.03, 128.17, 126.94, 126.78, 83.30, 59.87, 40.54, 34.62, 34.30, 23.76, 20.51, 17.41. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.32; H, 10.31; N, 5.40.

***N*-*tert*-Butyl-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylethyl)hydroxylamine (2).** 2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide radical (**6**) (100 mg, 0.65 mmol) and potassium (18 mg, 0.77 mmol) were dissolved in dry THF under an argon blanket (4 h). To the solution was added (1-bromoethyl)benzene (118 mg, 0.64 mmol). After stirring the reaction mixture for 7 h at 75 °C, the reaction was quenched by adding water and the mixture was extracted with CH_2Cl_2 (3X). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was further purified by flash column chromatography (hexanes/EtOAc=50:1) to afford alkoxyamine **2** as a mixture of two inseparable diastereomers (110 mg, 72%). R_f=0.39 (hexanes/EtOAc=50:1); ^{1}H NMR (300 MHz, $CDCl_3$, a mixture of both diastereomers) δ 7.7-7.1 (m, 20H), 4.91 (q, J=6.6 Hz, 2H, both diastereomers), 3.42 (d, J=10.5 Hz, 1H, major diastereomer), 3.29 (d, J=10.5 Hz, 1H, minor diastereomer), 2.29 (m, 1H, major diastereomer), 1.63 (d, J=6.6 Hz, 3H, major diastereomer), 1.54 (d, J=6.6 Hz, 3H, minor diastereomer), 1.35 (m, 1H, minor diastereomer), 1.31 (d, J=6.3 Hz, 3H, major diastereomer), 1.05 (s, 9H, minor diastereomer), 0.92 (d, J=6.3 Hz, 3H, minor diastereomer), 0.77 (s, 9H, major diastereomer), 0.54 (d, J=6.6 Hz, 3H, major diastereomer), 0.22 (d, J=6.6 Hz, 3H, minor diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$, a mixture of both diastereomers) 145.9, 145.2, 142.7, 142.5, 131.2, 128.2, 127.5, 127.4, 127.3, 127.2, 126.8, 126.5, 126.4, 126.3, 83.7, 82.9, 72.4, 72.3, 60.7, 60.6, 32.2, 31.8, 28.6, 28.4, 24.9, 23.3, 22.3, 22.1, 21.3, 21.2.

(1-Bromo-2-*tert*-butyldimethylsilyloxyethyl)benzene (7). A culture tube was charged with 2-bromo-2-phenyl-ethanol (500 mg, 2.5 mmol), pyridine (2 mL), DMAP (cat.) and dry CH_2Cl_2 (5 mL). To the solution was slowly added TBSCl (452 mg, 3.0 mmol) at 0 °C under argon atmosphere. After 3 h of stirring, the mixture was filtered through a short pad of silica gel. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography using hexanes. The product was obtained as colorless oil (473 mg, 74%). R_f=0.5 (hexanes); ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.40 (m, 5H), 4.97 (t, J=6.9 Hz, 1H), 4.14 (dd, J=11.1 and 6.9 Hz, 1H), 4.04 (dd, J=10.8 and 7.2 Hz, 1H), 0.082 (s, 9H), 0.018 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.50, 128.65, 128.31, 68.32, 54.97, 25.90, 18.42, -5.18, -5.29; Anal. Calcd for $C_{14}H_{23}BrOSi$: C, 53.33; H, 7.35, Found; C, 53.32; H, 7.35.

1-[2-(*tert*-Butyldimethylsilanyloxy)-1-phenylethoxy]-2,2,6,6-tetramethylpiperidine (8). TEMPO (990 mg, 6.34 mmol) and potassium (299 mg, 7.6 mmol) were dissolved in dry THF under an argon atmosphere. To the solution was added bromide **7** (2.00 g, 6.34 mmol). After stirring the reaction mixture for 3 h at rt, it was filtered through a short pad of silica gel. The filtrate was concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography using hexanes to yield a colorless oil (1.8 g, 72%). R_f=0.5 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H), 4.69 (t, J=5.7 Hz, 1 H), 4.06 (dd, J=9.9 and 5.1 Hz, 1H), 3.73 (dd, J=9.9 and 6.6 Hz, 1H), 1.1 – 1.51 (m, 6H), 1.44 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3 H), 1.09 (s, 3 H), 0.082 (s, 9H), 0.018 (s, 3H), -0.04 (s, 3H).

2-Phenyl-2-(2,2,6,6-tetramethyl-piperidin-1-yloxy)-ethanol (9). 1-[2-(*tert*-Butyldimethylsilanyloxy)-1-phenylethoxy]-2,2,6,6-tetramethylpiperidine **8** (315 mg, 0.95 mmol) was dissolved in dry THF under an argon atmosphere. Then a TBAF solution (1.0 M in THF, 0.6 mL, 1.9 mmol) was added at 0 °C. After 2 h, the reaction mixture was quenched by adding distilled water. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography using hexanes/EtOAc (6:1) to yield a colorless oil (219 mg, 83%). R_f=0.4 (hexanes:EtOAc=6:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H), 5.78 (d, J=9.3 Hz, 1H), 5.30 (dd , J=9.6 and 2.7 Hz, 1H), 4.22 (dd, J=12.3 and 9.6 Hz, 1H), 3.73 (dd, J=12.3 and 2.7 Hz, 1H), 1.1 – 1.51 (m, 6H), 1.44 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.08, 128.52, 128.07, 126.96, 83.74, 69.96, 61.89, 60.56, 40.59, 40.39, 34.79, 32.93, 20.91, 20.58, 17.33.

***N*-*tert*-Butyl-O-[2-(*tert*-butyldimethylsilanyloxy)-1-phenylethyl]-*N*-(2-methyl-1-phenylpropyl)-hydroxylamine (11).** To a solution of 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide free radical (**6**) (287 mg, 0.91 mmol) in dry THF (10 mL) was added potassium (43 mg, 1.09 mmol) under an argon atmosphere and the mixture was stirred at rt until it makes a homogeneous solution. After adding 1-bromoethylbenzene (200 mg, 0.91 mmol), the mixture was heated at 75 °C for 3 h. The reaction was quenched by adding water (1 mL), and the mixture was extracted with CH_2Cl_2 (× 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified by flash column chromatography using hexanes/CH_2Cl_2 (95:5) to yield alkoxyamine **11** as two separable diastereomers in a ~1:1 ratio (combined yield=305 mg, 74%). *Diastereomer 1*: R_f=0.47 (hexanes: CH_2Cl_2=95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.29 (m, 10H), 4.78 (t, J=4 Hz, 1H), 4.09 (dd, J=10.5 and 4 Hz, 1H), 3.90 (dd, J=11 and 3.5 Hz, 1H), 3.41 (d, J=10.5 Hz, 1H), 2.47 (m, 1H), 1.28 (d, J=6.5 Hz, 3H), 0.83 (s, 9H), 0.81 (s, 9H), 0.51 (d, J=6.5 Hz, 3H), - 0.15 (s, 3H), - 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 142.6, 141.8, 131.6, 127.8, 127.6, 127.4, 126.9, 126.4, 87.2, 72.5, 66.4, 61.1, 31.3, 28.4, 26.0, 22.3, 21.3, -5.66, -5.69. *Diastereomer 2*: R_f=0.43 (hexanes:CH_2Cl_2=95:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.48 (m, 10H), 4.90 (t, J=6 Hz, 1H), 4.18 (dd, J=9.6 and 5.1 Hz, 1H), 3.84 (dd, J=9.6 and 6.6 Hz, 1H), 3.35 (d, J=10.5 Hz, 1H), 1.50 (m, 1H), 1.11 (s, 9H), 0.90 (d, J=6.6 Hz, 3H), 0.83 (s, 9H), 0.27 (d, J=6.6 Hz, 3H), - 0.07 (s, 3H), - 0.10 (s, 3H).

2-[*N*-*tert*-butyl-*N*-(2-methyl-1-phenylpropyl)-aminooxy]-2-phenylethanol (12). Alkoxyamine **11** (270 mg, 0.59 mmol) was dissolved in dry THF (5 mL) under an argon atmosphere. To the solution was added TBAF (1.18 mmol, 1.2 mL) at 0 °C. After stirring the reaction mixture for 3 h, water (1 mL) was added. The mixture was extracted with CH_2Cl_2 (× 3). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography using hexanes/EtOAc (6:1) to yield alkoxyamine **12** (136 mg, 68%). Alkoxyamine **12** from *diastereomer 1* of **11**: R_f=0.43 (hexanes:EtOAc=6:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.14 (m, 10H), 4.91 (t, J= 4.5 Hz, 1H), 4.07 (t, J=5.4 Hz, 2H), 3.46 (d, J=10.5 Hz, 1H), 2.32 (m, 1H), 1.29 (d, J=6.3 Hz, 3H), 1.15 (s, 3H), 0.85 (s, 6H), 0.54 (d, J=6.3 Hz, 3H). Alkoxyamine **12** from *diastereomer 2* of **11**: R_f=0.43 (hexanes:EtOAc=6:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.12 (m, 10H), 5.16 (t, J=5.1 Hz, 1H), 4.14 (dd, J=11.4 and 7.8 Hz, 1H), 3.83 (dd, J=11.7 and 3.9 Hz, 1H), 1.84 (m, 1H), 1.15 (s, 9H), 1.02 (d, J=6.3 Hz, 3H), 0.32 (d, J=6.6 Hz, 3H).

Succinic acid mono-(methyl-PEG)yl ester (15). Poly (ethylene glycol) mono-methyl ether (M_n=5,000 g/mol, 5.00 g, 1.0 mmol), succinic anhydride (120 mg, 1.2 mmol), pyridine, and DMAP (cat.) were dissolved in dry toluene under a nitrogen blanket. The solution was heated at reflux and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel using THF as an eluent. The filtrate was dripped into diethyl ether at 0 °C to precipitate the desired polymer. The precipitates were dried under vacuum overnight to provide the carboxy terminated PEG polymer **15** as a white cake (5.0 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) : δ 2.64 (t, J=4.5 Hz, 4H), 3.38 (s, 3H), 3.4-3.8 (br s, -OCH_2CH_2O-), 3.88 (t, J=5.1 Hz, 4H), 4.26 (t, J=4.5 Hz, 2H).

Polymer (16). The procedure was the same as the procedure described above for polymer **13**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (t, J=4.5 Hz, 4H), 3.38 (s, 3H), 3.4 – 3.8 (br, -CH_2CH_2-), 3.88 (t, J=5.1 Hz, 4H), 4.26 (t, J=4.5 Hz, 2H).

Macroinitiator (17). Succinic acid mono-(methyl-PEG)yl ester **15** (5,000 g/mol, 2.9 g, 0.8 mmol), 2-phenyl-2-(2,2,6,6-tetramethyl-piperidin-1-yloxy)-ethanol **9** (200 mg, 0.72 mmol) were dissolved in dry CH_2Cl_2 under an argon atmosphere. DCC (178 mg, 0.86 mmol) was slowly added to the solution at 0 °C. After 2 h of stirring, the reaction mixture was filtered through a short pad of silica gel with CH_2Cl_2. The filtrate was dripped into diethyl ether at 0 °C to precipitate the desired polymer. The precipitates were dried under vacuum overnight to provide the macroinitiator **17** as a white solid (2.75 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (t, J=6 Hz, 1H), 4.62 (dd, J=11.1 and 5.4 Hz, 1H), 4.26 (t, J=4.5 Hz, 2H), 3.88 (t, J=5.1 Hz, 4H), 3.4 – 3.8 (br, -CH_2CH_2-), 3.38 (s, 3H), 2.54 (t, J=3.6 Hz, 4H), 1.1 – 1.51 (m, 6H), 1.44 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3 H), 1.09 (s, 3 H).

Macroinitiator (18). The procedure was the same as the procedure described above for macroinitiator **17**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (t, J=6 Hz, 1H), 4.62 (dd, J=11.1 and 5.4 Hz, 1H), 4.26 (t, J=4.5 Hz, 2H), 3.88 (t, J=5.1 Hz, 4H), 3.4 – 3.8 (br, -CH_2CH_2-), 3.38 (s, 3H), 2.54 (t, J=3.6 Hz, 4H), 1.1 – 1.51 (m, 6H), 1.44 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3 H), 1.09 (s, 3 H).

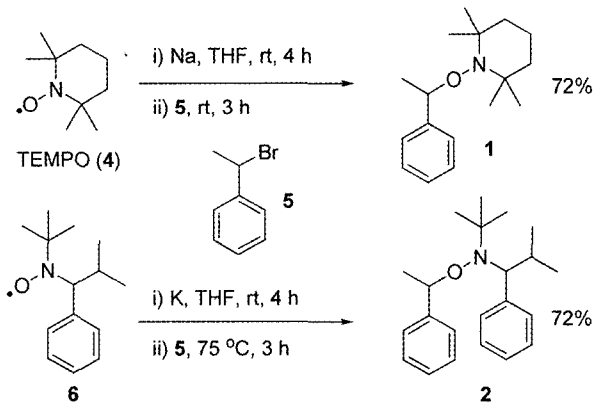
General NMRP for Block Copolymers (19) and (20). A Schlenk flask was charged with argon by three vacuum and charging cycles. After inhibitor-free styrene (2.0 g, 20 mmol) and macroinitiator **17** (500 mg, 0.1 mmol) were placed in the flask, the mixture was deoxygenated by three freeze-pump-thaw cycles. After sealing the flask, the solution was heated at 120 °C for 6 h while stirring. After cooling the reaction mixture to rt, the solution was diluted with THF (30 mL). The diluted solution was dripped into hexanes (200 mL) to precipitate the block copolymer. After filtration and vacuum drying, the PEG-*b*-PS polymer **19** was obtained as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.4-7.3 (br, Aromatic H), 3.4–3.8 (m, -CH_2CH_2-), 1.3-2.3 (br, -CH_2CH-); GPC: M_w=39,447 g/mol, M_n=34,455 g/mol, PDI=1.15, $M_{n,cal}$=25,800 g/mol. The triblock copolymer **20** was also prepared by the same procedure.

Results and Discussion

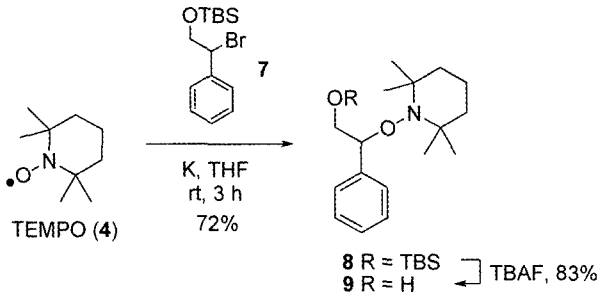
In order to test our proposed protocol, sodium metal (1.2 eq) was added to an orange solution of the commercially available 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, **4**) free radical in dry THF at rt. Sodium metal gradually became dissolved in 3~4 h to form a cloudy orange solution of the corresponding alkoxy anion. Then, (1-bromoethyl) benzene (**5**) was added to the reaction mixture and the resulting light yellow solution was allowed to stir for 3 h at rt. While the reaction was running, formation of yellow precipitates (NaBr) was observed, which indicates the substitution reaction was taking place. After a usual work-up procedure and purification by flash column chromatography on silica gel, the desired alkoxyamine initiator **1** was obtained in 72% yield (Scheme I). Based on this result, we next attempted to prepare initiator **2** under the same conditions. The necessary nitroxide stable radical **6** was prepared following the literature procedure.[13] Generation of the anion of this bulkier nitroxide was achieved by treatment with potassium metal at rt as in the case of TEMPO, but the subsequent alkylation reaction with (1-bromoethyl)benzene (**5**) did not take place at rt and only starting materials were recovered even after prolonged reaction time. After careful examinations, we discovered that the substitution reaction of this bulky species requires elevated temperature (75 °C), and the alkoxyamine initiator **2** was obtained in a comparable yield (72%) under these conditions (Scheme I). In general, the usage of potassium metal was favored than that of sodium metal because the reactivity of potassium is higher than sodium and the reaction time is shorter.

To explore the versatility of this protocol, next we have examined preparation of an initiator bearing an end functional OH group **9** (Scheme II). This initiator has been prepared by Hawker and coworkers[8b] and proved to be useful for preparation of various end-functional polymers and block copolymers. When TEMPO anion generated by treatment with potassium was subjected to the reaction with bromide **7** that had been prepared in two steps from styrene oxide,[14] the desired TBSO-functionalized alkoxyamine initiator **8** was obtained in 72% isolated yield, which is comparable to the case of nonfunctionalized alkoxyamine **1**. After deprotection of the TBS group (TBAF in THF), hydroxy functionalized initiator **9** was obtained in 83% yield.

Preparation of a hydroxy functionalized alkoxyamine initiator **12** derived from nitroxide **6** also worked in the same manner as shown in Scheme III. In principle, it is also possible that the nitroxide anion can be prepared from the hydroxy amine by treating with potassium metal by generating hydrogen gas. Indeed, the reaction proceeded well starting from hydroxy amine **10** instead of stable free radical **6**,



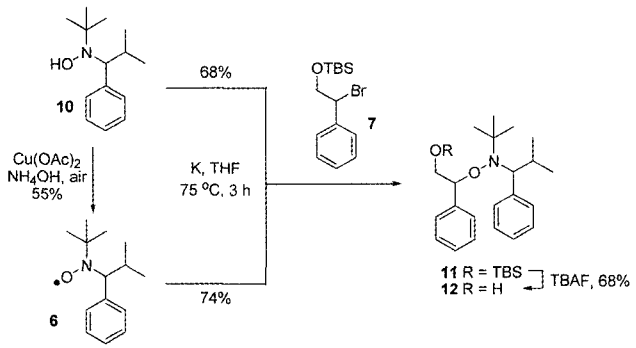
Scheme I. Synthesis of alkoxyamine initiators **1** and **2** under anionic conditions.



Scheme II. Synthesis of hydroxy functional alkoxyamine initiator **9**.

and yielded the desired TBS protected hydroxy functional alkoxyamine initiator **11** in 68% yield, which is comparable to the yield (74%) of the reaction where the nitroxide radical **6** was used (Scheme III). In the original procedure by Hawker *et al.*,[8b] they prepared the stable nitroxide radical **6** by air oxidation of the intermediate **10** in the presence of $Cu(OAc)_2$ catalyst in 71% yield (55% yield in our hands), and reacted the resulting nitroxide radical **6** with benzylic hydrazine in the presence of PbO_2 to afford the corresponding initiator **2** in 73% yield. Although this procedure provides the initiator in a reasonable yield, it requires the use of benzylic hydrazine that needs to be prepared from (1-bromoethyl)benzene and fuming hydrazine. Considering the limited accessibility of fuming hydrazine due to safety issues, the original procedure is rather impractical.

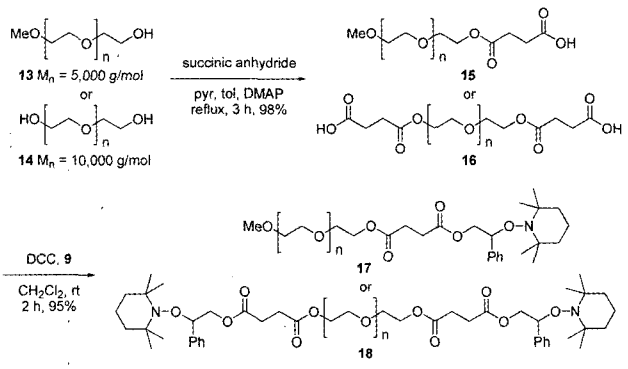
Having the hydroxy functional alkoxyamine initiator **9**, we next tested its ability for NMRP by synthesizing PEG-macroinitiators (Scheme IV) and by preparing block copolymers using these macroinitiators (Scheme V). Commercially available monomethyl poly(ethylene glycol) (Aldrich, M_n=5,000 g/mol, M_w/M_n=1.10[15]) and poly(ethylene glycol) (Aldrich, M_n=10,000 g/mol, M_w/M_n=1.10[15]) were subjected to functionalization with succinic anhydride in refluxing toluene in the presence of pyridine and 4-dimethylaminopyridine (DMAP) as a catalyst to produce carboxy-terminated PEGs **15** and **16**, respectively. The functionality



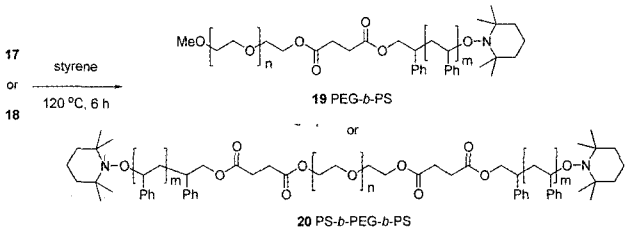
Scheme III. Synthesis of hydroxy functional alkoxyamine initiator **12**.

of each polymer was determined to be over 95% from 500 MHz ^{1}H-NMR spectroscopic analysis of the polymer by comparing the resonance integrals of $COCH_2CH_2CO_2H$ against that of OCH_3 (for **15**) or against that of CH_2OH (for **16**). The resulting functional polymers could be easily purified by precipitation in *t*BuOMe.

NMRP under typical conditions for polystyrene growing (neat, 120 °C) using the macroinitiators **17** and **18** was performed, and the desired PEG-*b*-PS (**19**) and PS-*b*-PEG-*b*-PS (**20**) block copolymers were obtained with good molecular weight and polydispersity control (Scheme V). Molecular weight analyses of these polymers are provided in Table I. After 6 h of reaction time, 86 and 83% conversions for the block copolymers were achieved by judging from ^{1}H-NMR analyses of the reaction mixture. Number average molecular weights of **19** and **20** were determined to be 34,500 g/mol and 48,800 g/mol by gel permeation chromatography (GPC) calibrated with polystyrene standards. While the molecular weight distribution of diblock copolymer **19** was fairly narrow (M_w/M_n = 1.15), that of triblock copolymer **20** was rather broad (M_w/M_n = 1.57). In order to determine the molecular weight of the resulting PS block more accurately, each block copolymer was cleaved by hydrolysis (K_2CO_3, THF/H_2O, reflux) to provide the polystyrene blocks by precipitating in MeOH, and they were analyzed by GPC. From the analyses, the molecular weights of the polystyrene blocks for **19** and **20** were determined to be 18,000 g/mol and 17,000 g/mol, respectively. The discrepancy between the molecular weights of the block copolymers from molec-



Scheme IV. Preparation of alkoxyamine macroinitiators using **9**.



Scheme V. Synthesis of PEG-*b*-PS (**19**) or PS-*b*-PEB-*b*-PS (**20**) block copolymers by NMRP.

Table I. GPC Characterization Data for Block Copolymers 19 and 20

Polymer	M_n[a] (g/mol)	M_w/M_n[a]	M_n (PEG)	M_n[b] (PS)	Conversion (%)
19	34,500	1.15	5,000	18,000	86
20	48,800	1.57	10,000	17,000	83

[a]Determined by GPC analysis using polystyrene as standards. [b]Determined by GPC analysis of the polystyrene generated by hydrolysis of block copolymers **19** and **20** using K_2CO_3 in THF/H_2O under refluxing conditions.

ular weights of PEG and PS segments (23,000 g/mol for **19** and 44,000 g/mol for **20**) and those directly obtained by GPC analysis (34,500 g/mol for **19** and 48,800 g/mol for **20**) seems to be arising from the different hydrodynamic volumes of the block copolymers in GPC solvent ($CHCl_3$).

Representative GPC traces of macroinitiator **17** and PEG-*b*-PS block copolymer **19** synthesized from **17** is shown in Figure 2. The GPC trace of **19** showed little trace of the macroinitiator **17**, which means that almost of the initiating PEG polymer chains were involved in the second polystyrene block growing.

Conclusions

We have demonstrated that the nitroxide anions can be generated by simple treatment of the stable nitroxide free radical or hydroxy amine with alkali metal in THF, and the subsequent reaction with benzylic bromide provides alkoxyamine initiators for NMRP in high yields. While the substitution reaction of TEMPO anion with benzyl bromide proceeded at rt, the reaction of bulkier nitroxide required elevated temperature. This protocol is easier and practical compared to other radical capturing methods because it employs cheap and easily accessible reagents and inherently prevents self-coupling or oligomerization reactions. It can be also applied to preparation of functional alkoxyamine NMRP initiators and the utility of those initiators were demonstrated by practically synthesizing PEG-*b*-PS and PS-*b*-PEG-*b*-PS block copolymers with molecular weight and polydispersity control starting from commercially available PEGs.

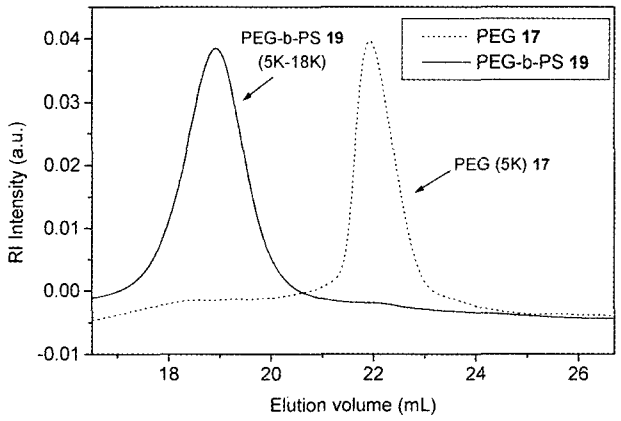


Figure 2. Comparison of the GPC traces of macroinitiator **17** and PEG-*b*-PS diblock copolymer **19** grown from **17**.

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