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A One-Step Synthesis of Monoprotected Polyethylene Glycol Ethers

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In conjunction with our research in the area of liquid-phase organic synthesis (LPOS), we required ready access to multigram quantities of monoprotected poly(ethylene glycol) (PEG).[1] Since the only monosubstituted PEG diol available is monomethoxy PEG (MPEG), the need for an efficient synthesis of monoprotected PEG with a synthetically manipulable endgroup exists. Furthermore, an efficient entry into monoprotected PEG would allow preparation of heterofunctional PEGs (e.g., monoamino PEG) which cost $100/g or more. We report herein an inexpensive and high yielding preparation of monoprotected PEG.

While commercially available PEG diol would be the ideal starting material for our purposes, no practical multigram-scale methods have been reported for the selective protection of only one of the two hydroxyl termini for PEG of molecular weight greater than 1000 amu. Tedious, labor intensive purifications[2] or the use of hazardous reagents[3] make this approach suitable only for small quantities of monoprotected PEG.

Well-defined heterofunctional PEG has been prepared by anionic polymerization of ethylene oxide and a functionalized initiator.[4] However, we are aware of only one example of monoprotected PEG diol prepared by an anionic polymerization.[5] In this report by Ito, 2-(*tert*-butyldimethylsiloxy)ethanol was deprotonated with potassium naphthenylide and the resulting alkoxide was used to initiate polymerization with ethylene oxide. Quenching with benzyl chloride and removal of the silyl group afforded PEG monobenzyl ether. While this method generates PEG monobenzyl ether in two steps, it suffers from several drawbacks. The starting material, while easily made,[6] is not commercially available. The TBDMS group is discarded, adding to the cost of the final polymer. Most importantly, the process does not generate the polymer directly. Our attempts at forming a monosilylated PEG diol in one step using this method was complicated by significant loss of the TBDMS group upon quenching with Amberlyst IR-120(+).

We then examined commercially available 2-(benzyloxy)ethanol (**1**) as the initiator alcohol to synthesize **2** in one step. Initial attempts to produce PEG monobenzyl ether from **1** using potassium naphthenylide as the base resulted in contamination by significant amounts of diol presumably formed by the slow radical anion induced cleavage of the benzyl ether.

We found potassium hydride to be the ideal base for generation of the alkoxide initiator,[7] and this alkoxide reacted smoothly with ethylene oxide in THF to give high yields (95−99%) of pure PEG monobenzyl ethers **2a**−**c** (Scheme 1). The polymerization was quenched with Amberlyst IR-120(+) and filtered from the resin directly into cold diethyl ether to precipitate the product. Polymerizations were routinely performed on a 10−20-g scale to generate PEG monobenzyl ethers of molecular weights[8] 1000 (**2a**), 2000 (**2b**), and 4500 (**2c**) amu with polydispersities (M_w/M_n) of 1.04 or less.[9] This polymerization reaction is conceptually simple; however, it should be pointed out that it is technically demanding. All solvents and reagents must be rigorously dried and degassed to obtain consistent results, and the purity of the potassium hydride is critical, since KOH contamination will lead to formation of PEG diol.

To demonstrate that these polymers were monosubstituted, **2c** was converted to the PEG mono(*tert*-butyldimethylsilyl) ether **4a** via a two-step sequence (Scheme 2). The presence of a single hydroxyl proton was visible in the ^{1}H NMR (DMSO-d_6)[10] of polymers **2a**−**c** and **4a**, and for differentially protected derivative **3**, the ratio of 5 (aromatic) and 2 (benzylic) protons to 9 (*tert*-butyl) and 6 (dimethyl) protons shows that we did indeed have pure monosubstituted PEG. Furthermore, PEG diol would be visible by mass spectral analysis if present; however, only one polymeric species is observed in **2a**−**c**.

While PEG monobenzyl ether can be converted other monoprotected PEG ethers as shown above, this procedure is not limited to the monobenzyl ether of PEG since generation of the initiator with potassium hydride will tolerate a range of functionality in the protected terminus. In addition to PEG monobenzyl ether, two other monoprotected PEG ethers were also prepared by this method. PEG mono(*tert*-butyldimethylsilyl) ether **4b** (MW 2000) was prepared from 2-(*tert*-butyldimethylsilyloxy)ethanol **5** and PEG mono(tetrahydropyranyl) ether

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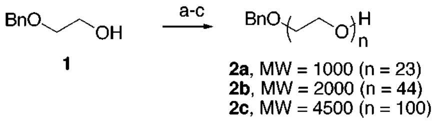
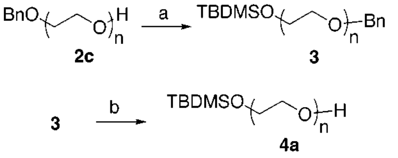
Scheme 1[a]



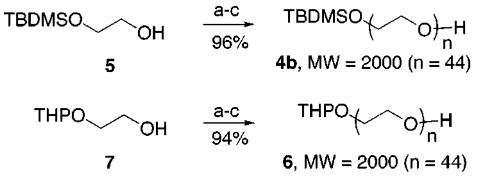
[a] Key: (a) KH, THF; (b) ethylene oxide; (c) Amberlyst IR-120(+) (96−99%).

Scheme 2[a]



[a] Key: (a) NaH, TBDMSCl (95%); (b) H_2, 10% Pd/C (96%).

Scheme 3[a]



[a] Key: (a) KH, THF; (b) ethylene oxide; (c) 10% aq. K_2CO_3.

6 (MW 2000) was prepared from 2-(tetrahydropyranyloxy)ethanol **7** (Scheme 3). Due to acid lability of the endgroups, an alternative workup was developed. Quenching with aqueous potassium carbonate and extraction with methylene chloride followed by precipitation provided the polymers in excellent yields.

In summary, we have developed an efficient and low cost synthesis of monoprotected PEG ethers. Furthermore, this procedure will allow access to a wide range of other heterosubstituted PEG derivatives by simple modification of the endgroups. Due to these considerations, we believe that our one-step procedure will find general application for the preparation of monoprotected PEG.

Experimental Section

General Methods. THF was distilled from sodium benzophenone ketyl, stirred over LAH, degassed by several (3−5) freeze−pump−thaw cycles, and then distilled by vacuum transfer before use. Dichloromethane was distilled from calcium hydride. Diethyl ether was distilled from sodium benzophenone ketyl. 2-(Benzyloxy)ethanol was obtained from Aldrich and distilled from calcium hydride. 2-(*tert*-Butyldimethylsilyloxy)ethanol (**5**) was prepared according to the procedure of McDougal et al.[6] and distilled from calcium hydride. 2-(Tetrahydropyranyloxy)ethanol (**7**) was prepared according to the procedure of Nishiguchi et al.[11] and distilled from calcium hydride. Ethylene oxide (CAUTION) was distilled by vacuum transfer from calcium hydride three times and used immediately. Amberlyst IR-120(+) acidic ion-exchange resin was washed sequentially with 1 M HCl, distilled water, ethanol, and diethyl ether and then dried under vacuum. Potassium hydride was purchased as a 35 wt. % dispersion in mineral oil and washed with distilled hexane under argon. All other reagents were obtained from Aldrich and used without further purification.

Poly(ethylene glycol) Monobenzyl Ether (MW 1000) (2a). To a suspension of potassium hydride (605 mg, 15.9 mmol, 1.06 equiv) in degassed THF (125 mL) was added 2-(benzyloxy)ethanol (**1**) (2.28 g, 15 mmol, 1 equiv) and stirred for 4 h. The solution was degassed by three freeze−pump−thaw cycles and then ethylene oxide (15.31 g, 347 mmol, 23 equiv) was introduced and the resulting solution was stirred at ambient temperature for 24 h. The reaction was quenched by the addition of Amberlite IR-120(+) resin (20 g) and stirred until the reaction was no longer basic by litmus. Filtration from the resin directly into diethyl ether (1 L) at 0 °C afforded the product PEG monobenzyl ether **2a** as a white powder (13.67 g, 78%) with an additional lower MW fraction collected from the ethereal filtrate (3.2 g, total 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.22 (m, 5H), 4.51 (s, 2H), 3.75−3.45 (m, 123H); 1H NMR (500 MHz, DMSO-d_6) δ 7.35−7.20 (m, 5H), 4.55 (bs, 1H), 4.48 (s, 2H), 3.65−3.30 (m, 106H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.2, 127.5, 127.4, 73.0, 72.3, 70.4, 70.2, 69.3, 61.5.

Poly(ethylene glycol) Monobenzyl Ether (MW 2000) (2b). To a suspension of potassium hydride (320 mg, 8 mmol, 1.02 equiv) in degassed THF (125 mL) was added 2-(benzyloxy)ethanol (**1**) (1.18 g, 7.8 mmol, 1 equiv) and stirred for 4 h. The solution was degassed by three freeze−pump−thaw cycles and then ethylene oxide (14.88 g, 337 mmol, 43 equiv) was then introduced and the solution was stirred at ambient temperature for 24 h. The reaction was quenched by the addition of Amberlite IR-120(+) resin (10 g) and stirred until the reaction was no longer basic by litmus. Filtration from the resin directly into diethyl ether (1 L) at 0 °C afforded the product PEG monobenzyl ether **2b** as a white powder (15.54 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 4.55 (s, 2H), 3.81−3.45 (m, 190H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35−7.20 (m, 5H), 4.57 (bs, 1H), 4.48 (s, 2H), 3.70−3.35 (m, 190H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 128.1, 127.6, 127.4, 73.0, 72.3, 70.3, 70.2, 69.2, 61.5.

Poly(ethylene glycol) Monobenzyl Ether (MW 4500) (2c). To a suspension of potassium hydride (0.14 g, 3.49 mmol, 1.1 equiv) in degassed THF (125 mL) was added 2-(benzyloxy)ethanol (**1**) (0.48 g, 3.15 mmol, 1 equiv) and the mixture was stirred 4 h at ambient temperature. The solution was degassed by three freeze−pump−thaw cycles, ethylene oxide (13.8 g, 313 mmol, 99 equiv) was added and the resulting solution was stirred at ambient temperature for 24 h. The reaction was quenched by the addition of Amberlyst IR-120(+) resin (8 g), and the mixture was stirred until it was no longer basic to litmus. The solution was filtered into diethyl ether (1 L) at 0 °C to afford the product PEG monobenzyl ether **2c** as a white powder (13.6 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 4.53 (s, 2H), 3.78−3.40 (m, 389H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40−7.35 (m, 5H), 4.57 (bs, 1H), 4.48 (s, 2H), 3.70−3.35 (m, 405H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.2, 127.6, 127.4, 73.1, 72.4, 70.4, 69.3, 61.6.

TBDMSO−PEG-OBn (3). To a solution of monobenzyl PEG **2c** (5.0 g, 1.1 mmol) in CH_2Cl_2 (50 mL) was added TBDMSCl (0.5 g, 3.3 mmol), Et_3N (0.49 mL, 3.5 mmol), and DMAP (27 mg, 0.22 mmol), and the resulting solution was stirred overnight at ambient temperature. The reaction was concentrated, and the residue was dissolved in THF (50 mL), filtered through Celite, and precipitated into diethyl ether at 0 °C (800 mL). The white precipitate was collected to afford the product as a white solid (4.98 g, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.2 (m, 5H), 4.55 (s, 2H), 3.80−3.45 (m, 438H), 0.87 (s, 9H), 0.04 (s, 6H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.4−7.2 (m, 5H), 4.48 (s, 2H), 3.80−3.2 (m, 365H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.3, 127.6, 127.4, 73.1, 72.5, 70.4, 69.3, 62.6, 25.8, 18.3, −5.3.

Poly(ethylene glycol) Mono(*tert*-butyldimethylsilyl) Ether (MW 4500) (4a). To a solution of **3** (1.4 g, 0.325 mmol) in 4:1 EtOAc:CH_2Cl_2 (25 mL) was added 10% Pd/C (100 mg), and the mixture was agitated under H_2 (55 psi) for 3 h. The solution was filtered through Celite and concentrated to provide a clear oil which was taken up in THF (10 mL) and precipitated from diethyl ether (200 mL) at 0 °C to give the product **4a** as a white powder (1.3 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80−3.43 (m, 452H), 0.86 (s, 9H), 0.03 (s, 6H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (t, J = 5.5 Hz, 1H), 3.70−3.22 (m, 404H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.4, 70.4, 62.6, 61.6, 25.8, 18.2, −5.3.

Poly(ethylene glycol) Mono(*tert*-butyldimethylsilyl) Ether (MW 2000) (4b). To a suspension of potassium hydride (0.26 g, 6.5 mmol, 1.1 equiv) in degassed THF (125 mL) was

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added 2-(*tert*-butyldimethylsilyloxy)ethanol (**5**) (1.04 g, 5.9 mmol, 1 equiv), and the mixture was stirred for 1.5 h at ambient temperature. Ethylene oxide (11.32 g, 257 mmol, 44 equiv) was added, and the resulting solution was stirred at ambient temperature for 24 h. The reaction was quenched by addition of 10% aq. K_2CO_3 (50 mL), the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was taken up in warm THF and precipitated into diethyl ether (1 L) at 0 °C to afford the product PEG mono(*tert*-butyldimethylsilyl) ether **4b** as a white powder (11.90 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70−3.40 (m, 194H), 0.80 (s, 9H), −0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.3, 70.2, 70.0, 62.4, 61.3, 25.7, 18.0, −5.4.

Poly(ethylene glycol) Mono(tetrahydropyranyl) ether (MW 2000) (6) from 7. To a suspension of potassium hydride (0.18 g, 4.3 mmol, 1.1 equiv) in degassed THF (125 mL) was added 2-(tetrahydropyranyloxy)ethanol (**7**) (0.57 g, 3.92 mmol, 1 equiv), and the mixture was stirred 1.5 h at ambient temperature. Ethylene oxide (7.56 g, 172 mmol, 44 equiv) was added, and the resulting solution was stirred at ambient temperature for 24 h. The reaction was quenched by addition of 10% aq. K_2CO_3 (50 mL), the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was taken up in warm THF and precipitated into diethyl ether (0.8 L) at 0 °C to afford the product PEG mono(tetrahydropyranyl) ether **6** as a white powder (7.68 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (t, J = 3.3, 1H), 3.84−3.80 (m, 2H), 3.74 (t, J = 5 Hz, 2H), 3.70−3.52 (m, 204H), 3.46 (t, J = 5 Hz, 2H), 1.82−1.77 (m, 1H), 1.70−1.65 (m, 1H), 1.58−1.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 72.4, 70.5, 70.2, 66.5, 62.1, 61.6, 30.4, 25.3, 19.3.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and mass spectral data for **2a**−**c**, **3**, **4a**−**b**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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