An Expedient Synthesis of Monodispersed Oligo(ethylene glycols)

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Abstract: A convenient approach to the synthesis of oligo(ethylene glycols) under phase transfer conditions is described. Oligo(ethylene glycols) (x = 7–12) are obtained in excellent yields and high purity via modular, bi-directional elongation of readily available ethylene glycol bis-tosylates.

Keywords: oligo(ethylene glycols), alkylation, phase transfer catalysis, chain elongation, nucleophilic substitution

Oligomers of ethylene glycol have found widespread applications in a number of areas of chemistry, including the synthesis of crown ethers and podands, use as surfactants and more recently as biocompatible polymers which are capable of modifying the properties of a variety of substrates. Even though poly-dispersed oligomers of ethylene glycols are readily available, the commercial availability of monodispersed oligomers (Figure 1) is limited beyond x = 6 (hexaethylene glycol). We were recently required to access a range of monodispersed ethylene glycol oligomers (1) up to x = 12. The synthesis of higher oligomers was therefore pursued.

Despite their widespread utility, the synthesis of monodispersed oligo(ethylene glycols) remains a challenging task. Reported syntheses are typically time consuming and low yielding processes, often complicated by competing elimination reactions. The level of difficulty in the synthesis and isolation of oligo(ethylene glycols) also typically increases with an increase in chain length, placing further limitations on the available methods.

In the first instance, we pursued the synthesis of the required oligo(ethylene glycols) using 2-bromoacetic acid derivatives as latent functionality to ethylene glycol monomers. Such an approach has previously been reported in the literature for the mono-directional elongation of ligated oligo(ethylene glycols) as well as for the bidirectional elongation of branched ethylene glycol derivatives. However, to the best of our knowledge this approach has not been applied to the synthesis of monodispersed oligo(ethylene glycols). Hence, readily available oligo(ethylene glycols) (1, x = 4–6) were treated with isopropyl bromoacetate (2) in the presence of sodium hydride to afford the corresponding bis(esters) 3 in moderate yields following purification over a short column of silica (Scheme 1). Subsequent reduction of 3 (x = 4–6) with LiAlH4 furnished the desired x+2 extended oligomers (1', x = 4–6). The results of these studies are shown in Table 1.

![Scheme 1](image)

**Table 1** Isolated Yields of Bis-esters 3 and Ethylene Glycols 1' using Reduction/Elimination Strategy

<table>
<thead>
<tr>
<th>Entry</th>
<th>x</th>
<th>Yield of 3 (%)</th>
<th>x+2</th>
<th>Yield of 1' (%)</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>51</td>
<td>6</td>
<td>70</td>
<td>35</td>
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<tr>
<td>3</td>
<td>6</td>
<td>42</td>
<td>8</td>
<td>56</td>
<td>24</td>
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<tr>
<td>4</td>
<td>7</td>
<td>46</td>
<td>9</td>
<td>30</td>
<td>14</td>
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</table>

As evident from Table 1, the elongation/reduction strategy was successfully employed for the synthesis of monodispersed oligo(ethylene glycols), however the overall yields were deemed unacceptable for our purposes. Whilst isolated yields for the elongation step were consistently between 40% and 50%, a significant drop in the yield of the reduction step was observed with increasing chain-length (entry 4). The observed decrease in yield is attributed, in part, to the high solubility of products in water during the aqueous workup of the reduction. An additional drawback of the elongation/reduction approach is the lack of potential for modular assembly of monodispersed oligo(ethylene glycols). Thus the synthesis of higher oligomers (e.g. x = 12) requires the synthesis of all intermediate oligomers, rendering the process laborious and
inefficient, particularly in view of the low yields observed with increasing chain length.

In the literature, bidirectional chain elongation of oligo(ethylene glycols) has been classically achieved starting from an appropriately bis-activated ethylene glycol derivative [e.g. bis(tosylate)\(^{6,10}\) or bis(mesitylate)\(^{11}\)] and two molar equivalents of a suitably mono-protected ethylene glycol derivative (Scheme 2). Our attempts to reproduce these syntheses using 2-allyloxethanol (4) and the corresponding bis(sulfonates) derived from pentaethylene glycol (5 and 6, \(m = 5\)) were met with frustrating results as poor conversion to the elongated products persisted. Further investigation revealed this was also the case for elongation using some of the lower bis(sulfonates), particularly for the \(m = 1\) system where extremely low conversion to the elongated products persisted. As poor conversion to the desired systems (7) was observed (Table 2) along with evidence of competing elimination reactions.

\[
\text{R=Ts (5)} \quad \text{R=Ms (6)} \quad \text{Conditions} \quad \text{Conversion to 7 (%)}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(m)</th>
<th>(R)</th>
<th>Conditions</th>
<th>Conversion to 7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Ts</td>
<td>NaH, THF, r.t., 96 h(^6)</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Ms</td>
<td>NaH, THF, Reflux, 30 h(^{11})</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Ms</td>
<td>NaH, DMF, 80 °C, 30 h(^{12})</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Ts</td>
<td>NaH, THF, r.t., 96 h</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Ms</td>
<td>NaH, THF, Reflux, 30 h</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>Ts</td>
<td>NaH, THF, r.t., 96 h</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>Ms</td>
<td>NaH, THF, Reflux, 30 h</td>
<td>&lt; 20</td>
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</table>

Gratifyingly, nearly all reactions proceeded to give near quantitative conversion to the corresponding bis-protected elongated ethylene glycol oligomers 7. The only exception to this was in the case of the \(m = 1\) system (Table 3, entry 1) where, in addition to the formation of 7, elimination of the bis-tosylate was observed (ca. 10%), the remaining material being starting bis(tosylate) 5. It is thought that the low conversion to the extended systems in this case is due to the very low solubility of the 5 (\(m = 1\)) under the reaction conditions.

The remaining extended systems were isolated in excellent yields following purification through a short column of silica. Analysis of the purified bis-allyl ethers by ESI-MS showed no evidence of lower oligomers such as the starting mono-allyl ethers, or products resulting from hydrolyzed bis(tosylate) and unsymmetrical alkylation.

Removal of the allyl protecting groups was readily achieved in refluxing MeOH using 10% Pd/C and catalytic amount of toluenesulfonic acid\(^{15}\) to give quantitative conversion to the desired monodispersed oligo(ethylene glycols) 1 which were isolated in excellent yields by simple filtration (Table 3). Longer reaction times were required for complete deprotection for the higher homologues (\(x = 9–12\)), however reactions were usually complete within 24 hours.

In summary, we have demonstrated the efficient and convenient bidirectional elongation of oligo(ethylene glycols) up to \(n = 12\). This simple and effective phase transfer method offers several advantages to existing literature preparations of monodispersed oligo(ethylene glycols), including comparatively short reaction times, minimal use

\[
\text{Scheme 2}
\]

\[
\text{Scheme 3 Reagents and conditions: a) } \text{-BuOK, Allyl bromide, THF, r.t., 24 h. b) 5 (m = 1–4), KOH, TBAB (20 mol%), toluene, 110 °C, 120 min. c) 10% Pd/C, TsOH (5 mol%), MeOH–H}_2\text{O (24:1), reflux, 2–24 h.}
\]

Whilst the use of bis(mesitylates) was purported to give improved yields of the elongated systems,\(^{11}\) in our hands only very low conversion to products was observed. Owing to the difficulties encountered using the literature methods, we sought to improve the conditions for the bi-directional elongation of oligo(ethylene glycols) and turned our attention to the use of phase transfer catalysis. Addition of quaternary ammonium salts to the reactions where alkoxydes were generated using sodium hydride failed to significantly improve conversion to the desired elongated oligo(ethylene glycol) systems. However, we were encouraged by reports in the literature in which bis(tosylates) of di- and tri-ethylene glycols were used in the synthesis of dianhydrohexitol dimers using KOH and tetrabutyl-ammonium bromide (TBAB).\(^{13}\) The reported method was considered advantageous as the reaction uses only minimum volumes of solvent and the work-up procedure avoids any use of water, the inorganic salts being removed by simple filtration. We considered such a protocol as an attractive alternative to the existing methods for ethylene glycol elongation and undertook an investigation to assess its applicability to the synthesis of oligo(ethylene glycols) 1 where \(x = 7–12\).
of solvents, simple work-up procedures, shorter deprotection times and ease of isolation.

^1_H NMR and ^13_C NMR spectra were recorded on a spectrometer operating at 400 MHz for ^1_H and 100 MHz for ^13_C nuclei. Chemical shifts are reported as the shift in parts per million (ppm) from tetramethylsilane (TMS, 0.00 ppm) which was used as an internal standard and used to reference ^1_H NMR spectra. ^13_C NMR spectra were referenced to the central peak of the CDCl3 triplet at 77.0 ppm. Coupling constants J are quoted in Hz and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet) q (quartet), m (multiplet). Infrared spectra were recorded as thin films on KBr discs. Absorbances are reported as in reciprocal centimeters (cm⁻¹) and the band intensity is described as follows: s (strong), m (medium), w (weak). Low resolution and high resolution mass spectra were recorded on a Q-TOF spectrometer using the electrospray ionisation technique.

All chemicals and reagents were readily available from common companies and were used as purchased except in the following cases. Monoallylated oligo(ethylene glycols) (4 where n = 2, 3, and 4 were synthesized according to literature procedures¹⁴ as was the bis(tosylate) derived from ethylene glycol (5, x = 1).²⁵

<table>
<thead>
<tr>
<th>Entry</th>
<th>m</th>
<th>n</th>
<th>x</th>
<th>Yield of 7 (%)</th>
<th>Yield of 1 (%)</th>
<th>Overall Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>&lt;40%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>&gt;90%</td>
<td>–</td>
<td>–</td>
</tr>
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<td>12</td>
<td>79</td>
<td>82</td>
<td>65</td>
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</table>

* Approximate percentage conversion to 7 determined by ^1_H NMR spectroscopy.

Bidirectional Elongation of Oligo(ethylene glycols); General Procedure

Freshly powdered KOH (1.31 mmol) was added to a stirred suspension/solution of the appropriate monoaallylated oligo(ethylene glycol) (1.31 mmol), oligo(ethylene glycol) bis-tosylate (0.62 mmol) and TBA in toluene (0.25–1 mL). The resulting reaction mixture was heated at 100 °C for 2 h and after this time the reaction was allowed to cool to r.t., whereupon CH2Cl2 (10 mL) was added to the reaction mixture. The resulting suspension was filtered and the solid was washed with CH2Cl2. The filtrate was concentrated in vacuo to afford the crude elongated systems as pale yellow-orange oils, which were purified by flash column chromatography.

Heptaethylene Glycol bis(allyl ether) (7, x = 7)

The title compound was prepared using the general method from diethylene glycol monoallyl ether (191 mg, 1.31 mmol), bis(toluene-sulfonetyl) triethylene glycol (284 mg, 0.62 mmol), KOH (74 mg, 1.31 mmol), TBAB (40 mg, 0.124 mmol) and toluene (1 mL). Heptaethylene glycol bis(allyl ether) was isolated as a colorless oil (204 mg, 81%) following purification by flash column chromatography: Rf 0.2 (EtOAc).

IR: 2868 (s), 1640 (w), 1458 (m), 1399 (m), 1297 (w), 1255 (w) 1115 (s), 925 (m) cm⁻¹.

^1_H NMR (400 MHz, CDCl3): δ = 3.23–3.66 (m, 16 H), 3.95 (d, J = 6 Hz, 2 H), 5.11 (dd, J = 10, 1 Hz, 1 H), 5.28 (dd, J = 17, 1 Hz, 1 H), 5.91 (ddt, J = 17 Hz, 10 Hz, 6 Hz, 1 H).

^13_C NMR (100 MHz, CDCl3): δ = 69.7, 70.44, 70.49, 72.1, 117.0, 134.6


Octaethylene Glycol Bis(allyl ether) (7, x = 8)

The title compound was isolated as a colorless oil (246 mg, 88%) following purification by flash column chromatography; Rf 0.2 (EtOAc).

IR: 2872 (s), 1640 (w), 1461 (m), 1294 (w), 1249 (w), 1108 (s), 927 (m) cm⁻¹.

^1_H NMR (400 MHz, CDCl3): δ = 3.30–3.66 (m, 16 H), 3.95 (d, J = 6 Hz, 2 H), 5.11 (dd, J = 10, 1 Hz, 1 H), 5.20 (dd, J = 17, 1 Hz, 1 H), 5.84 (ddt, J = 17 Hz, 10 Hz, 6 Hz, 1 H).

^13_C NMR (100 MHz, CDCl3): δ = 69.7, 70.44, 70.49, 72.1, 117.0, 134.6


Nonaethylene Glycol Bis(allyl ether) (7, x = 9)

The title compound was isolated as a colorless oil (260 mg, 85%) following purification by flash column chromatography; Rf 0.2 (EtOAc).

IR: 2877 (s), 1643 (w), 1457 (m), 1351 (m), 1301 (w), 1244 (w), 1109 (s), 925 (w) cm⁻¹.

^1_H NMR (400 MHz, CDCl3): δ = 3.30–3.66 (m, 18 H), 3.95 (d, J = 6 Hz, 2 H), 5.10 (dd, J = 10, 1 Hz, 1 H), 5.22 (dd, J = 17, 1 Hz, 1 H), 5.85 (ddt, J = 17 Hz, 10 Hz, 6 Hz, 1 H).

^13_C NMR (100 MHz, CDCl3): δ = 69.3, 70.43, 70.48, 72.1, 117.0, 134.6

The title compound was isolated as a colorless oil (307 mg, 79%) following purification by flash column chromatography; Rf < 0.1. The title compound was isolated as a colorless oil (289 mg, 80%) following purification by flash column chromatography; Rf < 0.1.

Undecaethylene Glycol Bis(ally ether) (7, x = 11)

The title compound was isolated as a colorless oil (289 mg, 80%) following purification by flash column chromatography; Rf < 0.1. The title compound was isolated as a colorless oil (289 mg, 80%) following purification by flash column chromatography; Rf < 0.1.

Undecaethylene Glycol Bis(ally ether) (7, x = 12)

The title compound was isolated as a colorless oil (307 mg, 79%) following purification by flash column chromatography; Rf < 0.1. The title compound was isolated as a colorless oil (307 mg, 79%) following purification by flash column chromatography; Rf < 0.1.

Deprotection of Oligo(ethylene glycol) Bis(ally ethers); General Procedure

To a stirred solution of the appropriate oligo(ethylene glycol) bis(ally ether) 7 (1 equiv) in MeOH–water (24:1, 5 mL/mmol) was added p-toluensulfonic acid (0.05 equiv), and 10% Pd/C [equal mass to that of protected oligo(ethylene glycol)]. The resulting reaction mixture was refluxed under an atmosphere of nitrogen and monitored by 1H NMR spectroscopy for the disappearance of 7 (2–24 h). Upon complete consumption of starting material, the reaction was filtered through a cotton plug and the filtrate was concentrated in vacuo to afford the elongated oligo(ethylene glycols) in high purity as colorless oils in 82–95% yield as indicated in Table 3. All the oligo(ethylene glycols) are known compounds.6,10

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References