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Convenient multigram synthesis of monodisperse oligo(ethylene glycols): effective reaction monitoring by infrared spectroscopy using an attenuated total reflection fibre optic probe ☆

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ABSTRACT

A convenient approach for the synthesis of monodisperse oligo(ethylene glycols) up to 12 units is described. A novel cleavage protocol replacing laborious hydrogenolysis is introduced to achieve a fast, inexpensive and widely applicable procedure. In addition to the synthetic part, Fourier transform infrared (FTIR) spectroscopy using a fibre optic attenuated total reflection (ATR) sensor was applied to monitor the formation of sensitive key intermediates, resulting in optimized reaction times. By applying this in-line technique, the possibility of real-time analysis under inert conditions was impressively demonstrated.

Oligomers of ethylene glycol (PEGs) have a wide range of applications in many fields of science and industry. They can be applied as synthons for crown ether-type derivatives,[1] non-ionic surfactants,[2] templates for the synthesis of porous inorganic materials,[3] and more recently, functional mono-layers were used to develop biocompatible material.[4] In the field of biomedical engineering 'hydrogels' prevent unspecific adsorption of proteins from biological media. Another application field is bioconjugation of proteins, in order to increase the water solubility, which serves as one of the most effective drug delivery systems.[5] As a matter of fact, the physical and chemical properties of these modified materials often depend significantly on the number of repetition units of the PEG tether.

As part of our ongoing research on PEG-grafted polystyrene resins,[6] a series of novel polystyrene-oligo(oxyethylene) graft copolymers containing monodisperse PEG units (n = 2–12, even numbers) have been synthesized and examined regarding their applicability for gel-phase ^{13}C NMR spectroscopy.[7] A stronger correlation than expected between the graft length and the line widths in the gel-phase spectra was observed. As a consequence, the demand arose to synthesize monodisperse PEGs most efficiently.

For the preparation of the resins mentioned above, we required access to well-defined oligo(ethylene glycols) of up to 12 units.[6] Despite the widespread utility of PEGs, their synthesis remains a challenging task. The published synthetic methods for commercially unavailable or expensive representatives (n >4) are usually time-consuming or include extensive purification procedures.

To the best of our knowledge, the most promising approach was published by Keegstra et al.,[8] who applied bidirectional chain elongation. Taking this sequence as a starting point, we intended to optimize the key steps in order to shorten reaction times from periods as long as several days to more acceptable values. Eliminating this major disadvantage would result in an easy to handle, fast and low-cost synthetic procedure for well-defined oligo(ethylene glycols).

The first reaction step shown in Scheme 1 (deprotonation of mono-trityl protected glycols **1a**–**b**) is reported to take at least 18 h to reach completion.

To verify this, it was necessary to monitor the conversion in an inert, anhydrous reaction medium. Encouraged by recent studies,[9] a mid-IR fibre optic probe was chosen for fast in-line monitoring of the chemical reaction under investigation. The ATR fibre system consisted of the FTIR spectrometer Bruker Matrix F® in connection with an ATR fibre probe (A.R.T. Photonics, Berlin; Ø 12 mm) and a MCT (mercury cadmium telluride) detector (Belov Technology, Co., Inc.). The probe was directly inserted through the ground neck of

☆ Dedicated to Professor Peter Stanetty on the occasion of his 65th birthday.

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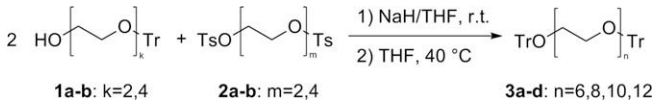


Scheme 1. Synthesis of glycols **3a–d**; monitoring via ATR-IR-sensor spectroscopy.

the reaction vessel and comprised two 1 m silver halide fibres (Ø 1 mm) connecting to a conical two bounce diamond ATR element housed in a rod of hastelloy. Using this set-up it was possible to follow the reactions to be studied in real-time covering a spectral range from 600 to 2000 wavenumbers.

The major advantage of in-line versus at-line ATR-IR-spectroscopy is that monitoring takes place inside the reaction system, thus eliminating steps such as workup of samples prior to analysis, which avoids the risk of contamination or a loss of inertness. In our work we focus on the deprotonation of the monoprotected glycols **1a–b**. The progress of these reactions can either be determined by tracking changes in absorbance values at selected wavenumbers or applying modern chemometric methods, which process the entire spectral information. Among these multivariate curve resolution, alternating least squares (MCR-ALS) needs to be mentioned.[10] This technique decomposes the recorded data set into smaller matrices containing information on the spectra and the concentration profiles of each component involved in the reaction. A recently available user friendly interface for Matlab facilitates this type of data analysis.

Indeed, measurements indicated a rapid conversion of glycols **1a–b** to the corresponding alkoxides. Absorbance values at characteristic wavenumbers for the substrate and the product, respectively, are plotted versus reaction time in Figure 1. The blue curve derives from substance **1b**, the green graph originates from deprotonated **1b**. Monitoring here did not employ the more complex MCR-algorithm, but just non-overlapped single band monitoring. The graph clearly shows that after 90 min no significant changes of absorption values can be observed, thus being an indicator for the end of the reaction.

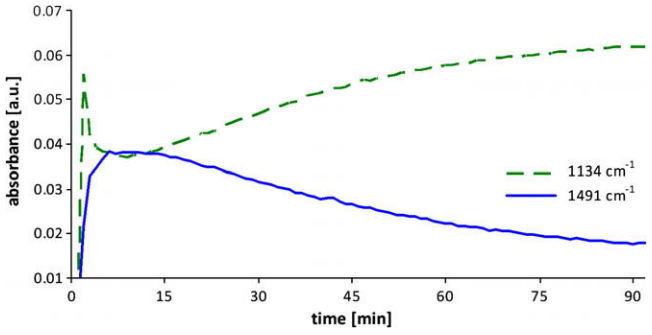


Figure 1. ATR-IR in-line monitoring for the deprotonation of monoprotected glycol **1b**. Distortions for $t \leqslant 10$ min are attributed to equilibration effects (temperature and concentration).

In fact, we could prove that this step is completed after a reaction time of 90 min for glycol **1b** and 210 min for **1a**, respectively.

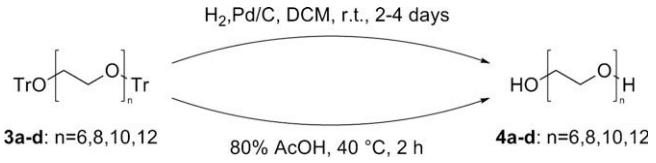
According to the original procedure, the subsequent nucleophilic reaction of the alkoxide with the tosylated glycols **2a–b** has to be performed at room temperature. Refluxing the reaction mixture in THF as a solvent to increase conversion rates leads to products, which were dark in colour and contaminated by inseparable impurities. However, optimization studies showed that performing the reaction at 40 °C shortens the time from 96 h to 58–80 h avoiding the formation of unwanted by-products[11] (Table 1).

Table 1
Reaction times and yields for the preparation of **3a–d**

Entry	Glycol **1**	Tosylate **2**	Time[a] (h)	Product **3**	Yield[b] (g)	Yield[b] (%)
1	**1a**	**2a**	4/84	**3a**	18.8	98
2	**1a**	**2b**	4/84	**3b**	165.4	97
3	**1b**	**2a**	2/60	**3c**	23.2	98
4	**1b**	**2b**	2/60	**3d**	24.6	95

[a] Times given refer to deprotonation and overall reaction time, respectively.
[b] Isolated yields.

To obtain the desired oligo(ethylene glycols) **4a–d**, the protecting groups have to be cleaved off. Virtually all published procedures use hydrogenolysis under high-pressure conditions in the presence of palladium for several days to achieve this final transformation (Scheme 2). Aside from long reaction time, this procedure suffers from some more disadvantages. The most serious one is the need for equipment allowing to perform gas reactions under high pressure, which might be a limiting factor. Furthermore, the reaction was never quantitative in our hands, always leaving small amounts of protected glycols in the product. Finally the use of halogenated organic solvents, for example, dichloromethane and transition metal catalysts might become troublesome, if the final product is intended to be used in the field of pharmaceutics or biology, especially when the procedure is performed on industrial scale.



Scheme 2. Synthesis of glycols **4a–d**; hydrogenolysis versus acidic cleavage.

Our approach was to substitute this deprotection step against a safe, fast and inexpensive procedure. To the best of our knowledge, the well known acidic cleavage of trityl groups was not reported for this substance class until now. This is quite surprising, as we could show that the usage of aqueous acetic acid leads to pure products **4a–d** in nearly quantitative yields avoiding any tedious workup or implementation of chromatographic methods (Table 2).[12] It is worth mentioning, that it is necessary to stick to the given reaction conditions (time and temperature) to prevent the formation of the corresponding diacetates.[13]

Comparing this new protocol to hydrogenolysis, the advantages are clearly visible: dramatically shortened reaction times (2 h vs 4 days), easier workup and higher product quality (purity determined by ^{1}H NMR; compared to products synthesized in our lab according to literature). Moreover, nearly the theoretical amount of triphenylmethanol (pure according to combustion analysis) is isolated during workup and can simply be transformed to tritylchloride[14] enhancing the atom efficiency of the entire synthetic route.

In summary, we have reported an optimized protocol for the synthesis of monodisperse poly(ethylene glycols) up to 12 units. In contrast to other approaches described in literature, neither special equipment for high pressure hydrogenolysis nor any chromatographic purification is needed for the key steps of the sequence, making it attractive for especially large scale or industrial applications. In-line ATR-IR spectroscopy was shown to be a powerful analytical tool for the effective monitoring of 'problematic' processes. Due to the non invasive nature, this promising technology might arise as *the* solution for examining reactions

Table 2
Yields for the preparation of **4a–d**

Entry	Tritylate **3**	Product **4**	Yield[a] (g)	Yield[a] (%)
1	**3a**	**4a**	5.5	98
2	**3b**	**4b**	53.2	96
3	**3c**	**4c**	9.0	98
4	**3d**	**4d**	10.8	99

[a] Isolated yields; reaction conditions: 80% AcOH, 40 °C, 2 h.

under inert conditions. The scope of possible applications is widespread. In the field of organic chemistry one can imagine to apply this technique to, for example, metalation reactions, deprotonations, catalytic reactions under inert atmosphere (transition metal assisted coupling, olefin metathesis), etc. Experimental work covering some of these projects is already in progress. Furthermore, the possibility of elucidation of reaction mechanisms by monitoring transition states is clearly visible. This field of application is more sophisticated and will therefore be the aim of future projects.

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Supplementary data

Supplementary data (experimental details and compound characterization data of substances **3a–d** and **4a–d**, copies of spectra (^{1}H NMR, ^{13}C NMR, IR)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.010.

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11. Synthesis of 1,1,1,27,27,27-hexaphenyl-2,5,8,11,14,17, 20,23,26-nonaoxaheptacosane **3b**. Under argon, a 4-neck round bottom flask equipped with mechanical stirrer, reflux condenser, thermometer (and dropping funnel, respectively) and the ATR-IR Probe inlet was charged with sodium hydride (12.00 g, 500 mmol, 2.5 equiv) and dry THF (500 mL). To the well stirred suspension was added a solution of mono-trityl protected glycol **1a** (139.38 g, 400 mmol, 2.0 equiv) in dry THF (500 mL) at room temperature. After completion of the reaction according to IR-monitoring (4 h), the mixture was cooled to 0 °C and a solution of di-tosylated glycol **2b** (100.52 g, 200 mmol, 1.0 equiv) in dry THF (500 mL) was added. The temperature was adjusted to 40 °C and the suspension was stirred for 80 h. For workup, the reaction mixture was poured onto ice water (1200 mL)/chloroform (800 mL). The phases were separated and the aqueous phase was extracted with chloroform (500 mL). The combined organic layers were washed with brine (500 mL) and dried over sodium sulfate. After removing the solvent under reduced pressure, the title compound was obtained as a clear, slightly orange, viscous oil. Yield: 165.36 g (97%). ^{1}H NMR (200 MHz, DMSO-d_6) δ = 7.48–7.15 (m, 30 H), 3.67–3.39 (m, 28 H), 3.06 (t, J = 4.8 Hz, 4 H); ^{13}C APT NMR (50 MHz, DMSO-d_6) δ = 143.8 (s), 128.2 (d), 127.8 (d), 126.9 (d), 85.9 (t), 70.1 (t), 69.9 (t), 69.85 (t), 69.82 (t), 69.77 (t), 69.7 (t), 63.0 (t). Anal. Calcd for $C_{54}H_{62}O_9$ (855.09): C, 75.85; H, 7.31. Found: C, 76.15; H, 7.15; N, <0.05.
12. Synthesis of 3,6,9,12,15,18,21-heptaoxatricosane-1,23-diol **4b.** Compound **3b** (128.26 g, 150 mmol) was stirred with 80% acetic acid (1200 mL) at 40 °C. After 2 h the reaction was completed according to HPLC analysis. The mixture was allowed to cool to room temperature and poured onto ice water (600 mL). The precipitate was filtered off over a glass sinter funnel. The filtrate was concentrated under reduced pressure leaving a cloudy oil. The crude product was mixed with cold water (500 mL) and the suspension was again filtered over the same glass sinter funnel, still containing the bed of triphenylmethanol formed during the first filtration. The filter cake was washed with cold water, giving 77.02 g (99%) of pure triphenylmethanol after drying at 40 °C/15 mbar. The solvent of the filtrate was removed under reduced pressure (0.05 mbar) to afford the title compound as a clear, slightly orange oil. Yield: 53.20 g (96%). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.62–3.38 (m, 32 H), 3.30 (br s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 72.2, 70.15, 70.10, 69.9, 61.1. Anal. Calcd for $C_{16}H_{34}O_9$ (370.44): C, 51.88; H, 9.25. Found: C, 51.81; H, 9.34; N, <0.05.
13. Increasing reaction temperature from 40 °C to reflux and prolonging reaction times from 2 h to 3 d results in almost a quantitative formation of the corresponding diacetates. However, these can be converted into the desired glycols by sodium methanolate-catalyzed transesterification.
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