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A practical synthesis of (11-mercaptoundecyloxy)-triethylene glycol: a valuable precursor for multicomponent self-assembled monolayers

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$HSC_{11}EG_3OH$ (**1**) is an important component for formation of protein-resistant self-assembled monolayers on gold. Chromatography of small molecules containing oligoethylene units, such as **1** and its synthetic intermediates, are typically complicated by smearing on TLC, making separation tedious. We have developed a convenient modification for synthesis of **1** by using a UV–visible intermediate facilitating column chromatography of the desired compound.

Keywords: thiolates; SAM; chromatography; antifouling; chromaphore

1. Introduction

Self-assembled monolayers (SAMs) are part of a maturing technology platform for developing bioanalytical devices, in particular for protein biomarkers (*1*). Compound $HSC_{11}EG_3OH$ (**1**, Figure 1), first developed by Whitesides, is a valuable precursor for making SAMs (*2*, *3*). In these earlier studies by Whitesides, compound **1** was shown to have the minimum number of repeating ethylene glycol units (three) required for protein resistance. The shorter length of the triethylene glycol termini affords higher surface density of SAMs on the gold surface. Compound **1** has been extensively used either by itself or as part of a mixture for the preparation of SAMs, where it serves as the key component for resisting non-specific protein binding to the exposed monolayer surface (*4*–*7*). Previous research in our group has shown compound **1** to be particularly effective as a co-thiol in mixed SAMs incorporating aptamers that bind proteins (*8*). Aptamers are artificial receptors composed of DNA or RNA sequences that are evolved *in vitro* (*e.g.* by SELEX methods (*9*)) toward binding target molecules of interest such as proteins, cells, and small molecules (*10*). Findings from our group have shown that not only does compound **1** provide effective protein anti-fouling resistance, it also facilitates higher surface density of aptamer-containing thiols compared with other co-thiols such as the commonly used mercaptohexanol (*8*).

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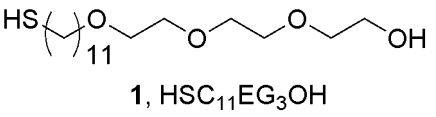

1, $HSC_{11}EG_3OH$

Figure 1. Compound **1**: (11-mercaptoundecyloxy)-triethylene glycol (or $HSC_{11}EG_3OH$).

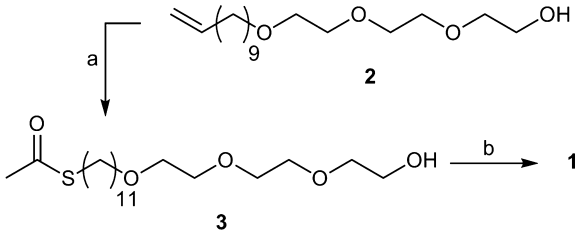

Figure 2. Initial strategy towards the synthesis of thiol $HSC_{11}EG_3OH$ **1**[1]: (a) AcSH, AIBN, hν, 88%; (b) 0.1 M HCl, 90%.

As part of an ongoing program of aptamer-based surface sensors, a practical synthetic procedure was developed to facilitate the synthesis of compound **1**.

Compound **1** is typically prepared by the addition of thiolacetic acid to terminal olefin **2** to form thioester **3**, followed by saponification to give thiol **1** (Figure 2) (*2*, *11*).[1] The products are purified by silica gel chromatography, although none of the compounds (**1**, **2**, or **3**) incorporate a UV chromophore. The lack of a chromophore is typically not a concern; however, these molecules streak during TLC and are hard to resolve cleanly. This smearing, combined with difficulty in visualization, makes silica-gel chromatography tedious.

2. Results and discussion

We have found that a simple modification of the procedure using thiobenzoic acid in place of the thiolacetic acid provides an easily purified reaction sequence suitable for preparation of **1** (Figure 3). The thiobenzoate provides a UV chromophore (making both reactions in scheme 2 easier to monitor by TLC) resulting in a dramatically easier purification. The R_f values for the thiobenzoic acid intermediate is roughly similar to that of the thiolacetic acid derivative (approximately 0.5 for both in a mixture of 95:5-methylene chloride:methanol); however, there is always significant overlap of compounds **3** and **4** with compound **2**. The advantage of compound **4** is that UV visualization during chromatography allows for much cleaner resolution, while separation of **3** from **1** often requires multiple separations to obtain a clean product. The thiobenzoate also makes the characterization simpler as the aromatic protons are easily distinguishable in the ^{1}H NMR.

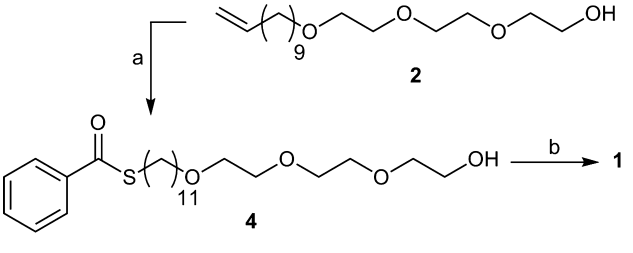

Figure 3. Improved synthesis of thiol $HSC_{11}EG_3OH$ **1**: (a) BzSH, AIBN, hν, 76%; (b) NaOH, 91%.

While the replacement of the thioacetate with a thiobenzoate is a modest change, this simple modification greatly facilitated the synthesis of compound **1** through faster separation of the product mixtures. This factor, coupled with the lower volatility and stench of thiobenzoic acid compared with thiolacetic acid, makes this new approach an attractive alternative to the existing procedure. For these reasons, we believe that this simple sequence will find utility for preparation of this and similar thiol-terminated SAM precursors. Furthermore, this methodology should be equally applicable for other polyethylene glycol containing substrates.

3. Experimental

3.1. *Materials and methods*

Starting materials were used as purchased. Olefin **2** was prepared according to the procedure of Whitesides and coworkers (*2*). All solvents were deoxygenated by sparging nitrogen flow through the solvents. Irradiation was done with a medium pressure mercury UV pen lamp powered by a Spectroline model SCT-1 power supply.

3.2. *Synthesis of precursor thiobenzoic acid S-(11-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-undecyl) ester 4 (Scheme 2)*

Olefin **2** (177 mg, 0.48 mmol, 1.0 eq.) was placed into a 20 ml scintillation vial with magnetic stirring. MeOH (5 ml) was added, followed by thiobenzoic acid (169 μl, 1.45 mmol, 3.0 eq.) and AIBN (ca. 5 mg). The vial was purged with argon and irradiated with a medium pressure mercury UV lamp for 17 h, resulting in a yellow solution with white solids. The solution was filtered through a plug of SiO_2 (ca. 200 mg) and concentrated *in vacuo*. Radial chromatography (95:5 chloroform:methanol) afforded a clear oil (160 mg, 0.36 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.5 (m, 1H), 7.40 (m, 2H), 3.58 (m, 12H), 3.4 (t, 2H), 3.02 (t, 2H), 2.88 (s, 1H), 1.60 (m, 4H), 1.51 (m, 2H), 1.23 (m, 12H). ^{13}C (75 MHz, $CDCl_3$): δ91.2, 137.1, 133.0, 128.4, 126.9, 72.3, 71.4, 7.4, 70.2, 69.8, 61.5, 44.2, 33.9, 33.2, 29.4, 29.3, 29.2, 28.9, 28.8, 26.7, 25.9. $C_{24}H_{41}O_5S$, mass (calc.) 441.2669, mass (found) 441.2666.

3.3. *Preparation of 2-{2-[2-(11-mercapto-undecyloxy)-ethoxy]-ethoxy}-ethanol 1 (Scheme 2)*

Thiobenzoate **4** (56 mg, 0.13 mmol) was placed into a scintillation vial with magnetic stirring under argon. Methanol (5 ml) and THF (5 ml) were added, followed by the addition of aqueous 0.2 M NaOH (2.5 ml). The reaction was stirred for 1 h, then the reaction was diluted with sat. $NaHCO_3$ (20 ml), extracted with CH_2Cl_2 (3 × 25 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude product (69 mg). Chromatography (2:98 methanol:methylene chloride) yielded the product as a clear oil (39 mg, 0.12 mmol, 91%). Spectral data matched that of **1** prepared earlier. ^{1}H NMR (300 MHz, $CDCl_3$p: δ3.65 (m, 12H), 3.44 (t, 2H), 2.52 (m, 4H), 1.6 (t, 4H), 1.35(m, 14H). ^{13}C (75 MHz, $CDCl_3$): δ 72.5, 71.6, 70.6, 70.3, 69.9, 61.7, 34.0, 29.5, 28.3, 26.0, 24.6. $C_{17}H_{37}O_4S$, mass (calc.) 337.2407, mass (found) 337.2414.

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Note

1. Other syntheses have been published to overcome difficulties with the radical addition; however, we did not experience any significant problems with the addition other than slightly lower yields than those reported in (*1*).

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