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EFFICIENT TWO-STEP SYNTHESIS OF 11,11'-DITHIOBIS[1-(2-BROMO-2-METHYLPROPIONYLOXY)UNDECANE], A CONVENTIONAL INITIATOR FOR GRAFTING POLYMER BRUSHES FROM GOLD SURFACES VIA ATRP

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11,11'-Dithiobis[1-(2-bromo-2-methylpropionyloxy)undecane], a conventional initiator for grafting polymers from gold surfaces, was synthesized in two steps from 11-mercapto-1undecanol in 88–92% overall yield. Oxidative dimerization of 11-mercapto-1-undecanol with a catalytic amount of sodium iodide and 30% hydrogen peroxide in ethyl acetate proceeded in 96% yield. Esterification with 2-bromoisobutyryl bromide in dichloromethane was clean and almost quantitative (92% yield) with pyridine used as base, whereas triethylamine gave a messy reaction (64% yield). Alternatively, esterification with 2-bromo-2-methyl-propanoic acid in dichloromethane occurred readily under Steglich's conditions with N,N-dicyclohexylcarbodiimide (DCC) and a catalytic amount of dimethylaminopyridine (DMAP; 88% yield).

Keywords: Atom transfer radical polymerization (ATRP); gold surface; self-assembled initiator monolayer; Steglich esterification

INTRODUCTION

The seminal discovery by Nuzzo and Allara^[1] at the Bell Laboratories that gold surfaces can be conveniently functionalized with self-assembled monolayers of alkanethiols gave a tremendous boost to the field of surface engineering.^[2] In the course of our ongoing investigations^[3,4] on the synthesis of triblock copolymers by "grafting from" gold surfaces, we were in need of an efficient synthesis of the atom transfer radical polymerization initiator 11,11′-dithiobis[1-(2-bromo-2-methylpropionyloxy)undecane] (3) (Scheme 1). A previously reported pioneering synthesis^[5] (synthesis I; Scheme 1) relied on the dimerization of 11-mercapto-1-undecanol **1** with toxic bromine as a first step, followed by acylation of the resulting diol **2** with 2-bromoisobutyryl bromide and triethylamine as base. 2-Bromoisobutyryl bromide is a very strong acylating agent which may react with the excess of triethylamine and/or the disulfide bridge present in diol **2**. The moderate reported yield of 64% led us to presume that uncontrolled collateral reactions had taken place. In fact, this

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Scheme 1. Syntheses of 11,11'-dithiobis[1-(2-bromo-2-methylpropionyloxy)undecane] 3: Synthesis I (Ia) $Br_2/DCM/10\%$ KHCO₃/25°C; (Ib) TEA/DCM/0–25°C/24 h; synthesis II (IIa) cat. NaI/30% H₂O₂/AcOEt/0–5°C/1 h; (IIb) method A cat. DMAP/DCC/DCM/24 h; method B Py/DCM/0–25°C/24 h.

was the case when we repeated Shah's procedure^[5] (synthesis I). Lowering the initial reaction temperature to -70 °C did not improve the yield. We therefore conducted a more thorough investigation, which resulted in a satisfactory improvement of the yield. Details of the strategy are discussed in the following article.

RESULTS AND DISCUSSION

The synthesis of the diol **2** from 11-mercapto-1-undecanol **1** has been previously reported using sodium borate (92% yield),^[6] stochiometric iodine in methanol (90% yield),^[7] N-phenyltriazolinedione in toluene (61% yield),^[8] or starting from 11-bromoundecanol using sodium thiosulfate and iodine in water/ethanol.^[9]

We went a step further and applied a recently described mild and general method for dimerization of thiols reported by Kirihara et al.,^[10] who used a

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catalytic amount of sodium iodide and hydrogen peroxide in ethyl acetate. When we subjected the precursor 11-mercapto-1-undecanol (1) (Scheme 1; synthesis II) to Kirihara's conditions, the reaction was strongly exothermic and terminated in a few minutes. When we repeated the reaction at 0-5 °C, there was no exothermic effect, the product precipitated gradually from the reaction mixture, and the reaction was completed after 1 h. To ensure high purity and yield, we ultimately crystallized the product from methanol. With these modifications, the desired diol **2** was obtained in 96% yield.

In the second step, we observed a messy reaction when using the strong acylating agent 2-bromoisobutyryl bromide and triethylamine as base according to the seminal procedure by Shah et al.^[5] (synthesis I), which was cited and utilized for the synthesis of diester **3** in numerous subsequent publications^[3,4,11–26] without substantial modification.

To improve the yield of this step, we envisaged two strategies: changing the acylating agent and changing the base (synthesis II, methods A and B). We therefore applied Steglich's esterification conditions^[27] using 2-bromo-2-methyl-propionic acid, a catalytic amount of DMAP, and a slight excess of DCC (synthesis II, method A) in analogy to a previously reported synthesis^[28] of structurally related polymerization initiator 2,2'-dithiobis[1-(2-bromo-2-methylpropionyloxy)ethane] (5)^[29-41] (Scheme 2).

In contrast to diester **3**, which has been synthesized always by the same procedure, diester **5** was synthesized according to three different protocols, namely Shah,^[29,30,34,38] Tsarevsky,^[28,31,35,39,41] and Matsuura.^[32,33,36,40]

2-Bromo-2-methyl-propanoic acid reacted with DCC exothermically and afforded the corresponding isourea derivative in situ. A catalytic amount of DMAP smoothly catalyzed the esterification at 5 °C but because it was difficult to assess the endpoint of the heterogeneous reaction, stirring at room temperature was continued overnight to assure complete conversion. The reaction mixture was directly poured on a column of silica gel, which had previously been conditioned with dichloromethane, and the product was eluted in high purity and yield. Other by-products in the reaction mixture spotted by thin-layer chromatography (TLC) were not eluted and did not contaminate the desired diester $\mathbf{3}$, which was gratifyingly obtained in 88% yield. The diester $\mathbf{3}$ was sensitive to oxydative degradation upon sustained exposure to air and should thus be stored under nitrogen.

Triethylamine is often replaced by the more expensive but sterically more hindered N-ethyldiisopropylamine (Hünig's base),^[42] which has proven to be effective in alkylations and acylations. Pyridine is less basic and more nucleophilic because of the sp² character of the lone electron pair on the nitrogen. In research, pyridine is widely used for acylations especially in combination with acid anhydrides. Matsuura^[32] obtained 82% yield when using pyridine as base for the synthesis of the shorter chain analogous polymerization initiator **5** (Scheme 2, Matsuura's method). By applying Matsuura's conditions to the diol **2**, we obtained the desired diester **3** in 92% yield (synthesis II, method B). Thus, most likely the real culprit for the diminished yield in Shah's procedure^[5] is triethylamine and not 2-bromoisobutyryl bromide. In fact, these two reagents, when mixed in the absence of the diol **2**, gave rise to a brown tar, which was found to be a multicomponent mixture by ¹H NMR.



Scheme 2. Syntheses of shorter chain polymerization initiator 5: Matsuura's method $Py/CHCl_3/0-25$ °C/24 h; Tsarevsky's method cat. DMAP/DCC/THF.

CONCLUSIONS

In summary, we have developed a practical and efficient two-step synthesis for the gold surface polymerization initiator 2-bromo-2-methyl-propanoic acid 11-[[11'-(2-bromo-2-methyl-1-oxopropoxy)undecyl]dithio]undecyl ester (3) by exploiting procedures established for shorter chain anolog 5. To our knowledge, these procedures have not been applied productively to the synthesis of the longer chain analog 3. We did not see an obvious reason why researchers had continued to use the procedure described by Shah et al.^[5] despite its nonoptimized yield. This triggered us to search for improvements, and here we suggest a solution.

EXPERIMENTAL

11,11'-Dithiobis-1-undecanol (2)

11-Mercapto-1-undecanol (1) (10.2 g, 48.4 mmol) and a catalytic amount of sodium iodide (73 mg, 0.484 mmol) were dissolved in AcOEt (100 mL) under nitrogen and cooled in ice. Then 30% hydrogen peroxide (5 ml, 48.4 mmol) was added

slowly from a dropping funnel. The product started to precipitate partially a few minutes after the addition of hydrogen peroxide. The reaction temperature did not rise. Cooling and stirring in ice was continued for 1 h. AcOEt, which partially dissolved the product, was evaporated from the suspension. Then MeOH (100 mL) was added, and the suspension was stirred in ice for 15 min. The solid was filtered off, washed twice with cold MeOH (2×20 mL), and thoroughly dried first at $20 \text{ mbar}/25 \,^{\circ}\text{C}$ for 1 h and then at 0.01 mbar/40 $^{\circ}\text{C}$ overnight to afford 9.5 g (96%) of white crystals. Mp 83 $^{\circ}\text{C}$. ¹H NMR (400 MHz, CDCl₃) δ =1.22–1.42 (m, 30 H, CH₂), 1.56 (quin, 4 H, CH₂CH₂S), 1.66 (quin, 4 H, CH₂CH₂O), 2.67 (t, *J*=8 Hz, 4 H, SCH₂), 3.63 (t, *J*=8 Hz, 4 H, OCH₂). MS (ESI+): *m/z*=429 (M+Na)⁺. MS (ESI-): *m/z*=441 (M+Cl)⁻. TLC on silica gel in hexane–AcOEt 2:1, R_f=0.23.

11,11'-Dithiobis[1-(2-bromo-2-methylpropionyloxy)undecane] (3)

Method A. 11,11'-Dithiobis-1-undecanol (2) (5 g, 12.3 mmol) was suspended under nitrogen in DCM (100 mL). 2-Bromo-2-methylpropionic acid (4.3 g, 25.8 mmol) and N,N'-dicyclohexylcarbodiimide (DCC) (5.33 g, 25.8 mmol) were added, the latter in portions. These two reagents reacted exothermically, leading to a rise in temperature of 10 °C. The reaction mixture was cooled in ice and treated with a catalytic amount of 4-dimethylaminopyridine (DMAP) (315 mg, 2.58 mmol). Stirring in ice was continued for 5 h, and then the mixture was allowed to warm to room temperature overnight. The reaction mixture was directly purified by chromatography on silica gel (column 12 cm high, 8 cm in diameter) in DCM to afford 7.6 g (88%) of colorless oil.

Method B. 2-Bromoisobutyryl bromide (1.36 mL, 10.8 mmol) was added dropwise to a stirred suspension of 11,11'-dithiobis-1-undecanol (2) (2 g, 4.9 mol) and dry pyridine (0.975 mL, 10.8 mmol) in dry dichloromethane (40 mL) at 0-5 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0-5 °C for 2 h and then at room temperature for 24 h. Afterward, the mixture was diluted with DCM (60 mL) and extracted with cold 1 N HCl (2 × 100 mL), saturated NaHCO₃ (2 × 100 mL), and saturated NaCl (1 × 100 mL). All aqueous phases were back-extracted with DCM (1 × 100 mL). The crude product (3.7 g) was purified by chromatography on silica gel in hexane/DCM 1:1 to afford 3.2 g (92%) of colorless oil.

¹H NMR (400 MHz, CDCl₃) $\delta = 1.28$ (s, 20 H, CH₂), 1.37 (m, 8 H, CH₂ CH₂CH₂O/S), 1.64 (m, 8 H, CH₂CH₂O/S), 1.93 (s, 12 H, CH₃), 2.67 (t, J = 8, 4 H, SCH₂), 4.16 (t, J = 8, 4 H, OCH₂). ¹³C NMR (100 MHz, CDCl₃) $\delta = 26.21$ (CH₂), 28.77 (CH₂), 28.95 (CH₂), 29.59 (CH₂), 29.64 (CH₂), 29.65 (CH₂), 29.89 (CH₂), 31.22 (CH₂), 39.59 (CH₂S), 56.44 (C), 66.58 (CH₂O), 172.16 (C=O). MS (ESI+): m/z = 727 (M + Na)⁺. MS (ESI-): m/z = 783 (M + Br)⁻. TLC on silica gel in hexane/DCM 1:1, R_f = 0.33.

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