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COMMUNICATION

**Preparation of 7-azidocarbonyl-2,4,9-trithiaadamantane by a new thioacetal crown synthetic method**

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A new method for synthesizing thioacetal crown is reported for the effective synthesis of 7-methoxycarbonyl-2,4,9-trithiaadamantane. Application of this intermediate in the synthesis of 7-azidocarbonyl-2,4,9-trithiaadamantane, a photoreactive surface linker for photolithographic chemical patterning on self-assembled monolayers on gold surfaces, is also reported.

*Keywords:* 2,4,9-trithiaadamantane; 7-methoxycarbonyl-2,4,9-trithiaadamantane; 7-azidocarbonyl-2,4,9-trithiaadamantane

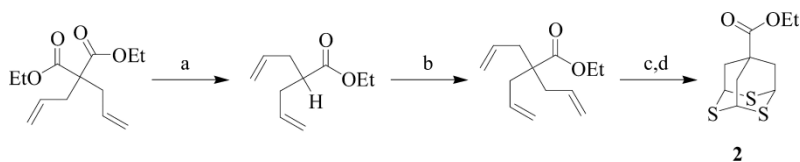
As a part of our continuous effort in the design and synthesis of sulfur containing ligands for self-assembled monolayers on gold surfaces [1, 2], we recently reported the utilization of 7-diazomethylcarbonyl-2,4,9-trithiaadamantane (**1**) as a surface anchor for the preparation of photo-labile SAMs on a gold surface [3]. The trithiaadamantane moiety of **1** served as a chelating ligand for the polycrystalline Au (111) surface and the diazomethylcarbonyl group displayed typical photo-induced Wolff rearrangement reactivity on a gold surface. Subsequent dark reactions at the UV-exposed surface allowed photolithographic chemical patterning on the gold surface effectively. The high chemical stability of the surface anchor and the high reactivity of the end groups in the corresponding SAMs provided a robust solution for photolithographic attachment of organic and biomolecules on gold films. A limitation of using diazomethylcarbonyl compounds is the generation and use of diazomethane which is highly toxic, explosive and volatile. Similar to the Wolff Rearrangement, carbonyl azides undergo photo- and thermal dissociation rearrangement to form isocyanates. Known as the Curtius Rearrangement, it is also a common method for photochemical cross-linking. In this report, we describe an improved synthesis of the key intermediates 2,4,9-trithiaadamantane (**2** and **3**) and the synthesis of the corresponding 7-azidocarbonyl-2,4,9-trithiaadamantane (**4**) as a new surface photoreactive anchor. In addition to the SAM applications, we found that the tridentate sulfur ligand coordinates to several transition metals and metal clusters, which show much potential for use in supramolecular coordination assemblies and homogeneous catalysis.

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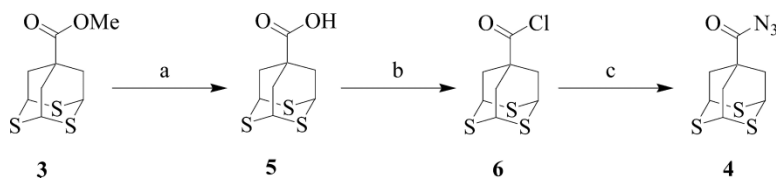
The new synthesis of 2,4,9-trithiaadamantane derivatives will provide essential materials for the future explorations of this novel ligand.

The 7-substituted 2,4,9-trithiaadamantane derivatives are difficult to synthesize due to the major limitations in the thioacetal crown formation from ethyl or methyl triallylacetate using the method reported by Lindgren (Scheme 1) [4, 5]. The reagents used in the reaction, including HCl, H<sub>2</sub>S and ZnCl<sub>2</sub>, are difficult to quantify and handle. Usually less than 5% of the desired product is produced in a complex reaction mixture. Separation and purification of the reaction product require multiple flash column chromatography or HPLC. We sought a new thioacetal synthesis method to replace the Lindgren synthesis to improve the efficiency of the overall synthesis. We found that a better yield of thioacetal crown (15–20%) can be achieved by treating the ozonolysis product (Scheme 1, c) with P<sub>4</sub>S<sub>10</sub> in refluxing acetonitrile (Scheme 1, d). Recently, methods for synthesizing thioacetal crowns using Lawesson's reagent were reported. Several bowl shaped crown thioacetals were thus produced using this new method [6–8]. However, when this approach was applied to the Lindgren's synthesis, only a little thioacetal crown was produced as indicated by TLC and crude NMR monitoring (less than 2% by NMR). It was discovered that a combination of Lawesson's reagent and boron trifluoride etherate in refluxing methylene chloride was necessary to promote the crown thioacetal formation. Under the optimized reaction conditions, product **2** was obtained in 30–40% yields with common flash chromatographic techniques using silica gel. The exact mechanism of action for BF<sub>3</sub> in the reaction is unclear. Lindgren's method used H<sub>2</sub>S as the sulfur source and HCl/ZnCl<sub>2</sub> as the acid. In our case, Lawesson's reagent serves as the sulfur source and BF<sub>3</sub> serves as the acid. Usually, Lawesson's reagent also serves as the Lewis acid in such reactions to pick up the oxygen due to the strong O=P bond. The use of ZnCl<sub>2</sub> in the Lindgren's method may not be optimum because of the strong S–Zn interaction. In addition, the high solubilities of Lawesson's reagent and BF<sub>3</sub> in the reaction mixture seem to be vital for the reaction to proceed effectively. The combination of the Lawesson's reagent with a Lewis acid is a new synthetic methodology for introducing sulfur atoms into organic molecules.

For the synthesis of the photoactive surface linker, 7-methoxycarbonyl-2,4,9-trithiaadamantane (**3**) was prepared from dimethyl diallylmalonate (Scheme 2). We initially explored the synthetic sequence (Scheme 1) using diethyl diallylmalonate as the starting material. We eventually chose the homologous dimethyl diallylmalonate because the decarboxylation reaction proceeds much faster with the methyl ester, which reduced the decarboxylation reaction time from 100 h to 25 h (Scheme 1, a). The change from the ethyl ester to the methyl ester did not seem to have any adverse effect on the overall synthesis. Hydrolysis of **3** was almost quantitative when carried out in a mixed solvent of THF : methanol : water using LiOH · H<sub>2</sub>O as the base. The resulting acid (**5**) from the hydrolysis and neutralization was converted to the corresponding acid chloride (**6**) upon treatment with thionyl chloride in CH<sub>2</sub>Cl<sub>2</sub>. The acid chloride was allowed to react with NaN<sub>3</sub> in water at 0 °C to furnish the 7-azidocarbonyl-2,4,9-trithiaadamantane (**4**) as a white crystalline solid. The overall synthetic



SCHEME 1 Synthesis of 7-ethoxycarbonyl-2,4,9-trithiaadamantane; a) NaCl, H<sub>2</sub>O, DMSO, Δ, 100 h; b) LDA, allyl bromide, HMPA, THF, –78 °C, 2 h then NH<sub>4</sub>Cl, r.t.; c) O<sub>3</sub>, Ethanol, –78 °C PPh<sub>3</sub> then r.t.; d) H<sub>2</sub>S, HCl.CH<sub>3</sub>CH<sub>2</sub>OH, reflux.



SCHEME 2 Reagents and conditions: a)  $\text{LiOH} \cdot \text{H}_2\text{O}$ ,  $\text{THF} : \text{MeOH} : \text{H}_2\text{O}$  (3 : 3 : 1), r.t. then reflux,  $\text{HCl}$  (6 M); b)  $\text{SOCl}_2$ ,  $\text{CH}_2\text{Cl}_2$ , reflux 30 min; c)  $\text{NaN}_3$ ,  $(\text{CH}_3)_2\text{CO} : \text{H}_2\text{O}$ ,  $0^\circ\text{C}$ , 2 h.

sequence is straightforward and effective without a protection group and with minimum separation and purifications. During these reactions the sulfur crown displayed chemical stability that is unmatched with other gold surface anchors such as alkyl thiols.

The development of the new synthetic method for the thioacetal crown allowed us to produce several derivatives of the 7-substituted-2,4,9-trithiaadamantane in appreciable quantities. Just as shown in the synthesis of the photoreactive surface linkers for photolithographic chemical patterning on self-assembled monolayers on gold surfaces, these compounds represent a new class of tridentate ligand for transition metals, metal clusters and surfaces. The effective syntheses of the key intermediates described in this report should provide essential materials for the future development of the tripodal ligand.

## 1. Experimental section

### 1.1 General procedures

All air and/or moisture sensitive reactions were conducted under an argon atmosphere. Common reagents were purchased from Aldrich and ACROS and used as received. All solvents were reagent grade. All  $^1\text{H}$  NMR (300 MHz) and  $^{13}\text{C}$  NMR (75 MHz) spectra were recorded on a Varian Gemini-300 spectrometer. NMR spectra were recorded in  $\text{CDCl}_3$ . IR spectra were recorded on a Nicolet NEXUS 870 FT-IR spectrometer equipped with a Thunderdom ATR accessory.

### 1.2 Synthesis of 7-methoxycarbonyl-2,4,9-trithiaadamantane (3)

To a solution of methyl triallyl acetate (**1**) (2.85 g, 13.70 mmol) in methylene chloride (100 mL) at  $-78^\circ\text{C}$  was bubbled through an ozone/oxygen mixture from an ozone generator until the reaction mixture displayed a light blue colour. Excess ozone was removed by bubbling argon through the reaction mixture for 10 min. Dimethyl sulfide (3.5 mL, 41.10 mmol) was added to the reaction mixture at  $-78^\circ\text{C}$  and the resulting reaction mixture was allowed

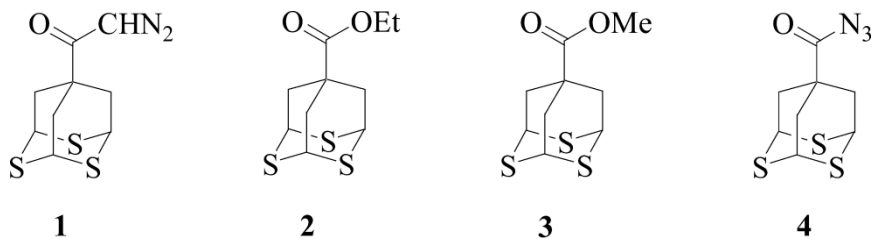


Figure 1. 7-Substituted 2,4,9-trithiaadamantane derivatives.

to slowly warm up to the ambient temperature. To the above reaction mixture, methylene chloride (100 mL), Lawesson's reagent (5.54 g, 13.70 mmol) and boron trifluoride (5.80 mL, 41.10 mmol) were added respectively. The reaction mixture was then refluxed for 100 h. Additional methylenechloride was added (100 mL) during the reflux. The reaction mixture was then treated with aqueous  $K_2CO_3$  (3 mL, 5.0 M) while cooling. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The resulting mixture was purified by column chromatography using 30% methylenechloride in hexane to give 7-methoxycarbonyl-2,4,9-trithiaadamantane (**3**) (1.23 g, 38% yield). M.P. 149–151 °C.  $^1H$  NMR  $\delta$ : 4.33 (t, 3H, SCHS), 3.76 (s, 3H, OCH<sub>3</sub>), 2.92 (d, 6H,  $J = 3.60$  Hz, CH<sub>2</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 4.33 (t, 3H, SCHS) ppm;  $^{13}C$  NMR  $\delta$ : 38.69, 40.05, 41.38, 52.62, 175.62 ppm; FTIR: 2944, 2923, 1740, 1724, 1446, 1430, 12840, 1276, 1267, 1212  $cm^{-1}$ .

### 1.3 Synthesis of 7-hydroxycarbonyl-2,4,9-trithiaadamantane (**5**)

To a solution of **3** (175 mg, 0.66 mmol) in a solvent mixture of tetrahydrofuran : methanol : water (2 mL, 3 : 3 : 1 volume) in a 10 mL pear-shaped flask connected to a reflux condenser was added LiOH·H<sub>2</sub>O (140 mg, 6.6 mmol). The reaction mixture was stirred at room temperature for 1 h and refluxed for 15 min. The reaction mixture was diluted with water (2 mL), cooled with an ice bath and acidified to pH ~ 2 with aqueous HCl (6M). Filtration and vacuum drying overnight afforded a light yellow solid of 7-hydroxycarbonyl-2,4,9-trithiaadamantane (**5**) (140 mg, 90% yield). M.P. 235–237 °C.  $^1H$  NMR  $\delta$ : 4.36 (t, 3H, CH), 2.96 (d, 6H, CH<sub>2</sub>) ppm;  $^{13}C$  NMR  $\delta$ : 202.11, 42.09, 39.41, 38.90 ppm; FTIR: 2933, 2920, 1695, 1445, 1421, 1300, 1277, 1184, 1103, 1042, 1000, 930, 830  $cm^{-1}$ .

### 1.4 Synthesis of 7-azidocarbonyl-2,4,9-trithiaadamantane (**4**)

To an ice-cooled solution of **5** (140 mg, 0.59 mmol) in methylene chloride (2 mL) was added thionyl chloride (1.5 mL, 3.0 mmol, 2.0 M in methylene chloride) dropwise. The resulting reaction mixture was refluxed for 2 h. After evaporation of the solvent and excess of thionyl chloride under vacuum, a yellow crystalline was produced. The yellow solid was dissolved in acetone (2 mL) and to the resulting solution was added sodium azide (47 mg, 0.72 mmol) in water (1 mL) at 0 °C. After stirring for 2 h, 10 mL of water was added to the reaction mixture. The resulting mixture was then extracted with methylene chloride (3 × 5 mL). The organic layers were combined and dried over anhydrous sodium sulfate. After the solvent was removed by a rotatory evaporator, **4** was produced as a white crystalline solid (141 mg, 91% from **5**). The compound is sensitive to light and heat and must be kept in a cool and dark place. M.P.: 106–107 °C (decomposed).  $^1H$  NMR  $\delta$ : 2.87 (d, 6H, CH<sub>2</sub>), 4.34 (t, 3H, SCHS), 2.87 (d, 6H, CH<sub>2</sub>) ppm.  $^{13}C$  NMR  $\delta$ : 182.80, 44.47, 41.30, 40.58, 39.97, 39.38 ppm. FTIR 2922, 2148, 1698, 1447, 1425, 1286, 1248, 1173, 1148, 1100, 1007, 960, 920, 858, 732, 707  $cm^{-1}$ .

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