

Clayton Scruggs was awarded the prize for best paper in the Physical & Applied Sciences category.

# **Clayton Scruggs**

## **A Quantitative Comparison of Three Cost-Effective Thioacetate Deacetylation Reactions**

**Faculty Sponsor**

Dr. William Alexander

Twenty-seven thiols (nine unique) were synthesized from their corresponding thioacetates using three different deacetylation methods utilizing NaOH, HCl, and hydroxylamine as hydrolyzing agents. These thioacetate deacetylations were analyzed for their respective percent yields using UV/Vis. Results from UV/Vis showed generally reasonable yields (50-75%) for the reactions using NaOH and HCl, while the hydroxylamine reactions typically had poor yields. Thiols produced in this fashion may be suitable as cheap and easy alternatives to much higher priced, unstable thiols purchased directly.

## 1. Introduction

Within the past two decades, the field of self-assembled monolayers (SAMs) has exploded with growth and new developments. [3-6, 8, 10] The first recognized SAMs were developed at Bell Laboratories in 1983[1,2]; these SAMs were comprised of organic molecules adsorbed on cleaned metal surfaces. A major disadvantage was quickly noticed: the organic molecules were moisture sensitive, and thus a requirement for a new surfactant arose. This requirement was met again in 1983 at Bell Laboratories when Allara and Nuzzo demonstrated the SAM-forming capability of dialkyl disulfides by adsorption onto gold surfaces. [2]

Since the 1983 discovery of SAM formation utilizing sulfur-containing functional groups, many different headgroups have been studied and found to be useful in the formation of SAMs. More refined methods of SAM formation, as well as more comprehensive techniques for their characterization, have been established since the initial work at Bell Laboratories [3-6] with alkylthiols remaining the most studied [7-9]. Recently, however, there has been a growing concern among SAM researchers about the reactivity of the sulfhydryl group.

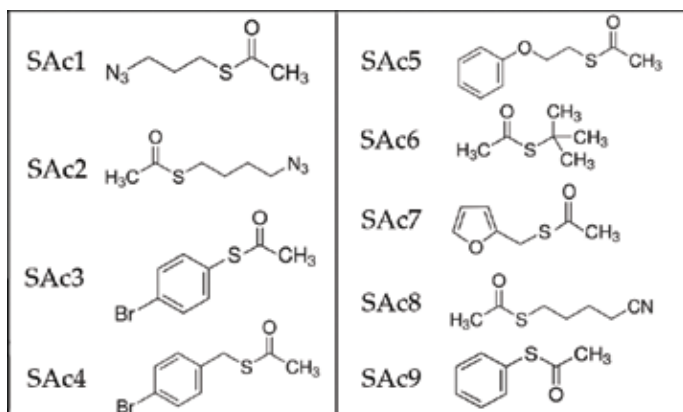
Free thiols can react through various pathways, including intramolecular cyclization, intermolecular polymerization, and the thiol-ene click reactions, all of which can prove to be detrimental for SAM formation and stability. [10,11] There have been recent efforts to protect the free thiol group to prevent these harsh effects. [11] A number of approaches have been developed for this purpose, including using sulfides, disulfides, thiocyanates, and thials. [10-13] However, a more recently-developed and less-studied functional group is being used more frequently: thioacetates. [13] Previous research has determined that thioacetates have slower SAM

formation kinetics and form less ordered, less densely packed SAMs. This leads to SAMs which are consistently less thick than the analogous thiol SAMs. [12] In spite of these facts, thioacetates are more shelf-stable, are typically more cost-effective, and are far less prone to the previously mentioned detrimental side reactions which free thiol groups are susceptible to. [10,12] This leads to a consequent need for the development of a method of SAM formation to bypass all of these shortcomings.

In this paper, we describe three simple synthesis methods for the formation of thiols from their corresponding thioacetates. These methods exploit not only the lower cost of the starting material, but also both the chemical and shelf-stability of molecules with a thioacetate headgroup which possesses the ability to form free thiol molecules for potential use in forming densely packed, well-ordered monolayer surfaces. A number of thioacetates are deacetylated to their complimentary thiol. Following this, the resulting product is characterized by ultraviolet/visible spectrometry to determine the effectiveness of these various methods. We then attempt to provide a general, overarching pattern seen among these assorted alkylthiol products for the effectiveness of their synthesis.

## 2. Experimental Section

**2.1 Materials.** S-(-3-azidopropyl) thioacetate (SAc1, 95%), S-(-4-azidobutyl) thioacetate (SAc2, 97%), 4-bromophenyl thioacetate (SAc3, 97%), 4-bromo- $\alpha$ -toluene thioacetate (SAc4, 97%), S-(-2-phenoxy-ethyl) thioacetate (SAc5, 98%), S-tert-butyl thioacetate (SAc6, 98%), S-furfuryl thioacetate (SAc7, 99%), S-(-4-cyanobutyl) thioacetate (SAc8, 97%), S-phenyl thioacetate (SAc9, 98%) and 5,5'-dithiobis-(2-nitrobenzoic acid) (Ellman's Reagent) ( $\geq 98\%$ ) were all obtained from Sigma Aldrich and were used as obtained. The structure for the thioacetates are shown in Scheme 1.



**Scheme 1.** The structures of the various thioacetates used in the deacetylation reactions.

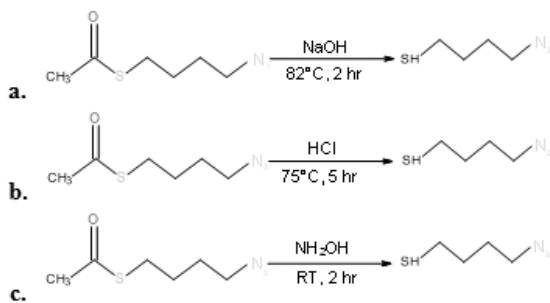
**2.2 Synthesis of Thiols.** All thiols were synthesized in one step from their corresponding thioacetates using either NaOH, HCl, or hydroxylamine as a hydrolyzing agent. A general reaction scheme for each of these reactions is provided below in Figure 2.

The following reactions are the general procedures used for all of the previously mentioned thioacetates with their respective yields shown in Table 1.

**Base-Promoted (NaOH) Deacetylation of Thioacetates.** The thioacetate (1.2mmol) was placed in ethanol (10mL) and stirred until fully dissolved. To this solution, 0.5M NaOH/H<sub>2</sub>O was added (4mL) and refluxed at 82°C for 2 h. The solution was then washed with hexanes (3x15mL), dried over sodium sulfate and decanted.

**Acid-Catalyzed (HCl) Deacetylation of Thioacetates.** The thioacetate (1.2mmol) was placed in methanol (15mL) and stirred until fully dissolved. To this solution, concentrated HCl was added (1mL) and the resulting solution was refluxed at 77°C for 5 h. The solution was then washed with hexanes (3x15mL), dried over sodium sulfate and decanted.

**Hydroxylamine Catalyzed Deprotection of Thioacetates.** Each thioacetate (1.2mmol) was dissolved in ethanol (10mL) and allowed to fully dissolve. Hydroxylamine (1.4mmol) was weighed and placed in this solution, which was then reacted for 2 h at room temperature with vigorous stirring. The solution was washed with hexanes (3x15mL), dried over sodium sulfate and decanted.



**Scheme 2.** General reaction schemes for: a. NaOH-promoted deprotection, b. HCl-catalyzed and c. hydroxylamine-catalyzed deprotection.

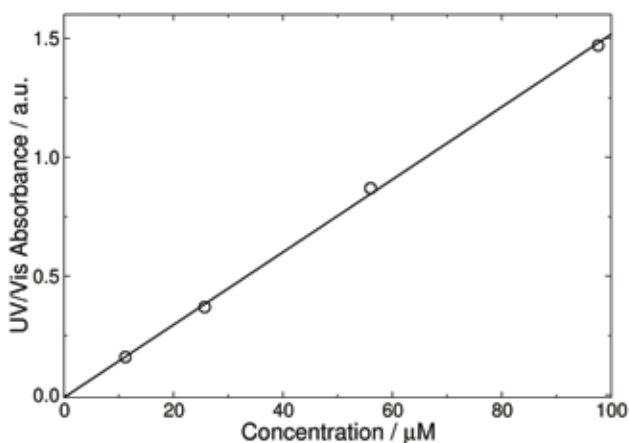
**2.3 Characterization of Thiol Yield.** Ellman's reagent was employed to quantify the concentration of free thiols. A buffer solution was made using a 95:5 ethanol:deionized water solution which was brought to a pH of around 8 using a 0.1M NaOH solution, with the pH being measured by litmus papers. 25mg of Ellman's reagent was then added to this solution and it was allowed to equilibrate for 10 minutes until the solution possessed a very faint yellow color. Following this, a 4mL aliquot of a single reaction's recovered hexane layer was placed in a 100mL volumetric flask along with 6mL ethanol and the flask was filled to the line with the Ellman's buffer solution and the volumetric flask was shaken for 5 minutes at room temperature. A cuvette was then filled with the resulting solution and was immediately characterized by UV/Vis spectroscopy on an Ocean Optics spectrophotometer. The samples were immediately characterized due to an unknown source of frosting on each plastic cuvette that appeared over time if the solution was allowed to remain in the cuvette.

**2.4 UV-Visible Spectroscopy (UV/Vis).** An Ocean Optics UV/Vis spectrophotometer was employed to obtain UV/Vis spectra to determine the concentration of free thiols in solution. Free thiol concentrations were calibrated relative to standard Ellman's reagent/1-undecanethiol solutions (11.2 $\mu$ M, 25.68 $\mu$ M, 56 $\mu$ M, 97.6 $\mu$ M) and absorbances were measured at 425nm. A solvent shift from the typical wavelength used for quantification employing Ellman's reagent, 412nm, was noted. Calculated concentrations were determined using the equation for the line of best fit for the calibration curve.

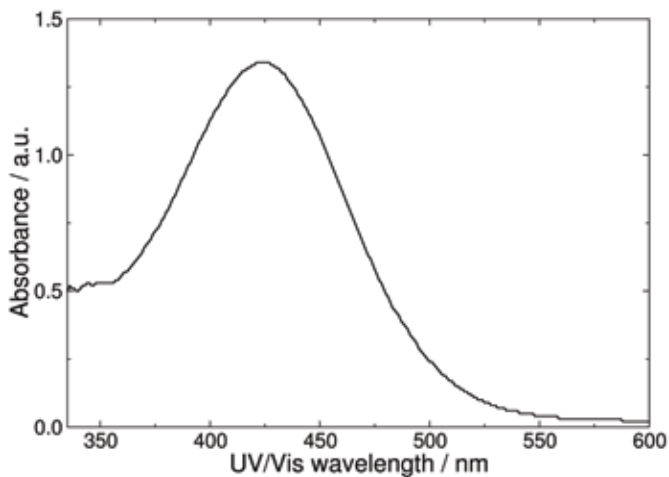
### 3. Results

**3.1 Deacetylation Synthesis Yield.** The percent yield for each deacetylation reaction was determined from measurements taken on a UV/Vis spectrophotometer using a calibration plot made from known standard solutions of Ellman's reagent reacted with 1-undecanethiol. Table 1 shows the yields for deacetylation using NaOH, HCl and hydroxylamine for each thioacetate species.

**3.2 Ellman's reagent calibration curve and representative spectrum.** Figure 1 shows the data obtained from the calibration curve using octadecanethiol reacted with Ellman's reagent as a calibration standard. Figure 2 shows a sample spectra obtained from the product S10 resulting from the deacetylation of SAc10.



**Figure 1.** Calibration curve obtained from octadecanethiol reaction with Ellman's reagent



**Figure 2.** Sample UV/Vis spectra of a reaction product S10 after reaction with Ellman's reagent

**Table 1.** Percent yield for Deacetylations of Thioacetates

Compound	Yield1	Yield2	Yield3
S1	*	<15%	<15%
S2	37.00%	68.00%	15.00%
S3	<15%	69.00%	<15%
S4	43.00%	39.00%	<15%
S5	68.00%	66.00%	18.00%
S6	25.00%	<15%	*
S7	73.00%	75.00%	76.00%
S8	76.00%	76.00%	<15%
S9	50.00%	72.00%	35.00%

Yield1-percent yield for NaOH hydrolysis. Yield2-percent yield for HCl hydrolysis. Yield3-percent yield for hydroxylamine deprotection. \* denotes an inability to obtain quality yield data.



## 4. Discussion

The calibration curve obtained from octadecanethiol reacted with Ellman's reagent demonstrated a good correlation, with  $R^2 = 0.9991$ . This allowed for an accurate determination of yields based on the equation of the line of best fit of these points.

Overall, yields for the NaOH and HCl reactions were reasonable, while yields for the hydroxylamine reactions were relatively poor, with most percent yields for similar reactions being between 85-100% [14], [15], [16]. Low yields for hydroxylamine reactions are thought to be primarily due to side reactions. This can be seen throughout nearly every reaction, sans S7 and S9.

Less than expected yields for both the NaOH and HCl hydrolysis reactions are believed to be caused by the synthetic constraints we put in place for the reactions; specifically, forgoing an inert and water-free atmosphere. Although yields calculated may appear to be acceptable overall, it is possible that side reactions may have occurred on the functional groups of a number of the compounds, specifically bromo- and cyano-functionalized compounds. Relevant factors might be the fact that bromine-terminated compounds may react with the newly formed thiols to form a thioether, which also cleaves the bromine from the compound. Cyano groups are also at risk of side reactions; HCl can hydrolyze these nitrile groups, while NaOH may assist in the nucleophilic addition of ethanol onto the nitrile group.

However, these reactions may still go on to deacetylate the thioacetate. Therefore, using Ellman's reagent as a method of quantification will provide good cursory data on the percent yield of the deacetylation of the thioacetates, but it cannot provide data on the structures of the resulting species. Further investigation is therefore needed using NMR to confirm side reactions as well as structures of important products.

## 5. Conclusion

In this paper, we have shown that our thiol syntheses, in general, were successful and resulted in reasonable yields for NaOH promoted and HCl catalyzed reactions, given our self-induced constraints.

Yields for the hydroxylamine reactions ranged from poor to abysmal, this being theorized as a result of possible side reactions with hydroxylamine and the functional group of the specific compound. NaOH and HCl hydrolysis reactions may also be susceptible to side reactions.

For future experiments many steps may be taken to increase yields and purity of the product, including: further purification of the product or reactant if necessary, performing NMR analysis to verify any potential side reactions, investigating unwanted solvent effects from ethanol or methanol, and performing the syntheses in an inert, water-free environment.

Our products from these reactions have been saved for SAM formation and analysis in the future to determine the quality of the SAMs that can be made from these thiols. If the SAM produced from these solutions is deemed to be of high quality, the methods detailed in this paper will provide a cheap and simple alternative to much more expensive thiols currently used in research involving SAMs.

## **Acknowledgement**

I thank Nikishia Parehk for assistance during early stages of this work. Materials were purchased through funds from the 2013 Memphis-CRESH program and a 2013 College of Arts and Sciences Faculty Research Grant. Finally, I am grateful for the financial and laboratory support for these studies provided by Prof. William Alexander's faculty start-up funds in the Department of Chemistry.

## References

- [1] Maoz, R.; Sagiv, J. J. *Colloid Interface Sci.* 1984, 100, 465.
- [2] Nuzzo, R. G.; Allara, D. L. *J. Am. Chem. Soc.* 1983, 105, 4481.
- [3] Mrksich, M.; Chen, C. S.; Xia, Y.; Dike, L. E.; Ingber, D. E.; Whitesides, G. M. *Proc. Natl. Acad. Sci. U.S.A.* 1996, 93, 10775.
- [4] Tidwell, C. D.; Ertel, S. I.; Ratner, B. D.; Tarasevich, B.; Atre, S.; Allara, D. L. *Langmuir* 1997, 13, 3404.
- [5] Knoll, W.; Zizlsperger, M.; Liebermann, T.; Arnold, S.; Badia, A.; Liley, M.; Piscevic, D.; Schmitt, F. J.; Spinke, J. *Colloids Surf., A* 2000, 161, 115.
- [6] Vergheese, T. M.; Berchmans, S. *Mater. Chem. Phys.* 2004, 83, 229.
- [7] Dubois, L. H.; Nuzzo, R. G. *Annu. Rev. Phys. Chem.* 1992, 43, 437.
- [8] Grunze, M. *Phys. Scr.* 1993, 7, 711.
- [9] Jung, D. R.; Czanderna, A. W. *CRC Crit. Rev. Solid State Mater. Sci.* 1994, 19, 1.
- [10] Troughton, B.; Bain, C. D.; Whitesides, G. M. *Langmuir* 1988, 4, 365.
- [11] Zhang, M.; Anderson, M. R. *Langmuir* 1994, 10, 2807.
- [12] Hagenhoff, B.; Benninghoven, A.; Spinke, J.; Liley, M.; Knoll, W. *Langmuir* 1993, 9, 1622.
- [13] Schlenoff, J. B.; Li, Ming; Ly, Hiep J. *Am. Chem. Soc.* 1995, 117, 12528.
- [14] Woodward, R. B. *J. Am. Chem. Soc.* 1956, 78, 2023.
- [15] Barua, N. *Eur. J. Org. Chem.* 2006, 1722.
- [16] Woodward, R.B. *J. Am. Chem. Soc.* 1952, 74, 4223.