Optimization of the Synthesis of *n*-Phthalimidoalkylthiols as Precursors for ω-Aminoalkylthiols as Prepared by Undergraduate Chemistry Students

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Abstract: The synthesis of *n*-phthalimidoalkylthiols from phthalimide and *n,m*-dibromoalkane was demonstrated as a general approach to short and medium chain (x = 1 to 12) functional alkylthiols in an undergraduate laboratory setting. The reaction conditions were demonstrated to be mild enough to directly synthesize *n*-phthalimidoalkylthiols with a carbon chain containing either double or triple bonds. The syntheses of each of these alkylthiols can be completed in less than 24 h (over a few laboratory periods) with at least a 50% overall yield. Reactivity of *n,m*-dibromoalkane with phthalimide was monitored with ^{1}H-NMR to determine the length of time needed for the reaction to reach completion avoiding the inaccurate use of thin layer chromatography. Based on this result, reaction times were reduced by two-thirds from those previously reported in the literature, which was necessary to prepare a method that will accommodate the duration of second year introductory organic or organic spectroscopy courses.

Introduction

Alkylthiols and their derivatives are a common synthetic target as the key component for preparing self-assembled monolayers (SAMs) on the surface of metals, semiconductors or making linkers to add molecular functionality (e.g., fluorescent tags or chemotherapeutic agents) to proteins and other biomolecules [1-3]. Their utility in these areas of study, for example, are due to their ease of assembly on gold surfaces, which render them very attractive molecular targets [4-7]. The hydrocarbon backbone of the alkylthiols is anchored by the thiol head group to these surfaces modifying the chemical properties of the original surfaces, while

the terminal group (e.g., amine, acid or alkynes) can be used as a specific receptor/anchor for biofunctional molecules ranging from proteins to sugar moieties [8-10]. As an example, ω-aminoalkylthiols can serve as linkers to bind biofunctional molecules to nanoparticles or to quantum dots for the purposes of tracking or drug delivery [2, 11]. Alkylthiols and their derivatives have also recently received a large amount of attention as precursors to sulphorane derivatives used as potential antitumor agents [12].

In this paper, we describe a facile synthesis of *n*-phthalimidoalkylthiols, the main precursors to ω-aminoalkylthiols in an undergraduate laboratory setting. We developed a three step synthesis of short to medium length (i.e. 3 to 12 carbon chain) alkylthiols, which can be completed by undergraduate students over a few short laboratory periods. This synthesis is particularly interesting for the relatively mild reaction conditions that could be applied to the derivatization of biofunctional molecules, or acid and base sensitive molecules with alkylthiols. This synthesis is also valuable, since it introduces two main functional group manipulations from readily available alkyl halides through the Gabriel synthesis and the thiolation reaction.

Experimental

All reagents and solvents were purchased from Aldrich and used without further purification. ^{1}H-NMR spectra were recorded on a Bruker 400 and 500 MHz spectrometer and were referenced to the residual chloroform ($CDCl_3$) resonance at 7.24 ppm or DMSO-d_6 at 2.50 ppm. All IR spectra were recorded on a Bomem MB-Series FTIR Model B-100 using KBr pellets or on a PerkinElmer UATR Two Fourier transform spectrophotometer. The TLC plates (Macherey-Nagel MN818333, Alugram Xtra SIL 60, UV 254, 0.2 mm) and the silica gel (Silica Gel 60, 230 - 400 Mesh) were purchased from Canadian Life Sciences. Melting points were recorded

using a Barnstead Mel-Temp capillary melting point apparatus and are uncorrected. The CI-MS or EI-MS spectra were recorded on a Varian 4000. The analytical data of all compounds were identical to those described in the literature. When the compounds were novel or missing analytical data in the literature (**1f, 2c, 2d, 2e, 2f**) a full characterization has been obtained and are reported herein.

General procedure for the synthesis of *N*-(*n*-bromoalkyl)-phthalimide. Phthalimide (1 equiv.) was suspended in dry acetone, along with potassium carbonate (3 equiv.), and tetrabutylammonium bromide (0.1 equiv.). To this mixture was added the desired *n*-dibromoalkane (3 equiv.) and the reaction was allowed to stir at room temperature over a period of 8 h. After 8 h, the solvent was evaporated under vacuum and the residue was partitioned between dichloromethane (DCM) and water. *(The residue was first dissolved in DCM and then washed with water to avoid any emulsion formation.)* The organic layer was separated and the aqueous layer was further extracted with two portions of DCM. The combined organic phases were dried over sodium sulfate (Na_2SO_4), and the solvent was removed under vacuum, to yield a crude product, which was further purified by column chromatography on silica gel. The excess *n*-dibromoalkane can be partially recovered by eluting the column with pure hexanes previous to eluting the desired *N*-(*n*-bromoalkyl)-phthalimide with a more polar solvent (*vide infra*).

General procedure for the synthesis of *n*-phthalimidoalkylthiol. *N*-(*n*-bromoalkyl)-phthalimide (1 equiv.) and thiourea (1 equiv.) were dissolved in dry EtOH, and the mixture was refluxed overnight. After cooling the reaction to room temperature, the solvent was removed under vacuum and the resulting *pseudo*-thiourea solid was used in the subsequent step without further purification. The resulting solid was dissolved in water, sodium metabisulfite (2 equiv.) and dichloromethane were added, and the biphasic mixture was refluxed for few hours until the TLC indicated a complete reaction of the *pseudo*-thiourea derivative: the UV active spot will disappear from the aqueous phase, and should be replaced by a UV active spot of higher R_f in the organic phase. The reaction was cooled to room

temperature, and the organic layer was separated. The aqueous layer was further extracted with dichloromethane and the combined organic phases were dried over sodium sulfate, and the solvent was evaporated under vacuum. The crude product was purified by column chromatography on silica gel to yield the desired thiol.

General procedure for the completion of the synthesis as part of an undergraduate laboratory course. While the given procedures outlined above are for an optimized synthesis, in the setting of an undergraduate laboratory course the duration of each synthesis can be shortened especially since the isolation of the intermediate and the final product relies on column chromatography. A plan for the entire synthesis is proposed as follows:

Laboratory Period #1: Students mix the reagents for the synthesis of the *N*-(*n*-bromoalkyl)-phthalimide derivatives and leave them to stir overnight. This typically will not require a full laboratory period as it only requires ~30 min of preparation. The students can either start this process while working on another laboratory exercise, or arrange to stop by the laboratory and start the reaction under the supervision of a Teaching Assistant.

Laboratory Period #2: Extraction, purification and characterization of the *N*-(*n*-bromoalkyl)-phthalimide derivative (~4 h). This laboratory period is also dedicated to teaching the students the proper use of TLC (Thin Layer Chromatography), column chromatography, removal of solvent using a rotary evaporator, and preparation of NMR samples.

Laboratory Period #3: Students mix the reagents for the synthesis of the *pseudo*-thiourea derivative and reflux this solution overnight (or 8 h if performed during the day). Typically, this step involves ~15 min of sample preparation and does not require a full laboratory period. Under the supervision of a Teaching Assistant, the students must ensure the reflux set-up is safe and properly secured, and check that the ethanol based solution has started to reflux before leaving the laboratory.

Laboratory Period #4: Synthesis of *n*-phthalimidoalkylthiol. The reflux period can be shortened to few hours *(a significant amount of the product is observed after a reflux period of 2 h)* followed by the separation and purification of this product. Typically, the column chromatography is fast as a single compound is prepared by this synthesis.

***N*-(3-bromopropyl)-phthalimide (1a)**: Yield: 76%; recovery of 1,3-dibromopropane: 28%. R_f = 0.50 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.71-7.83 (m, 4H), 3.84 (t, *J* = 6.8 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.30 (quin, *J* = 6.8 Hz, 2H) ppm.

***N*-(5-bromopentyl)-phthalimide (1b)**: Yield: 60%; recovery of 1,5-dibromopentane: 46%. R_f = 0.54 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.85 (m, 4H), 3.70 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 6.7 Hz, 2H), 1.92 (quin, *J* = 6.7 Hz, 2H), 1.72 (quin, *J* = 7.4 Hz, 2H), 1.5 (quin, *J* = 7.9 Hz, 2H) ppm.

***N*-(10-bromodecyl)-phthalimide (1c)**: Yield: 77%; recovery of 1,10-dibromodecane: 77%. R_f = 0.45 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.70-7.80 (m, 4H), 3.67 (t, *J* = 7.3 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 1.84 (quin, *J* = 7.4 Hz, 2H), 1.67 (quin, *J* = 7.2 Hz, 2H), 1.40 (quin, *J* = 6.9 Hz, 2H), 1.28-1.30 (m, 10H) ppm.

***N*-(12-bromododecyl)-phthalimide (1d)**: Yield: 62%; recovery of 1,12-dibromododecane: 56%. R_f = 0.62 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.70-7.83 (m, 4H), 3.67 (t, *J* = 7.3 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 1.85 (quin, *J* = 7.2 Hz, 2H), 1.67 (quin, *J* = 7.2 Hz, 2H), 1.41 (quin, *J* = 7.2 Hz, 2H), 1.25-1.32 (m, 14H) ppm.

***N*-[(*E*)-4-bromobut-2-enyl]-phthalimide (1e)** [13]**:** Yield: 65%; recovery of 1,4-dibromobut-2-ene: 50%. R_f = 0.43 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500

MHz, $CDCl_3$): δ = 7.87-7.73 (m, 4H), 5.90-5.30 (m, 2H), 4.29 (dd, *J* = 20, 4.3 Hz, 2H), 3.93 (d, *J* = 7.3 Hz, 2H) ppm.

***N*-(4-bromobut-2-ynyl)-phthalimide (1f)** [14]**:** Yield: 64%; recovery of 1,4-dibromobut-2-yne: 55%. mp = 98-101 °C. R_f = 0.33 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.90-7.75 (m, 4H), 4.52 (t, *J* = 2.1 Hz, 2H), 3.88 (t, *J* = 2.1 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 166.96, 134.24, 131.97, 123.60, 80.17, 78.17, 27.35, 13.87. IR (ATR) *v* = 3014, 2971, 1770, 1708, 1391, 1118, 718, 707 cm^{-1}. MS (EI) *m/z*: 277 & 279 (Molecular Ion).

3-Phthalimidopropylthiol (2a): Yield: 60%. R_f = 0.47 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.73-7.85 (m, 4H), 3.83 (t, *J* = 7.7 Hz, 2H), 2.55 (q, *J* = 7.1 Hz, 2H), 2.00 (quin, *J* = 6.9 Hz, 2H), 1.60 (t, *J* = 8.2 Hz, 1H) ppm. MS (CI) *m/z*: 222 ($(M + H)^+$, 100%).

5-Phthalimidopentylthiol (2b): Yield: 66%. R_f = 0.55 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.70-7.85 (m, 4H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.51 (q, *J* = 7.4 Hz, 2H), 1.68 (m, *J* = 7.6 Hz, 4H), 1.45 (m, 2H), 1.33 (t, *J* = 7.8 Hz, 1H) ppm. MS (CI) *m/z*: 250 ($(M + H)^+$, 100%).

10-Phthalimidodecylthiol (2c): Yield: 60%. mp = 41-44 °C. R_f = 0.65 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.70-7.85 (m, 4H), 3.67 (t, *J* = 7.3 Hz, 2H), 2.50 (q, *J* = 7.8 Hz, 2H), 1.67 (m, 2H), 1.59 (quin, *J* = 7.4 Hz, 2H), 1.17-1.34 (m, 13H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.55, 133.90, 132.13, 123.19, 38.08, 34.09, 29.44, 29.18, 29.05, 28.63, 28.38, 26.86, 24.72 ppm. IR (ATR) *v* = 9909, 2847, 1697, 1404, 1069, 719, 710, 530 cm^{-1}. MS (CI) *m/z*: 320 ($(M + H)^+$, 100%).

12-Phthalimidododecylthiol (2d): Yield: 80%. mp = 45-49 °C. R_f = 0.64 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.70-7.84 (m, 4H), 3.67 (t, *J* = 7.3 Hz, 2H), 2.51 (q, *J* = 7.3 Hz, 2H), 1.67 (m, 2H), 1.60 (quin, *J* = 7.4 Hz, 2H), 1.25-1.34 (m, 17H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 168.46, 133.82, 132.19, 123.14,

38.08, 34.06, 29.51, 29.47, 29.45, 29.18, 29.06, 28.60, 28.38, 26.86, 24.67 ppm. IR (ATR) *v* = 2911, 2847, 1769, 1698, 1394, 718, 710, 530 cm^{-1}. MS (CI) *m/z*: 348 ($(M + H)^+$, 100%).

4-Phthalimidobut-2-enylthiol (2e): Yield: 70%. mp = 102-105 °C. R_f = 0.42 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.88-7.73 (m, 4H), 5.91-5.66 (m, 2H), 4.30 (d, *J* = 6.1 Hz, 2H), 3.16 (t, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.8 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 167.87, 134.00, 133.15, 132.11, 124.62, 123.32, 38.89, 26.12. ppm. IR (ATR) *v* = 2926, 2560, 1770, 1703, 1389, 1114, 940, 718, 708, 529 cm^{-1}. MS (CI) *m/z*: 234 ($(M + H)^+$, 100%).

4-Phthalimidobut-2-ynylthiol (2f): Yield: 67%. mp = 106-108 °C. R_f = 0.36 (SiO_2, EtOAc:Hexanes, 1:3, v/v). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.90-7.73 (m, 4H), 4.48 (t, *J* = 2.1 Hz, 2H), 3.26 (dt, *J* = 7.5, 2.2 Hz, 2H), 1.98 (t, *J* = 7.5 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 167.10, 134.19, 132.04, 123.55, 81.15, 75.99, 27.437, 12.41 ppm. IR (ATR) *v* = 2926, 2560, 1770, 1703, 1390, 1114, 940, 718, 708, 529 cm^{-1}. MS (CI) *m/z*: 232 ($(M + H)^+$, 100%).

5-phthalimidopentyl isothiuronium bromide (3b): Quantitative yield, mp 184 to 189 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.82-9.00 (br d, 4H), 7.68-7.77 (m, 4H), 3.45 (t, 2H, *J* = 6.92 Hz), 3.04 (t, 2H, *J* = 7.28 Hz), 1.47-1.59 (m, 4H), 1.23-1.31 (m, 2H), ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 170.85, 168.72, 135.09, 131.76, 123.55, 37.66, 30.64, 28.32, 27.86, 25.56 ppm. IR (ATR) v = 3259, 3024, 2946, 2722, 1769, 1697, 1645, 1399, 1044, 724 cm^{-1}.

Results and Discussion

Previous syntheses of *n*-phthalimidoalkylthiols involved the use of hydrogen sulfide (a toxic and flammable gas) or thioacetic acid derivatives as a thiolation reagent, or

other cumbersome and lengthy procedures using a strong bases (NaOH or NaH) or acid (HCl) [15, 16]. In order to accommodate undergraduate students in an instructional laboratory, our approach establishes a relatively quick procedure for the synthesis of alkylthiols with a variety of chain lengths and under relatively mild reaction conditions. The reaction requires only three steps to synthesize the desired final product: i) reaction of *n,m*-dibromoalkane with phthalimide to form *N*-(*n*-bromoalkyl)-phthalimide; ii) isolation of the phthalimide derivative and its reaction with thiourea to afford the *pseudo*-thiourea bromide salt; and iii) reduction of the *pseudo*-thiourea derivative with sodium metabisulfite under biphasic conditions to produce the desired thiol.

The *N*-(*n*-bromoalkyl)-phthalimides were prepared (Scheme 1) for a variety of chain lengths (x = 1, 3, 8 and 10). Each of these syntheses started by dissolving phthalimide (1 equiv.) in dry acetone at room temperature, followed by the addition of potassium carbonate (3 equiv.) and tetrabutylammonium bromide (TBABr) (0.1 equiv.). Subsequently, *n,m*-dibromoalkane (3 equiv.) was added and the mixture was stirred for a minimum of 8 h. The choice of the chain length was purely based on the price and availability of the starting materials: as the chain length increases so does the price per gram of the dihalo compound, which can make it impossible to accommodate large organic chemistry classes.

To unambiguously establish the minimum reaction time, the reaction of 1,12-dibromododecane with phthalimide was monitored at one-hour interval over the course of 10 hours using ^{1}H-NMR spectroscopy (Figure 1). As the reaction proceeded, a new triplet appeared at 3.70 ppm, that is characteristic of the methylene group adjacent to the nitrogen of *N*-(12-bromododecyl)-phthalimide. The reaction progress can be readily monitored by following the change in relative intensity of the triplet at 3.70 ppm (CH_2 α to the nitrogen) to the triplet at 3.40 ppm (CH_2 α to the bromine). The reaction was complete when the relative intensity (the ratio of the integrated values) between the peaks of these two triplets remained constant. The ^{1}H-NMR study indicated that the reaction was complete after ~7 h,

dramatically reducing the reaction time from the 24 h previously reported in the literature [17]. This monitoring method is easily applied in an undergraduate laboratory as a replacement for thin layer chromatography (TLC). In some cases, such as the reactions demonstrated herein, TLC can be inaccurate to judge the completion of a reaction. When the starting materials do not carry strong chromophores or are difficult to stain, reverting to ^{1}H-NMR spectroscopy is almost always the best option especially if one of the reagents is in excess or the reaction doesn't go to completion. The generation of a stacked plot by second or third year undergraduates can also be readily achieved, and would provide the students with information on the reaction kinetics, yields and the characteristic peaks of the new compounds in solution that can be used to assist with future reaction monitoring or scale-up.

The reaction was allowed to run to completion for the purposes of this study, such as to assist with assessing the extent to which it is possible to optimize yields of the isolated products. After 8 h of reaction, the solvent was removed under vacuum and the isolated residue was partitioned between dichloromethane (DCM) and water. The aqueous layer was further extracted with DCM and the combined organic layers were dried over sodium sulfate (Na_2SO_4), and the solvent was removed under vacuum. The resulting solid was purified by chromatography on a column of packed silica gel. A rinse with hexanes eluted the unreacted dibromoalkane, which was recovered with an efficiency of up to 70% based on the anticipated quantity of unreacted material. Subsequent elution with a mixture of ethyl acetate:hexanes (1:3, v/v) yielded the desired naphthalimide derivative (**1a-1d**). It is important to note that as the chain length increases, the solubility of the phthalimide derivative decreases, which could be challenging when loading the sample onto the silica gel column. This relatively low solubility was minimized by dissolving the product in a minimum amount of pure ethyl acetate instead of a mixture of ethyl acetate:hexanes (1:3, v/v), prior to separation by column chromatography. Dry packing the chromatography column was also demonstrated to be an effective option. The sample was dissolved in a minimum amount of ethyl acetate to which was added a

small amount of silica gel. This mixture was evaporated to dryness and the resulting dry powder transferred to the top of the pre-packed column.

Thiolation of the *N*-(*n*-bromoalkyl)-phthalimide derivatives was achieved in a two-step fashion (Scheme 2) [18]. In the first step *N*-(*n*-bromoalkyl)-phthalimide (1 equiv.) and thiourea (2 equiv.) were dissolved in anhydrous ethanol, and the mixture was refluxed for 10 h. The solvent was subsequently removed under vacuum and the resulting *pseudo*-thiourea (Scheme 3) derivative was used in the following step without further purification.

The collected solid was dissolved in water containing sodium metabisulfite (2 equiv.), DCM was subsequently added and the biphasic mixture was refluxed over a period of 4 h. The progress of the reaction was monitored by TLC: the UV active spot associated with the *pseudo*-thiourea derivative disappeared from the aqueous phase while a UV active spot associated with *n*-phthalimidoalkylthiols of higher R_f appeared in the organic phase. After 4 h, the reaction was cooled and the aqueous layer was extracted several times with DCM, the combined organic phases were dried over Na_2SO_4, and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel using a mixture of ethyl acetate:hexanes (1:3, v/v) to elute the desired *n*-phthalimidoalkylthiols (**2a-2d**). Interestingly enough either no or less than 5% (^{1}H-NMR detection limit) of the disulfide was observed over the course of this reaction.

In the case of 5-phthalimidopentylthiol, an analytical sample of the *pseudo*-thiourea 5-phthalimidopentyl isothiuronium bromide [19] was synthesized and isolated for further characterization by undergraduate students. A full characterization was necessary since these derivatives are rarely encountered in organic syntheses. The *pseudo*-thiourea derivatives' solubility can be challenging, so it was essential to expose the students to this intermediate. Some interesting features of this intermediate were easily followed using infrared (IR) and ^{1}H-NMR spectroscopies.

Using infrared spectroscopy, the students followed the reaction by obtaining IR spectra of the crude reaction products. Obvious differences were observed by looking at the IR stacked plot of the bromo compound, the *pseudo*-thiourea and the thiol. The presence of a strong C=N stretch at 1645 cm^{-1}, combined with strong N-H stretches between 2950 and 3300 cm^{-1}, clearly showed the presence of a *pseudo*-thiourea type structure. Interestingly, following this synthesis by IR spectroscopy was not ideal as many of the spectral features in the fingerprint region were not very informative: i) C-Br stretch was weak and observing its disappearance wasn't helpful; ii) the C-S and C-N stretches were embedded in the fingerprint region and not clearly distinguished from other the peaks; and iii) ultimately, the S-H stretch at 2573 cm^{-1} for the thiol is often relatively small and might be missed during the spectral interpretation.

Another approach for the students to follow the reaction sequence was through the use of ^{1}H-NMR spectroscopy. The most obvious change was the chemical shifts of the protons neighboring the electronegative atoms: nitrogen, bromine and sulfur. As seen in Figure 3, the expected changes in chemical shifts are present, and a clear difference between all three species can be unequivocally established using ^{1}H-NMR. Specifically, a clear difference of chemical shifts was observed for the deshielded triplets. The student's main concern when using this method to differentiate the products was the lack of solubility of the *pseudo*-thiourea in chloroform and the necessity to use dimethyl sulfoxide for their NMR analyses. This difference in the choice of solvents for each sample could lead to confusion when trying to interpret the relative change in the chemical shifts for the NMR spectra of each sample.

A final analysis to confirm the products consisted of the use of mass spectrometry. This study was used to specifically establish the formation of the desired thiol species as opposed to the disulfide species, which is a common side product that can occur during thiol syntheses. As seen in Figure 4, the mass spectrum of the crude oxidation mixture as analyzed by the chemical ionization (CI-MS) mode shows only

a base peak at 250 mu. This result is consistent with the ionized molecular ion $[M+H]^+$ of the thiol with no trace of the ionized disulfide species expected at 497 mu.

To further prove the mild conditions of this thiolation reaction, we investigated the thiolation of an alkene **1e** (1,4-dibromobut-2-ene) and an alkyne **1f** (1,4-dibromobut-2-yne). These reactions used commercially available derivative **1e** and a prepared derivative **1f**. The resulting unsaturated ω-aminoalkylthiols proved that the double or triple bonds were unchanged by the entire sequence of the reaction (Scheme 4), yielding the desired compounds **2e** and **2f**, respectively. Both products were isolated in good yield and high purity from their parent bromide compounds.

Conclusion

In summary, we have described a general synthesis of *n*-phthalimidoalkylthiols with short and medium alkyl chain lengths. The procedure to synthesize these *N*-protected aminoalkylthiols is simple, requires only three steps, and can be completed in less than 24 hours with at least a 50% yield. We demonstrate that this reaction can be performed in a few short laboratory periods by undergraduates as part of an organic chemistry curriculum. Undergraduate students can first follow the initial step of the synthesis -- the formation of *N*-(bromoalkyl)-phthalimide from the reaction of dibromoalkane with phthalimide -- by ^{1}H-NMR to determine the kinetics, time to reach completion, and to determine the crude yield. The subsequent steps in the reaction and purification of the products were performed in a separate laboratory exercise. The reaction conditions for the thiolation were extended to the synthesis of unsaturated alkylthiols, demonstrating the mildness of these synthetic methods. While most undergraduate laboratories tend to avoid thiolation reactions due to evident concerns for smell and toxicity of reagents, this method using thiourea is believed to avoid such problems in a larger laboratory setting. Using the methods demonstrated herein, undergraduate students could prepare *n*-

phthalimidoalkylthiols and related derivatives for modifying the surfaces of noble metals or for reaction with biomolecules to create their own molecular labels.

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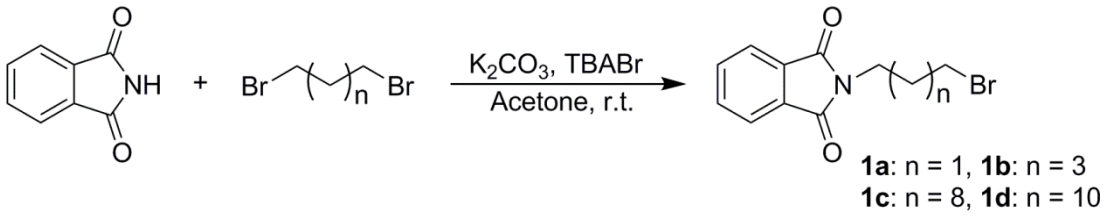
Figures and Schemes (presented in order of reference within the manuscript)



Scheme 1. General procedure for the synthesis of *N*-(*n*-bromoalkyl)-phthalimide.

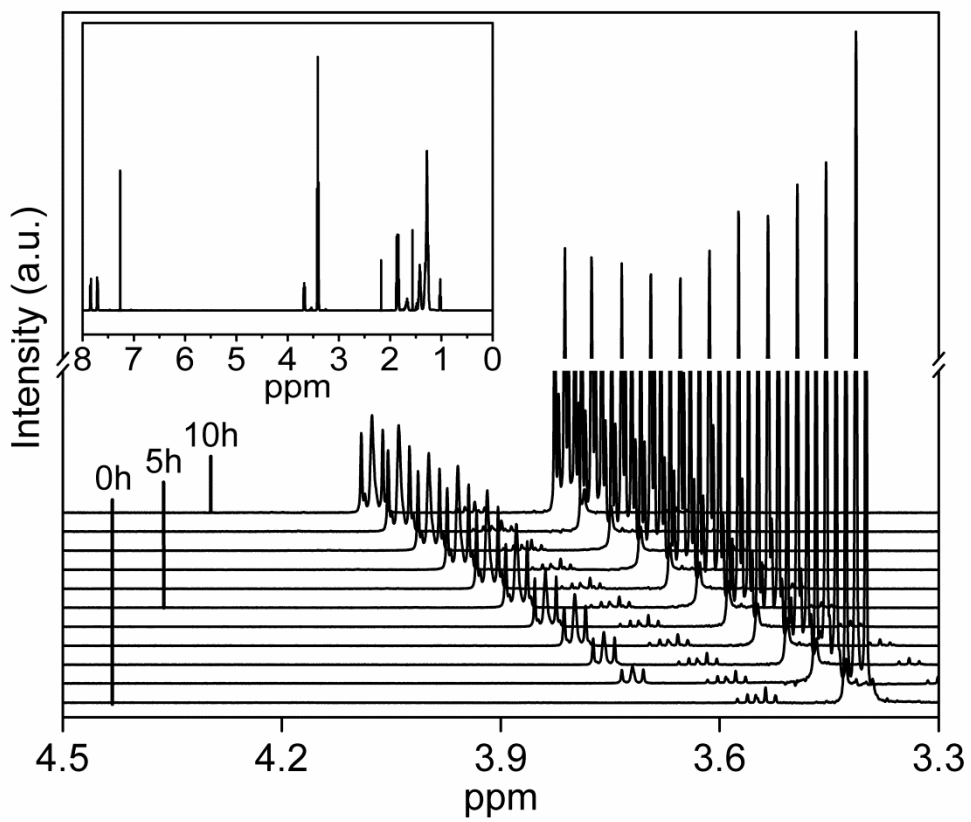
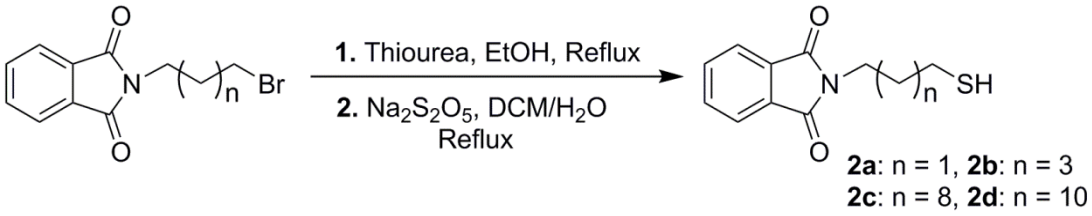
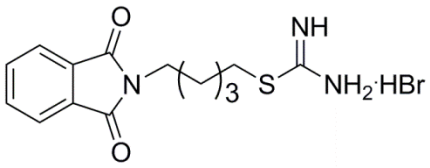


Figure 1. Stacked plot of ^{1}H-NMR (500 MHz, $CDCl_3$) spectra for aliquots of a reaction of phthalimide (1 equiv.) with 1,12-dibromododecane (3 equiv.) in a mixture of acetone/K_2CO_3/TBABr at room temperature; sampled at 1 h intervals according to the indicated times. (For clarity we have plotted only the region between 3.3 and 4.5 ppm and used a trimmed vertical axis as indicated above. A complete spectrum for the final product is plotted in the inset.)



Scheme 2. General procedure for the synthesis of *n*-phthalimidoalkylthiols.



Scheme 3. *pseudo*-Thiourea structure of 5-phthalimidopentyl isothiuronium bromide (**3b**).

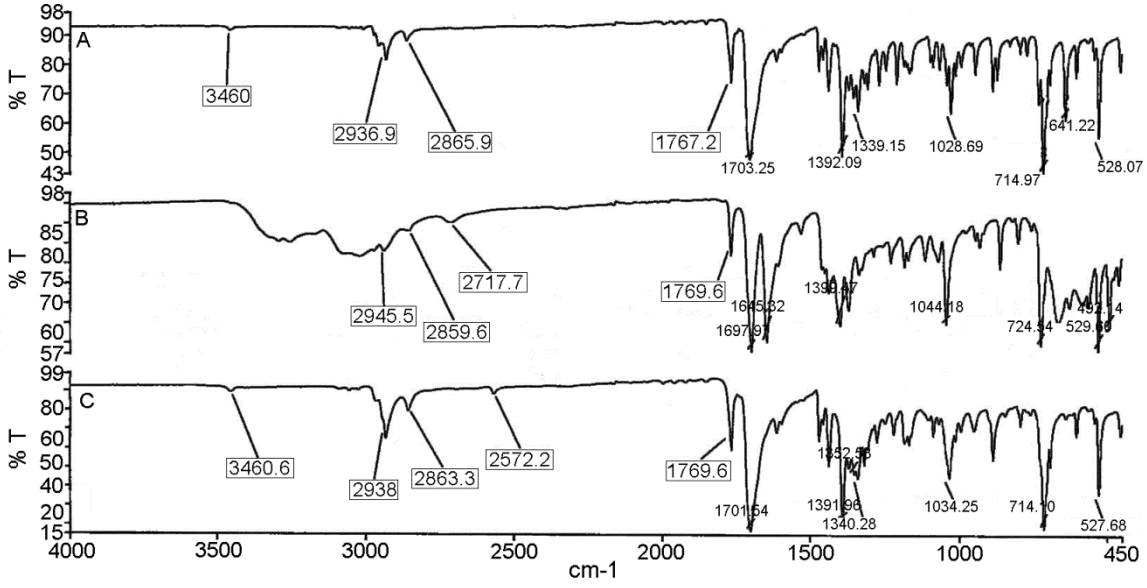


Figure 2. Stacked plot of IR spectra (ATR) for: (A) crude *N*-(5-bromopentyl)-phthalimide (**1b**); (B) crude *pseudo*-thiourea 5-phthalimidopentyl isothiuronium bromide (**3b**); and (C) crude 5-phthalimidopentylthiol (**2b**).

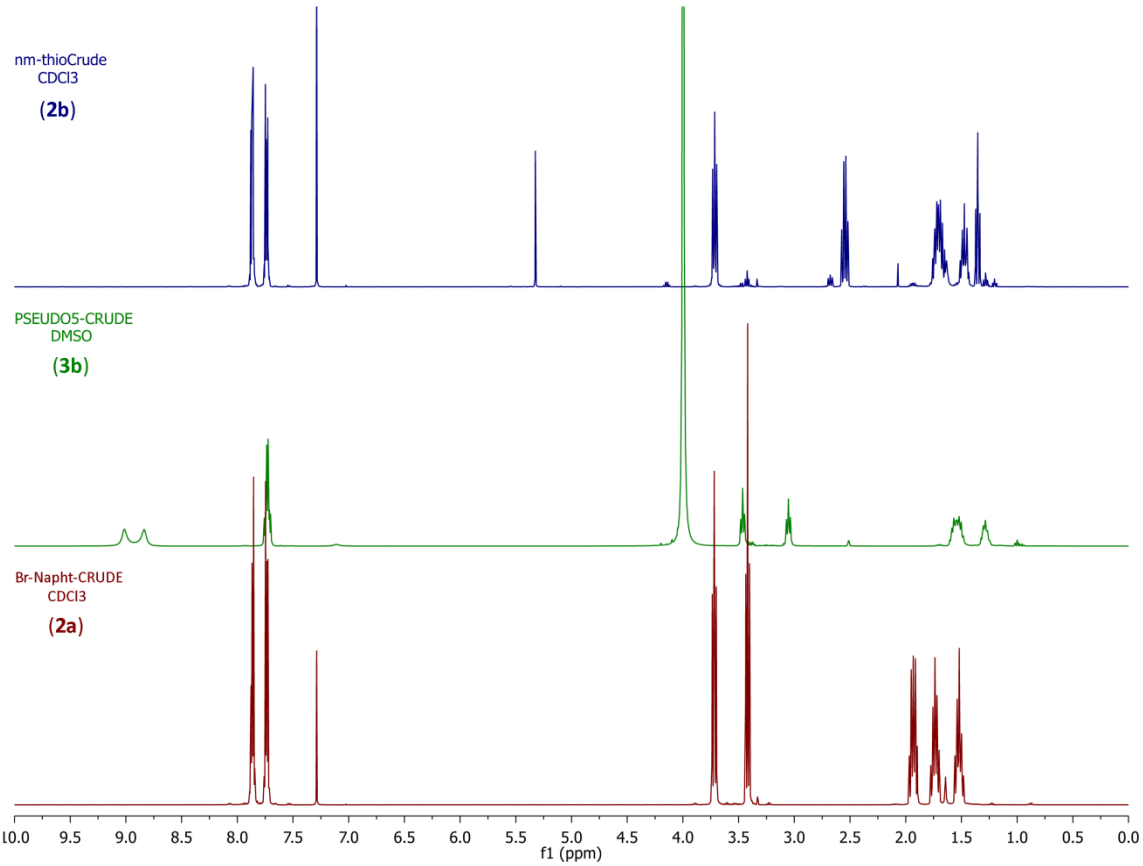


Figure 3. Stacked plots of the ^{1}H-NMR (400 MHz) spectra for the crude *N*-(5-bromopentyl)-phthalimide (**2a**) in $CDCl_3$, crude *pseudo*-thiourea 5-phthalimidopentyl isothiuronium bromide (**3b**) in DMSO d_6, and crude 5-phthalimidopentylthiol (**2b**) in $CDCl_3$.

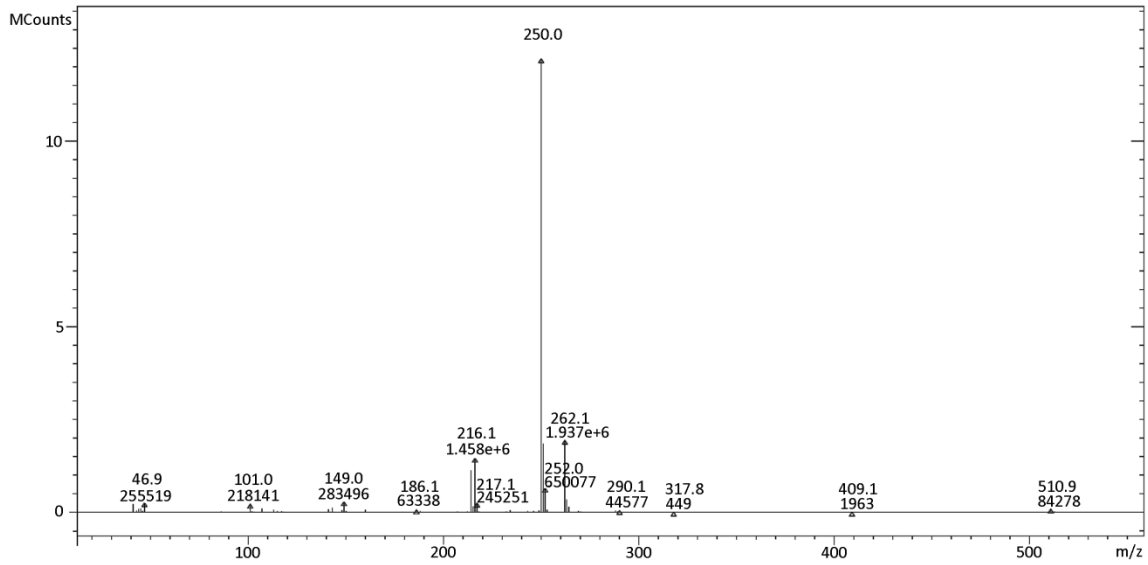
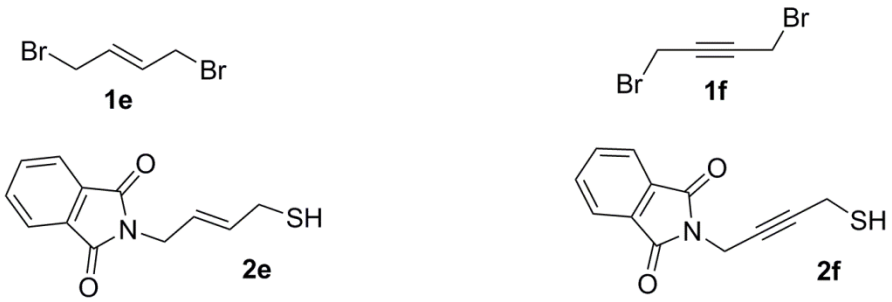


Figure 4. Mass spectrum (CI-MS) of crude 5-phthalimidopentylthiol.



Scheme 4. Structures of compounds **1e** and **1f**, as well as **2e** and **2f**.