Spring 2013

Novel synthesis of sulfur based ligands used in modeling biological hydrogen bonding interactions

Tyler Jesse Jacinto
University of New Hampshire, Durham

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Novel synthesis of sulfur based ligands used in modeling biological hydrogen bonding interactions

Abstract
Heme-thiolate proteins are known to have hydrogen bond donors proximal to the axial thiolate ligand. The specific roles of these conserved H-bond donors have not yet been elucidated. However, various sources agree upon the positive influence that increased X-H···S interactions have on protein redox potentials. For example, synthetic modeling studies of the cytochromes P450 show similar positive shifts in potential in iron-porphyrin-thiolate model systems. The ligands used in modeling the H-bonding interactions in the P450 cytochromes included a series of 2,6-substituted thiophenols, -S(2,6-(CX3CONH)2C6H3), where X = H, F, CH3. The current synthetic route to these ligands is vague and employs materials that are no longer commercially available. Seeking a new synthetic route to the precursor to this ligand series, bis(2,6-diaminophenyl)disulfide, 2,6-dinitrophenylsulfonyl chloride (14) has been synthesized and characterized by X-ray diffraction (XRD) and nuclear magnetic resonance (NMR). The steric contributions of these bulky ligands may have an effect on the redox potential and Fe-S bond length of the heme-thiolate complexes. This new idea prompted the synthesis of a putative precursor to the nearly isosteric bis-ester ligand series, -S-(2,6-(CX3COO) 2C6H3), where X is as specified above. Compound 18 and its intermediates were characterized by NMR.

Keywords
Chemistry, General, Chemistry, Inorganic, Chemistry, Organic, Chemistry

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NOVEL SYNTHESSES OF SULFUR BASED LIGANDS USED IN MODELING BIOLOGICAL HYDROGEN BONDING INTERACTIONS

by

Tyler Jesse Jacinto
B.A., College of the Holy Cross, 2010

Thesis

Submitted to the University of New Hampshire in Partial Fulfillment of the Requirements for the Degree of

Master of Science in Chemistry

May, 2013
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Professor of Chemistry

April 18, 2013
Date
Dedication

To my parents, Douglas and Marie, and my siblings Kaylie and Peter. I never would have been able to complete such a challenge without knowing the love of such a supportive family.
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Abstract

NOVEL SYNTHESSES OF SULFUR BASED LIGANDS USED IN MODELING BIOLOGICAL HYDROGEN BONDING INTERACTIONS

by

Tyler Jesse Jacinto

University of New Hampshire, May, 2013

Heme-thiolate proteins are known to have hydrogen bond donors proximal to the axial thiolate ligand. The specific roles of these conserved H-bond donors have not yet been elucidated. However, various sources agree upon the positive influence that increased X-H-•••S interactions have on protein redox potentials. For example, synthetic modeling studies of the cytochromes P450 show similar positive shifts in potential in iron-porphyrin-thiolate model systems. The ligands used in modeling the H-bonding interactions in the P450 cytochromes included a series of 2,6-substituted thiophenols, \( \text{S-} \left(2,6-(\text{CX}_3\text{CONH})_2\text{C}_6\text{H}_3\right) \), where \( X = \text{H}, \text{F}, \text{CH}_3 \). The current synthetic route to these ligands is vague and employs materials that are no longer commercially available. Seeking a new synthetic route to the precursor to this ligand series, bis(2,6-diaminophenyl)disulfide, 2,6-dinitrophenylsulfonyl chloride (14) has been synthesized and characterized by X-ray diffraction (XRD) and nuclear magnetic resonance (NMR). The steric contributions of these bulky ligands may have an effect on the redox potential and Fe-S bond length of the heme-thiolate complexes. This new idea prompted the synthesis of a putative precursor to the nearly isosteric bis-ester ligand series, \( \text{S-} \left(2,6- \)
(CX₃COO)₂C₆H₅, where X is as specified above. Compound 18 and its intermediates were characterized by NMR.
Introduction

Heme thiolates

The heme prosthetic group is one of nature's most versatile structures, found within many different proteins in plants, mammals, fungi, and bacteria. Heme proteins participate in a wide assortment of critical life processes such as catalysis, sensing, O$_2$ transport, and electron transfer.\(^1\) The most common of the heme structures is heme $b$, which consists of protoporphyrin IX (PPIX) coordinated to an iron ion (Figure 1). Axial ligands which typically bind to heme are endogenous peptide residues histidine,\(^2\) tyrosine,\(^3\) methionine,\(^4\) or cysteine,\(^5\) and, depending on protein function, exogenous small molecules such as H$_2$O, O$_2$, NO, CO, or CN$^-$.\(^6\),\(^7\) Differences in the axial substituents as well as the surrounding protein lead to the diverse range of biological functions exhibited by heme proteins.

Figure 1: Protoporphyrin IX coordinated to an iron atom. One or two axial ligands may be present ($L_1$ and $L_2$), with one above and below the porphyrin plane.
Members of the heme-thiolate class of proteins have an anionic cysteinate as an axial ligand, and exhibit both catalytic and sensing/transport activities. Heme-thiolates are further classified into two types; type 1 for those with catalytic functions, and type 2 for sensory and transport proteins. A non-labile axial cysteinate is a shared characteristic among type 1 heme-thiolates, such as chloroperoxidase (CPO) and the monooxygenase cytochromes P450. Upon substrate binding in catalytic heme-thiolates, the iron undergoes a switch from low- to high-spin. The conformational changes associated with substrate binding in turn cause the exogenous sixth ligand (usually a water molecule) to dissociate, which leads to the five-coordinate ferric species. In type 2 heme-thiolates, such as human cystathionine β synthase (hCBS) and the CO sensor CooA, the thiolate is present only in the ferric state and dissociates upon reduction. Both types of proteins tend to be six-coordinate in the low-spin resting states. Type 2 heme-thiolates generally function solely as six-coordinate centers. Upon reduction to the ferrous state the axial cysteinate is retained in type 1 heme-thiolates, while in type 2 heme-thiolates it is switched out for a neutral donor, most often an imidazole (Figure 2).
Figure 2: The axial cysteinate retains coordination to the iron throughout the catalytic cycle of type 1 heme thiolates. Upon reduction in type 2 heme thiolates a ligand switch occurs between the cysteinate and a neutral ligand, X.

The two types of heme-thiolates can be distinguished by examining the electronic spectra of their Fe^{II} carbon monoxide adducts. The Soret maximum that type 1 ferrous heme-thiolates exhibit is consistently around 450 nm, which is indicative of CO opposite a heme-cysteine(thiolate). Upon reduction in type 2 heme-thiolates the bound cysteinate may either become protonated or switched with another neutral ligand. This gives rise to a Soret band with $\lambda_{\text{max}} \approx 420$ nm. The differences in function and reactivity between the two types of heme-thiolates are thought to be largely influenced from the surrounding protein. Hydrogen bonding to the axial cysteinate is known to play a part in modulating redox potentials and the stability of the Fe-S bond. These interactions are thought to have unique effects on both classes of heme-thiolates.
Hydrogen bonding in heme-thiolates

In 1976 Sligar and Gunsalus observed that substrate binding to the camphor-hydroxylating \( \text{P450}_{\text{cam}} \) caused a change from low spin to high spin \( \text{Fe}^{III} \).\(^{10}\) This induced a positive shift in the \( \text{Fe}^{III}/\text{Fe}^{II} \) couple, leading them to the conclusion that substrate binding may alter the redox potential. More current synthetic modeling studies as well as site-directed mutagenesis provide support that hydrogen bonding to the thiolate may have a large influence on the redox potentials in heme-thiolate proteins.\(^{11,12}\) Conformational changes in proteins upon substrate binding may in turn result in the alteration of the hydrogen bonding environment proximal to the cysteinate.

Crystal structures of heme-thiolate proteins suggest nearby hydrogen bond donors to the sulfur in the active sites. In CPO, Cys\(^{29}\) is the axial ligand to the heme iron, with the sequence proximal including Pro\(^{30}\)-Ala\(^{31}\)-Leu\(^{32}\). There are two hydrogen bonds directed towards the sulfur donated by the amide N-H units of alanine and leucine (Figure 3).\(^{5}\)
Cytochromes P450 are a family of enzymes that are most known for catalyzing the stereoselective hydroxylation of unactivated C-H bonds. In light of the various other types of reactions performed, Coon deemed P450s "Nature's most versatile biological catalyst". Some of these include dehydrations, dehydrogenations, alcohol/aldehyde oxidations, N-, and S-oxidations, N-, S-, and O-dealkylations, alkene/arene epoxidations, and oxidative C-C cleavages. All of this chemistry occurs directly at the heme-thiolate site in the protein. Amino acid residues proximal to the complex are thought to assist in stabilizing heme-thiolate coordination upon substrate binding and with iron fluctuating oxidation states during catalysis. The general catalytic cycle of P450 enzymes is seen in Figure 4.
Figure 4: The catalytic cycle of cytochrome P450 monooxygenases. The distal substrate binding pocket is represented by the curved semicircle above the heme. The organic substrate to be oxidized is designated RH, and the product as R(O)H.

Starting with the top structure in Figure 4 and proceeding clockwise, the substrate enters the binding pocket on the distal side of the heme. This results in a change in the
iron center from low- to high-spin Fe$^{3+}$. One-electron reduction of this complex, normally performed in biology by reduced putidaredoxin, affords the active ferrous heme-thiolate. Dioxygen then binds to the ferrous iron and an irreversible cascade of reduction, protonation, and O-O bond scission results in Compound I.

The strong electron donating ability of the sulfur was proposed by Dawson et al. to assist in lengthening the O-O bond to be cleaved. This "push" effect is in contrast with non heme-thiolate oxygenases in which the O-O bond is activated via the hydrogen bonding network on the distal side of the heme. The "push-pull" effect observed between the axial histidine ligands and the hydrogen bond donors near the bound O$_2$ is known to assist in this bond breakage. In most P450 enzymes the distal side of the heme is fairly open due to the size of the substrate binding pocket. In turn, there is little assistance in this process from nearby amino acid residues. Thiolates are much stronger electron donors than neutral tertiary amines, so direct assistance from the protein environment is not necessary to facilitate O$_2$ cleavage.

Cytochrome P450$_{cam}$ is one of the more structurally studied of the P450 family of enzymes. The proximal sequence surrounding the axial cysteinate ligand in most P450s is conserved with three backbone amide N-H donors close to the sulfur. Most notably these amide N-H donors are found with the pattern Cys-X-Gly-Y, with X and Y being backbone-amide N-H containing amino acids. In Cytochrome P450$_{cam}$ this specific sequence is Cys$^{357}$-Leu$^{358}$-Gly$^{359}$-Gln$^{360}$. The crystal structure of the active site of this enzyme shows the amide nitrogen of Leu$^{358}$ to be in close proximity to the heme-thiolate sulfur, Cys$^{357}$ (Figure 5). The adjacent backbone nitrogens of Gly$^{359}$ and Gln$^{360}$ are also present, with Gly$^{359}$ having the shortest N⋯S distance (3.3 Å). The presence of these
hydrogen bond donors is thought to mitigate the charge localized on the sulfur and tune the electron donating ability of the thiolate to the heme iron.

![Figure 5: Crystal structure of the active site of cytochrome P450cam, showing hydrogen bonding between the proximal backbone amide N-H and the axial cysteinate. Nearby residues and backbone carbonyl oxygens were omitted for clarity. This image was generated from PDB file 1076 using Swiss-PdbViewer.](image)

One of the more common techniques for probing the function of a certain protein is site directed mutagenesis. In 2000, Morishima and coworkers replaced one of the three supposed amide N-H donors of the "cys pocket" of P450cam with proline, a tertiary amide. They substituted Leu\[^{358}\] with a residue that is incapable of hydrogen bond donation, making the L358P mutant.\(^{11}\) This mutation increased the amount of electron density on the thiolate relative to wild type P450cam. A corresponding effect on the redox potential and reactivity was observed. Enhanced O-O bond scission was detected for a variety of hydrocarbon substrates due to the added "push" effect from the more electron rich sulfur. Wild type P450cam has a reduction potential of \(-134\) (±3) mV, while L358P with one amide N-H donor removed has a potential of \(-170\) (±2) mV (calibrated with phenosafranine electrode, \(-252\) mV at 25 °C).\(^{20}\) The observed decrease in reduction
potential of the mutant is presumably due to the replacement of the supposed amide N-H
donor leucine with the tertiary amide proline.

The shift in potential (36 mV) is remarkably similar to those observed in
modeling studies carried out by Ueyama et al. in 1999. The active site peptide
sequences of the cys-pockets in both P450cam and CPO were complexed to synthetic
heme-thiolates and their redox properties were determined. The removal of one
hydrogen bond donor when comparing the tri- and tetra-peptide donor complexes led to a
decrease of 30-40 mV. Although hardly a direct comparison due to the model complex
lacking surrounding protein, this helps to illustrate that hydrogen bonding to the sulfur
may be a large factor in controlling the reactivity of heme-thiolates in nature.

Hydrogen bonding

Many different factors govern how proteins carry out their respective functions.
Hydrogen bonding is one of the main force attractions that lead to protein folding and
three-dimensional structure, as well as many other specific properties. The term
"hydrogen bond" was first mentioned in the chemical literature in 1920 by Latimer and
popularize the new concept. Pimentel and McClellan later defined this interaction in
their 1960 book, The Hydrogen Bond, with criteria that can be used to differentiate
between systems with and without H-bonds. Since this time there have been many
theoretical and experimental discoveries challenging the traditional definitions, leading to
debate in the literature as to what "hydrogen bonding" actually means. A more widely
accepted definition was needed in order to characterize a general hydrogen bonded system.

A technical report on a more modern classification of the hydrogen bond was issued by IUPAC in 2011. A collection of 14 authors with diverse backgrounds in chemistry defined the force as "an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation."25 A generalized depiction of a hydrogen bond can be X-H⋯Y-Z, where the acceptor of the hydrogen bond may be a lone pair on Y or a π-bond of Y-Z. Certain criteria were decided upon in support of their definition, with an emphasis on spectral characterization. According to the group of authors of this recommendation, the most widely accepted techniques for proving the existence of this interaction are 1H Nuclear Magnetic Resonance (NMR) and infrared (IR) spectroscopy.

Pimentel and McClellan described IR spectroscopy as the "most sensitive" technique for viewing the presence of a hydrogen bond.24 The X-H stretch typically undergoes a red shift with increasing peak intensity and broadening upon H-bonding. The magnitude of this shift quantifies the strength of the particular H-bonding interaction. This is highlighted in variable temperature IR studies by Gao et al. on hydrogen bond containing dendritic peptides (Figure 6).26 Above a certain threshold temperature these intermolecular attractions will not be present due to conformational fluxionality. As the sample cools the hydrogen bonds begin to form, with a corresponding red shift of the N-H stretch. These lower energy vibrations correspond to N-H bond lengthening, implying an N-H⋯Y interaction. Something else to note as the temperature cools is the presence
of another band intensifying at ~3080 cm⁻¹. This indicates the presence of the N-H···Y stretch, where Y may be a lone pair on a carbonyl O or amide N in the case of this system. Although this spectral feature is not always observed, the increasing intensity of the stretch with decreasing temperature provides additional support for the existence of hydrogen bonding.

![Figure 6: Temperature-dependent FT-IR studies performed by Gao et al. on amphiphilic dendritic peptides. As the sample cools to room temperature the characteristic red shift, broadening, and intensifying of the N-H stretch illustrate the existence of hydrogen bonding interactions.](image)

There are a few rare examples of an X-H···Y-Z interaction that actually result in a shortening of the X-H bond and a corresponding blue shift of the stretch in IR. These "blue shifting hydrogen bonds" are still classified as hydrogen bonds, but have only been seen in specific cases with electron deficient C-H donors.

In hydrogen bonded systems the X-H···Y-Z interaction leads to characteristic dispersions of NMR signals. The donor (X) and acceptor (Y) groups cause less electron density localized on the hydrogen atom through inductive effects giving rise to more downfield shifts. Although the word "concentration" is not used once in the IUPAC
account on the definition of the hydrogen bond, it is well known that modifying concentration of a hydrogen bond donor increases intermolecular attractions.\textsuperscript{28,29} A stronger acceptor could be provided either by modification of the molecule or changing the NMR solvent, resulting in relatively lower-field shifts. In addition to small molecules, hydrogen bonding within protein active sites can be elucidated using NMR.\textsuperscript{30}

X-ray crystallography is frequently used to probe the active site structures of proteins, although direct evidence of hydrogen bonding is not typically determined from this technique. Putative amino acid side chains or amide nitrogens near an active site H-bond acceptor, such as the cysteinate in heme-thiolates, may suggest the presence of these interactions. Various types of iron-sulfur proteins have been shown to contain backbone amide N atoms proximal to and, in many cases, directed towards the thiolate. This is observed in both heme-thiolates as well as iron-sulfur cluster proteins. Stephens and Warshel calculated the redox potentials of four unique iron-sulfur cluster proteins in an effort to confirm regulation of this property by hydrogen bonding.\textsuperscript{31} The presence of more amide groups closer to the clusters translated to relatively higher redox potentials. Synthetic model systems support this positive shift in redox potential in many iron-sulfur proteins, such as heme-thiolates.\textsuperscript{12,21}

**Modeling heme thiolates**

Heme-thiolate model complexes were first synthesized in the 1970s by Holm,\textsuperscript{32} and Collman.\textsuperscript{33} Collman et al. investigated the high- and low-spin ferric states of P450 enzymes using tetraphenylporphyrin (TPP) and benzenethiol/benzenethiolate as the axial ligands. Holm and coworkers prepared several five-coordinate ferric complexes using
PPIX and thiophenolate ligands. These were intended as simple models for the oxidized reaction states of P450 enzymes. The novel synthetic methodology, which involves air-free Schlenk techniques, was the basis for modeling more specific heme-thiolate active site complexes. With regards to hydrogen bonding, Ueyama and coworkers synthesized various heme-thiolate and non-heme iron-sulfur protein model complexes beginning in the early 1990s. A series of novel intramolecular hydrogen bond donor thiophenolate ligands were synthesized and complexed to various metals in order to model the protein environment around the axial cysteinate in iron-sulfur clusters and heme-thiolate proteins (Figure 7). The increased number and strength of the hydrogen bond donors was found to have a significant effect on the reactivity and properties of the model complexes.

![Figure 7: Thiophenolate ligands with flanking hydrogen bond donor amide groups. \((S-2,6-(\text{CX}_3\text{CONH})\text{C}_6\text{H}_3), \text{ and } (S-2-(\text{CX}_3\text{CONH})\text{C}_6\text{H}_4), \text{ where } X = \text{H, F, (CH}_3)\).](image)

A large collection of this work was performed using octaethylporphyrin (OEP) iron complexes with one or two ortho amide N-H donor ligands pictured in Figure 7. The crystal structures of both \([\text{Fe(OEP})](S-2-(\text{CF}_3\text{CONH})\text{C}_6\text{H}_4)\) and \([\text{Fe(OEP})](S-2,6-(\text{CF}_3\text{CONH})\text{C}_6\text{H}_3)\) suggest that the amide hydrogens are directed toward the sulfur atom, implying a hydrogen bonding interaction in the crystalline state (Table 1, Entries 3 and 5 respectively). This is supported by the orientation of the flanking amide C=O groups being practically coplanar with the phenyl ring. A lengthening of the Fe-S bond was also observed in these two crystal structures relative to the benzenethiolate complex. Ueyama et al. reported that this lengthening is due to intramolecular NH•••S hydrogen bonds.
decreasing π-donation of sulfur to iron, and does not involve steric effects. However, it is possible that steric interactions between the porphyrin plane and the bulky trifluoroacetyl groups of the amides may also be responsible for such an elongation.

Table 1: Selected physical properties of synthetic OEP heme-thiolate complexes modeling the effects of hydrogen bond donation to the sulfur.

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<th>Entry</th>
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<th>$E_{1/2}$*</th>
<th>Fe-S Bond (Å)</th>
<th>Oxidative Decomposition$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$SC_6H_5$</td>
<td>-0.68</td>
<td>2.29(9)</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>S-2-(tBuCONH)C$_6$H$_4$</td>
<td>-0.58</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>3</td>
<td>S-2-(CF$_3$CONH)C$_6$H$_4$</td>
<td>-0.52</td>
<td>2.32(7)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>4</td>
<td>S-2,6-(CH$_3$CONH)$_2$C$_6$H$_3$</td>
<td>-0.50</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>S-2,6-(CF$_3$CONH)$_2$C$_6$H$_3$</td>
<td>-0.35</td>
<td>2.35(6)</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>S-4-(CF$_3$CONH)C$_6$H$_4$</td>
<td>-0.67</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>S-2-MeC$_6$H$_4$</td>
<td>-0.72</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Redox potentials were measured in V vs. SCE in dichloromethane (2.5 mM, RT).
$^b$ Amounts (%) of producing Fe(OEP)$_2$O from Fe(OEP)L after exposure to air for 1 hr.

The presence of the ortho-hydrogen bond donor groups shift the redox potentials drastically to more positive values from that of benzenethiolate (Table 1). The observed trend increases with both the number of hydrogen bond donors and the electron-withdrawing ability of the alkyl group of the amide. Entry 5 in Table 1 had the most significant change in potential, with a positive shift of 0.33 V from the simple benzenethiolate complex (+0.68 V to +0.35 V). The strongly electron-withdrawing trifluoroacetyl group has the largest effect on the redox potential, but only when ortho to the sulfur. Entries 3 and 6 in Table 1 illustrate this most effectively. The ortho-substituted trifluoroacetamide complex (Entry 3) has a large positive shift of 0.16 V. The isomeric para-substituted trifluoroacetamide complex (Entry 6) has little to no effect on the redox potential, with a positive shift of 0.01 V. The electrochemical data is the most
convincing in showing that intramolecular NH···S hydrogen bonding may be present in these complexes, however it is not possible to rule out the contribution of steric effects until further studies are performed.

The oxidative stability of several of the Fe(OEP)-thiolate complexes were measured as a means of illustrating the stabilizing effects of the ortho substituents to the sulfur (Entries 1-5, Table 1). These percentages were determined by exposing the Fe(OEP)L complexes to air for one hour and measuring the relative amount of Fe(OEP)₂O produced via absorption spectroscopy. The presence of hydrogen bond donors and sterically hindering functional groups at the ortho positions to the sulfur correlate to more relatively air-stable Fe(OEP)L complexes. The simple benzenethiolate complex (Entry 1, Table 1) degraded by 40% after one hour. Entry 4 in Table 1, with two ortho N-acetamide functional groups, shows approximately twice the oxidative stability (20% degradation) when compared to the benzenethiolate complex. Entry 2 in Table 1 shows the effect of the more bulky ortho N-trimethylacetamide group in the protection of the Fe-S bond from oxidative dissociation, by only 7% conversion to Fe(OEP)₂O after one hour. Entry 5 in Table 1 showed no signs of decomposition even after 5 days at ambient conditions, showing the large stabilizing effects of the two ortho N-trifluoroacetamide groups. The proposed mechanism for degradation involves nucleophilic attack of molecular oxygen on the Fe(OEP)⁺ complex, with dissociation of thiolate and oxidation to disulfide:³⁵

\[ 2 \text{[Fe(OEP)]SAr} + \frac{1}{2} \text{O}_2 \rightarrow \text{[Fe(OEP)]}_2\text{O} + \text{ArSSAr} \] (1)
The steric hindrance of the functional groups at the ortho positions in addition to the possibility of hydrogen bonding help to explain the oxidative stability for these complexes.

Characterization of the existence of the intramolecular NH···S hydrogen bond was also attempted by NMR studies of the Fe(OEP)$^+$ complexes from Table 1. However, due to the paramagnetic Fe$^{III}$ center and anisotropy of the highly-conjugated porphyrin ring, several of the protons were absent in these spectra. In addition to some aromatic protons, the amide N-H protons were not present in the $^1$H NMR most likely due to peak broadening. Deuterium was exchanged with the amide N-H's in order to view these signals. There was a trend in varying the electronic nature of the amide alkyl substituents. $^2$H NMR allowed the ortho amide protons to be observed between -43 ppm to -24.8 ppm. The amide N-H peak for the para-substituted ligand (entry 6, Table 1) was at +30.4 ppm, far more downfield than any of the ortho amide complexes. The large discrepancy in dispersion between the amide N-H's of the ortho- and para-substituted complexes may be a result of being spatially further from the paramagnetic iron center and porphyrin ring. Overall the NMR studies carried out were unable to unequivocally determine presence of an intramolecular NH···S hydrogen bond in the ortho-substituted complexes.
Table 2: N-H stretching frequencies of the ligand disulfides, the [Fe(OEP)]⁺ complexes, and the difference of these measurements.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Fe(OEP)]L</th>
<th>v(N-H)_{disulfide} (cm⁻¹)</th>
<th>v(N-H)_{complex} (cm⁻¹)</th>
<th>Δv(N-H) (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L = S-2,6-(CF₃CONH)₂C₆H₃</td>
<td>3370</td>
<td>3278</td>
<td>-92</td>
</tr>
<tr>
<td>2</td>
<td>S-2,6-(CH₃CONH)₂C₆H₃</td>
<td>3385</td>
<td>3331</td>
<td>-54</td>
</tr>
<tr>
<td>3</td>
<td>S-2-(CF₃CONH)C₆H₄</td>
<td>3358</td>
<td>3235</td>
<td>-123</td>
</tr>
<tr>
<td>4</td>
<td>S-2-(tBuCONH)C₆H₄</td>
<td>3397</td>
<td>3331</td>
<td>-66</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>S-4-(CF₃CONH)C₆H₄</td>
<td>3320</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Δv(NH) was calculated from the change in N-H stretching frequency of the ligand disulfide vs. the Fe(OEP)⁺ complex. According to Ueyama, this quantifies the strength of the hydrogen bond. * No IR data was reported for this complex; IR data for this disulfide is provided from an alternate source, and also reported using KBr pellets for the IR studies.

The Δv(N-H) stretches (Table 2) were calculated between the conformationally "free" N-H of the disulfide of the ligand versus the model heme-thiolate complex. In the complexed form the amide N-H groups are thought to be more conformationally static and may stabilize the thiolate state from oxidative dissociation. According to Ueyama et al., this allowed for the strength of the potential hydrogen bonds to be determined. Entry 3 in Table 2 shows the strongest individual hydrogen bonding interaction, with a red shift of -123 cm⁻¹. This method of comparing the disulfide to the metal complex in determining hydrogen bond strength has no precedence in the literature, and has not been used since this report.

While the ortho substituted complexes are meant to exhibit some degree of intramolecular N-H···S interaction, the para substituted trifluoroacetamide (Entry 5, Table 2) was used as a control ligand for substituent electronic effects. The omittance of IR data of both this ligand and its Fe(OEP)⁺ complex raises some question as to the validity of the intramolecular N-H···S hydrogen bond observed in the ortho-substituted complexes. An unrelated source provided the disulfide of this ligand's IR spectrum,
reporting an N-H stretch of 3320 cm$^{-1}$. This N-H value is actually more red-shifted than any of the ortho-amide disulfides that Ueyama et al reported. Entry 3 in Table 1 was the most red-shifted of these disulfides, having an N-H stretch at 3358 cm$^{-1}$. The data reported for Entry 5 may potentially discredit the supposed N-H···S interactions viewed in the ortho-amides. The red shifts observed in the ortho-amide complexes may therefore be due to relatively weaker intermolecular H-bonding. Rationale for this discrepancy could be due to less sterically hindered intermolecular H-bonding in the para-amide complex. If IR data of the Fe(OEP)$^+$ complex of this ligand were reported, the data set would no doubt be more complete in illustrating these effects. Logical trends are observed with respect to the ortho-amide ligand series throughout the various spectral and physical characterizations. However, the observed increasing hydrogen bond strength may actually be a result of more intense intermolecular rather than actual intramolecular NH···S attractions.

Hydrogen bonding vs. steric interactions

Ueyama et al. synthesized the complexes $[\text{Fe(OEP)}(\text{S-2,4,6-Me}_3\text{C}_6\text{H}_2)]$ and $[\text{Fe(OEP)}(\text{S-2,4,6-(iPr)}_3\text{C}_6\text{H}_2)]$ in order to determine the effect that the hydrogen bond has relative to steric bulk.$^{37}$ They found that the alkyl substituted benzenethiolates were more prone to oxidation and corresponding iron reduction when compared to the relatively air stable complexes $[\text{Fe(OEP)}](\text{S-2,6-(CF}_3\text{CONH})\text{C}_6\text{H}_3)$ and $[\text{Fe(OEP)}](\text{S-2-(CF}_3\text{CONH})\text{C}_6\text{H}_4)$. Originally thought to provide a more bulky environment around the Fe-S bond, which may prevent attack from water or oxygen, these complexes were not as stable as the two trifluoroacetamide complexes.
Electron rich benzene rings lead to less acidic thiols, which are more susceptible to oxidation. This in turn means a more negatively shifted redox potential of the thiol-disulfide redox couple, as well as the metal-ligand complexes. The thiophenols with three alkyl donating groups have a more electron rich benzene ring which leads to less stable iron complexes than the N-trifluoroacetamide substituted thiophenols. However, the amide groups are themselves moderate electron donors to the benzene ring. The amide substituted thiolates are therefore relatively more electron rich than the control benzenethiolate. The mild electronic effect is overshadowed by either the hydrogen bonding or steric interactions between the amide groups and the sulfur. With respect to the benzenethiolate complex, the ortho-substituted N-H donor complexes all resulted in positively shifted redox potentials.

Dey and coworkers probed the Fe-S bond of P450 model complexes by ligand K-edge X-ray absorption spectroscopy (XAS) and density functional theory (DFT) calculations. They employed the same model intramolecular H-bond donor complexes for their calculations that Ueyama synthesized years earlier. These complexes are [Fe(OEP)](S-2,6-(CF₃CONH)C₆H₃) and [Fe(OEP)](S-2-(CF₃CONH)C₆H₄). Hydrogen bonding was found to have a notable effect on the electronic structure and redox potential of the complexes. The preedge feature of K-edge spectra can be used as a direct measure of ligand to metal bond covalency. The covalency of the Fe-S bond was therefore measured for the control benzenethiolate complex as well as the two intramolecular hydrogen bond donor thiolate complexes. Figure 8 shows the almost linear relationship of the covalency of the Fe-S bond with the redox potentials of the corresponding...
complexes. Hydrogen bonding reduces the covalency of the Fe-S bond by delocalizing electron density on the axial sulfur atom.

![Observed Fe-S Covalency](Figure 8: Dey and coworkers comparison of Fe-S bond covalency vs. redox potentials of the labeled Fe(OEP)-thiolate complexes.)

Modeling the effect that steric hindrance has versus that of hydrogen bonding on the heme-thiolate bond's properties may be more efficiently carried out by designing and complexing a ligand with similar dispersion and steric bulk as the already employed amide functionalities. Increasing the Fe-S bond length due to steric interactions may directly increase the reduction potential, as the iron atom has decreased electron donation from the anionic sulfur. A more appropriate control ligand for modeling steric hindrance vs. hydrogen bonding around the heme-thiolate active sites could be the ester functionality, seen in Figure 9. The environment around the thiolate would be very similar, and the mild electron donating ability of esters is comparable to that of amides. Since the diester ligands do not contain a hydrogen bond donor they are ideal candidates for comparison with the amide ligands. The diester series of ligands has not yet been prepared in the literature. Comparing the bond lengths and redox potentials of the ester
vs. the amide complexes could assist in proving the effects of steric interactions vs. H-bonding.

![Figure 9: Structures of the ligands to be complexed to [Fe(porphyrin)]^+, where X = H, F, (CH₃). The steric and electronic environments are relatively conserved between the two, except for the ability to donate a hydrogen bond.](image)

**Literature routes to bis-amide thiophenolate ligands**

The published route to the diamide series of ligands references bis(2,6-diaminophenyl)disulfide as the starting material. Neither this material nor its corresponding thiol are commercially available. The only published route to bis(2,6-diaminophenyl)disulfide involves ring opening of 7-aminobenzothiazole. No 7-substituted benzothiazoles are commercially available, and require several steps to synthesize. In the same reference that reports the synthesis of bis(2,6-diaminophenyl)disulfide, the compound 7-nitrobenzothiazole was synthesized from N-formyl-2-chloro-3-nitroaniline. This starting material is also not commercially available and requires multiple steps to synthesize. Reproducing this published chemistry is very difficult, as there is no indication from Ueyama's publications as to which method was used to prepare bis(2,6-diaminophenyl)disulfide. An alternate preparation of 7-nitrobenzothiazole was found in an earlier reference by Ward and Poesche, but the isolation of this compound is difficult, even with a fairly detailed procedure. The first step of this sequence involves the difficult isolation of a minor regioisomer from the nitration of benzothiazole, shown in Scheme 1.
Scheme 1: The nitration of benzothiazole results in a non-regioselective mixture of products. % yields were determined by chromatography and mixed melting point analysis, since the 6- and 7-isomers coelute.

As performed by Ward and Poesche, this reaction was run on a 31.5 gram scale. A maximum of 4.6 grams of 7-nitrobenzothiazole was reportedly isolated after several days of successive isolation and purification techniques. Chromatography was not practical for obtaining any of the minor isomers in quantity, and the 6- and 7- isomers coeluted. Crystallization of the filtered solids from ethanol gave largely 6-nitrobenzothiazole. The filtrate was concentrated and the resulting residue was steam distilled. Both the 6- and 7- isomers are slightly steam volatile, but this was a "tedious" means of separation, as commented by the authors. Further reacting the mixture of 6- and 7-nitrobenzothiazoles with methanolic sodium hydroxide followed by crystallization from ethanol allowed the isolation of 4.6 grams of the "almost pure" 7-nitro isomer.

The synthetic routes to the starting materials used to synthesize bis(2,6-diaminophenyl)disulfide appear to be wasteful, inefficient, and are poorly documented, so a new synthetic route was determined to be necessary.
Results and Discussion

Objective

Much of this thesis is dedicated to finding a more practical route to the disulfide precursor to the diamide derivatives of 2,6-diaminothiophenol. A synthesis to the disulfide precursor of the diester derivatives of 2,6-dihydroxythiophenol was also looked into in detail. Sulfur is nucleophilic and is known to compete with nitrogen and oxygen in acetylation reactions. The disulfides of each of these series of ligands is the actual objective so as to prevent possible acetylation at the sulfur. Complexation of the thiophenolate ligands to an iron porphyrin framework is the ultimate goal of this project, and progress towards this goal via the ligand syntheses is described in this thesis.

Synthesis of bis(2,6-diaminophenyl)disulfide

Several different approaches were taken in an attempt to synthesize the precursor to the ligand series, bis(2,6-diaminophenyl)disulfide. The following lettered synthetic routes (A through C) were attempted in chronological order and gave rise to several compounds previously unknown in the literature, but ultimately did not result in the isolation of the target compound. The final synthetic route (D) was the most promising in achieving the target. The main goal in each of the syntheses involved installing a sulfur in between two nitrogen functional groups, forming a symmetrical 1,2,3-trisubstituted benzene derivative. Benzene rings with this symmetrical substitution pattern are rarely described in the literature. The difficulty in achieving this arrangement of atoms is
largely due to steric interactions between functional groups and substituent directing effects.

A: Thiocarbamate cleavage route

A phenol can be converted into a thiophenol in three steps utilizing the Newman-Kwart rearrangement (Scheme 2). This is achieved by initial O-thiocarbamoylation in the presence of a base, followed by thermal rearrangement to the S-thiocarbamate, and subsequent cleavage under basic conditions. This is a widely used technique for installing the thiol functionality on aromatic rings.

Scheme 2: The Newman Kwart rearrangement, utilized to convert phenols to thiophenols in good yields.

A new synthetic route to the diamide ligand was designed with commercially available 2,6-dinitro-p-cresol. The first step of the proposed sequence involves conversion to the O-thiocarbamate. When this procedure was carried out in refluxing THF overnight a mixture of two products was produced and determined by thin layer chromatography (TLC). Starting material had been fully consumed, and $^1$H NMR indicated a mixture of both the O- and S-thiocarbarmates (Figure 10).
Figure 10: Crude NMR from the reaction of 2,6-dinitro-p-cresol and \(N,N\)-dimethylthiocarbamoyl chloride. Peak assignments are shown, with numbers corresponding to the O-thiocarbamate and letters to the S-thiocarbamate. Product distribution after 16 hours refluxing in THF was 2.7 : 1 S- : O-thiocarbamate.

One of the more intriguing spectral features in the \(^1\)H NMR of this mixture was the appearance of the two pairs of singlets at \(-3.44\) ppm and \(-3.05\) ppm (top left expansion, Figure 10). The protons of the \(N\)-methyl groups of both the O- and S-thiocarbamates are shown as two inequivalent singlets due to the energy barrier for rotation around an amide C-N bond. Generally, amides and thioamides are known to have restricted C-N rotation due to this barrier, but thiocarbamates are similar enough in structure to follow this trend.\(^{45}\) It is also known in the literature that the barrier to rotation around a thioamide C-N bond is greater than that of an amide C-N bond.\(^{46}\) This is directly evidenced in the \(^1\)H NMR spectrum in Figure 10. The shortening and broadening of the pair of peaks at 3.05 ppm is due to the \(N\)-methyl group protons.
approaching their coalescence point. The actual coalescence point occurs when the two groups are rotating faster than the timescale of the NMR experiment and appear as a single peak in the spectrum.

There is more restricted rotation around the C-N bond of the O-thiocarbamate because of the poor pi-overlap between the sulfur and carbon atoms. The lone pair on the nitrogen is in conjugation with the thiocarbonyl, and the resonance structure involving the C=\( \text{N} \) bond is the predominant form. This causes the methyl groups of the O-thiocarbamate to have a higher barrier to rotation resulting in sharper peaks relative to the S-thiocarbamate. This information was supported by Wiberg, who calculated the barrier for rotation of the C-N bond in thioformamide vs. formamide. His calculations reinforced the larger energy barrier in the thioformamide system, which implies that the C-N bond has more pi-character and is therefore more rigid. The larger size of sulfur relative to carbon is responsible for the poor C=S orbital overlap and consequently restricted C-N bond rotation.

The fact that this rearrangement is occurring at such a low temperature (85 °C) with respect to the typical literature range of 200-300 °C is due to an increased stabilization of the four-membered ring transition state. This positive result showed that there is no need to isolate or purify the O-thiocarbamate prior to thermal isomerization. This effectively skips a step in the proposed synthetic route to the 2,6-diaminothiophenol derivatives. The mechanism of rearrangement involves ipso nucleophilic attack of the sulfur forming a strained four-membered transition state. The temperature required for this process depends largely on the electronic nature of the ring and steric hindrance of the ortho positions. Electron deficient rings undergo nucleophilic substitution more...
readily than electron rich rings due to better resonance stabilization of the transition state, as seen in Figure 11. The Newman-Kwart rearrangement can actually proceed at room temperature for sufficiently electron deficient rings, but may require >300 °C for some electronically or sterically disfavored substrates.48

![Figure 11: The mechanism of the Newman-Kwart rearrangement. With very electron deficient rings, such as this system, the temperatures required for this process are drastically lowered.](image)

Removal of the thiocarbamate group is the next step in preparing the thiophenol. Basic hydrolysis is the most widely used method of thiocarbamate cleavage,44 but lithium aluminum hydride (LAH) has also been reported for sterically hindered thiocarbamates.49 Both methods when applied to 1 led to complex reaction mixtures upon attempted cleavage with trace organic-soluble impurities in the crude NMR. There are no published syntheses to produce 2,6-dinitrothiophenol, 2,6-dinitrothiocresol, or their respective disulfides in the literature. The reagents employed were not selective to the thiocarbamate and solely led to undesired side products observed by TLC and 1H NMR. The majority of these non-isolated byproducts were water soluble. The trace amount of a crude, organic soluble mixture obtained after workup was miniscule in comparison to the amount of starting material used in these attempts (Table 3).
Table 3: Conditions applied for the attempted cleavage of the thiocarbamate group in 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent - (Solvent)</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% NaOH - (MeOH)</td>
<td>Δ, 3 hr</td>
<td>Complex reaction mixtures, no starting material or desired products.</td>
</tr>
<tr>
<td>2</td>
<td>NaOMe - (MeOH)</td>
<td>RT, 2 hr</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄ - (THF)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H₂SO₄ - (H₂O)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
</tbody>
</table>

In addition to potentially cleaving the thiocarbamate group, LAH was found to be incompatible with the nitro groups of 1. Although it has been shown in certain cases to reduce nitro groups to amines,⁵⁰ this reagent is not commonly used due to many other more efficient and selective nitro reduction methods. LAH reductions have been shown in most aromatic systems to incompletely reduce the nitro compound, stopping at the diazo-coupled stage.⁵¹ When reacting an excess of this reagent with 1 in an attempt to fully reduce the nitro compounds to amines, the resultant crude mixture had no indication of amine protons, the thiophenol or the disulfide. The reaction mixtures consistently resulted in trace amounts of organic soluble material and were too complex by TLC and NMR to be of synthetic value.

Under hydrolytic conditions in methanol the S-thiocarbamate reacted very quickly, but gave rise to several undesired water-soluble byproducts. The yellow methanolic solution changed instantly to a deep purple upon addition of hydroxide. Starting material was consumed almost immediately at room temperature with several different products resulting as determined by TLC. Edwards and Pianka found on a similarly substituted system that, instead of thiocarbamate cleavage, methoxide immediately displaced the thiocarbamate group.⁵² They attributed the deep purple
reaction mixture to the formation of the 1,1-gem-dimethoxy-aci-nitro-salt, shown in

**Scheme 3.**

![Scheme 3: Pianka and Edward's attempted cleavage of a 2,6-dinitro-S-thiocarbamate led to ipso-substitution and loss of sulfur.](image)

The existence of this compound was determined by the authors via $^1$H NMR, although it re-aromatizes upon attempted isolation to the mono-methoxy-substituted derivative. The methoxy-substituted product was not isolated during hydrolysis of 1. When carried out only trace amounts of a complex mixture of organic soluble products were obtained, with the majority being water soluble. These reaction mixtures were not further analyzed or attempted to be separated. Although there is only one source in the literature citing cleavage under acidic conditions, this was also attempted. Acidic hydrolysis was attempted in hot sulfuric acid, but gave similar undesired results (Table 3).

Cleavage of 1 was unsuccessful at this stage, presumably due to the high reactivity of the ortho nitro groups. These were then reduced to amines, readily accomplished using iron metal powder in an acidic environment. After column chromatography eluting with dichloromethane (DCM) on alumina, 2 was isolated and subjected to a variety of thiocarbamate cleavage conditions (Table 4). The literature provided nuclear magnetic resonance (NMR) data for bis(2,6-diaminophenyl)disulfide in d6-acetone, so comparison to the reported chemical shifts was a means of determining the
success of these reactions. Contrary to the dinitro systems high reactivity, the diamino system was largely more stable to the cleavage conditions. Reaction mixtures resulted in decomposition to multiple undesired products, and also often contained unreacted starting material, as detailed in Table 4.

Table 4: Conditions applied for attempted cleavage of the thiocarbamate group in 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent - (Solvent)</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1M NaOH - (MeOH)</td>
<td>RT, 24 hr</td>
<td>Starting material, and/or decomposition</td>
</tr>
<tr>
<td>2</td>
<td>4M NaOH - (DMF)</td>
<td>Δ, 48 hr</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄ - (THF)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>N₂H₄ - (EtOH)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>H₂SO₄ - (H₂O)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
</tbody>
</table>

Compound 2 decomposes at high temperatures, with no indication of thiocarbamate cleavage. Utilizing hydrazine and attempting the same acidic conditions as applied on 1 (Entries 4 and 5 respectively in Table 4) each yielded similar undesired results. Rationale for this diminished reactivity towards cleavage and decomposition is thought to be due to the strongly electron donating free amino groups at the ortho positions to the thiocarbamate. Amides are much weaker electron donors than free amines due to the nitrogen lone pair being in conjugation with both the carbonyl carbon as well as the phenyl ring. The amines were readily protected via reaction with acetic and trifluoroacetic anhydrides to generate 3a and 3b, respectively, as seen in Scheme 4.
Scheme 4: Attempted synthesis of diamide ligand via Newman-Kwart rearrangement. Cleavage of the thiocarbamate was attempted at both the dinitro- and diamino- stages as well, and resulted in either unreacted starting material or a complex reaction mixture.

Attempts at cleaving the thiocarbamate group and generating the thiol at this stage resulted solely in amide hydrolysis back to the diamino precursor instead of thiocarbamate cleavage. Despite the successes of installing a sulfur in the first step of the sequence, the difficulties in removing the carbamoyl group eventually led to researching an alternate means of synthesizing the target ligand.

B: Xanthate cleavage route

The diazonium functional group is one of the most efficient leaving groups on a benzene ring, forming nitrogen gas when displaced. Conversion of an aryl amine to a diazonium salt is readily achieved in the presence of in situ generated $^+$N=O from strong acid and the nitrite anion, NO$_2^-$. Diazotization is often catalyzed by using the copper(I) salt of the nucleophile; however iodide, water, and sulfur compounds generally do not require this catalyst. Commercially available 2,6-dinitroaniline has the necessary
substitution pattern and was used as the starting material in this synthesis. The explosion hazards associated with working with polynitro aromatic compounds is increased even more by conversion to a potentially explosive diazonium salt. There are several Organic Syntheses preparations explaining diazotization using sulfur nucleophiles, and a procedure for generating the diazonium salt of 2,6-dinitroaniline in good detail.

(Scheme 5) Sulfur nucleophiles have been used extensively in diazotization reactions, but have not been reported in the literature on this system.

\[
\text{Scheme 5: Diazotization of 2,6-dinitroaniline. The diazonium salt in brackets was not isolated due to it being highly unstable and explosive. The strongly deactivated ring makes the aniline much less basic, necessitating a stronger acid source.}
\]

Diazonium salts can be explosive, shock sensitive compounds that are most practically generated in situ and reacted with immediately. The diazonium salt shown in brackets in Scheme 5 is generated, followed by reaction with an excess of nucleophile X. Attempts employing various sulfur nucleophiles resulted in complex reaction mixtures and no desired product (Table 5). Some may have decomposed upon addition of the extremely acidic diazonium salt solution, or may have been incompatible with the strongly deactivated ring. Xanthates in particular have been shown to decompose in sulfuric acid to yield carbon oxysulfide.
Table 5: Nucleophiles used in substituting the diazonium salt from Scheme 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KSCN</td>
<td>Complex reaction mixtures</td>
</tr>
<tr>
<td>2</td>
<td>Na₂S, S₈</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>KEX</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>KI</td>
<td>4, 79%</td>
</tr>
</tbody>
</table>

*KSCN = potassium thiocyanate, KEX = potassium O-ethyl xanthate, KI = potassium iodide.

The sulfur compounds employed did not successfully substitute during the diazotization procedure. Iodide was then used as the nucleophile and 2,6-dinitroiodobenzene (4) was isolated in 79% yield after crystallization from cyclohexane (Table 5). The iodide leaving group allowed for a similar framework to introduce a sulfur functional group without the harshly acidic conditions. There is little known on the reactivity of this compound towards sulfur nucleophiles, so a new procedure was developed.

Potassium O-ethyl xanthate was the first sulfur nucleophile employed in reacting with 4. Nucleophilic aromatic substitution reactions give rise to many charged intermediates in solution, so several different polar organic solvents were used in order to stabilize the charged intermediates formed during the mechanism of substitution. Optimization of the reaction solvent is shown in entries 1-3 in Table 6. It was found that N,N-dimethylformamide (DMF) gave the cleanest conversion to the xanthate under these conditions. The modest yield was improved by heating the reaction mixture up to 90 °C. Successful conversion of 4 to S-(2,6-dinitrophenyl)-O-ethyl xanthate (5) was found to be complete within one hour in DMF.
Table 6: Conditions applied for the nucleophilic substitution on 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time, Temperature</th>
<th>Result (1H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEG</td>
<td>5.5 hr, RT</td>
<td>Product and with byproduct</td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>5.5 hr, RT</td>
<td>Product and brown decomp.</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>5.5 hr, RT</td>
<td>5, 51%</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>16 hr, 90 °C</td>
<td>5, 52%</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>1 hr, 90 °C</td>
<td>5, 82%</td>
</tr>
</tbody>
</table>

All reactions were carried out on a 0.50 mmol scale using 1 equivalent of KEX and 1.5 mL of solvent. DEG = diethylene glycol, NMP = N-methyl pyrrolidinone, DMSO = dimethylsulfoxide.

Cleavage of the xanthate group to generate 2,6-dinitrothiophenol was not attempted at this stage. This is largely due to no literature precedence for the synthesis or characterization of this compound. All attempts to generate the same target during hydrolysis of 1 in the thiocarbamate cleavage route (A) resulted in undesired reaction with the nitro groups or even cleavage of the aryl-S bond. Reduction to S-(2,6-diaminophenyl)-O-ethyl xanthate (6) was therefore accomplished as before (route A) using iron in acetic acid, shown with the rest of the sequence in Scheme 6.

Scheme 6: Nucleophilic substitution route to the diamide ligand. All attempts to cleave the xanthate resulted in unreacted starting material and oxidative decomposition.
The xanthate group was thought to be a better means of introducing sulfur on the benzene ring relative to the thiocarbamate (Scheme 7). In route A to the diamide ligand series, the diamino thiocarbamate (2) was largely unreactive towards acidic and basic hydrolysis. Based on the relative reactivities of esters and amides and the resonance structures shown in Scheme 7, it seemed as though the xanthate group would be more readily hydrolyzed. Rotation about the C-N bond in amides and S-aryl thiocarbamates is hindered due to more π-character contribution, as seen in the left resonance structure. Rotation about the C-O bond in esters has a much lower barrier, and therefore leads to a more flexible functional group with less C-O π-character relative to amide systems. The dithiocarbonate (xanthate) group is expected to have weaker π-overlap between the carbonyl carbon and adjacent atoms, and therefore be more susceptible to cleavage conditions.

Scheme 7: Resonance structures shown for the thiocarbamate (left) and xanthate (right). The xanthate group is thought to be more susceptible to hydrolytic conditions due to the oxonium ion not being as representative of the bonding as the iminium ion.

Just as before in attempting to cleave the diamino S-thiocarbamate, all attempts to cleave the xanthate group to form the corresponding thiol were unsuccessful. Similar results were obtained in that the starting material was largely unreactive and darkened over time while heating. Table 7 shows the conditions applied for this reaction.
Table 7: Conditions applied for cleaving the diamino xanthate (6). Higher temperatures and longer reaction times resulted in faster decomposition, but no attempts yielded any desired product.

<table>
<thead>
<tr>
<th>Nucleophile - (Solvent)</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M NaOH - (EtOH)</td>
<td>RT, 24hr</td>
<td>Starting</td>
</tr>
<tr>
<td>4M NaOH - (EtOH)</td>
<td>Δ, 48 hr</td>
<td>material, with decomposition</td>
</tr>
<tr>
<td>4M NaOH - (DMF)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
<tr>
<td>N₂H₄ - (EtOH)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
<tr>
<td>LiAlH₄ - (THF)</td>
<td>Δ, 24 hr</td>
<td></td>
</tr>
</tbody>
</table>

The amines in the two ortho positions were then thought to have more of an effect on these aromatic sulfur compounds than originally thought. These 1,2,3-substituted benzenes are novel compounds, and thus their chemistry is largely undocumented. Since neither the xanthate nor the thiocarbamate sulfur protecting groups could be cleaved under these conditions, it was thought that the two ortho amino substituents on the benzene ring may be providing some type of undesired stabilizing effect. This may amount to certain interactions that prevent a nucleophile from cleaving both the thiocarbamate group in route A and the xanthate group.

**C: Benzothiazole ring opening route**

Routes A and B were similar in scope, involving attempts at cleaving different sulfur protecting groups in similarly substituted systems. A formal synthesis of bis(2,6-diaminophenyl)disulfide was decided upon as an altogether different approach. Since Ward and Heard determined that the synthesis of the target disulfide is dependent on the ring opening of 7-aminobenzothiazole, this was decided as a new target molecule (Scheme 8).
Scheme 8: The final step in the published route to bis(2,6-diaminophenyl)disulfide. According to Ward and Heard, ring opening by reaction with hydrazine followed by peroxide oxidation yielded the desired disulfide in 60% yield.

Ward and Heard reported that thiolation of N-formyl-2-chloro-3-nitroaniline resulted in formation of the desired target. This is due to substitution of the chloride by sulfide followed by condensation via thiolate attack of the amide carbonyl. Retrosynthetic analysis of 7-aminobenzothiazole led to the compound 2-chloro-3-nitroaniline. This compound has recently been synthesized in one step from 3-nitroaniline. In 2012, Gan et al. carried out electrophilic aromatic substitution using N-chlorosuccinimide (NCS) on various substituted aromatic and heterocyclic rings.

The compound 2-chloro-3-nitroaniline was reported to be the major regioisomer in the chlorination of 3-nitroaniline. Gan et al. isolated this compound in 77% yield after column chromatography. When designing a multi-step synthetic sequence, the first step is most desirably scalable. Necessitating chromatography as the means of purification in the first step is a drawback when having to troubleshoot and optimize several subsequent reactions with a small amount of material.

Upon examination of the $^1$H NMR reported for 2-chloro-3-nitroaniline in the supplementary information, starting material 3-nitroaniline was also found as a contaminant. This led to the presumption that starting material and the desired chlorinated product may be difficult to separate by chromatographic methods. This was the case when attempted under the published conditions. Determining the completeness
of the reaction was difficult by TLC due to the starting material and desired isomer coeluting. This led to utilizing \(^1\)H NMR to successfully monitor the completeness of the chlorination reaction. The reported length of time was 1 hour at 70 °C, however the reaction was found to be fully complete after 2 hours as confirmed by crude \(^1\)H NMR.

Purification of 2-chloro-3-nitroaniline (7) by chromatography in a multi-step synthetic sequence makes scaling up a wasteful, multiple-column task. Alternative means of isolation and purification were attempted since the desired chlorinated isomer was prepared in decent yield. Crystallization of the cooled reaction mixture was achieved upon diluting the reaction solvent volume six-fold with water. Since DMF and water are miscible but 2-chloro-3-nitroaniline is not water soluble, this led to gradual growth of yellow needles from the reaction mixture. The crystals were then filtered off, washed with water, and dried in vacuo. These were shown by \(^1\)H NMR to contain largely 2-chloro-3-nitroaniline, but also trace amounts of the other chlorinated regioisomers. Slow diffusion of hexanes into benzene solutions of this crude product was accomplished by setting up large scale 'crystal farms'. Over three to four days, yellow crystals of 2-chloro-3-nitroaniline were grown in several test tubes at room temperature and harvested. Although this did lead to very pure 7, the best overall yield attained by this method was 47%. These crystals usually took one week to grow overall and left potentially 30% of the desired product as halogenated waste. Smaller clusters of needles, identified to be an impure mixture of other chlorinated regioisomers, began to grow off of the original larger crystals after about one week. This was not the ideal method of purification, especially for the first step in a multi-step synthesis, but it eventually amounted to a sufficient amount of material. The subsequent transformations are shown in Scheme 9.
Scheme 9: Benzothiazole ring-opening route to the diamide ligand. Some drawbacks were the difficult purification in the first step as well as an inability to reproduce earlier results in the benzothiazole formation step.

Formylation of 7 would result in N-formyl-2-chloro-3-nitroaniline, which Ward and Heard have shown can be used to synthesize 7-nitrobenzothiazole, a precursor to bis(2,6-diaminophenyl)disulfide. However, the N-formylation of 2-chloro-3-nitroaniline was not successful after several attempts. Refluxing in formic-acetic anhydride, neat formic acid, and a silica catalyzed microwave procedure all resulted in sluggish reactions with poor solubility and undesired byproducts. Due to the slow process of purifying 7, the immediate unsuccessful formylation attempts were seen as wasteful. N-Acetylation was then performed due to higher solubility and cleaner, more rapid reactions. The reaction of 7 with acetic anhydride in acetic acid produced N-acetyl-2-chloro-3-nitroaniline (8) in good yield after recrystallization from toluene/hexanes. This compound was then subjected to thiolation, in a procedure modified for that reported for 7-nitrobenzothiazole. Battistoni et al. determined DMSO to be the best solvent for thiolation of various substituted ortho-nitro chlorobenzenes. These conditions were used in the thiolation of 8, which resulted in a 79% yield of 2-methyl-7-
nitrobenzothiazole (9). The thiolation-condensation reaction was complete after 16 hours at RT. When this mixture was heated in an attempt to increase the rate of conversion, premature reduction of the nitro group was observed. This is due to a known reaction between the sulfide ion and nitro groups, termed the Zinin reduction.\textsuperscript{61} The benzothiazole 9 was previously reported in the literature, but was prepared via a six-step sequence.\textsuperscript{62} Effectively producing 9 in three steps is a vast improvement over the only published route to this compound. Reduction of 9 to 7-amino-2-methylbenzothiazole (10) was accomplished as previously performed in routes \textit{A} and \textit{B} using iron in an acidic environment.

A large excess of hydroxide or hydrazine are typically used for ring opening of benzothiazoles. However, depending on the substitution pattern, the ring opening of the benzothiazoles may or may not occur.\textsuperscript{41} For example, the compounds 7-nitrobenzothiazole and 2-amino-6-nitrobenzothiazole both failed to react under either of these conditions when performed by Ward and Heard. There is no data in the literature with respect to ring opening of benzothiazoles 9 or 10. When conducted separately in both refluxing hydrazine and 30\% NaOH\textsubscript{aq}, there was no indication of thiol or disulfide in either of the crude reaction mixtures. Ring opening of this compound was only attempted twice due to an inability to replicate previous results in the benzothiazole formation step.

After optimizing conditions for 9, the procedure was then scaled up. Upon doing so, it was found that the starting material was reacting to a point and stopped once nearly half of it had been consumed. Increasing the temperature, or using an excess of sodium sulfide did not improve the conversion. Even prolonged reactions over several days did
not result in the complete consumption of starting material. Scaling up past 450 mg consistently led to a mixture of 7-nitrobenzothiazole and the starting N-acetyl-2-chloro-3-nitroaniline, while maintaining original concentration of the reaction mixture.

In conclusion, with the difficulties in isolation and purification of the first step of the sequence, 7, and the complications later encountered in reproducing the chemistry to synthesize 9, it was then decided to find a better means of synthesizing bis(2,6-diaminophenyl)disulfide.

D: Sulfonyl chloride formation and simultaneous reduction

After successfully introducing the sulfur atom on the benzene ring in a one-pot Newman Kwart rearrangement, cleavage of the thiocarbamate group was largely unsuccessful in route A. Removal of the thiocarbamate group was instead achieved via oxidation of the sulfur to the sulfonyl chloride. Thiols are known to be converted to the respective sulfonyl chlorides in the presence of acid and chlorine gas. In 2006 Nishiguchi et al. utilized a 1:5 2M HCl:MeCN solution of N-chlorosuccinimide as an oxidizing agent in the conversion of thiols, thioacetates, and thiocarbamates into sulfonyl chlorides. The reactions in Scheme 10 illustrate the two step process to generate chlorine in situ.

\[
\begin{align*}
\text{HOCI} & \rightleftharpoons \text{HCl} \quad \Rightarrow \quad \text{H}_2\text{O} + \text{Cl}_2 \\
\text{HOCI} + \text{H}_2\text{O} & \rightleftharpoons \text{N-H} + \text{HOCl}
\end{align*}
\]

Scheme 10: Generation of chlorine by NCS in 1:5 2M HCl:MeCN. This reagent rapidly oxidizes thiocarbamates to sulfonyl chlorides (~10-30 min).
Various functionalized aryl-thiocarbamates were converted to their respective sulfonyl chlorides in high yield (>90%) by this procedure. By applying the same conditions as Nishiguchi et al. on the S-(4-methyl-2,6-dinitrophenyl)-N,N-dimethylthiocarbamate (1) system, 1 was successfully converted to 4-methyl-2,6-dinitrophenylsulfonyl chloride (11) in decent yield (Scheme 11). The structure was confirmed by X-ray crystallography.

\[ \text{Scheme 11: Successful conversion of thiocarbamate (1) to sulfonyl chloride (11), followed by simultaneous reduction of the nitro and sulfonyl groups and subsequent oxidation to disulfide (12).} \]

Reduction of the sulfonyl chloride to the disulfide, and nitro groups to the amines do not have to be two separate reactions. Both sulfur and nitrogen are in their highest available oxidation states, and therefore are susceptible to a variety of reductive conditions. There are several procedures in the literature for the simultaneous reduction of these functional groups in the same molecules.\(^{65,66}\) A modified procedure of Robins et al. was used involving complete reduction to the thiol in concentrated HCl/ethanol using SnCl\(_2\). Crude \(^1\)H NMR indicated bis(4-methyl-2,6-diaminophenyl)disulfide (12) as the major product of the reaction mixture by comparison with the spectrum of bis(2,6-diaminophenyl)disulfide. The aryl meta protons and amine protons were in similar chemical shift ranges, and proton integrations agreed with their respective values.
The positive result attained with the para-methyl substituted system was then applied to the more complex 1,2,3-trisubstituted benzene system. 2,6-Dinitrophenol, as of a few months ago, is no longer commercially available. An old, previously opened container of the compound was obtained from Dr. Miller's research group. Conversion of the phenol to S-(2,6-dinitrophenyl)-N,N-dimethylthiocarbamate (13) was achieved in a similar manner as described for the synthesis of 1, and was identified by NMR and crystallography (Scheme 12). The one attempt in reacting 13 with NCS resulted in a 50% yield of a white solid, which was identified by crystallography to be 2,6-dinitrophenylsulfonyl chloride (14). There was also production of a yellow powder thought to be either elemental sulfur or the incompletely oxidized sulfenyl chloride, but so far no crystals have grown large enough to be successfully analyzed.

Scheme 12: Successful synthesis of the phenol to the thiocarbamate, and subsequent conversion to the sulfonyl chloride in a similar manner laid out in the para-methyl substituted system.

Conclusion

In conclusion, the synthesis of bis(2,6-diaminophenyl)disulfide is nearing completion. The unfortunate removal of 2,6-dinitrophenol from commercial availability mandates preparation of this compound in the synthetic route, adding a step to the overall synthesis. This is most likely achieved by diazotization of 2,6-dinitroaniline using water as the nucleophile, in a simplified manner to the first step in route B, and is under investigation by another group member at this time.
The ester series of ligands is meant to provide a control for steric effects with respect to the intramolecular hydrogen bond containing amide series. The iron porphyrin complexation studies carried out by Ueyama et al. were unclear in probing the effects of steric hindrance around the thiolate ligands, mainly due to employing inefficient alkyl-substituted thiophenolate models that were unstable. The diester ligands have not yet been synthesized in the literature, but there is one known route to 2-mercaptoresorcinol. This allows for disulfide formation and esterification of the phenols to be the only additional steps (Scheme 13).

\[
\text{HO-\text{SH}} \xrightarrow{I_2 (sat. aq.)} \text{HO-\text{S-S-}} \text{HO} \xrightarrow{\text{Anhydrides or acyl chlorides}} \text{X}_3\text{C-O-}\text{O-CX}_3 \quad X = \text{H, F, (CH}_3\text{)}
\]

Scheme 13: Conversion of 2,6-dihydroxythiophenol to its disulfide, followed by a series of O-acetylations.

**Synthesis and new characterization of intermediates**

Finding a synthetic route to the bis(2,6-dihydroxyphenyl)disulfide series of ligands was much more simple than the bis-amide series. One report contained all of the transformations necessary to synthesize 2-mercaptoresorcinol (2,6-dihydroxythiophenol, Scheme 13). This sequence suffers from harsh conditions inevitably leading to losses in yield due to decomposition, and complex purification methods. One of these steps makes use of a high-temperature Newman-Kwart rearrangement to install sulfur in the ring. These transformations are seen in Scheme 14.
Scheme 14: Modified literature route to 2-mercaptoresorcinol. Formation of the disulfide and acetylation are the only undocumented steps for producing the novel diester ligands.

Starting with 2,6-dimethoxyphenol and following the optimized conditions laid out by Moseley and Lenden with slight modification, O-(2,6-dimethoxyphenyl)-N,N-dimethylthiocarbamate (15) was obtained in 82% yield. Rearrangement to the S-thiocarbamate is achieved by heating the neat compound up to 280-300 °C for 30 minutes. This is in stark contrast to the 2,6-dinitro systems in 1 and 13, which rearranged in one pot at 85 °C. The strongly electron donating methoxy groups hinder the mechanism of rearrangement, which was shown to be a specialized nucleophilic aromatic substitution reaction. The conventional method for achieving these rearrangements involves immersing a flask of the neat compound in an oil bath at the necessary temperature for an extended period. Degradation due to reaction with trace impurities or molecular oxygen are common at higher temperatures, however, and safer methods were first attempted to obtain the rearranged product.

A microwave-assisted procedure for the conversion of electronically and sterically disfavored O-thiocarbamates was found to produce clean S-thiocarbamates in
good yields after workup. This involved performing the rearrangement in solvent (dimethylacetamide, DMA), and heating to 300 °C in a microwave reactor for 30 minutes. The workup for this reaction involved dilution of the DMA solution with a five-fold excess (v/v) of water to precipitate the S-thiocarbamate. The microwave reactor employed was a different model than that reported, and could only reach a maximum temperature of 268-270 °C under its maximum power output conditions. Upon dilution with H$_2$O, the off-white solid that slowly precipitated was determined by $^1$H NMR to be a 4:1 mixture of O- to S-thiocarbamate, as seen in Table 8.

Table 8: Conditions applied for the Newman-Kwart rearrangement of O- to S-thiocarbamate (15 to 16).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale</th>
<th>Temperature$^a$</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50 g (2 mL DMA)</td>
<td>270 °C, µW</td>
<td>20% 16, 80% 15$^b$</td>
</tr>
<tr>
<td>2</td>
<td>0.50 g (neat)</td>
<td>300 °C, µW</td>
<td>41% 16, 0% 15$^c$</td>
</tr>
<tr>
<td>3</td>
<td>2.00 g (neat)</td>
<td>280 °C, oil bath</td>
<td>49% 16, 37% 15$^d$</td>
</tr>
<tr>
<td>4</td>
<td>7.30 g (neat)</td>
<td>290 °C, oil bath</td>
<td>80% 16, sublimed</td>
</tr>
</tbody>
</table>

$^a$Time = 30 min for entries 1-3, 45 mins for entry 4.
$^b$Microwave would not heat up past 270 °C in the presence of solvent.
$^c$Largely resulted in decomposition.
$^d$Used improper glassware, led to starting material clinging to walls above the oil bath level.

Since the microwave was on its maximum power and temperature settings, it was determined that a modified procedure would have to be used for complete O- to S-thiocarbamate conversion. It was determined that the solvent prevented the internal temperature from approaching 300 °C, so the neat compound was then subjected to microwave conditions. Although the S-thiocarbamate was the major product of the reaction as determined by crude $^1$H NMR and, there was much decomposition to a brown-black oil and it was not easy to isolate the pure product by chromatographic or crystallization methods. This led to attempting the conventional procedure of heating the
neat compound in an oil bath up to 290 °C. The resultant product was still a brown oil, but after passing through a silica plug the eluent was concentrated and dried to a brown solid powder. This was then sublimed at reduced pressure (<200 mtorr) with heating to afford a white crystalline solid, 16, on the condenser and walls of the sublimation apparatus, leaving behind a brown residue.

After isolating the S-thiocarbamate, conversion to the benzoxathiolone was achieved using the method of Traxler\textsuperscript{67} by stirring in a melt of anhydrous pyridine hydrochloride at 200 °C. This procedure also led to some decomposition, and was contaminated with approximately 1:5 of the intermediate 4-methoxybenzoxathiolone to the target 4-hydroxybenzoxathiolone (17). This impurity was separated by chromatography, however monitoring this reaction by $^1$H NMR and longer reaction times may fully convert this impurity to 17 and improve the overall yield.

Ring-opening of 17 to 2,6-dihydroxythiophenol was achieved by following Traxler's method.\textsuperscript{67} Successful isolation of the thiol was confirmed by crude NMR. After purification by chromatography conversion to bis(2,6-dihydroxyphenyl)disulfide (18) was achieved by shaking a solution of the thiol with an aqueous solution of I$_2$. Disappearance of the thiol proton in the $^1$H NMR confirmed conversion to the disulfide, and 18 was obtained in 53% yield.

Conclusion

In conclusion, the route to bis(2,6-dihydroxyphenyl)disulfide was successfully completed following Traxler's procedure to 2,6-dihydroxythiophenol. Subsequent conversion to disulfide was achieved by oxidation using I$_2$. The structures of the
intermediates in this synthetic route were further characterized via \(^1\)H and \(^{13}\)C NMR as well as X-ray crystal diffraction. This is a vast improvement on the IR data and elemental analyses provided for these intermediates.
Experimental Section

General Experimental Section

Solvents

Diethyl ether, acetonitrile, dimethylformamide, toluene, tetrahydrofuran, dichloromethane, and methanol were purified by passing through an Innovative Technology Inc. Solvent Delivery System prior to use. Benzene and dimethylsulfoxide were purchased from commercial sources and used as received. Anhydrous solvents were obtained by storage over activated 3Å or 4Å molecular sieves. Molecular sieves were activated by heating in a 250 mL round bottom flask in a 900W microwave in 30 second bursts until a small portion began to melt and glow red. The flask was then covered with a rubber septum and subjected to high vacuum (≤200 mtorr) until cool enough to touch. The appropriate solvent was syringed in and left to stand for at least 24 hours prior to use.

When indicated, solvents were degassed by at least three cycles of pulling high vacuum while sonicating the flask for 15 seconds and refilling with N₂ (for more volatile solvents, such as diethyl ether and dichloromethane, multiple 5 second intervals were done to avoid excessive evaporation). When the flask begins to feel slightly cold due to solvent evaporation, pressure was reestablished with dry N₂. Dry and degassed solvents were handled under nitrogen and transferred either via cannula or syringe.
Reagents

All reagents were received from commercial sources and were used as received unless otherwise noted. Reagents were obtained from: Fisher Scientific (Acros), Alfa Aesar, Sigma-Aldrich, Strem Chemicals, and Cambridge Isotope Laboratories.

Reactions

All glassware and magnetic stir bars were stored in an oven at 150 °C prior to use. Reactions were conducted under a dry nitrogen atmosphere through a double manifold. When possible, solids were weighed in the oven-dried flask and the atmosphere purged by three high vacuum-N₂ refill cycles. Nitrogen was dried by passing through a tube of calcium sulfate, and was introduced through rubber vacuum tubing via either glass inlet adapters or rubber septa and needles. Either plastic or glass syringes were used for volumetric addition of solvents and reagents unless otherwise noted. Standard Schlenk techniques were used when indicated.

Chromatography

Flask column chromatography was performed with Silicycle SiliaFlash® P60 Flash Silica Gel with 40-63 μm particle size. Mobile phases were freshly prepared as described in the detailed experimental section. Thin layer chromatography (TLC) analysis was conducted on Whatman polyester-backed Silica Gel 60Å 250 μm thickness flexible plates with fluorescent indicator.
Instrumentation

Analysis by Nuclear Magnetic Resonance (NMR) spectroscopy was recorded on a Varian Mercury spectrometer operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C spectroscopy. The majority of NMR spectra were measured in deuterochloroform (CDCl$_3$), but deuterated dimethylsulfoxide (DMSO-d$_6$), acetone ((CD$_3$)$_2$CO), and methanol (CD$_3$OD) were all purchased from Cambridge Isotope Laboratories and used when indicated. All deuterated NMR solvents were stored over activated 3Å sieves. All $^1$H resonances were reported relative to an internal standard tetramethylsilane (TMS) ($\delta$ 0 ppm), unless otherwise noted. The following abbreviations were used to denote multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. Infrared Spectroscopy was conducted using a Thermo Nicolet iS10 FTIR with diamond ATR probe. Microwave-assisted reactions were conducted in a CEM Discover single-mode microwave reactor using a sealed reaction vessel. Crystal structure data was collected on a Bruker APEX-II CCD diffractometer.

Detailed Experimental Section

S-(4-Methyl-2,6-dinitrophenyl)-N,N-dimethylthiocarbamate (1)

To a 100 mL round bottomed flask equipped with magnetic stir bar was added 2,6-dinitro-$p$-cresol (0.991 g, 5.0 mmol) and DABCO (0.579 g, 5.1 mmol). The flask was capped with a rubber septum and evacuated (>200 mtorr) and refilled with N$_2$ three times. Dimethoxyethane (10 mL) was dried over 3Å molecular sieves and added via syringe. To a separate nitrogen flushed 10 mL flask was dissolved $N,N$-
dimethylthiocarbamoyl chloride (0.656 g, 5.3 mmol) in dimethoxyethane (5 mL). This solution was transferred via syringe to the 100 mL reaction flask. The septum was replaced with a water-cooled condenser, and the red-orange mixture was heated to reflux for 22 h. The reaction was quenched by the addition of H₂O (1 mL). This mixture was concentrated to a dark red resin, diluted with H₂O (20 mL) and extracted 5 times with equal volume DCM. The combined extracts were washed with NaHCO₃(Sat.), H₂O, and brine. The organic layer was dried over MgSO₄, filtered and concentrated to provide 1 as yellow block crystals (1.38 g) in 97% yield. Recrystallization from benzene/hexanes provides melting point: 127 °C. Yellow block crystals suitable for X-ray diffraction were grown from diffusion of pentane into a concentrated Et₂O solution. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 2H), 3.11 (br s, 3H), 2.99 (br s, 3H), 2.55 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.39, 154.14, 142.77, 128.17, 116.50, 37.54, 37.48, 21.36.

**S-(4-Methyl-2,6-diaminophenyl)-N,N-dimethylthiocarbamate (2)**

To a 100 mL round bottomed flask equipped with magnetic stir bar, 1 (1.14 g, 4.0 mmol) was partially dissolved in EtOH (8 mL) and acetic acid (8 mL), and H₂O (4 mL). The resultant yellow-orange mixture was cooled to 0 °C. Iron powder (1.79 g, 32 mmol) was added in batches. Once all of the iron was added the solution was slowly warmed to room temperature and stirred for 8 h. The original yellow color of the solution darkened over time to a brownish-red. The reaction was quenched with solid NaHCO₃ and filtered through a Celite plugged Büchner funnel. This was rinsed with chloroform and all volatiles were removed by rotary evaporation to give a red-brown mixture. This was diluted with H₂O (30 mL) and extracted 5 times with equal volume CHCl₃. The
combined extracts were washed with NaHCO$_3$(sat), H$_2$O, and brine. The organic layer was dried over MgSO$_4$, filtered and evaporated to yield a brown crystalline solid. Purification was achieved by column chromatography on alumina and elution with DCM to yield 2 as a white crystalline solid (0.685 g) in 76% yield. Solutions of this compound darken rapidly, forming colored impurities undetectable by $^1$H NMR. The neat solid darkens to a light brown color over several days, even when stored in a freezer at -78 °C. Colorless, square blocks suitable for X-ray diffraction were grown from slow evaporation of a CHCl$_3$ solution. Melting point: 140 °C. $^1$H NMR (400 MHz, CDCl$_3$)  δ 6.05 (s, 2H), 4.11 (br s, 4H), 3.18 (br s, 3H), 3.02 (br s, 3H), 2.16 (s, 3H).

**S-(4-Methyl-2,6-diacetylaminophenyl)-N,N-dimethylthiocarbamate (3a)**

To a 10 mL round bottomed flask with magnetic stirring was dissolved 2 (0.0673 g, 0.30 mmol) in EtOH:H$_2$O (2.0:0.5 mL). Acetic anhydride (0.0708 mL, 0.75 mmol) was added dropwise, and the solution was stirred at room temperature for 10 min. After this time a white solid began to precipitate, and the reaction mixture was cooled to 0 °C for 10 min. The white precipitate was isolated by filtration and washed with water (8 mL). This was dried under vacuum to yield 3a as a white powder (0.0872 g) in 94% yield. Melting point: 151 °C. $^1$H NMR (400 MHz, CDCl$_3$)  δ 7.94 (br s, 2H), 7.91 (br s, 2H), 3.24 (br s, 3H), 3.06 (br s, 3H), 2.39 (s, 3H), 2.18 (s, 6H).

**S-(4-Methyl-2,6-bis(trifluoroacetylamino)phenyl)-N,N-dimethylthiocarbamate (3b)**

To a 10 mL round bottomed flask equipped with magnetic stir bar was added 2 (0.0671 g, 0.30 mmol) and DCM (3 mL). To this solution was added triethylamine
(0.209 mL, 1.5 mmol), and the reaction mixture was cooled to 0 °C. Dropwise addition of trifluoroacetic anhydride (0.127 mL, 0.90 mmol) resulted in mild fuming. The ice bath was removed after the addition and the reaction mixture was stirred at room temperature for 1 h. After this time H₂O (10 mL) was added to quench the reaction, followed by DCM (7 mL). The aqueous portion was extracted twice with equal volume DCM, followed by washes of the combined extracts with NaHCO₃(sat), H₂O, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to afford 3b as an off-white crystalline solid (0.102 g) in 81% yield. Melting point: 189-190 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.99 (br s, 2H), 7.94 (s, 2H), 3.24 (br s, 3H), 3.08 (br s, 3H), 2.45 (s, 3H).

2,6-Dinitroiodobenzene (4)

2,6-Dinitroaniline was recrystallized from 95% EtOH, NaNO₂ was recrystallized from H₂O, and KI was recrystallized from H₂O prior to use. All of the following preparations were conducted behind a blast shield.

To a two-neck 100 mL RBF equipped with thermometer and stir bar was added conc. H₂SO₄ (13 mL). NaN₃ (1.37 g, 19 mmol) was then added portion-wise with stirring. If the sodium nitrite is added too rapidly brown nitric oxide gas evolves from the solution. This was dissolved by warming up to 60 °C for 10 min, then cooled back down to 25-30 °C.

To a separate 100 mL RBF was added 2,6-dinitroaniline (3.29 g, 18 mmol) and AcOH (35 mL). This was heated to almost boiling in order to dissolve. Carefully, the hot solution of 2,6-dinitroaniline was added dropwise to the sulfuric acid solution of
sodium nitrite at such a rate to maintain temperature below 40 °C. After this addition, the
temperature of the reaction mixture was maintained at 40 °C for 30 min.

During this time a solution of KI (3.28 g, 19 mmol) in H₂O (40 mL) was warmed
up to 70 °C with stirring in a 250 mL beaker. The diazonium salt solution was added in
portions over a period of 5 min. An instant yellow-orange precipitate and effervescence
was observed upon addition of the diazonium salt solution, with occasional precipitation
of a dark purple solid. Due to the oxidizing nature of sulfuric acid, some of the iodide
anion is inevitably converted into dark purple iodine upon addition of the diazonium salt
solution. In order to combat this oxidation and improve the overall yield, ~3 mL of a
saturated solution of Na₂S₂O₃(aq) was added to the aqueous solution prior to the addition.
After stirring this mixture for ~20 minutes at 70 °C, it was poured into a separate beaker
of H₂O (300 mL) and cooled in an ice bath. The yellow-orange powder was filtered off,
slurry-washed with H₂O (50 mL), and dried under vacuum to afford 4.59 g (87%) of an
orange solid. Crystallization from cyclohexane (~90 mL : 1 g), with a hot filtration
removing a small amount of a red solid, afforded 4 as a yellow crystalline solid (4.18 g)
in 79% yield. Melting point: 113 °C, (lit. 68 113 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.85
(d, 2H), 7.66 (t, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 156.39, 130.62, 127.05, 80.35.

S-(2,6-Dinitrophenyl)-O-ethyl dithiocarbonate (5)

To a 25 mL RBF was added solids 4 (0.498 g, 1.7 mmol), potassium O-ethyl
xanthate (0.284 g, 1.8 mmol), and a magnetic stir bar. This was dissolved in dry DMF (5
mL) and heated up to 90 °C. The reaction was monitored by ¹H NMR and was complete
after 1 hr. The reaction mixture was diluted with H₂O (25 mL) followed by extraction
with equal volume Et\textsubscript{2}O three times. The combined organic extracts were washed with Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3(sat)}, H\textsubscript{2}O, and brine, then dried over MgSO\textsubscript{4}. This was filtered and concentrated to afford a crude red oil. This was pre-purified by passage through a silica plug eluting with 1:1 DCM:hexanes and concentrated to afford 5 as a yellow oil (0.398 g) in 82% yield. This material was used without further purification. $^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.86 (d, 2H), 7.61 (t, 1H), 2.96 (q, 2H), 1.24 (t, 3H). $^{13}$C NMR (101 MHz, CDCl\textsubscript{3}) $\delta$ 155.43, 130.07, 129.14, 126.50, 31.71, 14.58.

\textbf{S-(2,6-Diaminophenyl)-O-ethyl dithiocarbonate (6)}

To a 50 mL RBF was added 5 (0.332 g, 1.2 mmol), EtOH (10 mL), and conc. HCl (5 mL). Fe powder (0.671 g, 12 mmol) was added at once, and the mixture was put under N\textsubscript{2} in a sonicator for 2 hrs. The light green reaction mixture was then filtered to remove excess iron. Upon basification of the reaction mixture with 3M NaOH to pH ~10, more iron salts crashed out of solution. This suspension was filtered through a pad of Celite to remove the iron, which was then washed copiously with DCM. The aqueous portion was extracted three more times with equal volume DCM. The combined organic extracts were washed with NaHCO\textsubscript{3(sat)}, H\textsubscript{2}O, and brine, then dried over MgSO\textsubscript{4}. This solution was filtered and concentrated to dryness to afford a crude brown oil. Purification was achieved by column chromatography on alumina eluting with 1:1 Et\textsubscript{2}O:hexanes to afford 6 as a colorless oil (0.192 g) in 73% yield. $^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 6.91 (t, 1H), 6.14 (d, 2H), 4.41 (br s, 4H), 2.68 (q, 2H), 1.22 (t, 3H). $^{13}$C NMR (101 MHz, CDCl\textsubscript{3}) $\delta$ 150.34, 130.59, 104.65, 102.14, 27.87, 15.45.
2-Chloro-3-nitroaniline (7)

N-chlorosuccinimide (NCS) was recrystallized from acetic acid, washed copiously with water until no more smell of the acid, and dried under vacuum. 3-nitroaniline was recrystallized from benzene/petroleum ether and dried under vacuum.

To a 250 mL RBF was added NCS (5.62 g, 42 mmol) and dry DMF (50 mL) with a magnetic stir bar. A separate DMF (50 mL) solution of 3-nitroaniline (5.81 g, 42 mmol) was prepared and added dropwise to the NCS solution. The yellow solution was heated to 75 °C under N\textsubscript{2} for 2 hrs. After this time the reaction mixture was gently poured into a 2 L Erlenmeyer flask containing warm (~50 °C) 1000 mL H\textsubscript{2}O. This mixture was left alone to crystallize overnight at room temperature. The following morning, yellow needles were filtered off, washed with water, and dried. These were pre-purified by passage through a silica plug eluting with DCM to remove a red baseline impurity, and concentrated to afford a yellow solid (4.65 g) in 64% yield. This was shown by \textsuperscript{1}H NMR to contain largely 7, but still a significant amount of several other regioisomers (~8:1 of the most prominent impurity). Purification was achieved by diffusion of petroleum ether into concentrated benzene solutions over one week to afford 7 as yellow crystals (3.43 g) in 47% yield. A yellow ribbon suitable for X-ray diffraction was grown from diffusion of pentane into a concentrated CHCl\textsubscript{3} solution. Melting point: 95 °C, (lit.\textsuperscript{59} 94-95 °C). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.19-7.14 (m, 2H), 6.97-6.92 (m, 1H), 4.42 (br s, 2H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 149.41, 145.19, 127.59, 118.71, 114.43, 110.76.
N-(2-Chloro-3-nitrophenyl)acetamide (8)

To a 100 mL RBF equipped with a magnetic stir bar was added 7 (1.35 g, 7.8 mmol) and AcOH (13 mL). A catalytic amount of H$_2$SO$_4$ (150 µL) was added to this mixture, followed by Ac$_2$O (1.47 mL, 16 mmol). The yellow reaction mixture was capped with a water-cooled condenser under N$_2$ and heated to reflux for 2 h. Over this time the reaction mixture turns colorless. As the reaction mixture cools to room temperature a white powder gradually precipitated out of solution. The reaction mixture was diluted with H$_2$O (20 mL) and NaHCO$_3$ (S at) (10 mL) with stirring. After 10 mins, this mixture was extracted with equal volume CHCl$_3$ three times. The combined organic extracts were washed with NaHCO$_3$(sat) three times, H$_2$O and brine, then dried over MgSO$_4$. This solution was filtered and concentrated to dryness to afford a white solid. This was purified by recrystallization from toluene/hexanes. Dissolution in the minimum amount of hot toluene (8.5 mL) was followed by slow cooling to room temperature while slowly layering hexanes (45 mL total) on top in 5 mL increments. Thick, colorless needles of 8 (1.42 g) were obtained in 85% yield. Melting point: 131 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.67 (br d, 1H), 7.79 (br s, 1H), 7.58 (dd, 1H), 7.42 (t, 1H), 2.30 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.81, 148.64, 136.75, 128.04, 125.06, 120.15, 115.26, 25.16.

2-Methyl-7-nitrobenzothiazole (9)

To a 25 mL RBF equipped with magnetic stir bar was added 8 (0.449 g, 2.1 mmol) and Na$_2$S·9H$_2$O (0.765 g, 3.1 mmol). The solids were dissolved in DMSO (9 mL), and upon dissolution the reaction mixture immediately took on a deep red color.
This was stirred at room temperature under N₂ for 16 h. The reaction was then poured into a 250 mL beaker with H₂O (90 mL) to create a lighter red colored solution. Upon the addition of 4M HCl (3 mL) a milky white solution resulted. This was slowly cooled in an ice bath and stirred for 20 mins while a white precipitate formed. The solid was filtered off, washed copiously with H₂O, and dried in a vacuum dessicator overnight. This was pre-purified by passage through a silica plug eluting with DCM to afford 9 as a white solid (0.319 g) in 79% yield, which was used without further purification. Melting point: 117-120 °C, (lit. 119-120 °C). ¹H NMR (400 MHz, CDCl₃) δ 8.38 (dd, 1H), 8.27 (dd, 1H), 7.64 (t, 1H), 2.91 (s, 3H).

7-Amino-2-methylbenzothiazole (10)

To a 25 mL RBF was added 9 (0.305 g, 1.6 mmol) and Fe powder (0.263 g, 4.7 mmol). These were suspended in EtOH : H₂O (4 : 1, 6.5 mL) and conc. HCl (0.220 mL). The mixture was put under N₂ and sonicated for 2 h. The suspension was then filtered through an alumina plugged fritted funnel, which was rinsed with EtOH (15 mL). The eluent was concentrated to afford a crude brown solid. Purification was achieved by column chromatography on alumina eluting with 0.1% MeOH in DCM to afford 10 as a white solid (0.154 g) in 60% yield. Melting point: 117 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (dd, 1H), 7.26 (t, 1H), 6.66 (dd, 1H), 3.88 (br s, 2H), 2.82 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 165.94, 154.94, 140.76, 127.21, 122.55, 113.48, 110.20, 20.49.
4-Methyl-2,6-dinitrophenylsulfonyl chloride (11)

To a 100 mL RBF equipped with magnetic stir bar was added NCS (2.81 g, 21 mmol) and MeCN : 2M HCl (5 : 1, 10 mL) to create a white suspension. This was cooled to 10 °C. To a separate vessel was dissolved 1 (1.49 g, 5.2 mmol) in MeCN (5 mL). This yellow solution was added dropwise to the cooled reaction mixture, and was stirred at 10 °C for 2 h. Over this time the reaction turned colorless with a white precipitate. The reaction was diluted with brine (10 mL) and H₂O (5 mL), followed by EtOAc (15 mL) to dissolve the precipitate. The aqueous layer was extracted three times with equal volume EtOAc. The combined extracts were washed with twice with brine, dried over MgSO₄, and concentrated to afford 11 as a white solid (1.21 g) in 83% yield. This was used without purification. Colorless plates suitable for X-ray diffraction were grown from gently layering pentane over a concentrated EtOAc solution. Melting point: 153 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 2H), 2.66 (s, 3H).

Bis(4-methyl-2,6-aminophenyl)disulfide (12)

To a 100 mL RBF equipped with magnetic stir bar was added anhydrous SnCl₂ (4.12 g, 22 mmol) and conc. HCl (6 mL). The mixture dissolved with stirring and was cooled to 0 °C. Solid 11 (0.483 g, 1.7 mmol) was added in batches, creating a warm, cloudy yellow solution. This was gradually warmed to room temperature and stirred for 1 h. H₂O (75 mL) was poured into the reaction mixture, and a small amount of a brown precipitate was filtered off and washed with EtOAc. The aqueous and organic portions were separated, and the aqueous portion was basified using 30% NaOH (aq) to pH 10. A large amount of white powder, presumed to be oxidized tin salts, crashed out during the
basification. These were filtered through Celite and washed with EtOAc. To the alkaline aqueous portion was added solid I$_2$ and shaken until the dark brown-purple color persisted. This was then extracted twice with EtOAc, creating a yellow organic layer. The combined extracts were washed with NaHCO$_3$(sat), Na$_2$S$_2$O$_3$(sat), H$_2$O, and brine, then dried over MgSO$_4$. This solution was filtered and concentrated to dryness to afford 12 as a crude brownish-yellow oil (0.121 g) in 46% yield, which smelled very similar to m-phenylenediamine. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.88 (s, 4H), 4.03 (br s, 8H), 2.11 (s, 6H).

**S-(2,6-Dinitrophenyl)-N,N-dimethylthiocarbamate (13)**

The 2,6-dinitrophenol used was from an old bottle, and was at one time moistened with 10% water to prevent shock-sensitive explosion during travel. The dry solid appeared brown with small yellow crystals, and amounted to about 1 gram of material. $^1$H NMR indicated several trace aromatic impurities. Purification was attempted by crystallization from benzene. This resulted in brownish-yellow crystals that were used in the following preparation without further purification.

To a 100 mL RBF was added solids 2,6-dinitrophenol (0.978 g, 5.3 mmol) and 1,4-diazobicyclo[2.2.2]octane (DABCO) (0.673 g, 5.8 mmol) with magnetic stir bar. Dry dimethylacetamide (DMA) (10 mL) was added to dissolve, creating an orange solution. $N,N$-dimethylthiocarbamoyl chloride was dissolved in DMA (5 mL) and added dropwise to the reaction vessel. The mixture was covered with a water-cooled condenser under N$_2$, and heated to reflux for 6 h. A white solid presumed to be DABCO·HCl gradually precipitated during this time. Upon completion, the reaction was poured into H$_2$O (90
mL) and left to crystallize overnight. An orange-yellow powder was filtered off and washed copiously with H$_2$O. Purification was achieved by column chromatography on silica eluting with 2:1 hexanes:EtOAc to afford a yellow solid (1.26 g) which was further purified by recrystallization from toluene/hexanes to afford 13 (1.15 g) in 80% yield. Yellow rhombic prisms suitable for X-ray diffraction were grown from gently layering hexanes over a concentrated benzene solution. Melting point: 116 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.07 (d, 2H), 7.73 (t, 1H), 3.13 (br s, 3H), 3.00 (br s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.01, 154.23, 130.73, 127.72, 120.41, 37.61, 37.53.

2,6-Dinitrophenylsulfonyl chloride (14)

This preparation is far from optimized, as it has only been conducted one time in the laboratory. However, with successful identification of 14 due to crystallography, the procedure is as follows.

To a 50 mL RBF equipped with magnetic stir bar was added NCS (1.89 g, 14 mmol) and MeCN : 2M HCl (5 : 1, 7 mL). This was stirred to create a white suspension. To a separate vessel was dissolved 13 (0.958 g, 3.5 mmol) in MeCN (6 mL). This solution was added dropwise to the reaction mixture, and was stirred at room temperature overnight. The reaction mixture did not turn from yellow to colorless as it did in the preparation of 11, perhaps due to running this reaction at room temperature instead of 10 °C. A bright yellow precipitate was noticed the next morning and was filtered off. Upon addition of H$_2$O (5 mL) more of the same yellow solid (confirmed by NMR) crashed out and was combined with the first (0.321 g, 34% of theoretical yield of sulfonyl chloride). Upon dilution of the reaction mixture with 20 mL more of H$_2$O, an orange-white
precipitate was observed and separately isolated (0.472 g, 50% theoretical yield of sulfonyl chloride). Crude NMR of these two solids indicates no presence of the thiocarbamate N-methyl protons, however they had noticeably different triplet-doublet patterns in the aromatic region. These resonances corresponding to the meta (d) and para (t) protons relative to the sulfur. Colorless crystals of 14 suitable for X-ray diffraction grew over several days by gently layering pentane over a concentrated acetone solution over several days. Melting point: 171 °C. The identity of the yellow precipitate is awaiting confirmation by crystallographic analysis. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (d, 2H), 7.98 (t, 1H).

**O-(2,6-Dimethoxyphenyl)-$N,N$-dimethylthiocarbamate (15)**

To a 250 mL RBF equipped with a magnetic stir bar was added solids DABCO (11.5 g, 99 mmol) and 2,6-dimethoxyphenol (11.7 g, 76 mmol). DMA (50 mL) was added and warmed to 50 °C to create a brown solution. To a separate vessel was dissolved $N,N$-dimethylthiocarbamoyl chloride (12.5 g, 99 mmol) and DMA (15 mL). This solution was added dropwise to the reaction mixture, which was maintained at 50 °C for 1.5 h. A white solid presumed to be DABCO·HCl gradually precipitated during this time. The reaction mixture was slowly poured into a 400 mL beaker containing 140 mL H$_2$O. The original white precipitate dissolved immediately, and the solution became cloudy with a new white precipitate. This was stirred with cooling in an ice bath for 30 minutes, filtered, washed with H$_2$O, and dried in a vacuum desiccator overnight to yield 15 as a white microcrystalline solid (14.9 g) in 82% yield. Colorless rhombic prisms suitable for X-ray diffraction were grown from slow diffusion of pentane into a
concentrated EtOAc solution. Melting point: 145 °C, (lit. 144-146 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, 1H), 6.64 (d, 2H), 3.83 (s, 6H), 3.46 (br s, 3H), 3.36 (br s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 187.96, 152.98, 132.32, 126.45, 105.28, 56.54, 43.74, 38.96.

S-(2,6-Dimethoxyphenyl)-N,N-dimethylthiocarbamate (16)

To a 100 mL Schlenk flask was added 15 (7.34 g, 30 mmol) with a magnetic stir bar. The flask was then subjected to five cycles of evacuation to ≤200 mtorr and refilled with N₂ to purge the atmosphere of O₂. Upon the last re-pressurization the flask was left open to N₂. An oil bath was heated up to 290 °C and the reaction vessel was submerged so the melted neat compound was below the level of the oil. This was stirred at this temperature for 45 minutes. Heat was then turned off and the hot dark oil was allowed to slow cool to room temperature. The resultant brown-black semi-solid was pre-purified by dissolving in the minimum amount of EtOAc (60 mL) and passing through a silica plug. The eluent was concentrated to afford a brown semi-crystalline solid (6.73 g) in 92 % yield. Purification was achieved by sublimation in batches at reduced pressure (~100 mtorr), with heating to about 120 °C over the course of several hours to afford 16 as a white crystalline solid (5.86 g) in 80% yield. Colorless diamonds suitable for X-ray diffraction were grown from slow diffusion of pentane into a concentrated EtOAc solution. Melting point: 127 °C, (lit. 127-128 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.36 (t, 1H), 6.61 (d, 2H), 3.86 (s, 6H), 3.18 (br s, 3H), 2.99 (br s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 165.91, 161.61, 131.95, 104.46, 56.62, 37.37, 37.10.
4-Hydroxy-1,3-benzoxathiol-2-one (17)

To a 100 mL Schlenk flask equipped with magnetic stir bar was added solids 16 (2.45 g, 10 mmol) and freshly prepared (see below) anhydrous pyridine·HCl (7.21 g, 62 mmol). This was placed in an oil bath at 200 °C and stirred vigorously for 1.25 hrs. Heat was then turned off and the mixture was allowed to slow cool to room temperature. The resultant brown oil was adsorbed onto silica gel and pre-purified by passage through a silica plug eluting with 7:3 EtOAc:hexanes. The eluent was concentrated to a light yellow crystalline solid (1.12 g) in 66% crude yield, shown by \(^1\)H NMR to contain ~8:1 17 to the intermediate 4-methoxy-1,3-benzoxathiol-2-one. Extended reaction time and monitoring by \(^1\)H NMR will undoubtedly lead to full conversion to 17. Purification was achieved by recrystallization from benzene/hexanes to afford 17 as white crystals (0.867 g) in 51% yield. Colorless rhombic prisms suitable for X-ray diffraction were grown from gently layering hexanes over a concentrated Et₂O solution. Melting point: 155-156 °C, (lit. 155-157 °C). \(^1\)H NMR (400 MHz, CDCl₃) δ 7.19 (t, 1H), 6.93 (dd, 1H), 6.71 (dd, 1H), 5.71 (br s).

Anhydrous pyridine·HCl

The only literature procedure for preparation of anhydrous pyridine·HCl utilizes dry HCl gas as the acid source. Since there was no HCl gas readily available in this research laboratory, an alternative means of generating it was looked into. Trialkyl silyl reagents are commonly used as protecting groups for the hydroxyl functionality. The reaction with methanol results in the more thermodynamically stable Si-OMe bond
forming rapidly. An equivalent of HCl is generated for each equivalent of trialkyl silyl reagent employed since the solvent is in large excess. If a base were dissolved in methanol it would undoubtedly deprotonate the in situ generated HCl. A novel procedure was developed to quickly produce the anhydrous hydrochloride salt of pyridine, but virtually any methanol soluble nitrogenous base could be used.

An oven-dried 500 mL Schlenk flask was equipped with stir bar and rubber septum. The atmosphere was then purged of O₂ and moisture by evacuating the flask (<200 mtorr) and refilling with dry N₂ three times. Syringed in dry pyridine (22.3 mL, 277 mmol), followed by dry MeOH (100 mL), and trimethylsilyl chloride (37 mL, 284 mmol). The homogenous mixture was stirred for 30 min at room temperature under N₂. Concentrating the mixture to dryness on the rotovap at 50 °C followed by further drying under high vacuum afforded a white solid (32.0 g, 277 mmol) in near quantitative yield.

Exposure of pyr·HCl to the atmosphere resulted in moisture adsorbing to the surface of the salt in seconds. This showed the materials deliquescent properties, which necessitates handling the anhydrous salt quickly in air. If preparing an exact amount for carrying out a particular reaction, the flask in which the salt is prepared could be used as the reaction flask directly after drying. This procedure is rapid and simple to operate on a high vacuum line. The workup simply consists of the removal of all volatiles, and since TMSCl is volatile a slight excess is used to ensure complete protonation of the base. As opposed to setting up a temporary apparatus to generate or deliver HCl gas, cheap and commonly available reagents were used to prepare the anhydrous salt. The utility of this procedure for generation of the hydrochloride salts of other nitrogenous bases has not been looked into, but certainly seems viable.
Bis(2,6-dihydroxyphenyl)disulfide (18)

To a 100 mL RBF equipped with magnetic stir bar was added 17 (0.867 g, 5.156 mmol). This was capped with a rubber septum, and purged of O₂ via three cycles of evacuation (≤200 mtorr), refilling with N₂ each time. To this mixture was syringed in H₂O (1 mL) with stirring to create a slurry, followed by 2M NaOH (9 mL) to create an orange solution with a small amount of suspended material. This was stirred at room temperature for 20 mins. Acidification with conc. HCl (1.5 mL) to pH 3 produced bubbles of presumably CO₂, and was extracted with Et₂O four times. The combined extracts were washed with brine twice and dried over Na₂SO₄. This solution was filtered and concentrated to afford a yellow oil, which was shown by crude NMR to indicate conversion to the thiol. Purification was achieved by column chromatography eluting with 2:1 hexanes:EtOAc and 0.05% AcOH. The thiol of 18 eluted fourth, and was oxidized by shaking with a saturated solution of I₂(aq), adding more I₂(s) as needed until the aqueous layer remained colored. The organic layer was washed with Na₂S₂O₃(aq), H₂O, and brine, followed by drying over Na₂SO₄. This solution was filtered and concentrated to afford 18 as a yellow powder (0.385 g) in 53% yield. Thiol melting point: 78 °C. ¹H NMR (400 MHz, CD₃OD) δ 7.04 (t, 2H), 6.35 (d, 4H), 4.88 (s, 4H). ¹³C NMR (101 MHz, DMSO) δ 160.18, 131.46, 110.04, 106.90.
References


(3) Fita, I.; Rossmann, M. G., Proceedings of the National Academy of Sciences 1985, 82, 1604-1608.


(60) Battistoni, P., et al., *Gazzetta Chimica Italiana* **1980**.


Appendices
Appendix A: Characterization of compounds
Crystal structure data of 1

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<th><strong>Compound name</strong></th>
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<td><strong>Crystal system</strong></td>
<td>triclinic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P\textsubscript{T}</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td>a = 8.3790(12) Å, b = 8.8777(12) Å, c = 9.0174(12) Å</td>
</tr>
<tr>
<td></td>
<td>α = 74.580(4)\degree, β = 88.516(4)\degree, γ = 87.425(4)\degree</td>
</tr>
<tr>
<td><strong>color/appearance:</strong></td>
<td>yellow/block crystals</td>
</tr>
</tbody>
</table>

![Structure diagram](image)
### Crystal structure data of 2

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound name</td>
<td>S-(4-Methyl-2,6-diaminophenyl)-N,N-dimethylthiocarbamate (2)</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{10}H_{15}N_{3}O_{1}S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>225.31</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P_{T}</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.6435(19) Å, α = 101.803(8)°, b = 8.2766(17) Å, β = 99.652(8)°, c = 9.852(2) Å, γ = 103.533(8)°</td>
</tr>
<tr>
<td>Color/appearance</td>
<td>colorless/block crystals</td>
</tr>
</tbody>
</table>
Crystal structure data of 7

<table>
<thead>
<tr>
<th>Compound name</th>
<th>2-Chloro-3-nitroaniline (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₆ H₅ N₂ O₂ Cl</td>
</tr>
<tr>
<td>Formula weight</td>
<td>172.57</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.130(7) Å</td>
</tr>
<tr>
<td></td>
<td>b = 3.768(3) Å</td>
</tr>
<tr>
<td></td>
<td>c = 11.815(9) Å</td>
</tr>
<tr>
<td>Color/appearance:</td>
<td>yellow/ribbon</td>
</tr>
</tbody>
</table>

α = 90°, β = 90.66°, γ = 90°
Crystal structure data of 11

<table>
<thead>
<tr>
<th>Compound name</th>
<th>4-Methyl-2,6-dinitrophenyl sulfonyl chloride (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C7 H5 N2 O6 S Cl</td>
</tr>
<tr>
<td>Formula weight</td>
<td>280.64</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁2₁2₁</td>
</tr>
</tbody>
</table>

Unit cell dimensions:

\[
\begin{align*}
    a &= 6.9547(12) \text{ Å} & \alpha &= 90°. \\
    b &= 10.646(2) \text{ Å} & \beta &= 90°. \\
    c &= 14.471(3) \text{ Å} & \gamma &= 90°.
\end{align*}
\]

Color/appearance: colorless/plate crystals
### Crystal structure data of 13

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound name</td>
<td>(S)-(2,6-Dinitrophenyl)-N,N-dimethylthiocarbamate (13)</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C9H15N3O5S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>271.25</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>(P2_1/c)</td>
</tr>
</tbody>
</table>
| Unit cell dimensions      | \(
| a = 7.8794(8) Å          | \(\alpha = 90^\circ\).                   |
| b = 21.3605(18) Å        | \(\beta = 116.901(3)^\circ\).            |
| c = 7.8848(8) Å          | \(\gamma = 90^\circ\).                   |
| Color/appearance:         | yellow/block crystals                      |
Crystal structure data of 14

<table>
<thead>
<tr>
<th>Compound name</th>
<th>2,6-Dinitrophenyl sulfonyl chloride (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₆H₃N₂O₆SCl</td>
</tr>
<tr>
<td>Formula weight</td>
<td>266.61</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.796(3) Å</td>
</tr>
<tr>
<td></td>
<td>b = 9.602(4) Å</td>
</tr>
<tr>
<td></td>
<td>c = 13.401(4) Å</td>
</tr>
<tr>
<td>Color/appearance:</td>
<td>colorless/plate crystals</td>
</tr>
</tbody>
</table>

α = 90°, β = 95.604(13)°, γ = 90°.
Crystal structure data of 15

<table>
<thead>
<tr>
<th>Compound name</th>
<th>O-(2,6-Dimethoxyphenyl)-N,N-dimethylthiocarbamate (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C11H15N03S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>241.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>PbcA</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a = 10.4413(8) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 10.6467(9) Å</td>
<td>β = 90°</td>
</tr>
<tr>
<td>c = 21.9070(18) Å</td>
<td>γ = 90°</td>
</tr>
<tr>
<td>Color/appearance:</td>
<td>colorless/rhombic prism</td>
</tr>
</tbody>
</table>

![Diagram of the molecule]
Crystal structure data of 16

<table>
<thead>
<tr>
<th>Compound name</th>
<th>S-(2,6-Dimethoxyphenyl)-N,N-dimethylthiocarbamate (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C11 H15 N O3 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>241.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 16.7250(15) Å, b = 11.8103(10) Å, c = 13.3194(13) Å, α = 90°, β = 113.441(3)°, γ = 90°</td>
</tr>
<tr>
<td>Color/appearance:</td>
<td>colorless/diamond</td>
</tr>
</tbody>
</table>
Crystal structure data of 17

<table>
<thead>
<tr>
<th>Compound name</th>
<th>4-Hydroxy-1,3-benzothiol-2-one (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C\textsubscript{7}H\textsubscript{4}O\textsubscript{3}S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>168.16</td>
</tr>
<tr>
<td>Temperature</td>
<td>300(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2\textsubscript{1}/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 5.4326(7) \text{ Å}) (\alpha = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(b = 13.4096(14) \text{ Å}) (\beta = 103.121(4)^\circ)</td>
</tr>
<tr>
<td></td>
<td>(c = 9.8850(13) \text{ Å}) (\gamma = 90^\circ)</td>
</tr>
</tbody>
</table>

Color/appearance: colorless/block crystals