APPLYING A LATE-STAGE LAWESSON’S CYCLIZATION STRATEGY TOWARDS THE SYNTHESIS OF 1,3,4-THIADIAZOLE-2-CARBOXYLATE THIOESTERS

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CHAPTER 1. INTRODUCTION

1.1 Introduction to liquid crystals

The two most common condensed phases of matter, crystals and liquids, are differentiated by the order of the molecules within each phase. The molecules in a crystal have both positional and orientational order, constrained to occupy certain regions of a lattice and point their molecular axes in specific directions, while the molecules of a liquid diffuse randomly throughout the sample with their molecular axes rotating in all directions. There exist in nature, however, phases with higher degrees of order than present in liquids, but less order than typical of crystals. These intermediate phases are collectively termed liquid crystal phases, since they possess properties normally associated with both liquids and crystals.¹

The most well-studied class of liquid crystals are thermotropic liquid crystals, which are pure substances whose phase behavior is dependent on temperature. Other liquid crystals exhibit different phases dependent on both temperature and their concentration as a component in a solvent. These systems are termed lyotropic liquid crystals.² Further subclassifications of thermotropic liquid crystals are made based on the structure of the molecules displaying the phases. Calamitic liquid crystal phases are formed by rod-like molecules, while discotic liquid crystal phases are formed by disk-shaped molecules.² This work examines calamitic liquid crystals. The general structure is
defined by a rigid core with flexible side chains; several examples are shown in Figure 1.1.

![Figure 1.1 Typical structures of calamitic liquid crystal molecules](image)

Defining liquid crystal phases is foundational to discussing their useful functions as well as synthesis of compounds displaying these phases. Several different parameters are used to describe the orientational and positional order of molecules in a liquid crystalline sample. Some phases possess both orientational and positional order, while others maintain a degree of orientational order, but lack positional order. As a substance warms and melts into a liquid crystal phase, some or all of the positional order is lost. As it warms into the liquid phase, the orientational order is lost. The amount of molecular order in a liquid crystal compared to a crystal is small; however, it is significant enough to manifest itself through mechanical and electromagnetic properties typical of crystals.¹

### 1.1.1 Liquid crystal phases

Several different types of molecules form liquid crystal phases, but they all possess anisotropy. In the case of calamitic liquid crystals (rod shaped), one molecular axis is much longer than the other. Interaction between these anisotropic molecules allow orientational and positional order in an otherwise fluid phase.¹ The simplest liquid crystal
phase is known as the nematic phase. While molecules lack positional order and are free to diffuse in all directions throughout the sample, they maintain a preferred orientational direction. This average direction is denoted as \( n \) and is called the director, which is used to define the order of various phases.

In addition to the nematic phase, other phases are common to calamitic liquid crystals. These are known as the smectic phases. In addition to a small amount of orientational order, these phases also display varying amounts of positional order. The centers of masses of molecules are arranged in layers, although molecules are still free to diffuse randomly within the layers. Molecules are still free to move between layers as well, although on average, they spend more time within the layers than between them. If the director is perpendicular to these layers, the phase is referred to as an orthogonal phase (for example, the smectic A and smectic B phases). If the director makes any angle other than \( 90^\circ \) to the layers, it is called a tilted phase (for example, the smectic C and smectic I phases). Essentially, the smectic C phase (SmC) can be thought of as a tilted smectic A (SmA) phase.

Figure 1.2 Schematic depicting the N, SmA, and SmC phases
Several theories have been proposed to explain the physical causes of the molecular tilt of the SmC phase. One primary theory advanced by McMillan in 1973 proposes that in the SmA phase, molecules are free to rotate around their long axes. As the molecules lose thermal energy, this rotation becomes limited and lateral outboard dipoles not orthogonal to the long axes tend to align and thus produce torque, tilting the molecules. A second theory, advanced by Wulf in 1975, instead proposes that the SmC tilt angle is the result of steric interactions between molecules. This model describes “zig-zag” shaped molecules (from obliquely placed side chains) as acquiring a tilt in order to maximize packing efficiency as they lose energy on cooling from the SmA to SmC phases. Neither of these two theories is individually satisfactory in explaining the SmC phase; in particular, Goodby et al. found the McMillan model to be inconsistent with experimental data by synthesizing molecules that still displayed the SmC phase, but where the outboard dipoles were replaced with aliphatic branching. However, despite lacking universality, these two original models are still helpful when visualizing the effect of molecular structures on tilted phase formation.

If the molecules forming a liquid crystal phase are chiral, then chiral phases exist in place of certain non-chiral phases. The nematic phase is replaced by the chiral nematic (N*) phase, in which the director rotates in a helical fashion about an axis which is perpendicular to the director. A helpful visualization of this phase is of layers of material, parallel to the long axis of the molecules, which rotate with respect to each other (Figure 1.3). The distance (measured parallel to the normal of these theoretical layers) along the helix through which the director rotates by 360° is called the pitch.
Pitch can be adjusted by mixing the two enantiomers in different ratios, or by doping the material with a chiral molecule soluble in it.\textsuperscript{7} Interesting optical effects occur when the wavelength of light passing through the material matches the pitch.\textsuperscript{1}

![Figure 1.3 Schematic of chiral nematic and smectic C phases](image)

Tilted smectic phases also exhibit chiral versions, in which the director rotates around an axis normal to the layer planes.\textsuperscript{1} Just as with the chiral nematic phase, chiral SmC (SmC*) phases possess a pitch, defined by the distance in which the director rotates around the layer normal axis by 360°. Chiral SmC materials have found many applications such as in optical switching and modulating devices, image scanners and printers, optical image and signal processing, and liquid crystal displays.\textsuperscript{7} The liquid crystal display (LCD) is one of the most ubiquitous pieces of technology in the modern world;\textsuperscript{8} it can be found in devices ranging from computer displays to kitchen appliances and handheld medical instruments. The obvious applications in displays beginning in the 1970s stimulated vast amounts of research in academic and industrial settings, such that in recent years LCD technology has become advanced and now remains primarily in industrial settings. Academic liquid crystal science has moved away from LCD research.
and focuses on potentially very different topics such as new optics, novel composites, and biotechnology. In order to understand the role liquid crystals play in displays and other applications, old and new, one must understand how liquid crystal materials interact with electric fields and polarized light.

1.1.2 Interaction of liquid crystals with electric fields and polarized light

Charged objects interact, with like charges repelling each other and opposite charges attracting each other. The charged objects need not be in contact with each other to experience this force, although the force is inversely proportional to the square of the distance separating the charges. An electric field describes the force experienced by a charge as a function of its location relative to some other charge. It is important to note that an electric field has a specific direction associated with it; if a positive test charge were placed in the field, it would either experience a force towards or away from the source of the field. Molecules with electric dipoles (uneven charge distribution), either permanent or induced, also interact with electric fields much like charged objects. This is the basis for how liquid crystals interact with electric fields, and is extremely important for their optical applications and controlling their physical behavior in general.

In the absence of an electric field, the permanent dipoles of liquid crystal molecules are not aligned, even if orientational order is present. This is true even of dipoles along the long axis of molecules because the molecules can be aligned along the director in either direction. The lateral dipoles also orient themselves randomly in any direction perpendicular to the director. If an electric field is applied, however, the charged
parts of the molecules (opposite ends of dipoles) experience opposite forces and cause the molecules to rotate until the charges align with the electric field. The larger dipoles, whether along the long or lateral axes, align with the field. In the N* phase, this is the mechanism of controlling the twist of molecules by applying an electric field perpendicular to the director. Similarly, in the SmC* phase, applying an electric field perpendicular to the helical axis (director) destabilizes and unwinds the spiral structure. In the N* phase, this is the mechanism of controlling the twist of molecules by applying an electric field perpendicular to the director. Similarly, in the SmC* phase, applying an electric field perpendicular to the helical axis (director) destabilizes and unwinds the spiral structure.

Figure 1.4 Schematic of linearly polarized light

Light, (visible spectrum electromagnetic radiation), consists of electric and magnetic field components perpendicular to each other and travelling in the same direction (conventionally the z-direction, Figure 1.4). Unpolarized light oscillates in every orientation about the axis of propagation. If the light is linearly polarized, however, its oscillation is confined to a single plane, and the transmitted intensity reduced to 50% of that of the original source. Multiple polarizers can be used in sequence to control the intensity of transmitted light. If two polarizers are oriented perpendicularly, no light is transmitted because linearly polarized light from the first polarizer strikes the second polarizer at 90°. Likewise, if the polarizers are parallel, all the light that passes through the first polarizer also passes through the second. This is the basis for “on” and “off” states in terms of light transmission.
Liquid crystals have an anisotropic molecular structure. This leads to properties such as birefringence, that together with the ability to precisely control the orientation of molecules in a liquid crystal phase using external electric fields, makes liquid crystals useful in controlling light. When polarized light enters a material in the SmC* phase, its plane of polarization is rotated due to the helical nature of the phase (described previously). If an electric field is applied perpendicularly to the director, the helical structure is disrupted and a non-zero electric polarization (electric dipole per unit volume) is established. Even with the removal of the electric field, this polarization tends to remain. This behavior is termed ferroelectric.

1.2 Nematic and smectic liquid crystal displays (LCDs)

A common application of ferroelectric liquid crystals (FLCs) is in surface-stabilized ferroelectric liquid crystal (SSFLC) displays. In these devices, an FLC material is sandwiched in a cell between two glass plates which promotes alignment of the director parallel to the plates. Perpendicular light polarizers are placed on either side of the plates so that light entering the cell is linearly polarized. Applying an electric field normal to the glass plates aligns the electric polarization of the liquid crystals; applying an electric field in the opposite direction reverses the electric polarization of the molecules (Figure 1.5 c, d). By selecting a careful combination of material birefringence of the liquid crystal molecules, cell thickness, and careful alignment, light entering the display may be rotated by 90° (“on” state, Figure 1.5 d) under an applied electric field.
Applying an electric field in the other direction causes the entering light not to be rotated and transmission is blocked by the second light polarizer (“off” state, Figure 1.5 c).²

![Figure 1.5 Schematic of light transmission mechanism by a TN cell vs. a SSFLC cell](image)

Good performance of SSFLC devices requires the suppression of the helical twist observed in the SmC* phase. To achieve this, the distance between glass plates of the cell is small (less than or equal to the pitch length of the liquid crystal material). The presence of the helical twist can negatively affect the performance of the device by introducing defects, lowering contrast, and disrupting molecular alignment.⁷

The predominant type of LCD employs the twisted nematic (TN) cell design (Figure 1.5, a, b). These devices also sandwich liquid crystal molecules (nematic in this case) between two glass plates, and have light polarizers oriented at 90° from each other in reference to their normal axis. The glass plates are prepared chemically or mechanically to cause the director of the liquid crystal molecules to lie parallel to the plates. The director of the molecules along the bottom plate, however, is perpendicular to
that of the molecules of the top plate such that between the plates the molecules twist through 90°. This is the configuration of the transmitting (“on”) state (Figure 1.5, a) when no electric field is applied to the plate. When an electric field is applied perpendicular to the plates, the liquid crystal molecules are electrically polarized along their long axes and the twist is disrupted; the linearly polarized light entering the cell no longer is rotated 90° and is blocked by the second polarizer (Figure 1.5, b).

The disadvantage of TN displays is slower switching times than SSFLCs. In order to restore the twist after an electric field has induced the off state, the field is turned off and the liquid crystal molecules relax back to their twisted configuration. Some delay is associated with this relaxation. In an SSFLC, however, the “off” and “on” states are induced by changing the direction of the electric field and this results in switching times which are faster by two or three orders of magnitude than observed with TN displays.²

1.3 Molecular structure of ferroelectric liquid crystal materials

![Figure 1.6 Typical structure of ferroelectric materials](image)

In order to produce ferroelectric materials, it is important to engineer molecules that display a tilted smectic phase. Figure 1.6 shows a typical structure of a material that exhibits tilted smectic phases. These molecules possess a rigid core, usually aromatic; strongly dipolar group in the core (central linkage) and at the ends of the core (terminal linkages); and flexible aliphatic side chains.⁷ Also, introducing a chiral center to the
molecules that display tilted phases reduces their symmetry and can induce ferroelectricity.\textsuperscript{2,7} Figure 1.7 summarizes the general effects of central and terminal linkages in causing tilted smectic phases. Structures synthesized in this work are highlighted in red.

![Diagram of central and terminal linkages in smectic liquid crystals](image)

**Figure 1.7 Series of central and terminal linkages in smectic liquid crystals (adapted from Goodby\textsuperscript{7})**

The Seed/Sampson research group has focused on synthesizing 5-membered sulfur-containing heterocyclic-core liquid crystals, namely thiophenes, 1,3-thiazoles, fluorothiophenes, and 1,3,4-thiadiazoles. Figure 1.8 outlines these structures. The rationale for pursuing these targets is consistent with the previous discussion about structures that form SmC phases. This work focuses on 1,3,4-thiadiazoles as potential ferroelectric mesogens. The 1,3,4-thiadiazole ring possesses a strong lateral dipole, narrow molecular width compared to fluorine-substituted benzene rings, and the most linear geometry of the common 5-membered sulfur-containing heterocycles. Each of these properties generally promotes the tilted smectic phase.\textsuperscript{2} Ester and thioester linking groups are also used, which tend to promote tilted smectic phases while being more
chemically stable than Schiff bases. Figure 1.9 provides a summary of the structural dimensions of the common 5-membered heterocycles.\textsuperscript{13}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.8.png}
\caption{General structure of potential liquid crystal core structures in the Seed/Sampson research group.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.9.png}
\caption{Bond angles and dipoles in common 5-membered sulfur-containing heterocycles.}
\end{figure}

1.4 Synthesis of 1,3,4-thiadiazoles in liquid crystal materials

1,3,4-Thiadiazoles are generally synthesized through either ring-forming or ring-modifying approaches. Each strategy offers advantages or disadvantages depending on the specific target molecules in which the heterocycle is incorporated. Substituents on the 1,3,4-thiadiazole ring determine which of the two approaches promises greater efficiency in the synthesis of the final material.
1.4.1 Ring-forming approaches to 1,3,4-thiadiazoles, 1,3-thiazoles, and thiophenes

The most common ring forming approach to five-membered sulfur heterocycles in the literature involves cyclizing 1,4-dicarbonyl species using a thionating agent. Although the strategies to synthesize these dicarbonyl compounds are extremely diverse, similar conditions can be employed to obtain 1,3,4-thiadiazole, 1,3-thiazole, and thiophene systems from these compounds, based on the identity of the 3- and 4- position bridging atoms. (Figure 1.10)

![Diagram](image)

**Figure 1.10 General strategy of approach to 5-membered heterocycles via cyclization of 1,4-dicarbonyl precursors**

Previous to the work in thionation chemistry published by Lawesson and coworkers in 1978,14,15 cyclization reactions were usually carried out using phosphorus pentasulfide (P₄S₁₀) under reflux conditions. Lawesson’s reagent (1) is generally considered to possess advantages over P₄S₁₀ in requiring shorter reaction times, fewer equivalents of the reagent, and superior reproducibility.16,17 Although the synthesis of 1 was first documented by Lecher in 1956,18 it was the systematic explorations of the compound by Lawesson and coworkers that resulted in it becoming arguably the most important agent in thionation chemistry. It is commercially available and synthesized by
heating anisole and P$_4$S$_{10}$ for several hours, giving yields of approximately 80\%. The species (1) is a nonreactive dimer that dissociates in solution into the monomer (2) before reacting. A proposed mechanism outlined a ring closure mechanism of 1,4-dicarbonyl compounds in which thionation of both carbonyl groups is the first step, followed by *in situ* cyclization and loss of H$_2$S. Figure 1.11 shows this mechanism for the 1,3,4-thiadiazole system, The same principle applies to thiophene and 1,3-thiazole systems, albeit with slightly different electron movements during the formation of (3) through intramolecular nucleophilic attack.
Recent literature has demonstrated the late-stage cyclization strategy of dicarbonyl compounds as approaches to columnar liquid crystals. Pathak et al.\textsuperscript{19} used the Lawesson’s cyclization ring forming approach to 1,3,5-triaryl “star-shaped” liquid crystals (Figure 1.12). Gallic acid was esterified with ethanol to obtain ethyl-3,4,5-trihydroxybenzoate, which was then alkylated using Williamson etherification techniques\textsuperscript{20} (bromoalkanes and potassium carbonate in DMF). The afforded trialkoxy esters (4) were converted to their respective hydrazides (5) by treating with hydrazine.
monohydrate. These hydrazides were then reacted with trimesic acid chloride in the presence of triethylamine, yielding the appropriate tri-N-benzoylbenzohydrazides. These compounds were cyclized to the corresponding 1,3,4-thiadiazoles (using Lawesson’s reagent) in moderate yield (31-49%). An important concept demonstrated in this strategic pathway is the incorporation of all ring substituents before cyclization.

Figure 1.12 Pathak's approach to "star-shaped" columnar liquid crystals

Han et al.\textsuperscript{21} also utilized the Lawesson’s cyclization methodology to synthesize precursors to rod and H-shaped liquid crystals (Figure 1.13). The final target molecules (111, 112) all contained a 2,5-diphenyl-1,3,4-thiadiazole group with an ester-linked 4-decyloxyphenyl moiety. The main purpose of the study was to develop 1,3,4-thiadiazole-
based liquid crystals with low temperature mesophase ranges and to compare the liquid
crystal behavior of dimers (H-shaped in this case) with that of their corresponding
monomers. 4-Substituted benzoic acids (6) were reacted with thionyl chloride affording
the appropriate 4-substituted benzoyl chlorides. 4-Methoxybenzoic hydrazide (7) was
then reacted with these acyl chlorides to yield the corresponding 1,4-dicarbonyl
compounds (8), which were then cyclized using Lawesson’s reagent. The resulting 1,3,4-
thiadiazole precursors were then deprotected to phenols and reacted with 4-
decyloxybenzoyl chloride to yield the final targets (11). One concept that can be observed
in this synthetic strategy is another common approach to 1,4-dicarbonyl compounds prior
to cyclization: the formation of the acyl chloride intermediate in situ. Another
observation that can be made is placing a phenyl “spacer” between the 1,3,4-thiadiazole
ring and the reacting moiety allows facile linking of side chains after the 1,3,4-thiadiazole
ring has been formed. This allows for a synthetically divergent strategy since many
different side chains can be linked to the heterocycle-containing core with a single
reaction. If, however, the side chains must be linked to the 1,3,4-thiadiazole ring directly
through other groups (e.g. ester/thioester), difficulties arise with this early-stage
cyclization strategy. Some of these issues were the basis of a significant amount of
experimental problem solving by prior researchers in our group and will be discussed
later.
Figure 1.13 Han's approach to 1,3,4-thiadiazole liquid crystals containing a central ester linkage (reproduced from Han\textsuperscript{21})

Kuo et al.\textsuperscript{22} also used an \textit{in situ} acyl chloride formation and late-stage cyclization strategy towards symmetric 1,3,4-oxadiazole and 1,3,4-thiadiazole-based calamitic liquid crystals (Figure 1.14). 6-Hydroxy-2-naphthoic acid (12) was subjected to Fisher esterification conditions (alcohol, acid catalyst), Williamson etherification (bromoalkanes, potassium carbonate, catalytic iodide salt in acetone), and hydrolysis with base to afford the corresponding 6-alkoxy-2-naphthoic acid (15). This compound was then reacted with thionyl chloride, followed by hydrazine monohydrate in THF to give symmetrical 2-naphtho-bis-hydrazides 16 in good yield (80\%). The bis-hydrazides were then cyclized to the corresponding 1,3,4-thiadiazoles in good yield (70-74\%) using phosphorus pentasulfide. This strategy demonstrates that good yields in these cyclization reactions can still be obtained (albeit with a 24 hour reaction time) using phosphorus
pentasulfide; however, in most cases yields can be easily matched and reaction time reduced significantly using Lawesson’s reagent.

![Chemical diagram](image)

**Figure 1.14** Kuo’s approach to symmetric 1,3,4-thiadiazole liquid crystals

Microwave assisted methods have been demonstrated to offer potentially useful and efficient approaches to 1,3,4-thiadiazoles. Our own group explored a family of thiophenes, 1,3-thiazoles, and 1,3,4-thiadiazoles (19) via cyclization of various dicarbonyl compounds (18, Figure 1.15). These compounds were mixed with Lawesson’s reagent, without solvent, and irradiated in a conventional microwave oven. All but two of twelve different compounds were synthesized with short reaction times and yields in excess of 83%. Two specific examples are shown in Figure 1.15. Han et al. also
demonstrated that microwave-irradiated Lawesson’s cyclizations towards 2,5-diaryl-1,3,4-thiadiazoles can be highly efficient (Figure 1.16). 1,4-Dicarbonyl compounds 21 were prepared from acid chlorides and hydrazides as previously mentioned. These precursors were then cyclized under solvent free conditions with Lawesson’s reagent via irradiation in a household microwave for approximately two minutes until the reagents turned to a liquid. The reaction mixture was removed immediately at this point to avoid decomposition of the products. After silica column purification, the 2,5-diaryl 1,3,4-thiadiazole products were afforded in high yield (80-91%). The advantages of microwave-assisted synthesis in these cases were very short reaction times and solvent-free conditions, eliminating the need for anhydrous hydrocarbon solvents. However, the reactions could be hard to scale up due to the possibility of local superheating of the reaction mixture, although several compounds (e.g. 19a, 19b) were synthesized by our group on a multigram scale without significant reduction in yields.

**Figure 1.15 Use of microwave-assisted Lawesson's cyclization of 5-membered sulfur-containing heterocycles**

![Diagram of cyclization process]
Figure 1.16 Han's microwave assisted Lawesson's cyclization approach to 1,3,4-thiadiazoles

Other examples can be found using late-stage cyclization strategies.\textsuperscript{25} Despite this growing category in the literature, there remain relatively few examples of the strategy being applied to synthesize 1,3,4-thiadiazoles with substitution other than aromatic groups. One of these examples can be seen in recent work by Deokar et al.\textsuperscript{26} as part of a study on the antimicrobial activity of some oxadiazole/thiadiazole compounds. Hydrazide 23 was refluxed in 2-propanol with carbamate 24 to afford a hydrazinecarboxamide 25, which was subsequently cyclized using Lawesson’s reagent in refluxing dioxane (Figure 1.17). The final product 26 includes an amine linkage between the 2-position on the 1,3,4-thiadiazole heterocycle and an aromatic moiety. However, most examples of halo-, amino-, nitrile-, and other substituted 1,3,4-thiadiazoles are found within the context of ring modifying approaches (see section 1.4.2).
Figure 1.17 Deokar's Lawesson's cyclization of antimicrobial compounds containing 1,3,4-thiadiazole-2-amino groups

1.4.2 Ring-modifying approaches to 1,3,4-thiadiazoles

In addition to synthetic methods that directly form substituted 1,3,4-thiadiazoles, many approaches exist which modify a 1,3,4-thiadiazole ring that is already in place. The inductive effects of the electronegative nitrogen heteroatoms make the 2- and 5-position carbons electron-deficient, and together with the aromaticity of the system, explains the lack of reactivity at C-2 and C-5 positions of unsubstituted thiazoles (practically unknown electrophilic substitution on carbon, difficult nucleophilic substitution). Substituted 1,3,4-thiadiazoles are reactive at the carbon atoms, with leaving groups displaced easily, and electrophilic substitution made possible with the presence of an electron donating group, most commonly an amino group, on the remote carbon atom.

Numerous examples exist of amino-substitution being paired with bromination to create useful substituted 1,3,4-thiadiazole compounds. In a study of liver-targeted
stearyl-CoA desaturase inhibitor to treat diabetes and obesity, Lachance et al. demonstrated that 2-amino-1,3,4-thiadiazole undergoes electrophilic substitution in the presence of bromine and acetic acid (Figure 1.18), although a yield was not reported. Similarly, Rao et al. used this same reaction in a study of histamine H₃ receptor antagonists as part of a treatment for diabetes. Figure 1.19 shows the general strategy employed to synthesize these compounds. 2-Amino-1,3,4-thiadiazole was brominated at the 5-position, followed by bromination of the 2-position via a diazonium intermediate to yield the dibromo compound (29). Sequential use of nucleophilic substitution then afforded the final products (31).

**Figure 1.18 Bromination of 2-amino-1,3,4-thiadiazole (Lachance)

**Figure 1.19 Rao’s bromination/substitution of 1,3,4-thiadiazoles (reproduced from Rao)

(a) Br₂, AcOH, NaOAc, room temperature, 12 h (91%). (b) CuBr₂, t-BuONO, MeCN, room temperature, 12 h (70%). (c) 4-Piperidinopiperidine, N,N-disopropylethylenimine, 1,4-dioxane, 120 °C, 2 h (63%). (d) Amines, N,N-disopropylethylenimine, PhCF₃-1,4-dioxane (2:1), microwave, 220 °C, 3 h (50-80%)
In addition to utilizing the amino substituents on the thiaiazole ring as electron-donating groups and as precursors to diazonium leaving groups, a common strategy is to convert them into Schiff-base linkages. This linkage is common in liquid crystals, being present in some of the earliest examples of compounds displaying stable nematic phases at room temperature, including MBBA. More recently, Tandel and Patel synthesized a series of liquid crystals derived from 2-amino-1,3,4-thiaiazole compounds and containing a Schiff-base linkage (Figure 1.20). Methyl p-hydroxybenzoate (32) was etherified and then subjected to 80% hydrazine hydrate in ethanol to afford the hydrazide compound 33. The hydrazide was then allowed to react with ammonium thiocyanate under anhydrous conditions to afford thiosemicarbazide 34; this compound was first reacted with acetyl chloride and then dehydrated with concentrated hydrochloric acid, affording 5-aryl-2-amino-1,3,4-thiaiazole 35. Reacting with a series of p-benzoyloxybenzaldehydes (36) gave the final products (37). Liquid crystal materials containing a Schiff base linkage in their core tend to strongly promote tilted smectic phases, as mentioned earlier. The materials synthesized by Tandel and Patel containing longer alkoxy tails did indeed display the SmC phase, albeit over a narrow range, likely in part due to the lateral methoxy group in the core. A disadvantage of the Schiff-base moiety is its chemical instability; utilizing linking groups with higher stability such as esters or thioesters is one method to produce more robust materials.
Gallardo et al.\textsuperscript{32} utilized the reaction of thiosemicarbazide (39) with a series of aryl nitriles (38) to produce a family of 2-amino-1,3,4-thiadiazole derivatives (40), which served as intermediates in the synthesis of a new series of 2,6-disubstituted imidazo-1,3,4-thiadiazole liquid crystals (Figure 1.15). The reaction of the 2-amino thiadiazoles with various α-bromo aryl ketones demonstrates another interesting use for the 2-amino group of thiadiazoles; that is, using it to incorporate 1,3,4-thiadiazoles into more complex heterocyclic structures.
It is clear that amino-substituted thiadiazoles are very popular building blocks due to their versatility. In contrast to the numerous examples of the use of amino-, aryl, and halo-substituted 1,3,4-thiadiazoles, very few examples of effective synthesis of 2-carboxy-1,3,4-thiadiazole compounds exist in the literature. One example of a methyl ester-substituted 1,3,4-thiadiazole was shown by Garfunkle et al. as part of the synthesis of inhibitors of fatty acid amide hydrolase (FAAH). The family of inhibitors included compounds containing different 5-membered heterocycles including 1,3,4-thiadiazoles such as 47 (Figure 1.22). Hydrazide compounds 43 were allowed to react with methyl oxalyl chloride to afford tricarbonyl compounds (45), which were subsequently cyclized with Lawesson’s reagent to give 2-carboxy-1,3,4-thiadiazoles (46). Organolithium or Grignard reagents were then used to convert the ester group into a ketone and afford the final products, such as 47. Although the ester moiety was not preserved in the target compounds and experimental details were scarce, the strategy demonstrates use of the 2-
carboxy ester substitution in an intermediate step. Even recently, however, other examples of these 1,3,4-thiadiazole-2-carboxylate esters remain virtually unseen outside of the work\textsuperscript{34,13} performed by our group.

**Figure 1.22 Garfunkle’s approach to the synthesis of FAAH inhibitors**

Our group has used the strategy of selectively cyclizing tricarbonyl compounds using Lawesson’s reagent to form the 1,3,4-thiadiazole moiety bearing the 2-carboxylate ester group already in place, followed by basic hydrolysis to yield the sodium carboxylate salt (57).\textsuperscript{34} The 2-carboxylic acid group readily decarboxylates, while the sodium carboxylate salt is bench stable with decarboxylation only occurring in solution. Previous to the work of Schmidt,\textsuperscript{35} these carboxylate salts were converted to acid chlorides and reacted with alcohols and thiols to form the final materials (see Figure 1.25). This methodology was moderately successful after the work of several researchers in our group,\textsuperscript{34,36} albeit experimentally demanding. Wallace\textsuperscript{37} attempted to extend the methodology to thioesters 62a-c (Figure 1.26) with very limited success, while Schmidt extended the strategy to aryl esters 63 (Figure 1.27). In the process, Schmidt developed the late-stage cyclization strategy (see Figure 2.1 of the next chapter) which demonstrated
good efficiency and utilized a significantly less demanding experimental procedure than the previously established strategy.

1.5 Overview of the Seed/Sampson research group’s work with preparation of 1,3,4-thiadiazole-2-carboxylate esters

1.5.1 Previous methodology for synthesis of alkyl 1,3,4-thiadiazole-2-carboxylate esters and thioesters

Several techniques exist for the formation of esters from the condensation of an alcohol with a carboxylic acid. Condensation of these groups directly can be achieved through reactions including acid-catalyzed Fischer esterification\(^{38}\) or Steglich esterification (DCC, catalytic DMAP)\(^{39}\) or by first converting the carboxylic acid to more reactive functional groups such as anhydrides or acid chlorides.\(^{20}\) Each of these techniques requires use of a stable carboxylic acid precursor. This is a challenge when working with 1,3,4-thiadiazoles because of the electron-deficient nature of the 2- and 5-position carbons on the ring. Decarboxylation of the carboxylic acid occurs readily,\(^{40}\) with a postulated pathway shown in Figure 1.23. Furthermore, electron-withdrawing groups substituted onto the 2- or 5-positions of the ring increases the rate of decarboxylation.\(^{41}\) Since the 1,3,4-thiadiazole structures synthesized by our group all contain phenyl substituents at the 5-position carbon, combating rapid decarboxylation of the 2-position has been an issue since we began developing methodology towards these targets.
Figure 1.23 Proposed pathway for decarboxylation of 1,3,4-thiadazole-2-carboxylic acids

Figure 1.24 Bradley’s approach to synthesis of 1,3,4-thiadiazole free acid (53)

Bradley, a former researcher in our group, first tried to develop synthetic strategies towards 1,3,4-thiadiazole-2-carboxylate esters (see Figure 1.24) that used the free acid (53) as a key intermediate. As previously mentioned, however, the free acid proved not to be bench stable and the use of this intermediate was not continued. Attempts were also made to transesterify the ethyl ester 52, but these pathways were not efficient. Bradley then probed the effectiveness of using sodium carboxylate salt 57 as the intermediate towards various esters (see Figure 1.25). This salt proved much more stable than the free acid, and conversion to the acid chloride \textit{in situ} followed by reaction with various alcohols at room temperature provided the first reasonably successful results (41% yield of aryl ester 58a from the corresponding carboxylate salt).34,42 Sybo34,36 then elaborated on Bradley’s work, determining that the main factor in controlling decarboxylation of the carboxylate salt was the reaction temperature. The esterification
reactions proceeded with the best yields when a temperature range of -8 to -6°C was maintained. Below this temperature range, the reaction did not occur, while above this range the rate of decarboxylation greatly increased. This caused the experimental procedure to be very tricky, as adding the alcohols would cause the temperature of the solution to fluctuate. Together with a long reaction time to completely hydrolyze the ethyl ester 56, the methodology starting after cyclization of the 1,3,4-thiadiazole ring proved to be quite demanding. Despite this, Sybo successfully synthesized a family of four liquid crystals (butyl, hexyl, octyl, and decyl esters) in moderate yield (51-61%, 1 step).

Figure 1.25 Strategy developed by Bradley/optimized by Sybo for the synthesis of 1,3,4-thiadiazole-2-carboxylate esters (58)

Wallace\(^{37}\) then attempted to further optimize Sybo’s\(^{36}\) work. By use of the corresponding alkoxides rather than alcohols, Wallace was able to increase the yields of ester products (see Figure 1.26). In particular, the yield of the octyl ester 61a was
increased to 78% from Sybo’s 54%. Wallace then attempted to extend the optimized methodology to the synthesis of thioesters, but this proved to be difficult. He was able to synthesize a nonyl thioester 62b in 31% yield, but was unsuccessful in synthesizing octyl and decyl thioesters (62a,c). It is unclear why a low yield was obtained for the nonyl thioester, since thiolates are more nucleophilic than the corresponding alkoxides.

**Figure 1.26** Wallace’s use of alkoxides/thiolates for the synthesis of 1,3,4-thiadiazole-2-carboxylate ester/thioesters (61, 62)

Schmidt\(^{35}\) attempted to use the strategy developed by Bradley, Sybo, and Wallace for the synthesis of aryl esters (Figure 1.27). However, due to the less nucleophilic nature of phenols compared to alcohols, low yields resulted. Decarboxylation of the 1,3,4-thiadiazole ring again became a significant issue with the best yield achieved around 17%. Use of the corresponding phenoxides instead of phenols resulted in even poorer yields. At this point, our group reevaluated the overall strategy that relied on the unstable carboxylate salt as a key intermediate. Schmidt examined a new pathway that left the formation of the most unstable group as the last step, essentially avoiding the carboxy intermediate altogether and resulting in higher efficiency. The retrosynthetic pathway for this strategy is compared to the previously established approach in Figure 1.27. Since
formation of the 1,3,4-thiadiazole ring was the very last step in the new synthetic pathway, the methodology was termed the “Late-Stage Lawesson’s Cyclization” strategy.

![Diagram of the reaction process]

**Figure 1.27** Retrosynthetic comparison of late-stage Lawesson’s cyclization to previously established synthesis of aryl 1,3,4-thiadiazole-2-carboxylate ester (63)

1.5.2 The late-stage Lawesson’s cyclization strategy for the preparation of aryl 1,3,4-thiadiazole-2-carboxylate esters

At the heart of the new strategy was the reaction of benzohydrazides (54) with various oxalyl chloride derivatives (65). The resulting tricarbonyl compounds (64) were then cyclized with Lawesson’s reagent to afford the final 1,3,4-thiadiazole-2-carboxylate esters. The steps beginning from the synthesis of the acid chlorides 65 and resulting in the final products are shown in Figure 2.1. Synthesizing oxalyl chloride ester derivatives is
described in the literature through different methods.\textsuperscript{43,44} Most commonly, oxalyl chloride is reacted with the appropriate alcohol or phenol in the presence of a base (to react with the HCl formed); more recently seen are neat reactions\textsuperscript{43,45} of alcohols and oxalyl chloride. Schmidt\textsuperscript{35} found the neat reactions of various \textit{p}-alkoxyphenols in oxalyl chloride to provide satisfactory results. These compounds were then allowed to react with 4-octyloxybenzohydrazide (54) in anhydrous THF at room temperature in the presence of triethylamine. The major impurity present was phenol 66. Several attempts were made to purify the 1,4,5-tricarbonyl intermediate 64, including a silica plug, column chromatography, recrystallization, and simply washing the soluble impurities away with diethyl ether. However, the highly polar and labile nature of 64 made these efforts ineffective; either purity was not greatly increased or decomposition was observed. As a result, the crude material was used in the next step without purification. This next cyclization step proved not to be adversely affected by the impurities present with the tricarbonyl compound. The best results were obtained by refluxing the crude tricarbonyl compound (64) with Lawesson’s reagent in toluene. This afforded the target 1,3,4-thiadiazole-2-carboxylate ester compounds (63), which were purified using column chromatography. Further purification by recrystallization from DME yielded material pure enough for mesogenic studies, and in modest yield (21-35\%, 3 steps).

1.6 Scope of the current work

This thesis research was focused on two main goals. First was the optimization of the late-stage cyclization strategy towards the 1,3,4-thiadiazole-2-carboxylate aryl esters
synthesized by Schmidt. A second goal was to directly apply the late-stage cyclization strategy to the synthesis of 1,3,4-thiadiazole-2-carboxylate thioesters, essentially finishing the work that Wallace had started, but proceeding via an alternate strategy, with the goal of generating a family of thioester liquid crystal targets. One compound (62b) had been synthesized by Wallace in low yield and displayed a broad SmC temperature range. A reasonable assumption therefore was that a family of these materials would display similar and potentially useful physical properties.
CHAPTER 2. RESULTS AND DISCUSSION

2.1 Attempted optimization of the late-stage cyclization strategy for the preparation of aryl 1,3,4-thiadiazole-2-carboxylate esters and application to new liquid crystal targets

2.1.1 Reproduction and attempted optimization of work by Schmidt

Figure 2.1 Late-stage Lawesson’s cyclization pathway towards aryl 1,3,4-thiadiazole-2-carboxylate esters (63a-c) first attempted by Schmidt

The first goal of the current work was reproducing the work by Schmidt in order to determine which steps in the late-stage cyclization strategy could be optimized. First, 4-octyloxyphenol (66a) was allowed to react with oxalyl chloride (0.5 g scale) yielding aryloxalyl chloride 65a. Without purification or characterization, this compound was added to 4-octyloxybenzohydrazide (54) in THF at room temperature, in the presence of triethylamine (~1.5 equivalents, to remove HCl from solution). Subsequent removal of the resulting ammonium chloride salts provided the tricarbonyl compound 64a. The main impurity determined by $^1$H NMR analysis was the phenol 66a. However, it was not clear
whether this impurity was forming during the reaction of the hydrazide and acid chloride or was starting material remaining from the formation of the acid chloride precursor, since this compound (65) had always been used without characterization. In this case, $^1$H NMR analysis revealed a tricarbonyl product to phenol byproduct ratio of 1.2:1. This was a poorer result than Schmidt’s$^{35}$ attempt at synthesizing the same compound (1.8:1) ratio, but nonetheless the overall results demonstrated decent reproducibility.

Cyclizing the crude tricarbonyl compound (64) with Lawesson’s reagent had been demonstrated to be a robust reaction; the same technique was used here. The tricarbonyl compound was refluxed in anhydrous toluene with Lawesson’s reagent (0.6 equivalents). $^1$H NMR analysis showed the reaction was complete after only 70 minutes. The final product 63a was purified by silica column chromatography (10% EtOAc/petroleum ether). Three distinct fractions were obtained; first to elute was the desired product 63a (A), second was a mixture of the product 63a and phenol byproduct 66a (B), and third were other byproducts from Lawesson’s reagent (C). Fraction A displayed very good purity by $^1$H NMR analysis, while fraction B contained a ratio of 1.3:1 of product: phenol byproduct. Approximately 0.18 grams of product was recovered from the column (~17% yield over 3 steps of synthetically pure product). Poor recovery from the column (0.54 g crude product loaded) was due primarily to low user proficiency. The eluent system used also did not offer good separation ($R_f$ difference of 0.1 between the product and phenol byproduct).

Base extraction was another possible method for separating the phenol byproduct 66a from the final product 63a, but was not attempted. Previous attempts by Schmidt$^{35}$ to
remove the phenol byproduct from the tricarbonyl \(64a\) by washing with base (5% KOH) had resulted in complete decomposition of the tricarbonyl product. Furthermore, when purifying the final product \(63a\) using column chromatography, pretreating the silica columns with base (trimethylamine, to prevent decarboxylation of the product postulated to be catalyzed by acidic sites on the silica gel) had also resulted in decomposition of the product. Therefore, no further attempts at purification beyond column chromatography were made.

**Figure 2.2 Synthesis of 4-octyloxyphenol (66a)**

Efforts were then focused on determining the source of the phenol byproduct. First enough 4-octyloxyphenol (66a, Figure 2.2) was synthesized to be able to carry out the synthesis of the tricarbonyl compound (64a) several times on a 0.5 gram scale. The synthesis of this compound involved a simple alkylation and purity rather than optimization of the yield was the primary goal; however both were achieved using standard techniques (see Figure 2.2). 4-Benzxyloxyphenol (67) was alkylated using Williamson etherification\(^{20}\) (potassium carbonate, \(n\)-bromoheptadecane, reflux in butanone) in good yield (85%) and the product was recrystallized from petroleum ether. The benzyloxy protecting group was then removed using hydrogen gas and palladium-on-carbon catalyst in EtOH and EtOAc as cosolvents. The material was then recrystallized from petroleum ether with good yield (92%).
Synthesis of hydrazide 64 was not required because Schmidt had synthesized the material on a large scale (~40 g); the compound itself is very robust and the amount of the remaining material was expected to last for the entirety of this project.

Characterization of the oxalyl chloride derivative 65a was then attempted. Since oxalyl chloride is not visible by $^1$H NMR analysis, the simplest method to explore the neat reaction of the phenol 66a with oxalyl chloride was to perform a time study with aliquots of the reaction mixture directly analyzed by $^1$H NMR. 4-Octyloxyphenol was refluxed in oxalyl chloride as previously described. At 2 and 5 hours after the start of reflux, aliquots were removed, avoiding contact with the air and moisture as much as possible. $^1$H NMR analysis showed a product to starting phenol ratio of 1:1.3 in the 2 hour aliquot, which progressed to a ratio of 1:0.35 at 5 hours. After an additional 2 hours of refluxing, the reaction was determined to be complete by $^1$H NMR analysis, showing complete consumption of starting phenol. The long reaction time was surprising considering the excess and reactivity of oxalyl chloride, but the product was very pure (aside from the presence of oxalyl chloride). After removal of the excess oxalyl chloride in vacuo, no evidence of the phenol byproduct was seen, and the conclusion was that the phenol byproduct observed as a contaminant in 64a was forming from the hydrolysis of the tricarbonyl or oxalyl chloride derivative during the subsequent reaction leading to 64a.

Attempts were next made to increase the efficiency of the reaction forming the tricarbonyl compound 64a. Solutions of the acid chloride 65a and hydrazide 54 in
anhydrous THF were prepared as previously described. The hydrazide solution was then added dropwise to the acid chloride solution. The reasoning behind reversing the order of addition of reagents was that this would allow the acid chloride compound to be in excess of other reagents throughout the addition; the triethylamine (1.5 equivalents and still added to the hydrazide solution) would react with the acid chloride first because of its greater nucleophilicity than the hydrazide, causing the ammonium chloride salt 69 to form. The hydrazide would then react with the salt (69) remaining in solution and with other acid chloride molecules.

$^1$H NMR analysis revealed an improved ratio of tricarbonyl product to phenol byproduct of 4:1. This represented a significant improvement over the previous attempt to synthesize the same compound, as well as Schmidt’s synthesis of the compound. In conclusion, reversing the order of reaction to add the nucleophile to the electrophile showed potential to improve efficiency, possibly in synthesis of all three targets that Schmidt had synthesized, but was not probed further due to time constraints.
2.2 Synthesis of new 1,3,4-thiadiazole thioester liquid crystals

Figure 2.4 Synthesis of 1,3,4-thiadiazole-2-carboxylate thioester targets (73a-c)

The late-stage cyclization strategy optimized in the previous section was then applied to the synthesis of 1,3,4-thiadiazole-2-carboxylate thioesters 73a-c (Figure 2.4). Wallace\textsuperscript{37} had attempted to synthesize the octyl, nonyl, and decyl thioesters (Figure 1.26, 62a-c) using the carboxylate salt 60, with limited success. The nonyl thioester was synthesized in 31\% yield (1 step), but he was unable to synthesize the octyl and decyl thioesters.

Synthesis of acid chloride thioester compounds similar to those presented here (71a-c) has been reported\textsuperscript{46} (Figure 2.5) by allowing thiols and oxalyl chloride to react at room temperature in dichloromethane. However, this work represents the first use of a neat reaction to synthesize these compounds. Consistent with the method described previously for the formation of aryl ester adducts (section 2.1.1), commercially available thiols 70a-c were refluxed in oxalyl chloride overnight under argon. The excess of oxalyl chloride was also removed by the same method as described previously to afford the corresponding acyl chlorides 71a-c. \textsuperscript{1}H NMR analysis of the octyl acyl chloride
confirmed that the product 71a was synthetically pure as was observed at this point with the aryl acyl chloride 65a. These compounds were then allowed to react under anhydrous conditions (in THF, 1.5 equivalents of triethylamine) with 4-octyloxybenzohydrazide to afford the tricarbonyl compounds 72a-c. The acyl chloride solution was added dropwise to the hydrazide solution (with ice bath cooling) despite the superior result obtained previously with a reverse addition approach so that a comparison could be made to the synthesis of the aryl esters, specifically the formation of byproducts. However, the crude tricarbonyl compounds 72a-c were nearly pure (not all solvent was removed, and a small amount of triethyl ammonium chloride was present by $^1$H NMR analysis), with no evidence of any alcohol or thiol byproducts. This led to the conclusion that, surprisingly, the aryl ester functional group in 64 or 65 is a significantly more labile functional group than the corresponding thioester moiety under the conditions employed.

![Figure 2.5 Synthesis of acid chloride thioester compounds (Togo46)](image)

The tricarbonyl products 72a-c were cyclized without further purification. Due to the fact they were cleaner than any of the corresponding aryloxy tricarbonyl compounds 64, which still underwent cyclization with good efficiency, there was reason to believe that similar efficiency would be observed during cyclization of compounds 72a-c. This was indeed found to be true; compounds 72a-c were refluxed in toluene overnight in the
presence of Lawesson’s reagent (0.6 equivalents), affording complete cyclization to 1,3,4-thiadiazoles 73a-c. Crude compound 73a was simply recrystallized from ethanol once to afford synthetically pure material in very good yield (73%, 1 step; 3 step yield from 70a-c was estimated to be ~65%). A second recrystallization from ethanol afforded mesogenically pure material. Compound 73b was first purified with a silica plug to remove most of the byproducts derived from Lawesson’s reagent, and then recrystallized from 1-propanol to afford mesogenically pure material in very good yield (65%, 3 steps). Compound 73c was similarly purified with a silica plug and recrystallized from 1-propanol to afford mesogenically pure material in very good yield (71%, 3 steps).

The late-stage Lawesson’s cyclization strategy has been proven to offer an efficient and remarkably experimentally facile approach to the synthesis of 1,3,4-thiadiazole-2-carboxylate thioesters. The previously developed synthetically demanding protocol gave thioester 73b in very low yield, and failed to afford compounds 73a and 73c. In contrast, the late-stage cyclization strategy gave the 1,3,4-thiadiazole thioesters 73a-c in high yield (65-79% over 3 steps). Further studies and optimization of the synthesis of aryl thioesters 63a-c still offers potential for improved yields, but overall the late-stage cyclization strategy offers in general the most effective route towards 1,3,4-thiadiazole-2-carboxylate esters.
2.3 Liquid crystalline properties

![Chemical structure]

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Figure 2.6 Transition temperatures (in °C) of the target 1,3,4-thiadiazole-2-carboxylate thioesters 73. The symbol “•” indicates the existence of the corresponding phase (upon melting), while the symbol “--” indicates the absence of the corresponding phase.

Figure 2.6 summarizes the transition temperatures and phase behavior of the target 1,3,4-thiadiazole-2-carboxylate esters 73. As anticipated, the materials exhibit wide SmC phases (~80°C wide ranges). These results are consistent with the expected results based on the phase behavior observed with the previously synthesized 1,3,4-thiadiazole carboxylate thioester 62b. The high melting points present an obstacle in display applications, but selective structural modifications could lower these temperatures, and the materials could be incorporated as single components to modify the properties of liquid crystal mixtures.

Figure 2.7 shows the transition temperatures of the analogous 1,3,4-thidiazole-2-carboxylate ester compounds 58d-e. Surprisingly, the thioester compounds display more stable and vastly broader SmC temperature ranges. It is uncertain how a single atom change causes such a significant difference in phase behavior of the compound. Certain
factors such as atomic size difference between the oxygen and sulfur atoms, resonance contribution differences between oxygen and sulfur towards the carbonyl group which could affect rigidity and rotations of the ester/thioester linkage, and differences of bond angle between the ester and thioester groups which would affect the bend angle of the whole molecule, work together to offer some explanations of the observed phenomenon.

Figure 2.7 Transition temperatures (in °C) of 1,3,4-thiadiazole-2-carboxylate esters 58a-b. The symbol “•” indicates the existence of the phase, while the symbol “--” indicates the absence of the phase. Parentheses “()” indicate the phase exists upon cooling.

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</table>

2.4 Future work

The simplest future work is to revisit the synthesis of 1,3,4-thiadiazole-2-carboxylate esters 74 (see Figure 2.8). Although these compounds can be potentially synthesized with good efficiency using the previously established route, the late-stage Lawesson’s cyclization still possesses the merits of experimental ease and reproducibility. Other possible targets are the 1,3,4-thiadiazole-2-carboxylate aryl thioester compound 75, which could be directly compared to the corresponding aryl esters 63a-c discussed in this work, both in their chemistry and physical behavior.
Figure 2.8 Potential future directions for the late-stage Lawesson's cyclization strategy
CHAPTER 3. EXPERIMENTAL

3.1 General Considerations

Solvents

*Tetrahydrofuran*. THF was dried by refluxing over sodium metal under argon as an inert atmosphere and benzophenone as an indicator.

*Toluene*. Toluene was dried by refluxing over sodium metal under argon as an inert atmosphere and benzophenone as an indicator.

*Triethylamine*. TEA was dried by refluxing over calcium hydride under argon as an inert atmosphere.

*Petroleum ether*. Petroleum ether was distilled from commercially available material and stored in amber containers.

Material Analysis

*$^1$H NMR spectra*. Spectra were obtained using a 400 MHz Bruker Avance 400 MHz spectrometer running Topspin version 2.1 software and with TMS as an internal standard.

*Thin layer chromatographic analysis*. TLC analysis was performed using aluminum backed silica gel plates (Sigma-Aldrich), 200 µm layer thickness, 2-25 µm particle size, 60 Å pore size, and were examined under UV light.

*Column chromatography*. Column chromatography was carried out using Fisher Scientific silica gel (Davisil™, 170-400 Mesh, Type 60A, Grade 1740).

*Optical microscopy*. Transition temperatures of the final products were measured using a Mettler FP82HT hot-stage and FP90 control unit in conjunction with a Leica Laborlux 12PoIS polarizing microscope.
Differential scanning calorimetry. DSC measurements were performed using a TA Instruments Differential Scanning Calorimeter 2920 at heating and cooling rates of 5 °C per minute with indium as internal standard.

3.2 Experimental details and schemes

Figure 3.1 Synthesis of 1,3,4-thiadiazole-2-carboxylate aryl ester

4-Octyloxyphenoxalyl chloride (65a)

Under argon, oxalyl chloride (10.0 mL, d = 1.5 g/mL at 20 °C, 118 mmol) was placed into an oven-dried, argon-cooled round bottom flask. While stirring, 4-octyloxyphenol (0.5072 g, 2.281 mmol) was added to the flask at room temperature and in a single portion. A reddish orange solution immediately formed. The solution was brought to reflux and allowed to react overnight. The next day (approx. 24 hours) the
solution had become a pale yellow color and the flask was removed from the heat. After cooling it was transferred as quickly and safely as possible to a rotary evaporator to minimize the time exposed to the air (any time the flask was being transported, a septum was used to cover it). The excess of oxalyl chloride was removed \textit{in vacuo} and the flask placed back under argon. The product solidified after several minutes, then was dissolved in anhydrous toluene (10.0 mL), which was then removed \textit{in vacuo} to ensure the removal of the rest of the oxalyl chloride. A waxy solid formed and the flask was placed back under argon, and used in the next step without purification (mass was not recorded).

\begin{align*}
\text{1-}(4\text{-Octyloxyphenoxalyl})-2\text{-}(4\text{-octyloxybenzoyl})\text{diazane (64a)}
\end{align*}

\begin{align*}
\text{4-Octyloxybenzohydrazide (0.6203 g, 2.346 mmol) was placed into an oven-dried, argon-cooled round bottom flask. Anhydrous THF (40.0 mL) was added with stirring, and anhydrous triethylamine (0.45 mL, d = 0.726 g/mL at 25 °C, 3.2 mmol) was added in a single portion at room temperature. A second solution was prepared by dissolving 4-octyloxyphenyl oxalyl chloride in anhydrous THF (20 mL) with stirring. Under argon, the solution of acid chloride in THF was added dropwise (room temperature) to the flask over a period of approximately twenty minutes. Immediately upon addition, a white precipitate formed. The reaction was allowed to continue with}
\end{align*}
stirring for an additional fifty-five minutes. The ammonium chloride salt was filtered off and the solvent was removed \textit{in vacuo} leaving a waxy yellow solid (0.45g). $^1\text{H}$ NMR analysis showed a product:phenol byproduct ratio of 2:1. The product was used in the next step without purification.

*4-Octyloxyphenyl 5-(4-octyloxyphenyl)-1,3,4-thiadiazole-2-carboxylate (63a)*

4-Octyloxyphenyl ($N$'- (4-octyloxyphenylcarbonyl)hydrazinecarbonyl)formate was dried in a vacuum desiccator overnight (P$_2$O$_5$, wax shavings). It (0.4171 g, 0.7714 mmol) was placed into an oven dried, argon cooled evaporating flask. With stirring, anhydrous toluene (50 mL) was added at room temperature. Lawesson’s reagent (0.1857 g, 0.4591 mmol) was then added at room temperature in a single portion and the mixture brought to reflux. The solid was observed to slowly dissolve over the length of the reaction. After 70 minutes, an aliquot was removed and analyzed by $^1\text{H}$ NMR, showing the reaction was complete. The reaction mixture was allowed to cool to room temperature and the solvent was removed \textit{in vacuo} and the resulting solid was dried with air overnight. $^1\text{H}$ NMR analysis showed the product to be the major component but further purification was needed. The material was purified by column chromatography (silica gel: 10% EtOAc in petroleum ether, wet loaded in CH$_2$Cl$_2$) to give three fractions. By $^1\text{H}$ NMR analysis, fraction A (0.11 g) was synthetically pure, while fraction B (0.11 g)
contained a significant amount of phenol byproduct. Another spot was present near the baseline of fraction B and C but was not visible by $^1$H NMR analysis.

A solvent system of 9% acetone, 6% dichloromethane and 85% petroleum ether was determined by TLC to offer better separation of the product from the phenol byproduct than the 10% EtOAc in petroleum ether used, but a column was not run with this eluent system. The approximate yield of material (adjusted for fraction B using $^1$H NMR integration) was 14% (3 steps). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.90 (t, 6H, $J = 7.2$ Hz), 1.22-1.42 (m, 16H), 1.42-1.53 (m, 4H), 1.74-1.88 (m, 4H), 3.97 (t, 2H, $J = 6.6$ Hz), 4.04 (t, 2H $J = 6.4$ Hz), 6.94 (d, 2H, $J = 8.8$ Hz), 7.01 (d, 2H, $J = 9.2$ Hz), 7.20 (d, 2H, $J = 9.2$ Hz), 8.00 (d, 2H, $J = 8.8$ Hz).
4-Benzyloxyphenol (12.089g, 60.376 mmol), potassium carbonate (16.57g, 119.9 mmol), and 1-bromooctane (10.38mL, d = 1.118 g/mL at 25 °C, 60.09 mmol) were placed in a 1000 mL round bottom flask. 2-Butanone (240 mL) was added with stirring, and the mixture was brought to reflux and allowed to react overnight (approximately 18 hours). The next day the solution was allowed to cool to room temperature. The reaction was determined to be complete by TLC. The potassium salts were then filtered off using vacuum filtration and the filtrate was successively washed with aqueous NaOH (1 M, 2 x 300 mL) and deionized water (2 x 300 mL). The final two washes with water resulted in emulsions, which were resolved by adding a small volume of brine. The combined organic washings were dried over magnesium sulfate, and the MgSO₄ was filtered off and the solvent removed in vacuo. After drying with an air stream for approximately one hour, ¹H NMR analysis revealed that the product showed no significant impurities (15.86g, 84% yield). The solid was then recrystallized from petroleum ether and dried in a vacuum desiccator overnight with P₂O₅ and wax shavings (9.35g, 50%), leaving a white solid. ¹H NMR (400 MHz, CDCl₃): δ 0.89 (t, 3H, J = 7.2 Hz), 1.20-1.39 (m, 8H), 1.39-1.50 (m, 2H), 1.75 (quint, 2H, J = 8.0 Hz), 3.90 (t, 2H, J = 6.4 Hz), 5.01 (s, 2H), 6.82 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 9.2 Hz), 7.28-7.46 (m, 5H).
**4-Octyloxyphenol (66a)**

![Chemical Reaction](image)

1-Benzyl-4-octyloxybenzene (6.042g, 19.34 mmol) was placed into a round bottom flask. Ethyl acetate and ethanol (140 mL, 1:1) were added to the flask, and palladium-on-carbon catalyst (10% w/w wet Degussa type; 0.429g) was added in a single portion with stirring. The flask was attached to a hydrogenation apparatus, degassed under house vacuum for 20 minutes, and placed under hydrogen gas overnight (saturated copper sulfate column). The next day the solution was filtered through celite and the solvent removed *in vacuo*, leaving a brown solid. The crude material was then recrystallized from petroleum ether and placed in a vacuum desiccator overnight (P₂O₅, wax shavings), leaving a white solid (3.96 g, 92% yield). ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.22-1.39 (m, 8H), 1.49-1.59 (m, 2H), 1.75 (quint, 2H, $J = 7.1$ Hz), 3.89 (t, 2H, $J = 6.6$ Hz), 4.46 (s, 1H), 6.75 (d, 2H, $J = 9.2$ Hz), 6.78 (d, 2H, $J = 9.2$ Hz).

**4-Octyloxyphenoxyal chloride (65a)**

![Chemical Reaction](image)

Oxalyl chloride (10 mL, d = 1.5 g/mL at 20 °C, 118 mmol) was added to an oven-dried, argon-cooled round bottom flask. 4-Octyloxyphenol was added in a single portion
with stirring, and a reddish orange solution formed immediately. The solution was brought to a gentle reflux. Two hours after the beginning of reflux, the heat was removed and the solution allowed to cool until reflux was no longer observed. An aliquot was taken and placed directly into an NMR tube and a sample for analysis was prepared (NMR tube and Pasteur pipette used were oven dried and cooled in a large 3 neck flask that was purged with argon; CDCl$_3$ used to prepare the sample had been dried over activated molecular sieves for 24 hours; a needle was used to purge the NMR tube with argon after the sample was prepared). $^1$H NMR analysis showed a product to starting material ratio of 1:1.3. Reflux was resumed and after an additional 5 hours, another aliquot was analyzed by the same method as previously described. $^1$H NMR analysis showed a product to starting material ratio of 1:0.35. Due to time constraints, reflux was not resumed but the solution was kept under argon and not stirred during this time. 48 hours later, the solution was observed to have changed from a slightly orange to a yellow color. It was gently refluxed for 2 hours and $^1$H NMR analysis (anhydrous sample preparation conditions as before) showed the reaction was complete, with synthetically pure product (aside from the presence of oxalyl chloride solvent, not visible by $^1$H NMR analysis). The excess of oxalyl chloride was removed in vacuo, leaving a yellow oil. This product was then dissolved in anhydrous toluene (10 mL) with stirring (10 minutes), and the toluene was removed in vacuo to ensure the complete removal of oxalyl chloride. $^1$H NMR showed synthetically pure product. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.89 (t, 3H, $J = 6.8$ Hz), 1.23-1.40 (m, 8H), 1.47 (quint, 2H, $J = 7.2$ Hz), 1.79 (quint, 2H, $J = 7.0$ Hz), 3.95 (t, 2H, $J = 6.8$ Hz), 6.92 (d, 2H, $J = 9.2$ Hz), 7.14 (d, 2H, $J = 9.2$ Hz).
4-Octyloxyphenyloxalyl chloride (0.40 g, 1.3 mmol) was placed into an oven-dried, argon-cooled round bottom flask. Anhydrous THF (16 mL) was added with stirring in one portion at room temperature. 4-Octyloxybenzohydrazide (0.323 g, 1.22 mmol) was added to a separate round bottom flask (oven-dried, argon-cooled), and anhydrous THF (24 mL) was added in one portion at room temperature with stirring. Anhydrous triethylamine (0.35 mL, d = 0.726 g/mL at 25 °C, 2.5 mmol) was then added in a single portion. The hydrazide solution was added to the acid chloride solution dropwise at room temperature under argon over a period of 20 minutes, then allowed to stir for an additional 40 minutes. The resulting ammonium chloride salt was removed (vacuum filtration) and the solvent removed in vacuo, leaving a yellow waxy solid (mass not recorded). $^1$H NMR analysis showed a product:phenol byproduct ratio of 4:1. Triethylammonium chloride was also present as an impurity.
S-Octyl 5-(4-octyloxyphenyl)-1,3,4-thiadazole-2-carboxylate (73a)

Oxalyl chloride (11.0 mL, d = 1.5 g/mL at 20 °C, 130 mmol) was placed into an argon-cooled, oven-dried round bottom flask. 1-Octanethiol (0.68 mL, d = 0.843 g/mL at 25°C, 3.9 mmol) was added in a single portion at room temperature (syringe/septum) with stirring. The solution was brought to reflux and allowed to react overnight. The reaction mixture was allowed to cool to room temperature and the excess of oxalyl chloride was then removed in vacuo, leaving a pale yellow oil. The product was then
dissolved in anhydrous toluene (10 mL) and stirred for approximately ten minutes. The
toluene was removed *in vacuo*, leaving a yellow oil, which was used in the next step
without purification.

4-Octyloxybenzohydrazide (1.035g, 3.92 mmol) was added to an oven-dried,
argon-cooled round bottom flask. Anhydrous THF (45 mL) was added to the flask with
stirring, in a single portion at room temperature. Triethylamine (0.84 mL, d = 0.726 g/mL
at 25 °C, 6.0 mmol) was added to the flask in a single portion at room temperature.
Anhydrous THF (25 mL) was added to the flask containing the oxalyl chloride derivative
at room temperature. This solution was then added dropwise to the hydrazide solution
over a period of approximately 25 minutes. An ice bath was used during addition (0.5 to
2.0 °C). The reaction was then allowed to continue for an additional 60 minutes. The
resulting ammonium salts were removed using vacuum filtration, and the solvent
removed *in vacuo*, leaving a pale yellow solid. The product was stored under house
vacuum overnight, and turned off-white when dry. 1H NMR analysis showed the only
major impurity to be triethylammonium chloride.

The crude tricarbonyl product was then placed into an oven-dried, argon-cooled
round bottom flask. Anhydrous toluene was added (70 mL) with stirring. Lawesson’s
Reagent (0.255 g, 0.630 mmol) was added in a single portion, and the solution was
brought to reflux and allowed to react overnight. The next day, the reaction mixture was
allowed to cool to room temperature and the solvent was removed *in vacuo*, leaving a pale
yellow waxy product. The product was then recrystallized from ethanol leaving a pale
yellow solid. A single clump of an insoluble impurity had been observed in the previous
recrystallization. The material was dissolved in boiling ethanol, the impurity removed with a spatula, and recrystallization allowed. $^1$H NMR analysis showed very pure product (0.52 g, 73% one-step yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.885 (t, 3H, $J = 6.8$ Hz), 0.892 (t, 3H, $J = 6.8$ Hz), 1.23-1.40 (m, 16H), 1.40-1.53 (m, 4H), 1.72 (quint, 2H, $J = 7.6$ Hz), 1.82 (quint, 2H, $J = 6.8$ Hz), 3.12 (t, 2H, $J = 7.6$ Hz), 4.03 (t, 2H, $J = 6.4$ Hz), 6.99 (d, 2H, $J = 8.8$ Hz), 7.96 (d, 2H, $J = 8.8$ Hz).

S-Decyl 5-(4-octyloxyphenyl)-1,3,4-thiadiazole-2-carboxylate (73b)

Oxalyl chloride (10.0 mL, $d = 1.5$ g/mL at 20 °C, 120 mmol) was placed into a 100 mL argon-cooled, oven-dried round bottom flask. 1-Decanethiol (0.60 mL, $d = 0.845$ g/mL at 25°C, 2.9 mmol) was added in a single portion at room temperature (syringe/septum) with stirring. The solution was brought to reflux and allowed to react overnight. The excess of oxalyl chloride was then removed in vacuo, leaving a pale yellow oil. The product was then dissolved in anhydrous toluene (10 mL). The toluene was then removed in vacuo, leaving a yellow oil (0.761g), which was used without purification.
4-Octyloxybenzohydrazide (0.774 g, 2.93 mmol) was added to an oven-dried, argon-cooled round bottom flask. Anhydrous THF (45 mL) was added to the flask in a single portion at room temperature. Triethylamine (0.65 mL, d = 0.726 g/mL at 25 °C, 4.7 mmol) was added to the flask in a single portion at room temperature. Anhydrous THF (25 mL) was then added in a single portion at room temperature to the flask containing the oxalyl chloride derivative. This solution was then added dropwise to the hydrazide solution over a period of approximately 25 minutes. An ice bath was used during addition (0.5 to 2.0 °C). The reaction was then allowed to continue for an additional 70 minutes (ice bath removed 20 minutes after addition). The resulting ammonium salts were removed using vacuum filtration, and the solvent removed in vacuo, leaving a pale yellow solid. The product was stored under house vacuum overnight, and turned off-white when dry. H NMR analysis showed the only major impurity to be triethylammonium salt. (Crude yield 1.53 g).

The crude tricarbonyl product was then dissolved in anhydrous toluene (140 mL) with stirring at room temperature. Lawesson’s Reagent (0.726 g, 1.79 mmol) was added in a single portion, and the solution brought to reflux and allowed to react overnight under argon. The next day, the reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo leaving a pale yellow waxy product. The product was then purified with a silica plug with dichloromethane as an eluent and recrystallized from propanol, leaving a pale yellow solid (0.93 g, 65% from decanethiol). ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 6.8 Hz), 1.22-1.40 (m, 20H),
1.40-1.52 (m, 4H), 1.72 (quint, 2H, \(J = 7.6\) Hz), 1.82 (quint, 2H, \(J = 6.8\) Hz), 3.12 (t, 2H, \(J = 7.2\) Hz), 4.03 (t, 2H, \(J = 6.8\) Hz), 6.99 (d, 2H, \(J = 9.2\) Hz), 7.96 (d, 2H, \(J = 8.8\) Hz).

\[ S{-}\text{Dodecyll 5-}(4\text{-octyloxyphenyl}){-}1,3,4\text{-thiadiazole-2-carboxylate (73c)} \]

Oxalyl chloride (10.0 mL, \(d = 1.5\) g/mL at 20 °C, 120 mmol) was placed into a 100 mL argon-cooled, oven-dried round bottom flask. 1-Dodecanethiol (0.60 mL, \(d = 0.845\) g/mL at 25°C, 2.5 mmol) was added in a single portion at room temperature with stirring (syringe/septum). The solution was brought to reflux and allowed to react overnight. The reaction mixture was allowed to cool to room temperature and the excess of oxalyl chloride was then removed \textit{in vacuo}, leaving a pale yellow oil. The product was then dissolved in anhydrous toluene (10 mL) and stirred for ten minutes. The toluene was then removed \textit{in vacuo}, leaving a yellow oil, which was used without purification.

4-Octyloxybenzohydrazide (0.670g, 2.53 mmol) was added to a 300 mL oven-dried, argon-cooled round bottom flask. Anhydrous THF (45 mL) was added to the flask in one portion at room temperature with stirring. Triethylamine (0.57 mL, \(d = 0.726\) g/mL at 25 °C, 4.1 mmol) was added to the flask in a single portion at room temperature. Anhydrous THF (25 mL) was then added to the flask containing the oxalyl chloride.
derivative. This solution was then added dropwise to the hydrazide solution over a period of approximately 25 minutes. An ice bath was used during the addition (0.5 to 2.0 °C). The reaction was then allowed to continue for an additional 45 minutes (ice bath removed 15 minutes after addition). The resulting ammonium salts were removed using vacuum filtration, and the solvent removed \textit{in vacuo}, leaving a pale yellow solid. The product was stored under house vacuum overnight, and turned off-white when dry. $^1$H NMR analysis showed the only major impurity to be triethylammonium chloride (Crude yield 1.53 g).

The crude tricarbonyl product was then dissolved in anhydrous toluene (140 mL) under argon with stirring at room temperature. Lawesson’s Reagent (0.482 g, 1.19 mmol) was added in a single portion, and the solution brought to reflux and allowed to react overnight. The next day, the reaction mixture was allowed to cool to room temperature and the solvent was removed \textit{in vacuo} leaving a pale yellow waxy product. The product was then purified with a silica plug using dichloromethane as an eluent. $^1$H NMR analysis showed some impurity, and recrystallization was attempted from petroleum ether but the material was too soluble. The petroleum ether was boiled off and the material recrystallized from 1-propanol, leaving a pale yellow solid (0.93 g, 72% from dodecanethiol). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.91 (t, 3H, $J = 6.8$ Hz), 0.92 (t, 3H, $J = 7.0$ Hz) 1.21-1.39 (m, 24H), 1.39-1.52 (m, 4H), 1.74 (quint, 2H, $J = 7.4$ Hz), 1.84 (quint, 2H $J = 6.6$ Hz), 3.15 (t, 2H, $J = 7.4$ Hz), 4.06 (t, 2H, $J = 6.6$ Hz), 7.01 (d, 2H, $J = 8.8$ Hz), 7.98 (d, 2H, $J = 8.8$ Hz).
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