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Proposed Route to Cyclopenta[c]thiophenes via Activated Methylene

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Proposed Route to Cyclopenta[*c*]thiophenes via Activated Methylene

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Proposed Route to Cyclopenta[*c*]thiophenes via Activated Methylene

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PROPOSED ROUTE TO CYCLOPENTA[C]THIOHENES

VIA ACTIVATED METHYLENE

Vineet V. Karambelkar August 2008 36 pages

Directed by: Dr. Chad A. Snyder

Department of Chemistry Western Kentucky University

The synthesis of cyclopenta[*c*]thiophenes has been sparsely reported in the literature owing to several difficulties involved in their synthesis. The present work involves the proposed synthesis of cyclopenta[*c*]thiophenes and their precursors using activated methylene. Cyclopenta[*c*]thiophene compounds show promise in the field of polymer and catalysis chemistry. These substituted polythiophenes are potential organic semiconductors and anti-tumor agents. The research presented shows the successful and novel conversion of 3,4-bis(chloromethyl)-2,5-dimethylthiophene and 3,4-bis(bromomethyl)-2,5-dimethylthiophene to a fused 5,5'-fused membered ring which is the precursor to cyclopenta[*c*]thiophene the sulfone ester, 5-carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene, in just two steps as compared to four steps previously reported in the literature. This valuable precursor intermediate currently made and proven by characterization is one synthetic step away from a substituted cyclopenta[*c*]thiophene.

A paper has been submitted to *Letters in Organic Chemistry* to report our work.

CHAPTER ONE

INTRODUCTION

Conductivity in Conventional Materials. Many types of materials have the ability to conduct electricity while others do not. The ability for a material to be conductive arises from its electrical properties, and can be grouped together into three categories, conductor, semiconductor and insulator. In the solid state, band theory explains these properties. The theory states that, the atomic orbitals of each atom overlap with the same orbitals, of their neighboring atoms in all directions, to produce molecular orbitals similar to those in small molecules.[1] Continuous energy bands result when there is a subsequent overlap in a given energy range. The band gap is defined as the energy gap between the highest occupied (valence band) and lowest unoccupied band (conduction band). If the band gap is small enough, then these materials possess electrical properties (e.g; electrical conduction) that are similar to metals. The original atomic orbitals depend on the relative energies and number of electrons these bands possess, (i.e., relative energy of the highest occupied and the lowest unoccupied bands and number of electrons).[1] Greater conductivity is the result of better or increased overlap of these bands. An insulator such as plastic can be described by a band that is empty and fully filled and do not permit conduction. The prerequisite for a conventional conductive material at room temperature is a band gap narrow enough to allow thermally excited electrons to migrate from the valence band to the conduction band. The sole basis of conductivity is this ability to move electrons, and in the process the material starts behaving like a semiconductor, as

depicted in (Figure **1.1**). Examples of semiconductors are silicon (Si), germanium (Ge) and gallium arsenide (GaAs). However, the material starts behaving like an insulator if the band gap is too large, and the valence electrons fail to migrate to the conduction band, as is depicted in the (Figure **1.1**). Conversely, highly conductive metals possess a zero band gap resulting a full valence band and empty conduction band (metal) or partially full valence band and empty conduction band, such as silver (Ag) and copper (Cu).

Conductive Polymer Background. As compared to metals, polymers or plastics generally behave in the opposite manner. In fact, to insulate people from electric shock, metal wiring is coated with insulating materials. While metals conduct electricity, these polymers should behave as insulators. Dr. Alan. J. Heeger, Dr. Alan.G. MacDiarmid, and Dr. Hideki Shirakawa discovered conductive polyethylene and thereby challenged the view of conducting polymers. Since they were discovered in 1977 by H. Shirakawa et al[2], conductive polymers have been extensively studied. Their discovery that charge transfer oxidative doping of polyacetylene could increase it's conductivity by 12 orders of magnitude is close to Shirakawa's work. Other groups however, have envisioned a new class of polymers that would have either a zero energy band gap (a single continuous band consisting of valence and conduction bands) or a very small band gap[3]. In an ideal situation, polymers possessing a single continuous band of overlapping valence and conduction bands should be conductive without the need for doping.

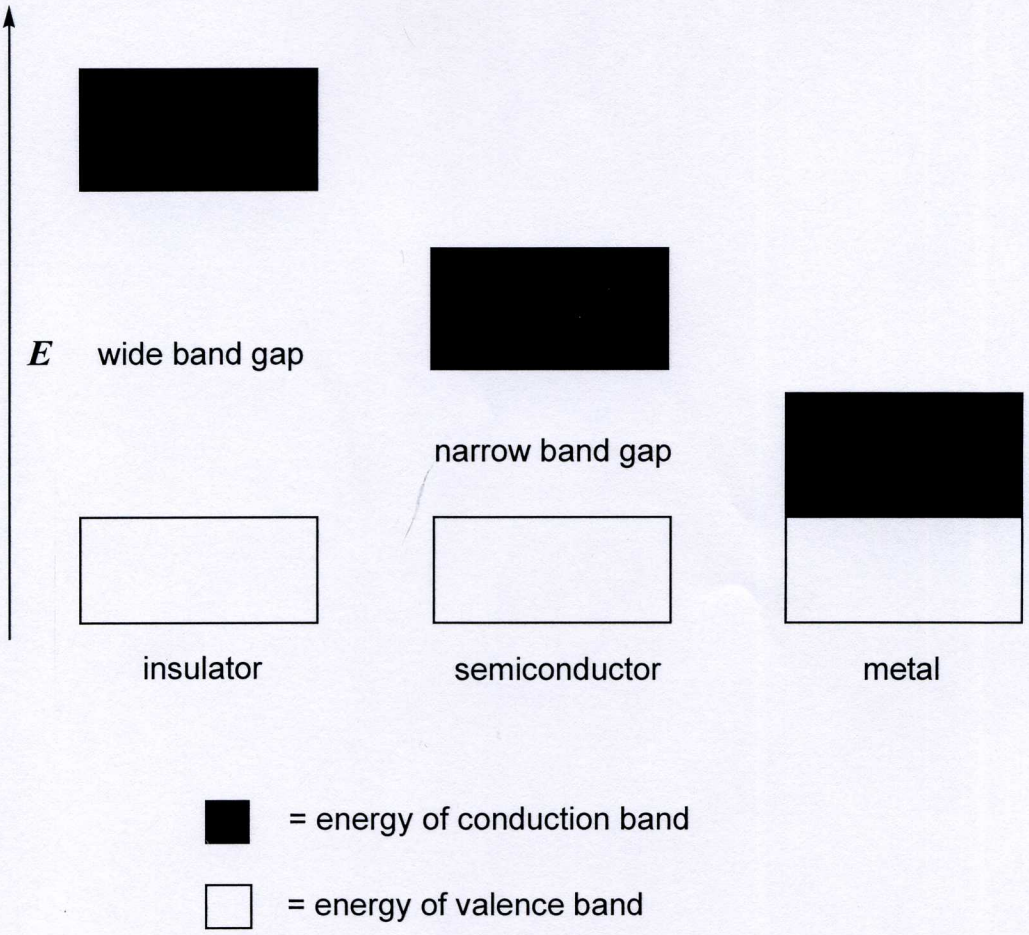


Figure 1.1. A molecular orbital illustration of an insulator, semiconductor, and conductor. [3]

Unless oxidized with chlorine, bromine, or iodine vapor,[3] polyacetylene is not conductive by itself ($10^{-15} - 10^{-14}$ S·m^{-1} with a band gap of 1.50- 1.7 eV)[4,5]. When doped, polyacetylene possesses a conductivity of 10^5 S·m^{-1}, as compared to silver (Ag) and copper (Cu) of 10^8 S·m^{-1}.

Polyacetylene is highly air-sensitive and oxidizes when exposed to molecular oxygen. However it is a promising organic electrical conductor. A commercial material requires O_2 and H_2O stability. In an effort to produce conductive polymers that are air-stable, tractable, and having a low band gap, a great deal of attention has been focused on heterocyclic aromatic polymers, such as polythiophene and polypyrrole. The positive charge of the p-doped polymers is stabilized by the lone pair of the heteroatoms[4]. This type of polymer is more resistant to O_2 and H_2O.

Owing to their synthetic ease[5] and myriad applications,[6-9] polythiophene (PT),[10,11] polypyrrole (PP)[5,12] and their derivatives (Figure 1.6) are the most reported polymers. PT and PP possess nondegenerate aromatic and quinoid states (Figure **1.2**). According to Brédas, as the contribution of the quinoidal structure increases, the band gap decreases.[13] Design of such systems as PT and PF would provide a source of new low band gap polymers.

Other advantages of PT's include environmental stability and structural versatility. A significant improvement in solubility is observed when PT's are alkylated to poly(3-alkylthiophenes) (PAT's) providing greater solubility in organic solvents. In order to make highly conjugated organic materials solution processable, it is necessary to introduce solubilizing groups. The thesis work presented herein focused on the synthesis of cyclopenta[*c*]thiophenes, a derivative of thiophene.

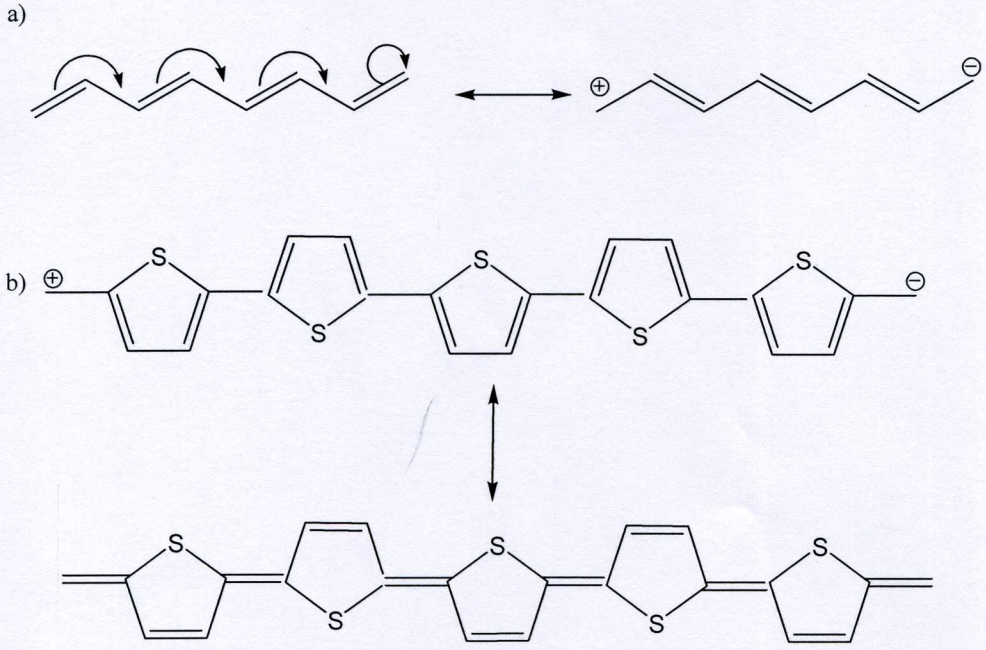


Figure 1.2. Examples of a (a) degenerate ground state configuration of polyacetylene and (b) nondegenerate ground sate configurations of polythiophene (top = aromatic form, bottom = quinoidal form).[13]

Cyclopenta[*c*]thiophenes, also known as thiapentalenes, are 5,5'-fused five membered ring compounds. They are natural terthienyl compounds and natural drug candidates for photodynamic destruction of the tumor cells[14]. They are also excellent potential conducting polymers.

The idea of synthesizing thiapentalenes was inspired by the previous work done by Palandoken and coworkers[20], who used an activated methylene to convert a dichloride to a 5,6-fused membered ring system. The research presented herein focuses on the synthesis of cyclopenta[*c*]thiophene that modeled Palandoken et al.

This route offers several benefits to the reported Wallace and Selegue 8-step Dieckmann route for thiapentalene synthesis. Their route suffers from many drawbacks including low yields, hazardous and corrosive chemicals and long, complex steps.

II. ATTEMPTED SYNTHESIS AND CHARACTERIZATION OF 1,3-DISUBSTITUTED CYCLOPENTA[C]THIOPHENE: ACTIVATED METHYLENE ROUTE

Introduction

Skramstad[16] first reported in 1969, the synthesis of 4*H*-cyclopenta[*c*]thiophene, also known as 2-thiapentalene (Figure 2.1.A) and its 1,3-dichloro derivative, 1,3-dichloro-4*H*-cyclopenta[*c*]thiophene (Figure 2.1.B).[16] 2-Thiapentalene (Figure 2.1.A) was prepared in a 9-step synthesis in their report. 2-Thiapentalene derivatives have also been reported in the literature. Wallace and Selegue[17] improved the synthesis of 1,3-dimethyl-4*H*-cyclopenta[*c*]thiophene (**9**, Scheme 2.1) in 1999, originally synthesized by Cantrell and Harrison (Scheme 2.2).[18] Bell and Snyder[19] showed that Wallace and Selegue's route[17] could be modified via Grignard chemistry to obtain thiapentalenes (Scheme 2.3). It has been well documented that a fused 5-membered ring to thiophene can bind to a redox active metal center. Complexes like these can be further oxidized or reduced. Unfortunately synthesizing cyclopenta[*c*]thiophenes or their organometallic complexes require long and tedious steps that often end in low yields. The problem has been concluded from 5,5'-fused ring strain that must be overcome.

The research goal presented in this thesis is to investigate cyclopenta[*c*]thiophene synthesis that require fewer steps than reported by Skramstad[16], Wallace and Selegue[17], and Bell and Snyder[19]. The idea came from a paper published by Palandoken and coworkers[20] where the authors converted a dichloride to an indan (5,6-fused ring system).

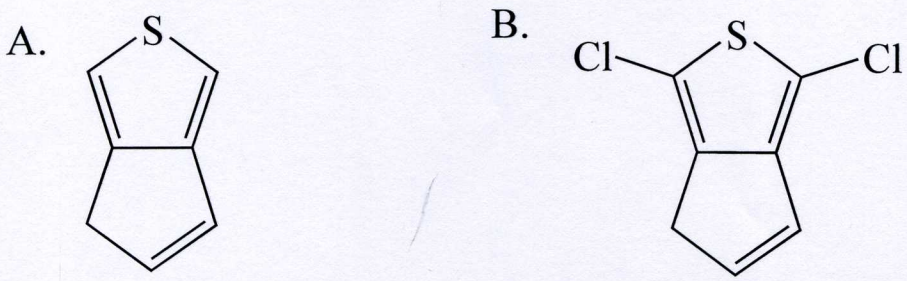
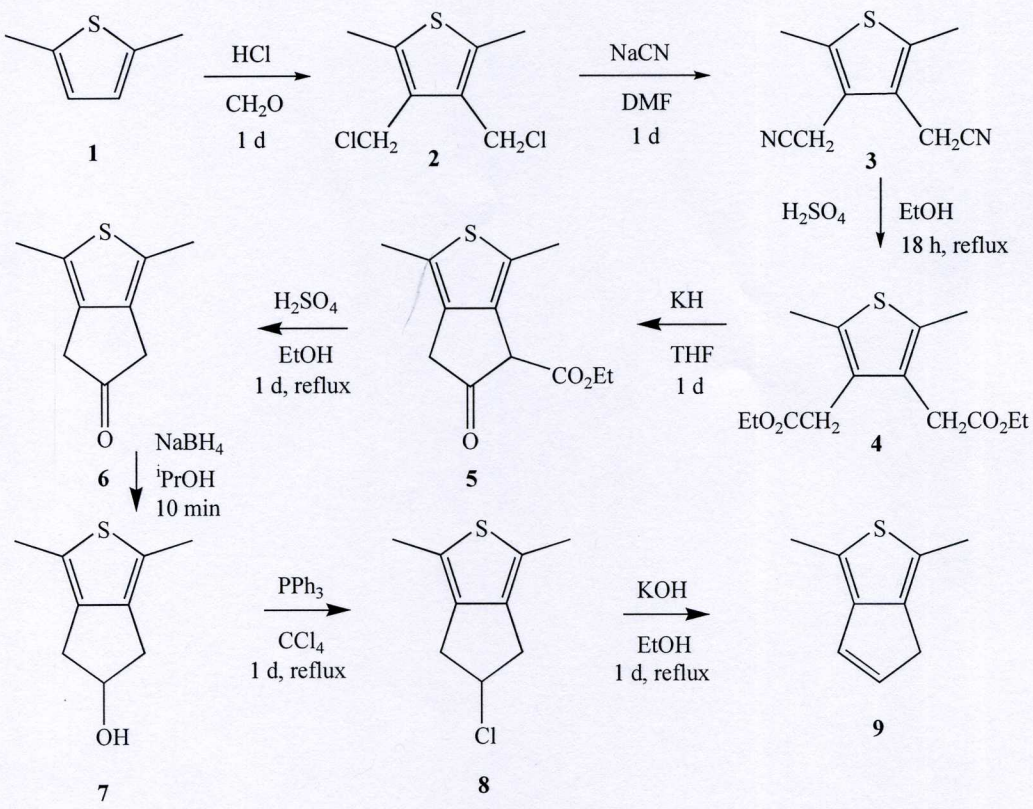
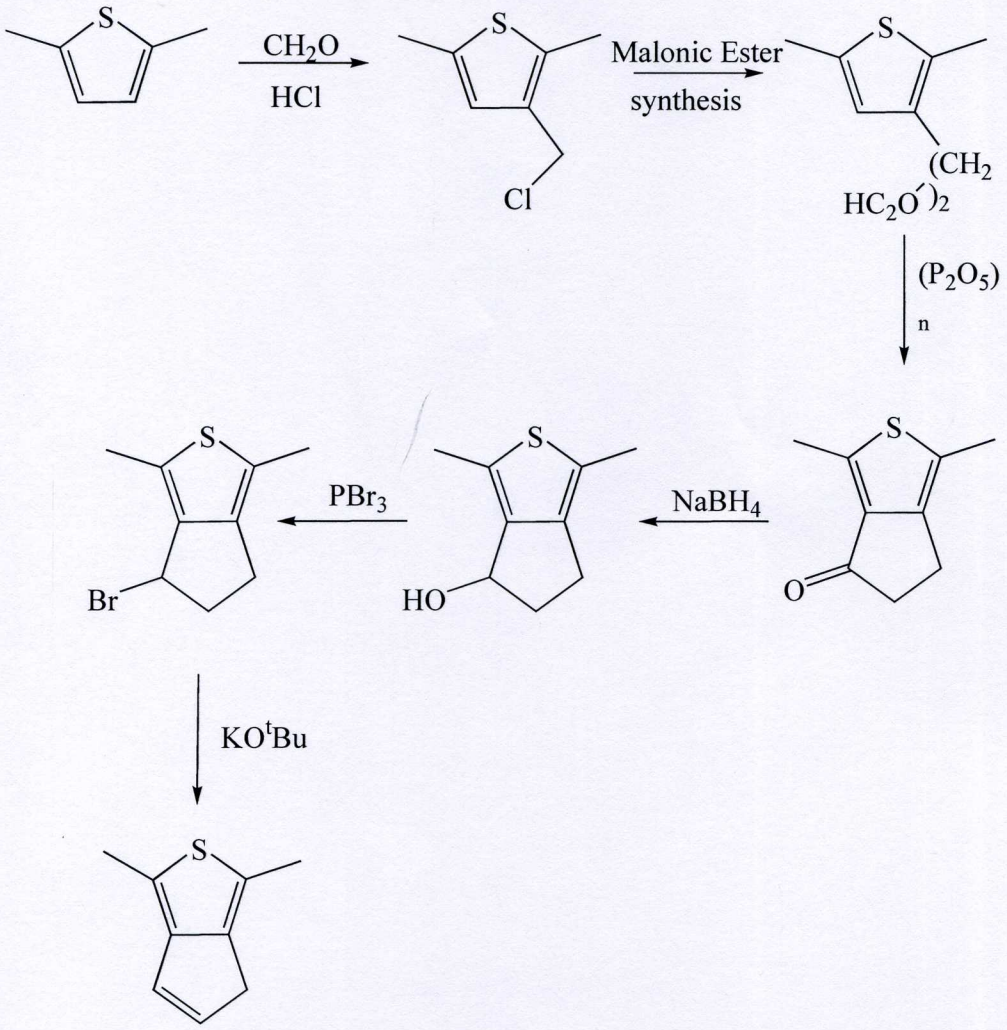


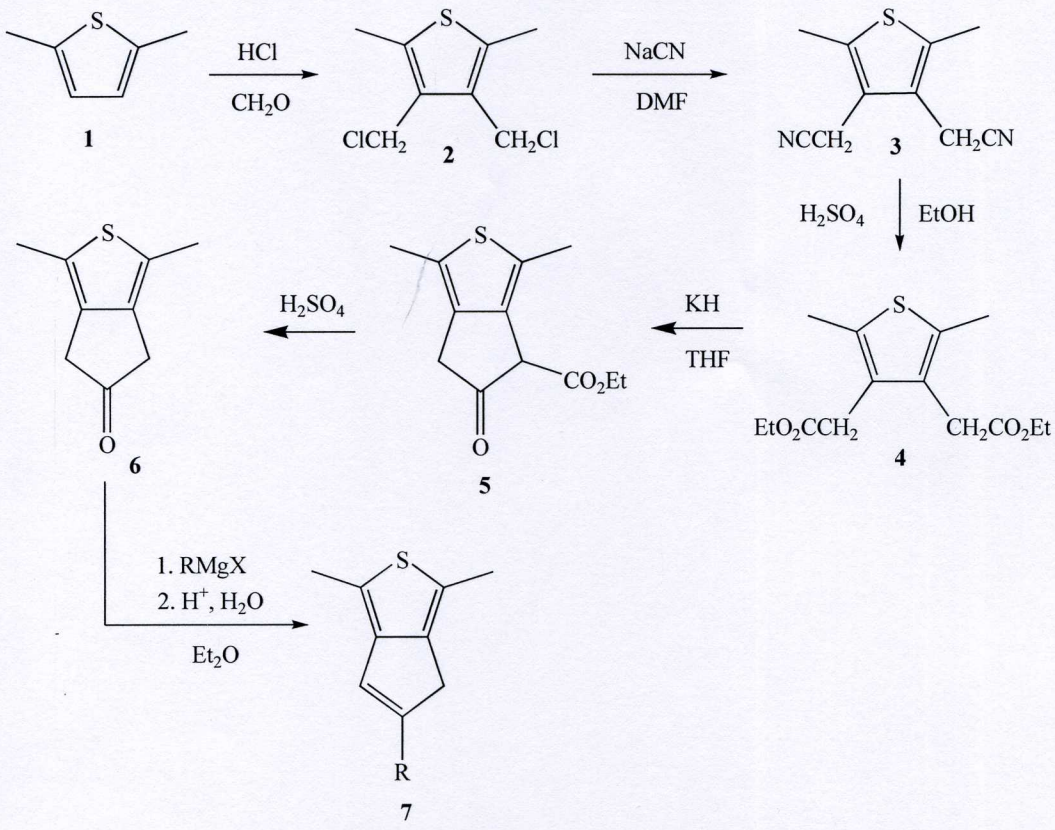
Figure 2.1. Structure of A. 2-thiapentalene and B. 1,3-dichloro-4*H*-cyclopenta[*c*]thiophene.[16]



Scheme 2.1. Wallace and Selegue route for synthesis of thiapentalenes.[17]

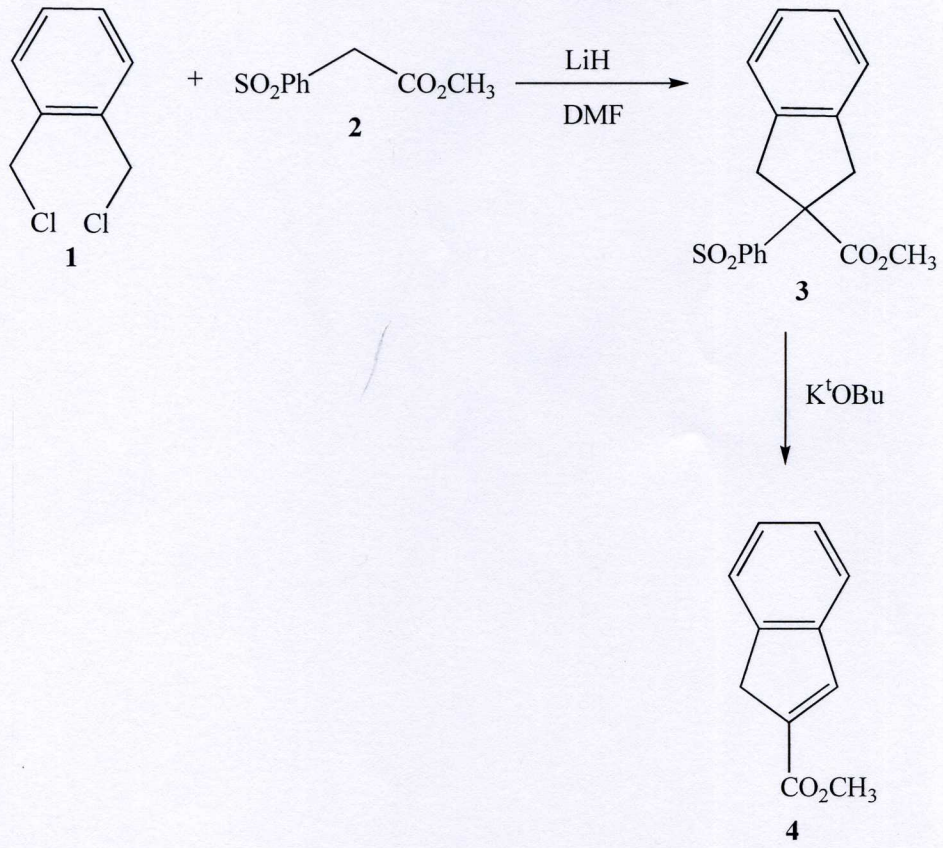


Scheme 2.2. Cantrell and Harrison synthesis of 2,5-dimethylcyclopenta[*c*]thiophene.[18]

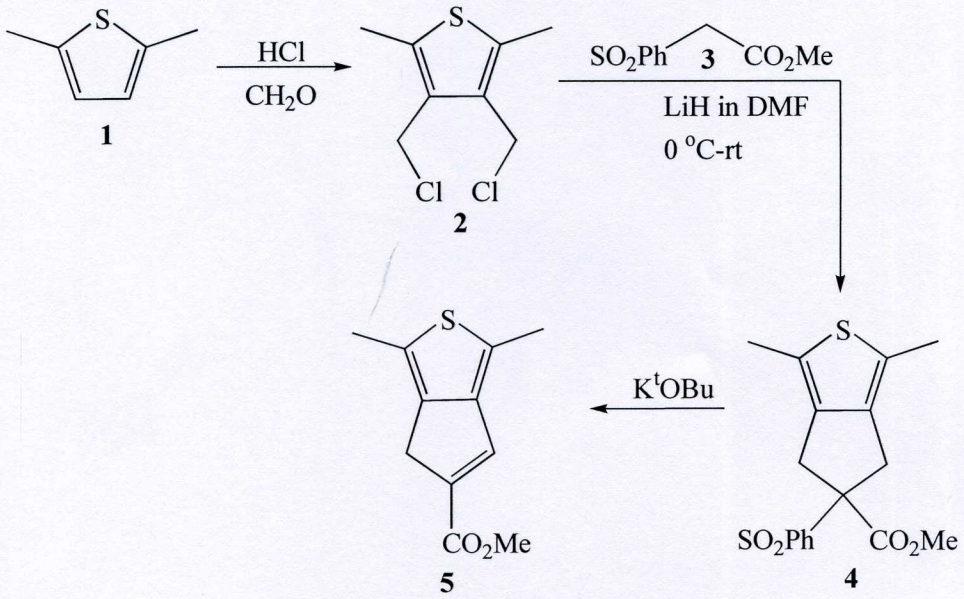


Scheme 2.3. Bell and Snyder Grignard route to substituted thiapentalenes.[19]

Their reaction involved 1,2-dialkylating bis(chloromethyl)benzene with methyl phenyl sulfonyl acetate in DMF to give 2-carbomethoxy-2-phenylsulfonylindan (Scheme **2.4**).



Scheme 2.4. 2-(Hydroxymethyl)indene synthesis from dichloride **1**.[20]



Scheme 2.5. Proposed 3-step route to substituted cyclopenta[*c*]thiophene (**5**) beginning with 2,5-dimethylthiophene (**1**).

III. EXPERIMENTAL

Reactions were carried out by using standard organic synthetic techniques under air unless otherwise noted. $CDCl_3$ was used without further purification. 2,5-Dimethylthiophene, 3,4-bis(chloromethyl)-2,5-dimethylthiophene and 3,4-bis(bromomethyl)-2,5-dimethylthiophene were prepared according to literature methods.[17,21] Aqueous formaldehyde (Eastman Chemicals), P_4S_{10}, (Aldrich), methyl phenyl sulfonyl acetate (Aldrich), LiH (Aldrich), and DMF (Acros Organics) were used without further purification. THF was dried over sodium benzophenone ketyl.

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer at ca. 22 ^0C and were referenced to residual solvent peaks. All ^{13}C NMR spectra listed are decoupled. Infrared spectra were recorded on an ATI-Mattson Galaxy^{TM} Series 5000 FTIR spectrometer. Melting points were taken on a standard Thermos-Hoover apparatus.

Preparation of 2,5–dimethylthiophene.

2,5-Dimethylthiophene (Scheme **1**, 2.1) was previously synthesized by Jean and Nord.[21] An improvement of their synthesis is reported here. A 250 ml Erlenmeyer flask was charged with P_4S_{10} (24.4 g, 0.133 mol). 2,5-Hexanedione (38.0 g, 0.333 mol) was added drop-wise by a pastuer pipette. After addition, the mixture was stirred at room temperature overnight. The mixture turned dark brown. After decanting and distillation (135 °C), a clear, colorless liquid was obtained (21.5 g, 0.244 mol, 73.0%).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ2.45 (s, 6H, Me), 6.51 (s, 2H, C*H*). **^{1}H NMR (200 MHz, $CDCl_3$, ppm)**: δ2.44 (s, 6H, Me), 6.55(s, 2H, C*H*).[33] **^{13}C NMR (125 MHz, $CDCl_3$, ppm):** δ15.4 (*C*H_3), 124.9, 137.6 (Ar).

Synthesis of 3,4-bis(chloromethyl)-2,5-dimethylthiophene.

Previously prepared 2,5-dimethylthiophene (10.0 g, 10.0 ml, 0.113 mol) was added to a solution consisting of conc. HCl (100 ml) and 37% aqueous formaldehyde solution (30.0 ml, 1.08 mol). This reaction mixture was stirred overnight at room temperature, turning bright blue-green, with a dark green solid precipitate. The dark green precipitate was dissolved in dichloromethane (200 ml) and added to the reaction mixture. The organic and the aqueous layer were separated using methylene chloride, CH_2Cl_2 (3x20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed by rotary evaporation yielding a pale yellow solid (17.4 g, 83.2 mmol, 93.0%). **^{1}H NMR (500 MHz, $CDCl_3$, ppm):** δ2.40 (s, 6H, Me), 4.75 (s, 4H, C*H*$_2$). **^{1}H NMR (200 MHz, $CDCl_3$, ppm)[17]:** δ2.38 (s, 6H, Me), 4.59 (s, 4H, C*H*$_2$). **^{13}C NMR (125 MHz, $CDCl_3$, ppm):** δ12.9 (*C*H_3), 37.4 (*C*H_2), 132.1, 136.1 (Ar).

Synthesis of 3,4-bis(bromomethyl)-2,5-dimethylthiophene.

To a solution of 48% HBr (100 mL) and 36.8% aqueous formaldehyde solution (27.4 mL 364 mmol) was added 2,5-dimethylthiophene (5.00 g, 5.10 mL, 44.6 mmol). The solution was stirred at 25 °C for 24 hours, turning green with a white solid precipitating. The crude mixture was extracted with dichloromethane (4 x 25 mL) and dried ($MgSO_4$). The combined organic extracts were reduced by rotary evaporation, yielding 3,4-bis(bromomethyl)-2,5-dimethylthiophene (6.98 g, 23.4 mmol) in 52.5%

yield. **^{1}H NMR (200 MHz, $CDCl_3$, ppm):** δ 2.35 (s, 3H, CH_3), 4.89 (s, 2H, CH_2). **^{13}C NMR (50 MHz, $CDCl_3$, ppm):** δ 12.8 (Me), 24.5 (*C*H_2Br), 131.9, 136.0 (Ar).

Synthesis of 5-carbomethoxy-5-phenylsulfonyl–1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene.

To a stirred solution of methyl phenyl sulfonyl acetate (0.90 g, 0.70 ml, 4.2 mmol) in DMF (35 ml) at 0 °C was added in one portion LiH (0.100 g, 12.5 mmol). After stirring 2 hours, 3,4-bis-(chloromethyl)-2,5-dimethylthiophene (1.0 g, 4.8 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction was recooled to 0 °C, after 48 hours, quenched by the careful addition of saturated NH_4Cl(aq), and then diluted with CH_2Cl_2 (30 ml) and water (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extract was washed with water, saturated brine, and dried ($MgSO_4$). The solvents were removed by rotary evaporation, to afford the crude product as an orange oil (76% crude). Methanol was added to the crude product and precipitated a white solid. The white solid was filtered and washed with cold methanol to yield 5-carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene. (4.00 mg, 2.38%). **M.p** = 88 °C- 92°C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 2.15 (s, 3H, C*H*$_3$), 3.31 (d, *J* = 16.6 Hz, 2H, C*H*$_2$), 3.31 (d, *J* = 16.6 Hz, 2H, C*H*$_2$), 3.71 (s, 3H, OC*H*$_3$), 7.51 (apparent t, *J* = 7.45 Hz, 2H), 7.64 (apparent t, *J* = 7.45 Hz, 1H), 7.79 (d, *J* = 8.05 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 13.2 (*C*H_3), 32.9 (*C*H_2), 83.9 (*C*CO_2Me), 53.8 (O*C*H_3), 126.5, 128.8, 129.8, 134.2, 136.4, 138.0 (*C*=*C*), 168.5 (*C*O). **IR (KBr, cm^{-1}): GCMS:** ***m/z*** 318 (M^+ – CH_4O), 290 (M^+ – CO, CH_4O), 152 (M^+ – SO_2PH, $C_2H_3O_2$).

Attempted synthesis of 5-carbomethoxy-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene.

To a solution of 5-carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene (100 mg, 0.285 mmol) was stirred for sometime and 20 ml THF was added to it while stirring. KO^tBu (1.05 g, 1.04 mmol, 1*M*, 1.05 ml) was cooled to -50 ^0C with liquid nitrogen and was added rapidly to the reaction mixture. When the addition was complete, the combined reaction mixture was stirred for 10 min. then quenched by the addition of saturated NH_4Cl. Dichloromethane was added to the solution and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic extract was washed with water (2 x 10 mL), saturated brine and dried with $MgSO_4$ The volatiles were removed using rotary evaporation to yield orange oil residue. ^1H NMR spectroscopy showed no indication of desired product.

IV. RESULTS AND DISCUSSION

2,5-Dimethylthiophene was previously synthesized by Jean and Nord[21]. Bell and Snyder[19] modified their procedure which was utilized for the reaction sequence presented in this thesis. Phosphorus pentasulfide was charged to an erlenmeyer flask and followed by careful drop-wise addition of 2,5-hexandione via Pasteur pipette. The reaction was allowed to sit for 48 hours giving 2,5-dimethylthiophene in 75% yield following distillation. ^{1}H and ^{13}C NMR analysis was performed on the product to verify its structure. The ^{1}H NMR spectra showed the expected two signals belonging to the methyl hydrogens (singlet, 2.44 ppm) and alkene proton (singlet, 6.55 ppm). The ^{13}C NMR spectra showed the expected three chemical shifts at δ 15.4 (CH_3), 129.7 and 137.6 (Ar).

3,4-Bis(chloromethyl)-2,5-dimethylthiophene was previously synthesized by Wallace and Selegue[17]. Bell and Snyder[19] modified their procedure which was utilized for the reaction sequence presented in this thesis. 2,5-Dimethylthiophene was added to a solution consisting of conc. HCl and 37% aqueous formaldehyde. The solution was allowed to stir at room temperature overnight, turned bright blue-green with a dark green solid precipitating out. The solid was extracted by adding dichloromethane, dried, using magnesium sulfate and purified through a silica plug to obtain a pale yellow solid. ^{1}H and ^{13}C NMR analysis was performed on the product to verify its structure. The ^{1}H NMR spectra showed the expected two signals belonging to the methyl

hydrogens (singlet, 2.40 ppm) and methylene protons (singlet, 4.75 ppm). The ^{13}C NMR spectra showed the expected four chemical shifts at δ 15.4 (CH_3), (CH_2), 129.7 and 137.6 (Ar).

3,4-Bis(bromomethyl)-2,5-dimethylthiophene was previously synthesized by Wallace and Selegue. Bell and Snyder modified their procedure which was utilized for the reaction sequence presented in this thesis. 2,5-Dimethylthiophene was added to a solution consisting of 48% conc. HBr and 37% aqueous formaldehyde. The solution was allowed to stir at room temperature overnight, turned green with a white solid precipitating out. The solid was extracted by adding dichloromethane, dried, and eluted through a silica plug to obtain a pale yellow solid. ^{1}H and ^{13}C NMR analysis was performed on the product to verify its structure. The ^{1}H NMR spectra showed the expected two signals belonging to the methyl hydrogens (singlet, 2.35 ppm) and methylene protons (singlet, 4.89 ppm). The ^{13}C NMR spectra showed the expected four chemical shifts at δ 12.8 (CH_3), 24.5 (CH_2), 131.9 and 136.0 (Ar).

Palandoken and coworkers[20] began with a six membered dichloride, α,α'-dichloro-*o*-xylene, and treated it with methyl phenylsulfonyl acetate (an activated methylene) in addition to LiH in DMF to provide 2-carbomethoxy-2-phenylsulfonylindan (**3**, Scheme **2.4**) in 81% yield. Purity was easily obtained from methanol recrystallization.

The dichloride 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**1**, Scheme **2.5**) is structurally and chemically similar to Palandoken and coworker's dichloride. This dichloride was treated under similar experimental conditions,

resulting in 5-carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene (**3**, Scheme **2.5**) in very low yield (2.38%) after purification.

It should be noted that the sulfone ester **3** had a much lower percent yield than Palandoken and coworker's[20] indan **3** (2.38% versus 81%, respectively). The difference in the percent yield most likely results from inherent difficulty in making 5,5-fused ring systems.[17,22] This is not uncommon as there have been several attempts to perform a 5,5'-fused synthesis with thiophene that resulted in no apparent product to low percent yields. The most recent reported was an attempt made using Meldrum's acid and 3,4-bis(chloromethyl)-2,5-dimethylthiophene[22].

5,5'-Fused ring synthesis is difficult and rarely reported in the literature. Meldrum's acid (**3**, isopropylidene malonate, 2,2-dimethyl-1,3-dioxane-4,6-dione, Figure **4.1**) was first reported by Meldrum in 1908.[23] It offers advantages over acyclic malonate esters in organic synthesis. The cyclic structure of Meldrum's acid leads to high acidity (pK_a = 4.97) of the malonate hydrogens, yet it's low steric profile makes it's anions very effective nucleophiles for C-alkylation and C,C-dialkylation[24].

A general synthesis of cyclopenta[3,4-c]thiophenes was attempted by dialkylating Meldrum's acid with 3,4-bis-(halomethyl)2,5-dimethylthiophenes (**1** & **2**) to give spiro compound (Scheme **4.1**). The idea for this reaction was taken from reacting *o*-xylene with Meldrum's acid that produced a 5,6-fused ring system (Scheme **4.2**).[25] However, when the authors treated Meldrum's acid

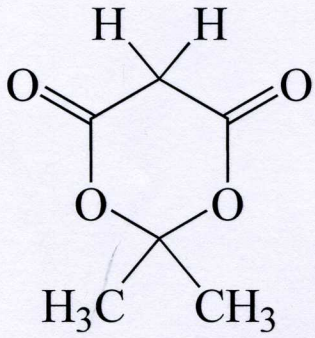
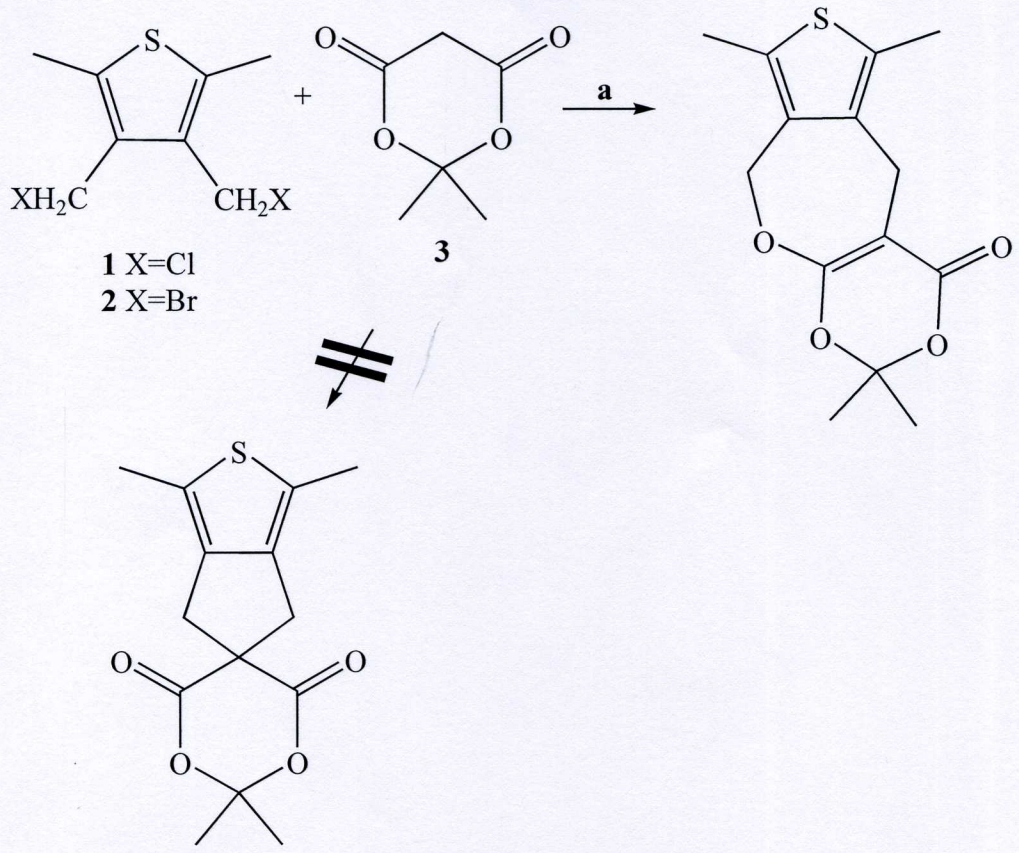
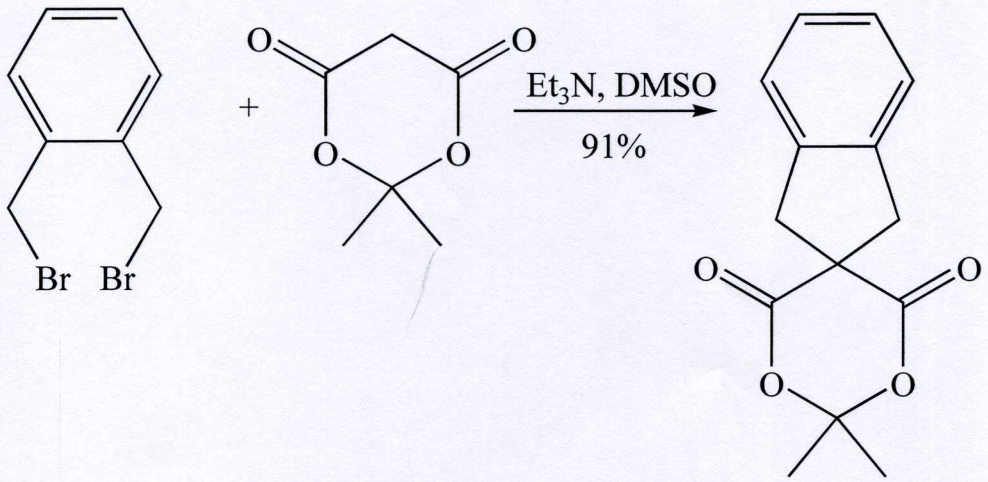


Figure 4.1 Structure of Meldrum's acid.



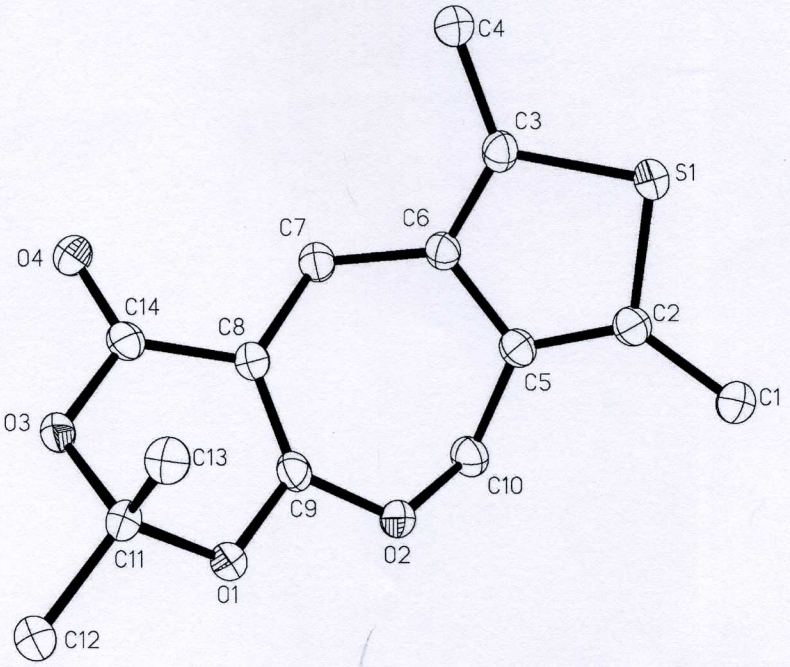
Scheme 4.1 Unusual C,O-dialkylation of Meldrum's acid.[22]



Scheme 4.2 Example of C,C-dialkylation using Meldrum's acid.[25]

with 3,4-bis(chloromethyl)-2,5-dimethylthiophene **1,** the kinetically favored C,O-dialkylation product, 1,3,7,7-tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one, was obtained (74% yield) instead of the desired saturated cyclopenta[*c*]thiophene. The structure (Figure **4.2**) for this unusual 5-7-6 fused ring system was verified by x-ray crystallography.

The sulfone ester (**3**, Scheme **2.5**, 5-carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene, was characterized by ^{1}H and ^{13}C NMR spectroscopy. It should be no surprise that the NMR results were very similar to Palandoken and coworker's reported indan spectra.[20] In the ^{1}H NMR spectra was observed a singlet (2.15 ppm) belonging to the substituted methyl groups attached to the thiophene ring. Two doublets (3.31 and 3.40 ppm, both J = 16.6 Hz) were observed belonging to both methylene groups. Palandoken and coworkers also reported two doublets (3.71 and 3.86 ppm, J = 14.7 and 16.8 Hz, respectively) for their methylene protons. Another singlet (3.71 ppm) was seen belonging to the methoxy group that closely matched the reported indan singlet (3.68 ppm). Finally, benzylic protons were observed as two apparent triplets (7.54 ppm, J = 7.45 Hz, 2H; 7.64 ppm, J = 7.45 Hz, 1H) and a doublet (7.79 ppm, J = 8.05 Hz, 2H). Palandoken and coworkers also reported two apparent triplets (7.54 ppm, J = 7.7 Hz, 2H; 7.68 ppm, J = 7.3 Hz, 1H) and a doublet (7.85 ppm, J = 7.5 Hz, 2H) corresponding to their benzylic protons. The ^{1}H NMR results were very satisfying supporting the sulfone ester structure. A comparison table is shown in Table **4.1.**



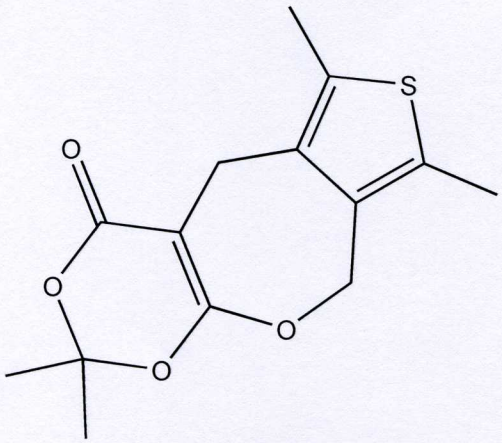
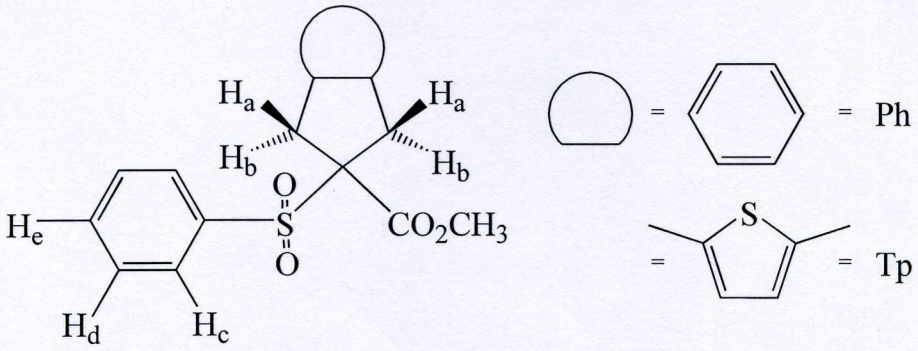


Figure 4.2 Molecular structure of 1,3,7,7-tetramethyl-4H,10H-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one. A drawing is included for clarity.[22]

Table 4.1. ^{1}H NMR Comparison of 5-Carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene (**3**, Scheme **2.5**) and 2-Carbomethoxy-2-phenylsulfonylindan (**3**, Scheme **2.4**).



System	Atom/Group	Chemical Shift (ppm)	Signal Pattern	*J* (Hz)
Tp	H_a	3.31	d	16.6
Tp	H_b	3.40	d	16.6
Tp	H_c	7.79	d	8.05
Tp	H_d	7.51	at	7.45
Tp	H_e	7.64	at	7.45
Tp	OCH_3	3.71	s	-
Ph	H_a	3.71	d	14.7
Ph	H_b	3.86	d	16.8
Ph	H_c	7.85	d	7.5
Ph	H_d	7.54	at	7.7
Ph	H_e	7.68	at	7.3
Ph	OCH_3	3.68	s	-

Solvent was $CDCl_3$.

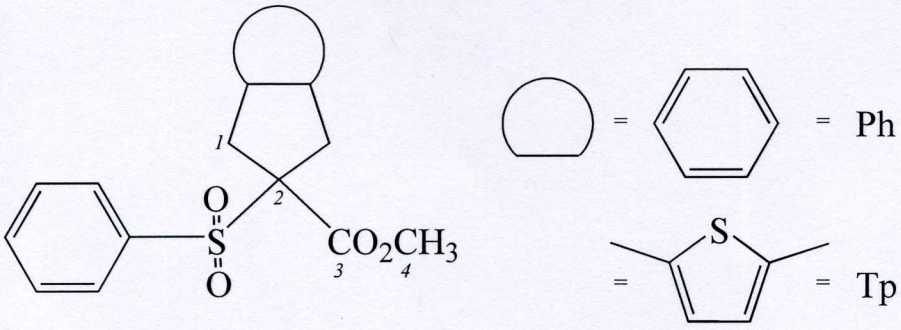
Similarly, the sulfone ester **3** ^{13}C NMR data was analyzed and compared to indan[20] results as shown in Table **4.2**. The methylene, the methoxy, and the benzylic carbons were contrasted for comparison purposes. The sulfone ester showed a signal at δ32.9 (CH_2) that closely matches Palandoken and coworker's δ38.4 (CH_2). The methoxy carbon was observed to be 53.8 ppm as compared to 53.4 ppm. Finally, benzylic ppm values were compared and were observed at δ126.5, 129.8 and 138.0 with respect to Palandoken and coworkers[20] values of δ127.2, 129.7, and 138.4.

IR analysis showed the sulfone ester to have stretches located at 1136.5, 1302.7 (S=O), 1736.2 (C=O), 2847.8, 2920.3 (C_{sp^3}–H), and 3072.5 (C_{sp^2}–H). IR data closely matches that of Palandoken and coworkers[20] reported values found (Table **4.3**) at 1136.5, 1302.7 (S=O), 1736.2 (C=O), 2847.8, 2920.3 (C_{sp^3}–H), and 3072.5 (C_{sp^2}–H).

However, the elimination of the sulfone ester to the desired cyclopenta[*c*]thiophene did not work out as expected. There was no evidence of thiapentalene in the ^{1}H and ^{13}C NMR to support elimination to alkene.

Attempts were made to improve the sulfone ester **3** yields by switching to the dibromide instead of dichloride. The results were only slightly better (within a percent). Attempts to increase or decrease the reaction temperature gave up to 4% yield.

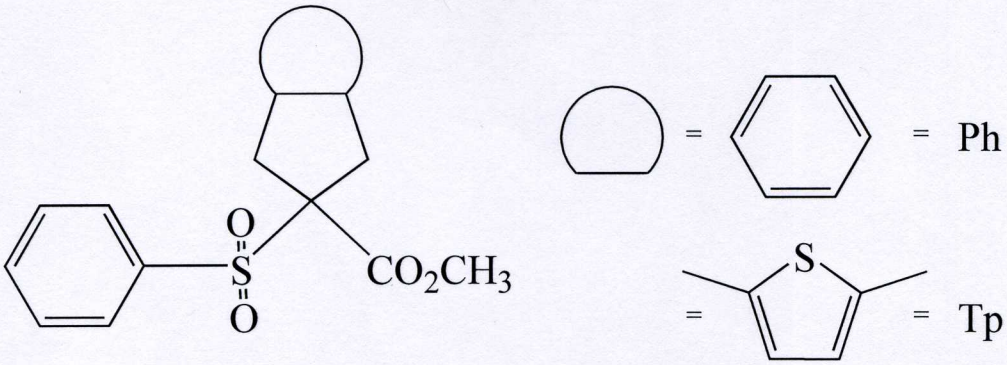
Table 4.2. ^{13}C NMR Comparison of 5-Carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene (**3**, Scheme **2.5**) and 2-Carbomethoxy-2-phenylsulfonylindan (**3**, Scheme **2.4**).



System	Atom/Group	Chemical Shift (ppm)
Tp	C_1	32.9
Tp	C_2	83.9
Tp	C_3	168.5
Tp	C_4	53.8
Tp	aromatic	134.2, 136.4, 138.0
Ph	C_1	38.4
Ph	C_2	78.9
Ph	C_3	168.5
Ph	C_4	53.4
Ph	aromatic	134.2, 136.4, 138.4

Solvent was $CDCl_3$.

Table 4.3. IR Comparison of 5-Carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene (**3**, Scheme **2.5**) and 2-Carbomethoxy-2-phenylsulfonylindan (**3**, Scheme **2.4**).



Stretch	**Tp wavenumber (cm^{-1})**	**Ph wavenumber (cm^{-1})**
S=O	1136.5 & 1302.7	1155.0 & 1324.0
C=O	1736.2	1736.0
C_{sp^3}-H	2847.8 & 2920.3	-
C_{sp^2}-H	3072.5	3071.0

KBr Matrix.

V. CONCLUSIONS

The objective of the research presented in this thesis was to synthesize substituted cyclopenta[*c*]thiophenes from 2,5-dimethylthiophene in fewer steps than previously reported by Wallace and Selegue[17] and Bell and Snyder[19] in their modified Dieckmann synthesis route to substituted cyclopenta[*c*]thiophenes. Although synthesized as potential semiconductors, the modified Dieckmann route suffered from some shortcomings like lesser yields, longer steps, and use of toxic /hazardous chemicals. The research goal set was to increase the yield, avoid contamination, avoid the use of toxic chemicals like sodium cyanide (NaCN) and triphenylphosphine (PPh_3), and synthesize substituted cyclopenta[*c*]thiophenes in just two steps instead of the 8-step Dieckmann route using an activated methylene.

The idea for this was inspired from the previously reported 2-step indene synthesis, by Palandoken and coworkers[20], using activated methylene that successfully synthesized a 5,6-fused ring system. Efforts were done to synthesize cyclopenta[*c*]thiophenes using a 5,5'-fused ring system using activated methylene under similar experimental conditions.

3,4-Bis(chloromethyl)-2,5-dimethylthiophene and 3,4-bis(bromomethyl)-2,5-dimethylthiophene were used to synthesize the precursor, the sulfone ester to substituted cyclopenta[*c*]thiophenes. One reason for using the bromide was having a better leaving group than chloride, thereby improving the product yield. It was

observed that dibromide increased the percent yield of the precursor. However, when dichloride was used, the percent yield was 2.38%, but the use of dibromide increased the percent yield marginally to 4% for the cyclopenta[*c*]thiophene precursor.

^{1}H and ^{13}C NMR spectra, as well as IR spectral analysis, confirmed the successful synthesis of this precursor, the sulfone ester. It was precipitated with methanol (CH_3OH), dried, weighed, and the precipitated sample was treated with potassium tert-butoxide ($K^{t}OBu$) to synthesize the desired cyclopenta[*c*]thiophene. Unfortunately no noticeable product was formed (using ^{1}H and ^{13}C NMR), and hence yield could not be taken.

VI. CONTINUING RESEARCH

Fortunately, the efforts to synthesize and purify the cyclopenta[*c*]thiophene precursor (5-carbomethoxy-5-phenylsulfonyl-1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene), were successful although in low yield. This was accomplished by treating 3,4-bis(halomethyl)-2,5-dimethylthiophene with activated methylene at room temperature.

For future research, the sulfone ester intermediate must be synthesized in greater yield. This can be accomplished by having a graduate student research the experimental conditions that would maximize product yield. The first idea would be to run a series of reactions at varying temperatures in an effort to provide greater amounts of 5,5'-fused product. It would make sense to increase the temperature as it was noted by Snyder and coworkers when using Meldrum's acid to synthesize their 5,5'-fused ring system. Additionally, more purification need to be performed. In the orange oil that results from this reaction there is probably more sulfone ester than what the cold methanol precipitates. Once those experimental conditions have been optimized, then the next step would involve eliminating the sulfone ester to the thiapentalene via an elimination reaction.

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VITA

The author was born in Nagpur, Maharashtra, India on June 21, 1980. He earned his Bachelor of Science degree from Hislop College, Nagpur University, India in the summer of 2001. In the fall of that year he enrolled at Hislop College, Nagpur University, India and earned his Master of Science degree in Chemistry majoring in organic chemistry in the summer of 2003. He then served as an Intern Chemist in National Environmental Engineering Research Institute (NEERI) Nagpur, India for two years, subsequently moving on to the graduate school at Shivaji Science College, Nagpur, India as a part-time instructor of organic chemistry for the fall 2006 semester. In January of 2007, he began his graduate school at the Western Kentucky University where he will earn his Master of Science degree in Chemistry working under Dr. Chad A. Snyder. He is expected to defend his thesis in the summer of 2008.

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(Author)

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