



KJE-3900

MASTER'S THESIS IN CHEMISTRY

**POTASSIUM SULPHIDE ON POTASSIUM-GRAPHITE
AS REAGENT IN THE PAAL-KNORR SYNTHESIS OF
2,5-DIMETHYLTHIOPHENE**

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April, 2009.

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List of Abbreviations and Symbols

η	eta
p	Para
σ	sigma
<	less than
>	greater than
A	alpha
β	beta
$\text{BF}_3 \cdot \text{C}_4\text{H}_{10}\text{O}$	boron trifluoride etherate
^{13}C	carbon-13
$\text{C}_4\text{H}_4\text{NH}$	pyrrole
$\text{C}_4\text{H}_4\text{O}$	furan
$\text{C}_4\text{H}_4\text{S}$	thiophene
C_8K	potassium graphite
Cs	caesium
FID	flame ionization detector
GC	gas chromatography
GIC	graphite intercalated compounds
^1H	proton
IR	infrared spectroscopy
K	potassium
K_2S	potassium sulphide
KOH	potassium hydroxide
MgSO_4	magnesium sulphate
MLR	multiple linear regression
MS	mass spectroscopy
NaCl	sodium chloride
R	alkyl, aryl etc.
SnCl_4	tin (IV) chloride
THF	tetrahydrofuran

ABSTRACT

This thesis describes a new principle for the synthesis of thiophene from diketone. Thiophene is a five-membered heterocyclic aromatic compound containing one sulphur atom. The thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds.

The procedure described in the thesis uses the combination of graphite and metallic potassium. When they are reacted together they form an interesting compound, potassium graphite, in which the metal atoms are intercalated between the sheets of the graphite. If the potassium graphite then is treated with elemental sulphur (flowers of sulphur), potassium sulphide is formed on the surface of the potassium graphite. The thiophene molecule is formed by heating the potassium sulphide with a 1,4-diketone followed by the addition of a dehydrating (water adsorbing) reagent.

Unfortunately, the procedure has so far given only moderate chemical yield, but the results show that the principle works. Further development may give a practically useful method.

Key Words: Thiophene, 2, 5-dimethylthiophene, graphite intercalated compound of Potassium , oxophilic Lewis acid, potassium sulphide, 2,5-hexanedione, Paal thiophene synthesis, factorial designs and response surface modelling.

CHAPTER 1

INTRODUCTION

Thiophene is the heterocyclic compound with the formula C_4H_4S . The simple thiophene consist of five-member ring, are stable liquids which closely resemble the corresponding benzene derivatives in boiling points and even in smell.^[1] Compounds analogous to thiophene include furan (C_4H_4O) and pyrrole (C_4H_4NH). Thiophene and its derivatives exist in petroleum or coal. Historically, Thiophene was discovered as a contaminant in benzene.^[2] It was observed that isatin (1H-indole-2, 3-Dione) forms a blue dye if it is mixed with sulfuric acid and crude benzene. The formation of the blue indophenin was long believed to be a reaction with benzene. Victor Meyer was able to isolate the substance responsible for this reaction. The compound was found to be a heterocyclic compound-Thiophene. Thiophene derivatives are also found in natural plant pigments. Biotin, a water-soluble B-complex vitamin, is a reduced thiophene derivative.

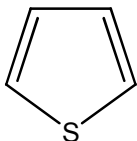


fig 1: Thiophene Structure

At room temperature, thiophene is a colorless liquid with a mildly pleasant odor reminiscent of benzene, with which thiophene shares some similarities. The high reactivity of thiophene toward sulphonation is the basis for the separation of thiophene from benzene, which are difficult to separate by distillation due to their similar boiling points (4 °C difference at ambient pressure). Thiophene is considered aromatic, although theoretical calculations suggest that the degree of aromaticity is less than that of benzene. This could be demonstrated by its ability to undergo substitution reaction. The "electron pairs" on sulfur are significantly delocalized in the pi electron system.^[3] Thiophene had a higher degree of stabilization than the analogous furan. This reasons being that sulphur has a lager bonding radius (length) and that sulphur could tolerates a positive charge better as a result of inductive pull towards sulphur.^[2] These contributions to its stability can be envisaged from the canonical form in fig 2a and 2b.

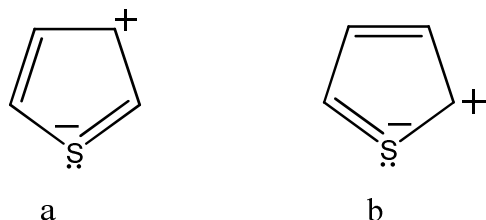


Figure 2: Canonical Structure of Thiophene

They are important heterocyclic compounds that are widely used as building blocks in many agrochemicals. ^[4] Thiophene is used as a solvent and chemical intermediate. Its derivatives are used in manufacturing dyes, aroma compounds and pharmaceuticals. They are used as monomers to make condensation copolymers. Organic conductive polymers are responsible for the important materials science in the application of polymer electro luminescence.

A method of preparing thiophene involves reacting an organic compound containing a chain of at least four carbon atoms linked by single or double bonds with a source of sulphur. The nature and type of the synthesized substituted thiophene compounds depends on the starting material. The choice of starting material controls the thiophene that is obtained. Thus, a starting material containing solely four carbon atoms in a straight chain will produce unsubstituted thiophene, while a starting material containing more than four carbon atoms will produce a substituted thiophene. Most Thiophene derivatives are either produced from ring synthesis or starting from Thiophene or simple alkyl thiophene.

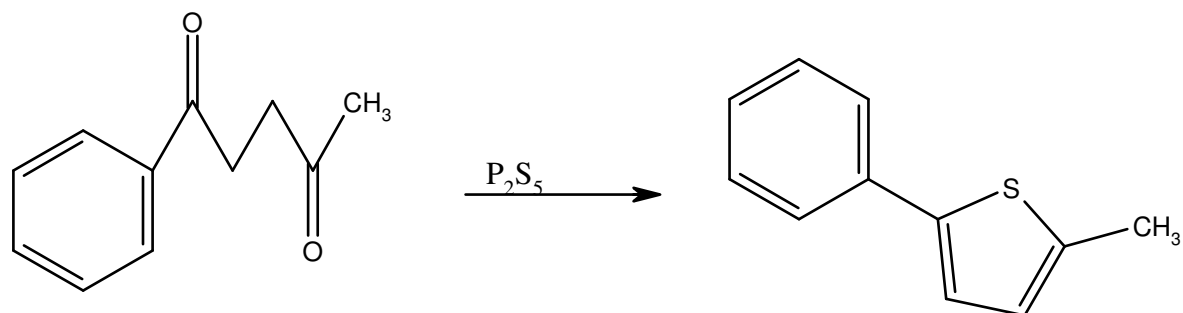
1.1 Aim of Study.

To develop new and optimum synthetic method for synthesizing 2, 5-dimethylthiophene from 1, 4-diketone (2,5-hexanedione) by using a sulphur source, potassium sulphide, different from the conventional use of phosphorus pentasulphide or phosphorus sesquisulphide.

1.2 Scope and Limitation of Study

There are reported synthetic methods to different types of substituted thiophene. The procedure describe in this thesis is similar to a method developed by Paal ^[5,6] for the

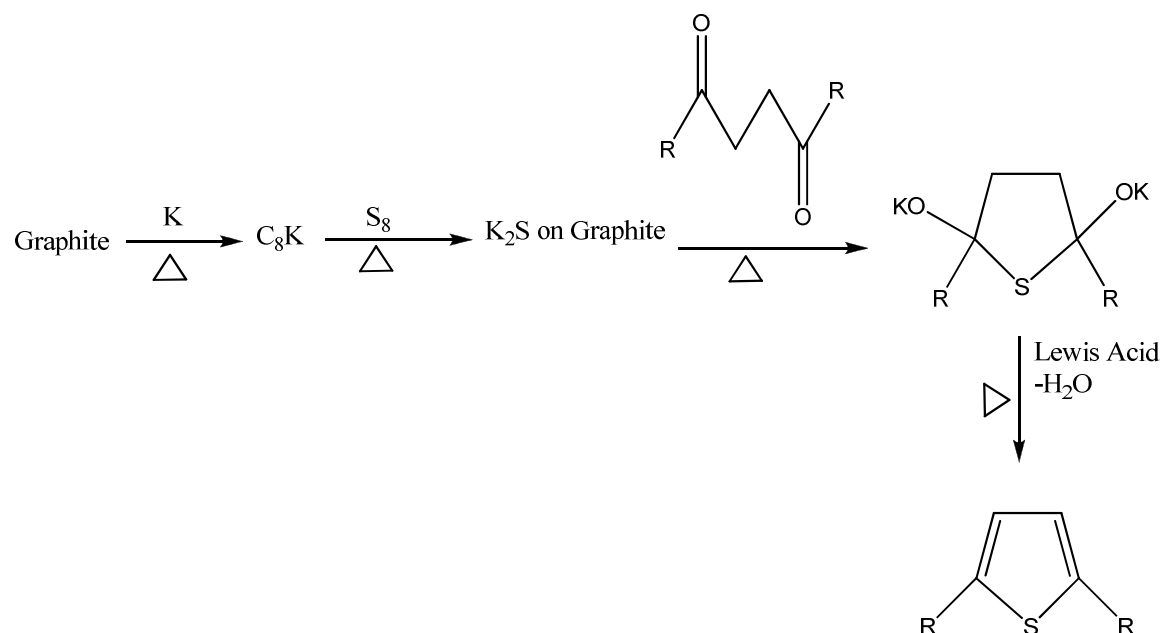
synthesis of 1-phenyl-5-methylthiophene from 1-phenyl-1, 4-pentadione with phosphorus pentasulphide as the sulphur source (Scheme 1)



Scheme 1: Paal Synthesis of 1-phenyl-5-methylthiophene from Phenyl-1, 4-pentadione

1.2.1 Procedure for the synthesis described in this project thesis.

The overall procedure involves melting metallic potassium in the presence of graphite to produce graphite potassium— C_8K in which potassium metal is intercalated between the layers of graphite. The valence electrons on potassium could easily be transported to the outer surface of the graphite. If elemental sulphur then is introduced to the potassium–graphite, a redox reaction occurs and potassium sulphide, K_2S , could be formed on the surface of the C_8K . (Scheme 2)



Where R = CH₃

Scheme 2: Proposed synthesis of alkyl substituted thiophene from K₂S on C₈K.

2, 5-hexanedione is introduced to the flask followed by an appropriate oxophilic Lewis acid (drying agent). Upon heating, 2, 5-dimethylthiophene is produced which could easily be separated from the reaction mixture by steam distillation. To establish suitable experimental condition, a two-level factorial design was used in a screening experiment followed by a response surface study. (Scheme 2)

CHAPTER 2

BACKGROUND OF STUDY/ LITERATURE REVIEW

2.0 General

This section gives a short review of materials (reagents) and compounds used in the present project. It would also emphasize on the established and reported synthetic methods leading to the formation of different types of substituted thiophene. Few words will also be mentioned on the theory behind the screening and the optimization procedure.

2.1 Graphite Intercalated Compounds (GICs)

Carbons can exist in two structural forms called allotropes of carbon. These allotropes are called diamond and graphite. This section describes the structure and properties of graphite and its potassium compounds.

2.1.1 Graphite

Graphite is the most stable form of carbon under standard conditions. It has a stacked structure where the carbon layers (graphene). They build up of annelated six-membered ring and are held together by weak van der Waals forces (fig 3). The presence of these layers allows a large, yet increasing number of Substances to be intercalated between the layers, forming lamella compounds in which monolayer of the guest species (intercalate) are separated by one, two or more graphene. This process resulted to macroscopic swelling due to the increase in the distance between the carbon layers.^[7] The outer shell electronic configuration of each carbon atom is: $2s^2 2p^2$.

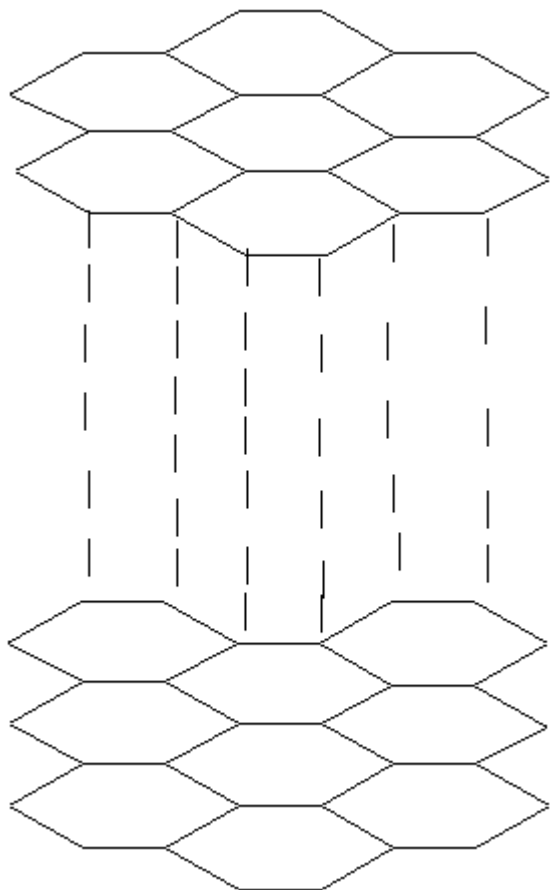


Figure 3: Structure of Graphite

The carbon in each carbon layer of the graphene is sp^2 -hybridised. This hybridization is responsible for its ability to form σ -bond with three neighboring carbon atoms in the same layer. The electron in the unhybridized $2p_z$ of each carbon becomes delocalized, thus generating weak Van der Waal forces between the carbon layers. It is this delocalized electron of graphite that accounts for the carbon electrical conductivity. ^[7, 8]

2.1.2 GIC's of Potassium Formation Process

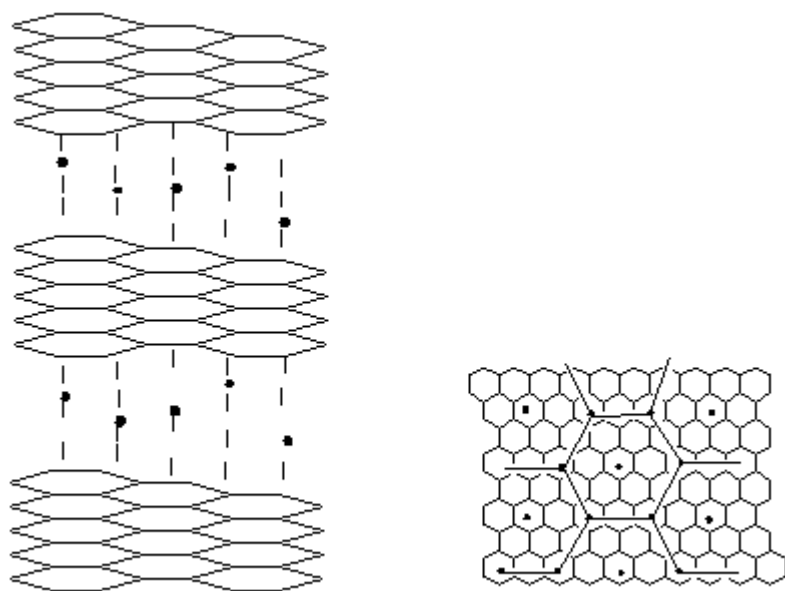
Intercalation is the insertion of ions, atoms or molecules (intercalants) into the voids or spaces between the planar carbon layers of graphite. The graphite carbon layers are capable of intercalating with certain substances, like alkali metals, to form lamella compound where the monolayer or single layer of the guest species (intercalants) are separated by one, two or more carbon layers (host). ^[8] Graphite readily forms

intercalation compounds with both electron donor and electron acceptor molecules by contributing their outer electrons.^[9] This charge transfer allows, precisely, the formation of a lamella compounds which exhibits iono-metallic bonding.^[10, 11] A theoretical and experimental study of the ground-state charge density of potassium GICs (C_8K) reveals that the intercalation is possible because of electronic states hybridization between carbon and potassium during the intercalation process. As a result of this, carbon atom in the graphite layer can accept a maximum of one electron from the potassium metal to its $2p_z$ orbital which had an initial one electron.^[7, 8, 12] This is the reason it falls under lamella compounds during classification of GICs. The most common stoichiometry for its formation is C_8K . However, the formula of GICs is not related to the common valences of the element involved in the formation of these compounds. The GICs formula is easily derived from structural data.^[8]

2.1.3 Structure of Potassium Graphite Compounds.

Historically, the discovery in 1926 by Fredenhagen and Cadenbach of the first stage graphite intercalation compound marks the departure point for much research work concerning the intercalation of the metallic elements into graphite.^[10]

The stage of a GIC is the number of graphene (carbon) layers which separate the intercalate (potassium). C_8K is a first stage GIC made up of alternating layers of potassium and graphene.^[13]



- Represent potassium atoms or ions.

Figure 4: The C_8K network from two orthogonal perspectives

Depending on the conditions for the preparation of GICs, several stages exist. In a second stage, two graphene layers separate two successive layers of intercalate (figure 5).

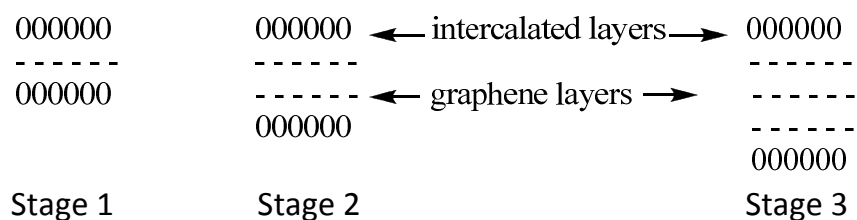


Figure 5: Different stages of GICs

Third stage GICs have guest specie monolayer being separated by three graphene layers. ^[8, 14] During the preparation of GICs, observation of the colour could be used to ascertain their formation. First stage GICs like C_8M ($M = K, Rb$ or Cs) are bronze-coloured; while second stage GICs compound like $C_{24}M$ are blue.

2.1.4 Preparation of C_8K

The synthesis of C_8K , a bronze-coloured powder, is achieved readily by melting potassium in the presence of graphite.^[11] The reaction is possible between 150 – 200 °C under an inert atmosphere of argon. Characteristically, the bronze – coloured C_8K is made up of potassium atoms or ions alternating with negatively charged carbon layers. (Fig 4). C_8K is a highly pyrophoric material. It can be stored in dried solvents like THF or diethyl ether under argon for at least 24 hours without appreciable decomposition.^[15]

2.1.5 Synthetic Applications of C_8K

C_8K had found a wide use in synthetic chemistry. It can be used as catalyst in polymerization reactions, as a reducing agent, and as a metallation agent in the alkylation of nitriles, esters, and oxazines. Other applications include treatment with phenyl halides to form biphenyl, reductive cleavage of carbon-sulphur bonds in vinylic and allylic sulphones etc. It has also found use in the preparation of active metals which are important in Reformatsky reactions, hydrogenation reaction reactions, debromination and preparations of allylic organometallic species.^[7, 11]

At a very high temperature (>350 °C), ternary graphite – potassium –chalcogen compounds could be synthesized. These chalcogens are unable by themselves intercalate into graphite. Hence, it is possible to form graphite –potassium –sulphur compound, graphite –potassium – selenium compounds.^[14]

The objective, as stated earlier of the project presented in this thesis was to determine whether, or not, potassium graphite can react with elemental sulphur to yield potassium sulphide, K_2S and to investigate if this potassium sulphide can be used as the source of sulphur in the synthesis of substituted thiophene from 1, 4-diketone. Prior to the addition sulphur, the temperature of the bronze-coloured C_8K should be adjusted, (>120 °C≤150 °C), in order to avoid total intercalation of sulphur into the preformed binary compound (C_8K).

2.1.6 Interaction of GICs with Solvents

Bronze-coloured C_8K is stable as suspensions in tetrahydrofuran (THF), diethyl ether, pentane or heptanes. However, THF allow better suspensions that are well dispersed. This is the reason THF produces a tractable and reactive suspension of potassium-graphite because they can penetrate and fill the interlayer spaces without intercalating with them. The incomplete dispersion of C_8K in other solvents like diethyl ether,

pentane or heptanes may contribute to why reaction in them might not go to completion.^[9]

2.2 Ring Synthesis of Substituted Thiophene Compounds

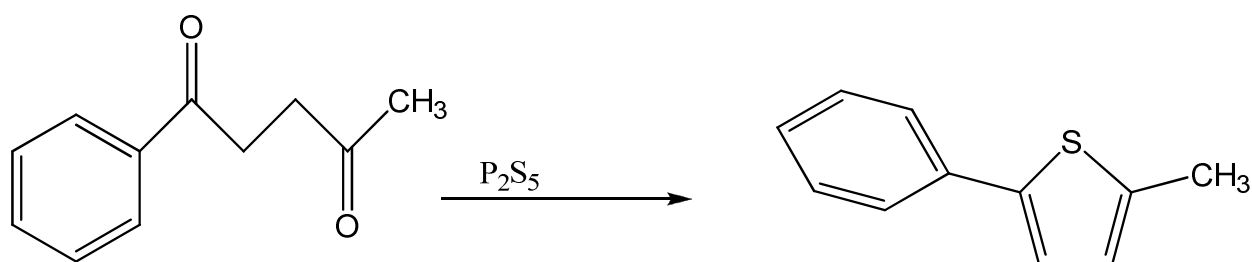
The general ways of synthesizing thiophene rings from non-heterocyclic precursors can be broadly divided into two categories:

- The construction of thiophene ring from appropriately substituted open chain precursors.^[16] That is, this synthesis involves the introduction of sulphur into a starting material containing the complete carbon skeleton. For example, the reaction of a sulphurizing agent with a diketone having 1, 4 arrangement.^[2]
- The functionalization at the positions α and β to the sulphur atom of the pre-constructed thiophene nucleus. This synthesis employ either the reaction of a mercapto acetate with a 1,3-dicarbonyl compound or the reaction of a thiodiacetate with a 1,2-dicarbonyl compound.^[2, 16]

These two categories of reaction pathway, leading to different substituted thiophene, had been exploited by many researchers. Among the known synthetic procedure includes: Paal thiophene synthesis, Gewald aminothiophene synthesis and Fiessemann thiophene synthesis.

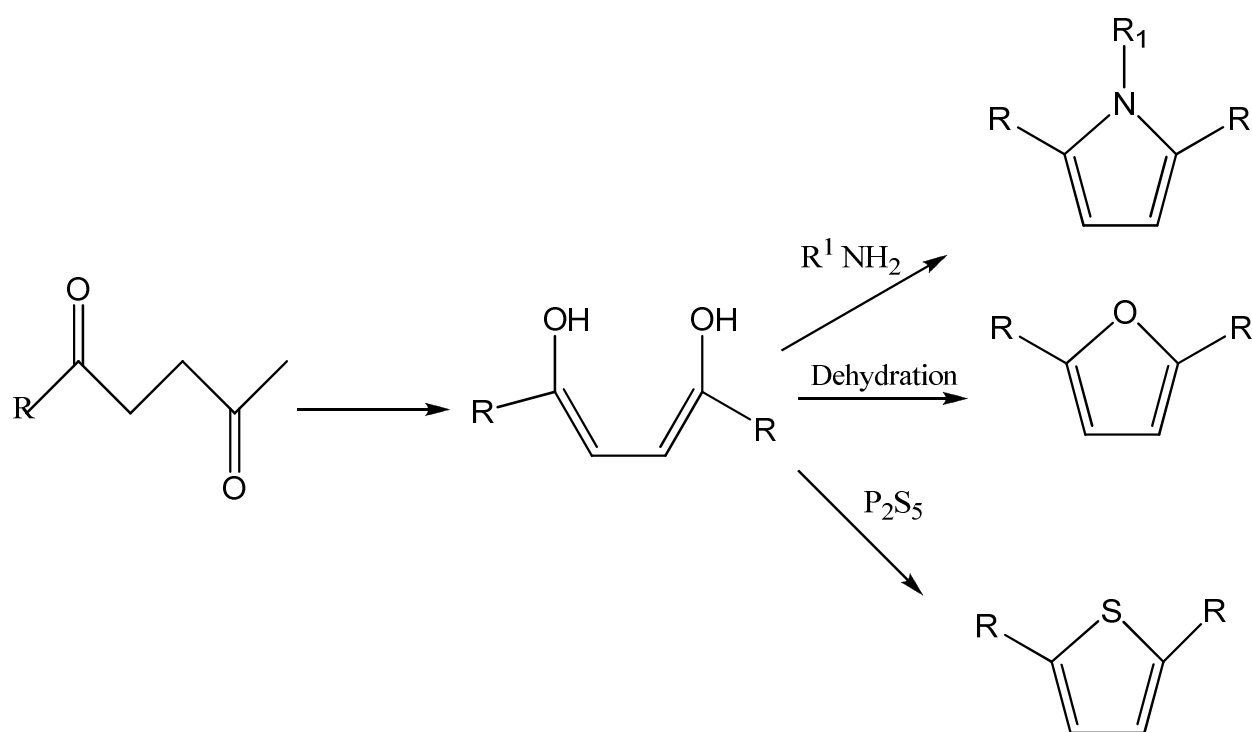
2.2.1 Paal Thiophene Synthesis

This synthesis involves the addition of sulphur atom to 1, 4-dicarbonyl compounds that is accompanied by subsequent dehydration. In 1885, Paal reported the synthesis of 2-phenyl-5-methylthiophene.^[5, 6] (Scheme 3)



Scheme 3: Paal synthesis of 2-phenyl-5-methylthiophene.

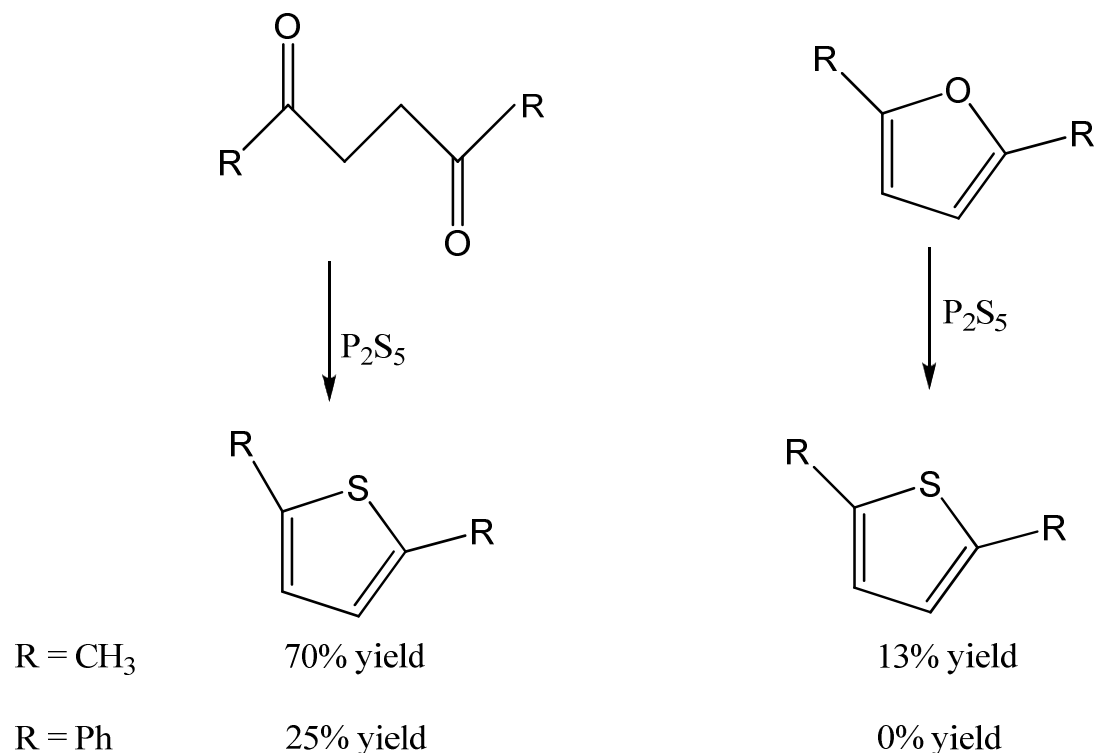
Separately, Paal and Knorr described the initial examples of condensation reactions between 1,4-diketones and primary amines, which became known as the Paal-Knorr pyrrole synthesis.^[6] The remote theme of this synthetic procedure involves cyclization of 1,4-diketones, either in the presence of a primary amine (Paal-Knorr pyrrole synthesis), in the presence of a sulphur(II) source (Paal thiophene synthesis), or by dehydration of the diketone itself (Paal Furan synthesis).^[5] (Scheme 4)



Scheme 4: Possible Paal-Knorr Synthesis of thiophene, furan and pyrrole.

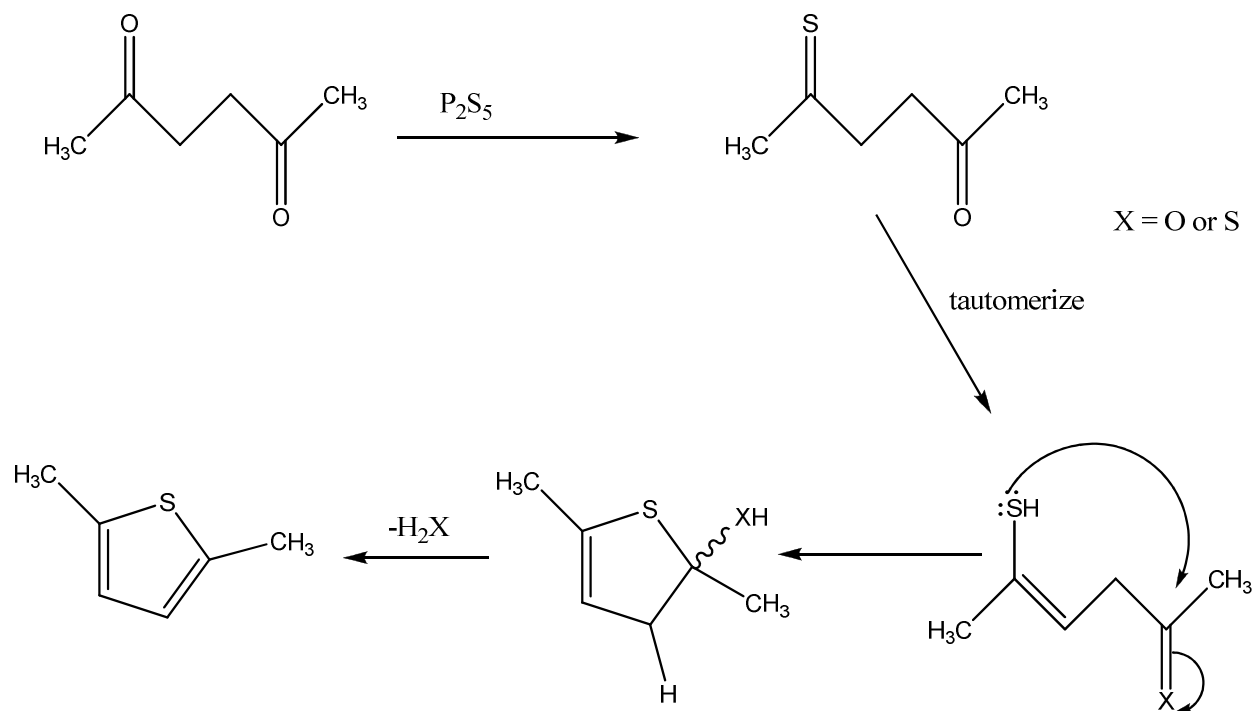
Earlier, it was assumed that Paal thiophene synthesis proceeds through the initial formation of furan via dehydration of the 1,4-diketone, followed by conversion of the furan to the thiophene because furans were often isolated as byproducts in the Paal thiophene synthesis. In 1952, Campaigne and coworkers^[17] was able to prove that Paal thiophene synthesis could not proceed via furan as intermediate. Instead it went through the formation of a thione. They conducted parallel experiments to prove this. Direct comparisons were made between the reactions of 2,5-hexanedione and 1,2-dibenzoylthane with P_2S_5 and the reactions of 2,5-dimethylfuran and

2,5-diphenylfuran under the Paal thiophene synthesis conditions. Reactions utilizing the diketones provided a greater yield of the thiophene suggesting that the furan is not an essential intermediate in the reaction pathway, but rather a by-product.^[17] (Scheme 5)



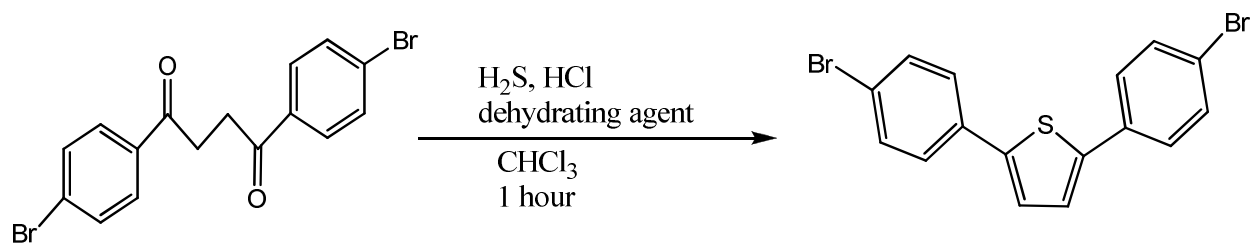
Scheme 5: Comparison of the reactions showing whether furan is formed as intermediate in the Paal thiophene synthesis.

Based on the above observations, it was then he proposed that the mechanism involves initial formation of thione (X = O or S), which is followed by tautomerization and Cyclization. Aromaticity drives the facile elimination of either H₂O or H₂S resulting in the thiophene product. (Scheme 6)



Scheme 6: A reaction mechanism showing the formation of thione as intermediate in Paal thiophene synthesis.

This synthetic method for thiophene had been subjected to considerable variations and improvements over time. The standard procedure for the Paal thiophene synthesis is to use phosphorus pentasulphide as the sulphur atom source. The product is always a mixture containing furan due to the dehydrating effect of P_2S_5 as an additional property. A number of other reagents had been developed to take care of the sulphur source and dehydration. Hydrogen sulphide, in the presence of an acid catalyst, was found to be more efficient than phosphorus pentasulphide at converting ketones to thione. It was thought that this system might prove more effective in the Paal reaction.^[5, 17] This above assumption forms the early work done by Campaigne and coworker. They treated 1, 2-di-*p*-bromobenzoyl ethane with hydrogen sulfide, hydrogen chloride and stannic chloride, to produce 2, 5-di-*p*-bromophenylthiophene in 73% yield. The stannic chloride was found to function as a dehydrating agent as illustrated in the results shown in Table 1. Most notable was the fact that furans were not isolated under this condition.^[17] (Scheme 7)



Scheme 7: Reaction of 1, 2-di-*p*-bromobenzoyl ethane with hydrogen sulfide using Paal procedure.

Dehydrating Agent	Yield, %	Recovered Diketone
None	0	80
Acetic anhydride	5	66
Zinc Chloride	56	38
Stannic Chloride	73	17

Table 1: Shows the yields obtained when different Lewis acids were used in the reaction between, 2-di-*p*-bromobenzoyl ethane with hydrogen sulfide using the Paal procedure.

In a related development, *p*-Methoxyphenylthionophosphine sulphide, commonly known as Lawesson's reagent, was developed in 1978 and proved effective for the transformation of a number of carbonyl compounds to their thiocarbonyl derivatives.^[18] (figure 7)

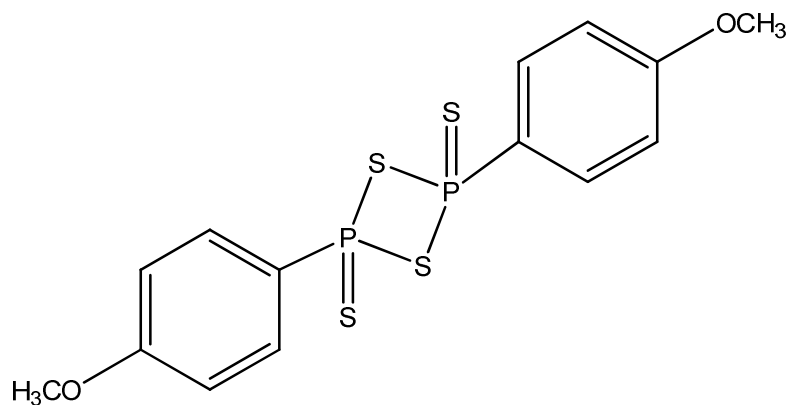
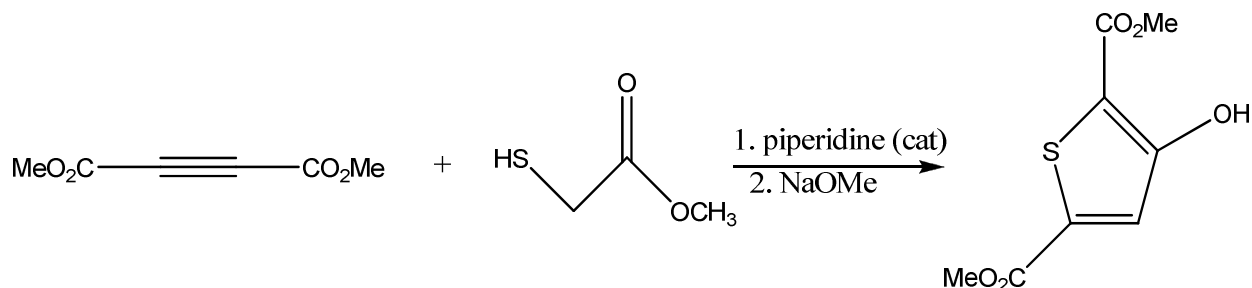


Figure 7: Structure of Lawesson's reagent

Thus, ketones, amides, and esters all produce the corresponding thiocarbonyl derivative in nearly quantitative yield on treatment with Lawesson's reagent. This has proven to be an effective replacement for the traditional use of the P_4S_{10} reagent system for the conversion of 1,4-diketones to thiophene. ^[18]

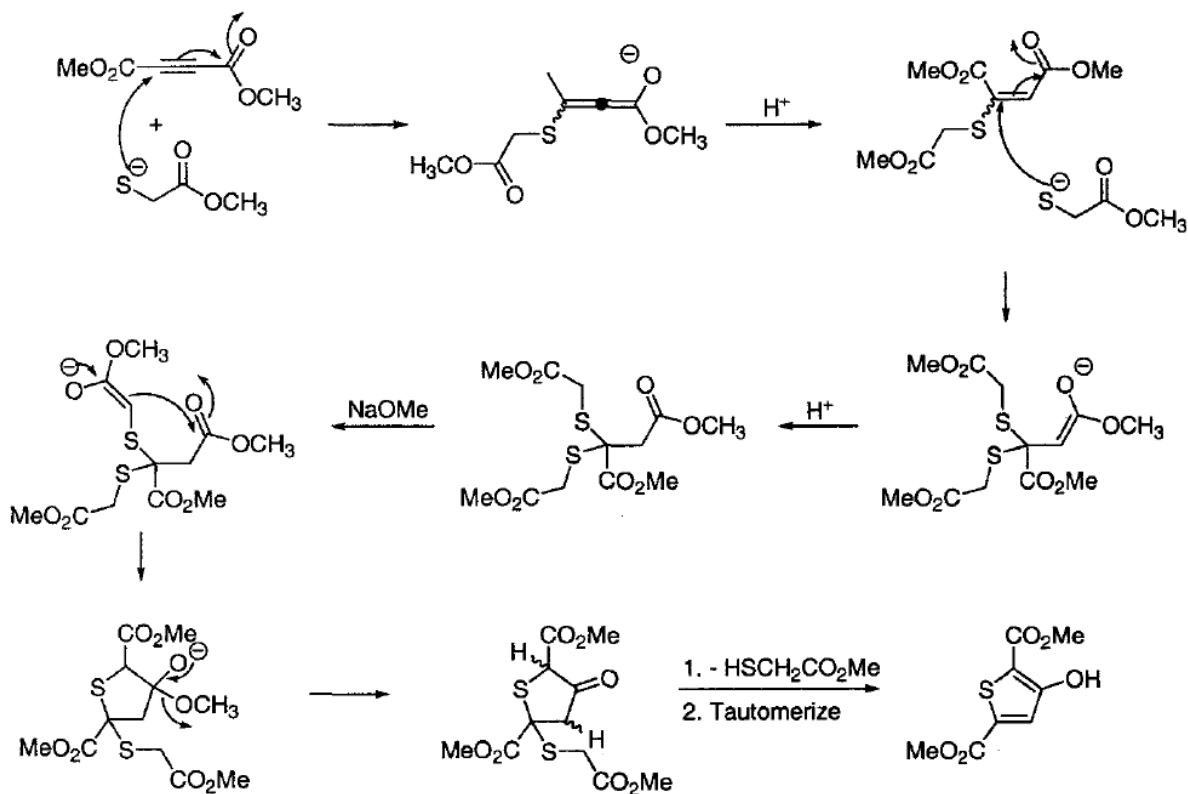
2.2.2 Fiesselmann Thiophene Synthesis

This is an extension of Woodward condensation of thioglycolic ^[19] acid and α , β -unsaturated ester in the presence of base to produce 2-carbomethoxy-3-ketotetrahydrothiophene. This synthetic method involves the condensation reaction of thioglycolic acid derivatives with α , β -acetylenic esters, which upon treatment with base results in the formation of 3-hydroxy-2-thiophenecarboxylic acid derivatives. (Scheme 8)



Scheme 8: Fiesselmann thiophene synthesis of 3-hydroxyl-2-thiophenecarboxylic acid derivatives.

Fiesselmann synthetic route proceeds through consecutive base-catalyzed 1, 4-conjugate addition reactions to form thioacetal. Treatment with stronger base results in the formation of an enolate. Intramolecular reaction through Dieckmann condensation leads to the formation of a ketone. Eliminating methylthioglycolate and tautomerization propelled by aromaticity provides the 3-hydroxyl thiophene dicarboxylate. (Scheme 9)

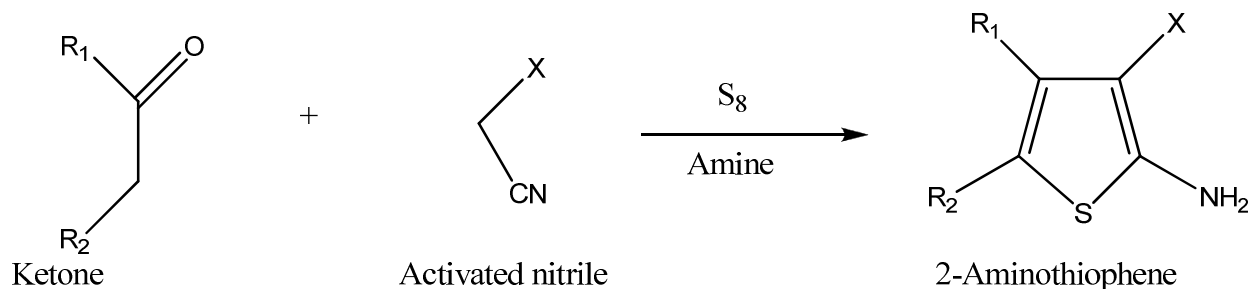


Scheme 9: Mechanism for Fiessemann thiophene synthesis.

In subsequent years, Fiessemann illustrated the applicability of this reaction for a number of related carbonyl systems. Thus, thiophene had been produced from reactions of thioglycolic acid derivatives and β -keto esters, α, β -dihalo esters and α - and β -halovinyl esters, along with the corresponding nitriles, ketones and aldehydes. Furthermore, a variety of α-mercaptocarbonyl systems can be used in place of the thioglycolic acid derivatives and this extends the applicability of this reaction. ^[5]

2.2.3 Gewald Aminothiophene Synthesis

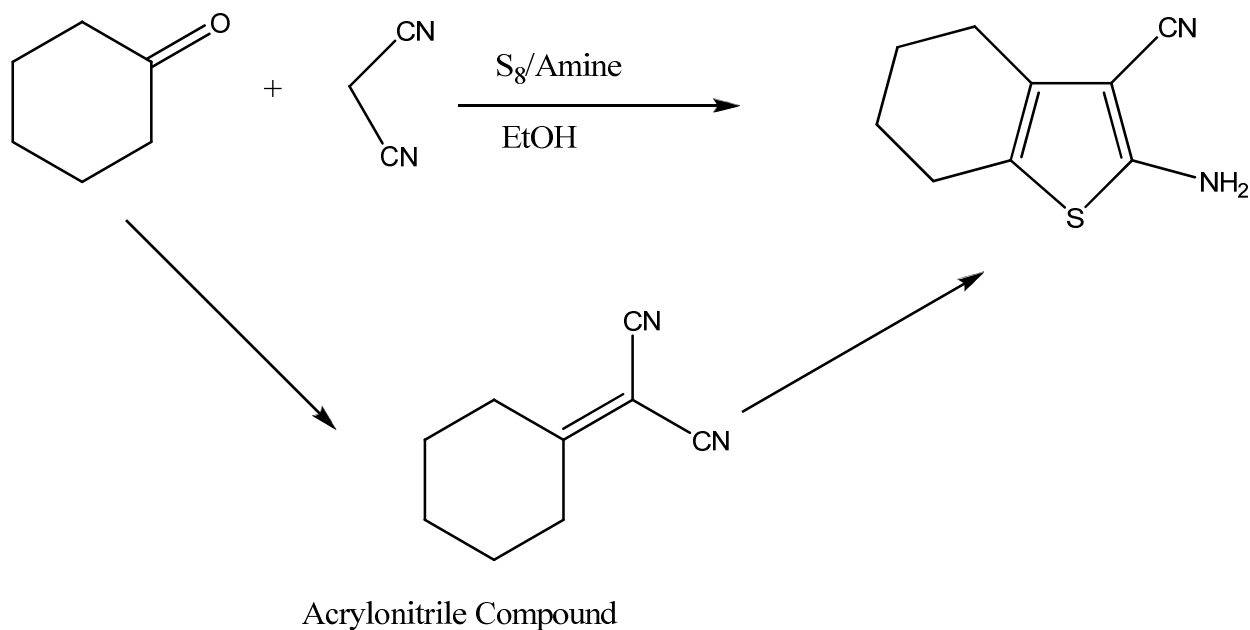
This method was reported by Gewald in 1966. ^[20 -23] It involves the condensation of aldehydes, ketones, or 1, 3-dicarbonyl compounds with activated nitriles such as malononitrile or cyanoacetic esters and elemental sulfur in the presence of an amine to afford the corresponding 2-aminothiophene at room temperature. (Scheme 10)



$\text{R}_1, \text{R}_2 = \text{H}, \text{alkyl}, \text{aryl}, \text{heteroaryl}, \text{CO}_2\text{R}$
 $\text{X} = \text{CN}, \text{CO}_2\text{R}, \text{COPh}, \text{CO-heteroaryl}, \text{CONH}_2$

Scheme 10: Gewald aminothiophene synthesis.

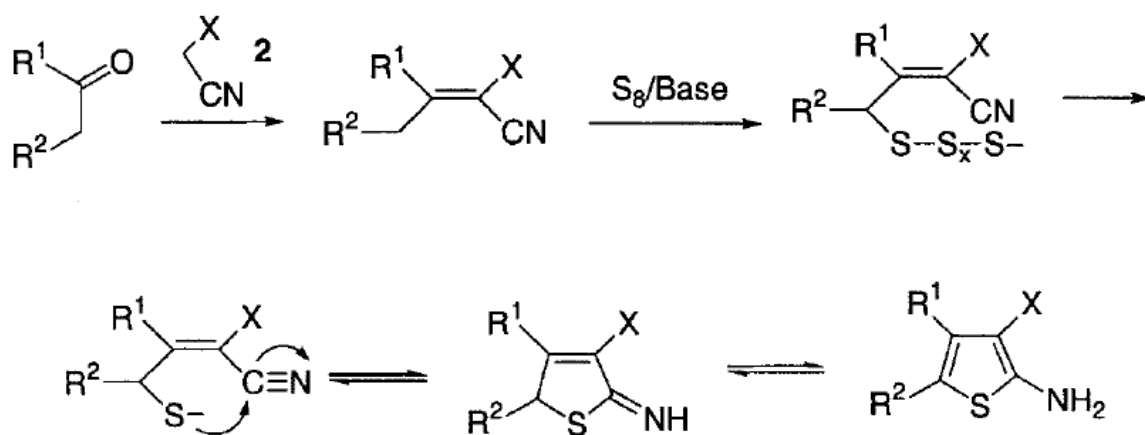
In a related procedure, cyclohexanone and malononitrile reacted to form cyclohexane annelated 2-aminothiophene in 86% yield. In an alternate procedure, the ketone and nitrile were condensed to form the acrylonitrile compound, which was then treated with sulphur and an amine to give thiophene in 90% yield. (Scheme 11)



Scheme 11: Other alternative route of Gewald aminothiophene synthesis

The first step in the mechanism of this reaction involves the Knoevenagel condensation of an activated nitrile with a ketone or aldehyde to produce an acrylonitrile. The product

of this condensation is then thiolated at the methylene position. The sulfurated compound initially decays to the mercaptide compound. This then undergoes a cyclization reaction via mercaptide attack at the cyano group. Base-catalyzed tautomerization affords the 2-aminothiophene. ^[5, 24] (Scheme 12)

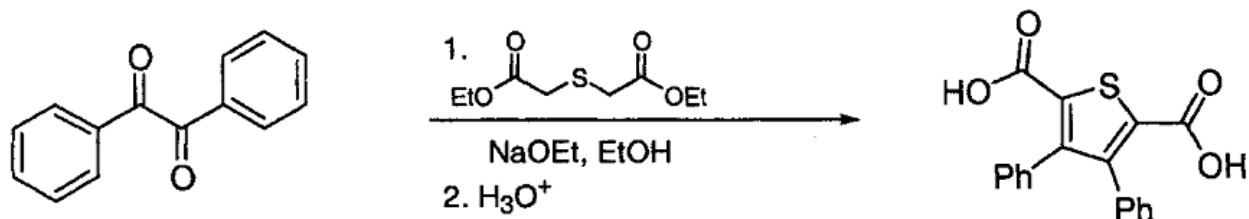


Scheme 12: Mechanism for Gewald aminothiophene synthesis.

This Gewald aminothiophene reaction had been used to produce different substituted 2-aminothiophenes. Among the substituted product produce includes: 5-alkoxy-2-aminothiophene, ^[25] 2,4-diaminothiophenes, ^[26] 4-alkyl-2-aminothiophene, ^[27] 5-alkyl-2-aminothiophene. ^[28]

2.2.4 Hinsberg Synthesis of Thiophene Derivatives

This Hinsberg synthesis of thiophene derivatives ^[29] involve the condensation of diethyl thiodiglycolate and α -diketones under basic conditions to produce 3, 4-disubstituted-thiophene-2, 5-dicarboxylic acids upon hydrolysis of the crude ester product with aqueous acid. (Scheme 13)



Scheme 13: Hinsberg Synthesis of 3, 4-disubstituted-thiophene-2, 5-dicarboxylic acids

2.3 Screening and Optimization

Screening experiment is a series of experiments that is carried out in order to find which experimental variables have a real influence on the yield or result. Prior to kick-off of any experiment, identification of the independent variables, (either continuous variables or discrete variables), needed in the experiment is very important. In order to explore the experimental procedure, the range of variation of the upper and the lower bound are specified in the case of continuous variables while nature of solvent and types of equipment and catalyst are specified for discrete variable. ^[30]

2.3.1 Factorial Designs

In a factorial design, each variable (factor) is investigated at predetermined fixed levels and this factorial design contains all combination of the factors at each level. A factorial design in which k factors are studied at r levels will thus contain r^k different experimental runs. That is, a two-level factorial design with k factors contains 2^k runs.

A two-level factorial designs are the most convenient and efficient way of carrying out a screening experiment if the number of experimental variables does not exceed four. A response surface model (Taylor expansion) can be established where all main effects of the variables and their interaction effects can be estimated. ^[30]

Other types of designs that can be used in screening experiment include: Plackett-Burman designs and D-optimal designs. ^[30]

2.3.2 Modelling

The yield observed, y , in a synthetic reaction will depend on the actual experimental conditions that were used. The experimental conditions can be specified by the detailed settings, x_i , of the experimental variables, i , and it is reasonable to assume that there is

some functional relationship between the observed response (yield) and the settings of the variables and that:

$$y = f(x_1, \dots, x_k) + e$$

In this equation, an error, e , has been introduced since the observed response, y , is not the true response, η . All experimental observations are victimized by a random error and at best, y , will be an estimator of η and

$$Y = \eta + e$$

Without error, the function, f , will depict the systematic variation induced by changing the experimental settings, x_i , and

$$\eta = f(x_1, \dots, x_k)$$

To derive an analytical expression for f , from physical chemical models is, in most cases, impossible. Provided that the range of experimental settings is not too vast, an approximation of f , can be obtained by a Taylor expansion and:

$$y = f(\mathbf{0}) + \sum_{i=1}^k \frac{\partial f(\mathbf{0})}{\partial x_i} \cdot x_i + \sum_{i=1}^k \sum_{j=1}^k \frac{1}{1 \cdot 2} \cdot \frac{\partial^2 f(\mathbf{0})}{\partial x_i \partial x_j} \cdot x_i x_j + \dots + R(\mathbf{x}) + e.$$

The Taylor expansion is more conveniently written as:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_k x_k + \beta_{12} x_1 x_2 + \dots + \beta_{ij} x_i x_j + \dots + \beta_{11} x_1^2 + \dots + \beta_{kk} x_k^2 + R(x) + e$$

The coefficients, $\beta_0, \beta_1, \beta_2, \dots, \beta_{ij}, \dots$, etc, in the polynomial model will be called parameters of the model. ^[30]

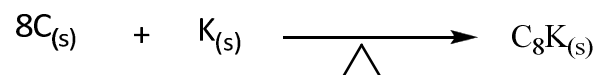
CHAPTER THREE

RESULT AND DISCUSSION

3.0 Synthesis of 2, 5-Dimethylthiophene

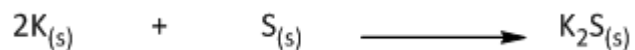
(a) Formation of Potassium Sulphide on C₈K

When pure potassium metal was added to pre-heated graphite under the flow of argon, a bronze-coloured powder was formed indicating the formation of graphite intercalation compound of potassium.



Scheme 14: Formation of potassium graphite.

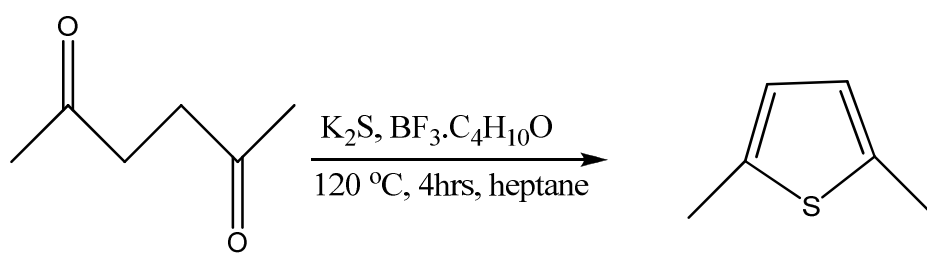
In order to obtain the desired sulphide, solid sulphur was added to the bronze-coloured C₈k inside the flask and the colour changes to black. In this reaction, a redox reaction occur where the oxidation number of potassium was increased from 0 to +1, and the oxidation number of sulphur decreases from 0 to -2 or in the alternative there was simultaneous loss of two electrons from the potassium and gain of two electrons by the sulphur. In this procedure, formation of ternary intercalated compound was avoided by reducing the temperature of the bronze-coloured C₈K before the introduction of the solid sulphur. This is because if the sulphur should have being added at a temperature above 200 °C, most of it would have reacted and intercalate with previous existing binary compound (C₈K) and this can make it unavailable on the C₈K surface as nucleophile (S⁻).



Scheme 15: Reaction of sulphur with potassium in C₈K.

(b) Addition of Diketone to the K_2S on C_8K

This is the important step leading to the formation of the desired product. The procedure was carried out “one-pot” and 2, 5-hexanedione and boron trifluoride etherate were introduced directly after the formation of K_2S . The potassium graphite with K_2S was suspended in heptane. However, only trace amount of 2,5-dimethylthiophene were formed according to GC. The starting ketone was mainly unreacted. (scheme 16).

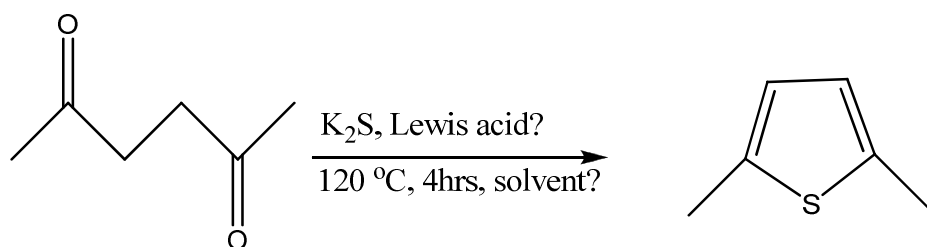


Scheme 16: Synthesis of 2,5-dimethylthiophene Using Heptanes (solvent) and $BF_3.C_4H_{10}O$.

Effort at using NMR in elucidating the product (thiophene) failed as it was only the starting ketone that was detected on the NMR. However, when the sample was subjected to MS analysis, it reveals the presence of 112.12 as the molecular ion and this value is equivalent to the molecular mass of 2,5-dimethylthiophene. This result from mass spectroscopy gave me an insight to look for better combination of the reacting materials.

When this reaction was repeated with the reaction time set to 6 hrs, 7 hrs and overnight (16 hrs), the GC and mass spectroscopic analysis could detect neither the presence of the starting material (ketone) nor the desired thiophene. This could be as a result of decomposition of these substances at $120\text{ }^\circ\text{C}$ with long reaction time. For this reason, all other test experiment was run at lower temperature ($< 120\text{ }^\circ\text{C}$) for 4 hours.

When the reaction was repeated with hexane as the solvent and boron trifluoride etherate as the drying agent, trace amount of 2,5-dimethylthiophene ($< 2\%$) was detected on the GC, while the recovered ketone was very high ($> 98\%$). (Scheme 19)



Scheme 19: Selecting better solvent medium and Lewis acid (Drying agent).

Only the starting ketone could be seen in the ^1H NMR spectra. I was discouraged using hexane.

In a similar procedure with diethyl ether as solvent with boron trifluoride etherate, only traces of the thiophene product were observed (GC). Diethyl ether was unselected as solvent.

Also, chloroform was used with boron trifluoride etherate; the reaction did not give more than trace amount of the product. The starting ketone was recovered.

But, when THF was used as the solvent with boron trifluoride etherate, there was an improvement of the yield. The GC analysis showed a 1:1 mixture of 2,5-dimethylthiophene and 2,5-hexanedione. The NMR and the MS shows both the product and the ketone.

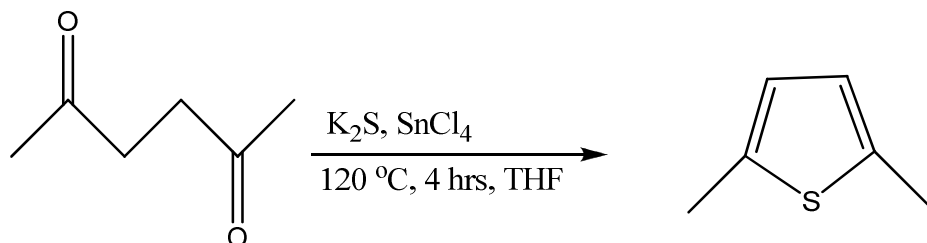
Due to the results from the reactions above, I decided to test other Lewis acids as drying agent.

When tin (IV) chloride or aluminum trichloride was used with heptanes, hexane and ether as solvent, the results obtained were not too different to what was observed with boron trifluoride etherate. When chloroform was used as the solvent and tin (IV) chloride as the Lewis acid, a yield of 18% of 2,5-dimethylthiophene was observed and 72% of unreacted ketone according to GC. Mass spectroscopic analysis confirmed this result. This was an improvement, but the result was not satisfactory. So I decided to try THF and tin (IV) chloride.

When tin (IV) chloride was used with THF as the solvent, the yield was improved and GC showed 78% of thiophene and 19% of the unreacted ketone. The GC/MS confirmed the result. From the above experiment, it was concluded that tin (IV) chloride and THF was the best combination so far. This good result could not be unconnected to fact that the THF can easily occupy the interlayer spaces of the C_8K . The ketone dissolves in THF can reach every part of the in C_8K structure where the sulphide might be trapped.

The encouraging results obtained with THF and tin (IV) chloride made it necessary to further explore the experimental conditions using a statistical experimental design. The yields obtained in the experiment were determined by GC using the internal standard technique. The calibration procedure is given in the Experimental section 5.4. From the design, a second order interaction model (linear terms and cross-product terms) was determined. Since only three variables were considered, a full factorial design with eight runs was convenient. The variables and the experimental design are presented in the next section.

3.1 Screening Experiments



2, 5-Hexanedione

2, 5-Dimethylthiophene

Scheme 20: Screening Experiment Using the Appropriate variable settings.

The three experimental variables studied: amount of sulphur, amount of Lewis acid (tin (IV) chloride) and temperature. The levels of their settings are summarized in the table 2

FACTORS/VARIABLES		LEVEL	
		-1(Low Level)	+1(High Level)
ABBREVIATIONS	NAME OF VARIABLE AND UNITS		
X_1	Amount of Sulphur (moles)	0.03	0.06
X_2	Amount of Lewis Acid (moles)	0.0043	0.0085
X_3	Temperature ($^{\circ}\text{C}$)	80	120

Table 2: Variables and Experimental Domain in the Formation of 2,5-dimethylthiophene.

The experimental design matrix and the yield obtained are showed in Table 3. Internal standard technique was used to estimate the yield (y) from gas chromatography whereby an accurate measured amount of tetralin (1.309g, 0.009905 moles) was added at the beginning of the reaction. The reaction time measurement begins when the Lewis acid addition was completed.

Experiment No.	X_1	X_2	X_3	$y_{(2)}$ (%)	$y_{(3)}$ (%)	$y_{(4)}$ (%)
1	-	-	-	1.45	1.75	2.62
2	+	-	-	1.92	2.73	3.16
3	-	+	-	2.34	5.35	7.66
4	+	+	-	3.43	6.36	10.70
5	-	-	+	2.93	5.89	10.60
6	+	-	+	4.82	7.21	10.88
7	-	+	+	5.15	9.75	17.46
8	+	+	+	9.56	11.48	12.96

Table 3: Design Matrix and Yields in the Formation of 2, 5-Dimethylthiophene.

In order to fit the model, a variable setting was assigned numerical values so that $X_i = -1$ indicating low level, and $X_i = +1$ indicating high level (table 3). A response surface model

which would account for the average or constant term, all main or linear effects and interaction effect could then be estimated. Table 4 shows a brief summary of name of the scaled variables and their abbreviation that was estimated and will be present in the response surface model.

FULL NAME	ABBREVIATIONS
YIELD (RESPONSE)	Y
CONSTANT OR AVERAGE TERM	CONSTANT
AMOUNT OF SULPHUR	X_1
AMOUNT OF LEWIS ACID	X_2
TEMPERATURE	X_3
AMOUNT OF SULPHUR AND LEWIS ACID	X_1X_2
AMOUNT OF SULPHUR AND TEMPERATURE	X_1X_3
AMOUNT OF LEWIS ACID AND TEMPERATURE	X_2X_3

Table 4: Linear and Interactions Terms in the Model

y is the measured response which cannot be equal to the true response η , because of the presence of systematic/random error.

Since function y describes the variation in response induced by the experimental variables, x_i . Therefore, in the presence of experimental error, the mathematical representation of the response surface model will thus be:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + e.$$

The coefficients, b_0, b_1, b_2, b_3 , are called the parameters of the model. The constant term, b_0 , will estimate the response when all variables are set to zero, corresponds to the centre of the experimental domain. The linear coefficients, b_1, b_2, b_3 will be the direct measure of the linear dependence of the corresponding variables. The cross product coefficient, b_{12}, b_{13}, b_{23} will be a measure of the two-function interaction effect between the variables. This interaction effect means that the effect of one variable depends on the setting of the others.

3.2 Estimation of Coefficients (Model Parameters) and Their Standard Error

The model parameters were estimated by a least-square fit of the model to the observed response. Let $y = (y_1, y_2, \dots, y_k)^T$ be the vector of the response in the experiments; let X be the model matrix; let $b = (b_0, b_1, b_2, b_3, b_{12}, b_{13}, b_{23})$ be the vectors of the model parameters to be estimated. A least-square fit is obtained by:

$$b = (X^T X)^{-1} X^T y.$$

Mathematically, the standard errors can be determined from the estimate of experimental error variance. When such estimate is multiplied by the dispersion matrix, the variance-covariance matrix of the estimated model parameters is obtained. Such an estimate is obtained from the least square fit as a residual mean square from the ANOVA table.

The model parameters and their standard errors were estimated using a computer programme called MODDE 8.0. The estimated coefficient and their standard errors are summarized in table 6, while the residual sum of squares, regression and F-ratio are shown in table 5 (ANOVA TABLE)

Y ₄	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE	F-RATIO
TOTAL	8	893.563	111.695	
REGRESSION	6	164.178	27.363	4.13039
RESIDUAL	1	6.6248	6.6248	

Y ₃	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE	F-RATIO
TOTAL	8	393.117	49.1396	
REGRESSION	6	74.0647	12.3441	683.888
RESIDUAL	1	0.0180499	0.0180499	

Y ₂	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE	F-RATIO
TOTAL	8	172.763	21.5954	
REGRESSION	6	47.4915	7.91526	17.5407
RESIDUAL	1	0.45125	0.45125	

Table 5: ANOVA TABLE

COEFFICIENT ABBREVIATION	COEFFICIENT AND THEIR STANDARD ERRORS		
	Y ₄	Y ₃	Y ₂
b ₀	9.51 ± 0.91	6.32 ± 0.05	3.95 ± 0.23
b ₁	-0.08 ± 0.91	0.63 ± 0.05	0.98 ± 0.23
b ₂	2.69 ± 0.91	1.92 ± 0.05	1.17 ± 0.23
b ₃	3.47 ± 0.91	2.27 ± 0.05	1.67 ± 0.23
b ₁₂	-0.29 ± 0.91	0.06 ± 0.05	0.39 ± 0.23
b ₁₃	-0.97 ± 0.91	0.13 ± 0.05	0.59 ± 0.23
b ₂₃	-0.46 ± 0.91	0.11 ± 0.05	0.57 ± 0.23

Table 6: Estimated Coefficient and Their Standard Error

The model parameters obtained after 4 hours (y_4) will be used to analyze the response surface.

From the above table, the approximate Taylor's expansion for the response surface model is:

$$y = 9.5 - 0.08x_1 + 2.7x_2 + 3.5x_3 - 0.3x_1x_2 - 1.0x_1x_3 - 0.5x_2x_3 + e$$

This model was obtained after rounding to one decimal place. It is observed that the reaction temperature, x_3 , is important and should be set to its high level (120 °C should be maintained). The amount (concentration) of Lewis acid is also important and should be set to its high level. The presence of sulphur as the sulphurizing agent is needed in the reaction, but its concentration at a higher level is seldom important as revealed in the response surface model. The model also shows that the interaction effects are small.

Figure 8 shows the coefficient plot of the response surface model. This plot displays the regression (MLR) coefficients with their confidence interval. The size of each coefficient represents the change in their response when a factor is varied in accordance to their experimental domain, while the other factors are kept at their averages.

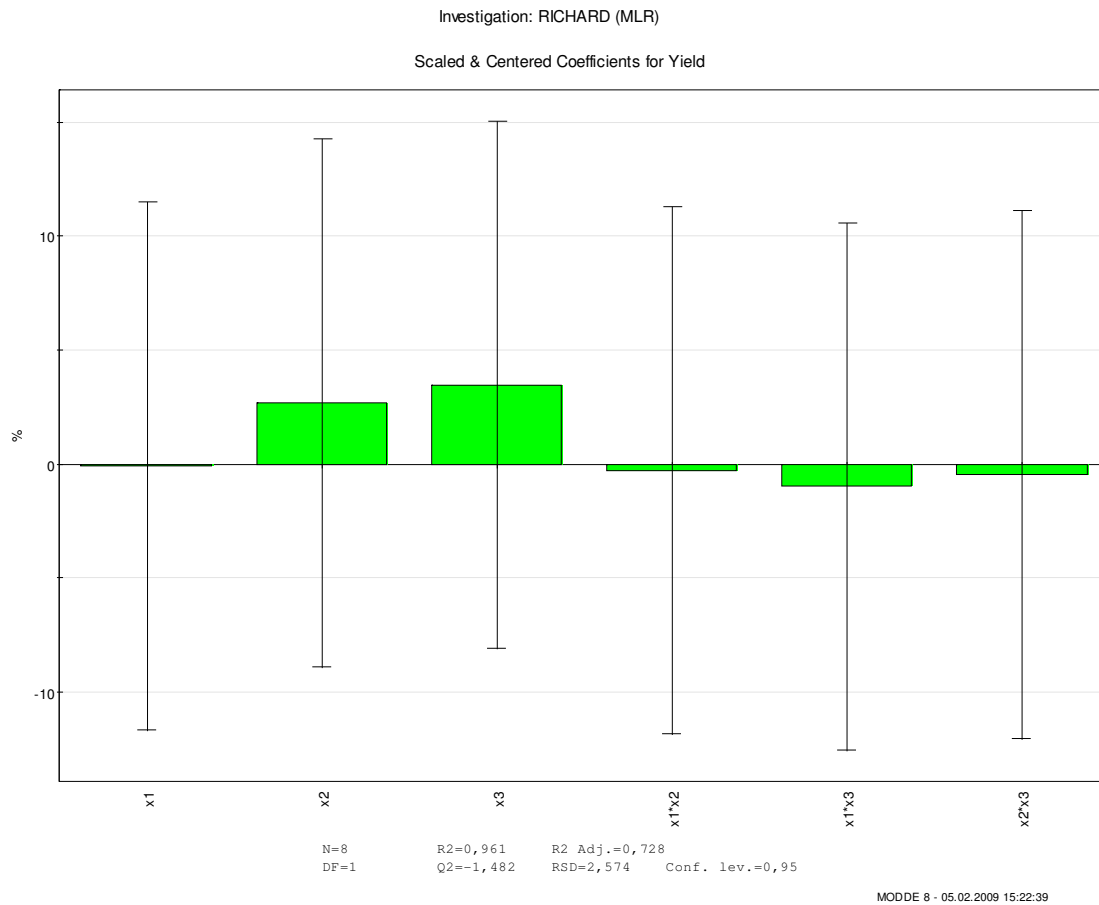
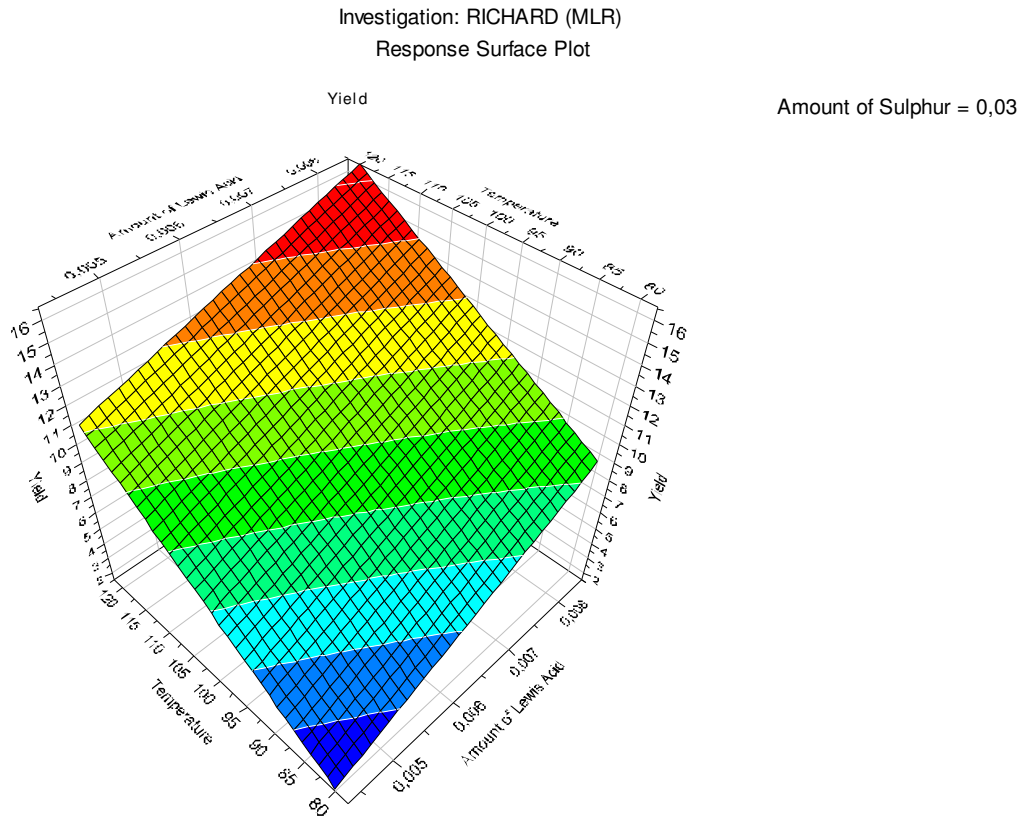


Figure 8: Coefficient Plot of the Response Surface Model.

The coefficient for variable x_2 and x_3 are positive. The coefficient for variable x_1 is small. This means that the variation of the amount of sulphur is not important, but it's presence is necessary as it is the source of sulphide needed for the formation of the thiophene.

Plots of the response surface versus X_2 and X_3 are shown figure 9, 10. A contour plot is shown in figure 11. This plot would give a prediction of how the yield would be when two of the important variables are varied and the other is kept constant.

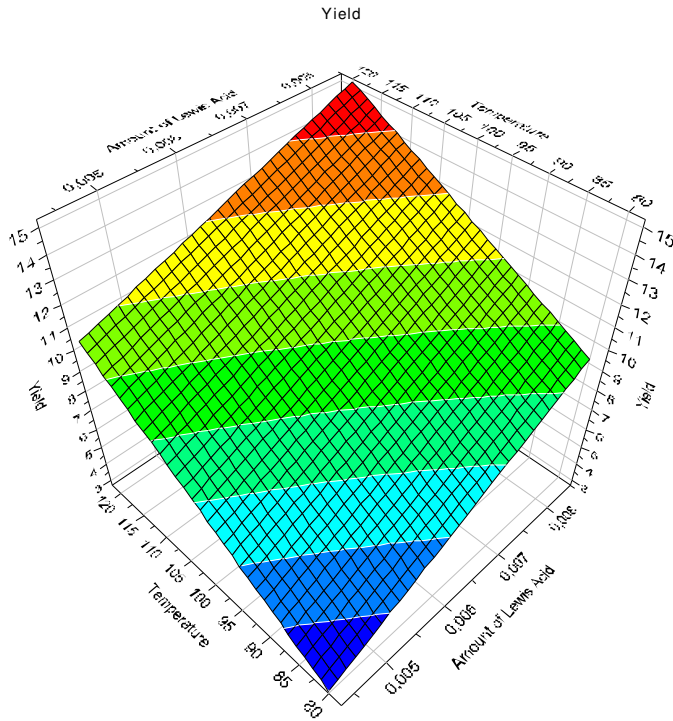


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Figure 9: Response Surface Plot at a Constant $x_1=0.03$ moles

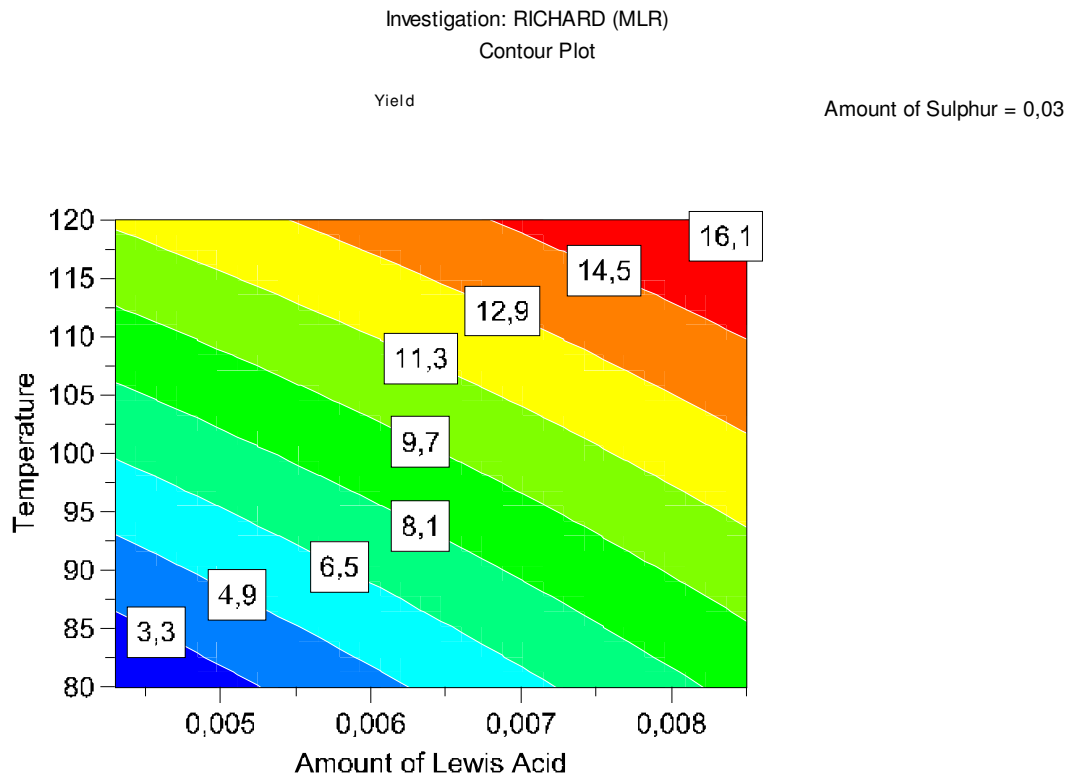
When the X_2 and X_3 was varied, at a constant level of $x_1 = 0.03$ moles in figure 9, the yield obtained was higher when compared to constant level of $x_1 = 0.045$ moles in figure 10

Investigation: RICHARD (MLR)
Response Surface Plot



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Figure 10: Response Surface Plot at a Constant $x_1=0.045$ moles



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Figure 11: Response Surface Contour Plot

From the response surface plot and contour plot, it is seen that increasing variable X_2 and X_3 will increase the yield.

From the analysis so far, it could be concluded that two variables, x_2 (amount of Lewis acid) and x_3 (temperature) have positive linear coefficients and they should be set to their high levels. Variable x_1 is also important but higher amount (concentration) of it is not significant. The best result, from the screening experiment, is 17.5% in experiment number 7 after running for 4 hours. However, care must be taken when setting variable x_3 (temperature). Increasing the temperature above 120°C may lead to product decomposition. Therefore, 110 °C - 120°C should be maintained when adjusting the other variables.

The reaction was then run in the absence of the internal standard using the optimum conditions from screening experiment. A yield of 18.1% of 2,5-dimethylthiophene was distilled between 125°C-135°C when the reaction was run with 0.013 moles of ketone. When the reaction was repeated using higher amount (concentration) of Lewis acid (0.021 mol), a yield 22% of 2,5-dimethylthiophene was obtained.

VARIABLE SETTINGS			YIELDS OBTAINED (%) IN 4HRS
AMOUNT OF SULPHUR (MOLES)	AMOUNT OF LEWIS ACID (MOLES)	TEMPERATURE (°C)	
x_1	x_2	x_3	y
0.03	0.0085	120°C	18.10
0.03	0.021	120°C	22

Table 6: Yields Obtained in Optimum Conditions with Their Variable Settings.

Though the yield are very low, the information from the response surface shows that temperature and drying agent(Lewis acid) concentration are important factors for achieving a better yield when elemental sulphur on C_8K is used in the preparation of 2,5-dimethylthiophene from 2,5-hexanedione.

CHAPTER 4

CONCLUSION AND RECOMMENDATION

A method for the synthesis of 2, 5-dimethylthiophene, with potassium sulphide on potassium graphite as the sulphur source has been investigated. The highest yield obtained was 22%. This result is not impressive since much higher yield can be achieved by using the standard procedure with phosphorus pentasulphide.

The use of a factorial design to investigate the adjustment of experimental condition of the procedure with K_2S on potassium graphite shows that higher temperature ($\leq 120^\circ C$) and increasing the amount of Lewis acid (drying agent) increased the yield. The variation of the amount of sulphur does not seem to have large influence on the yield of thiophene. It may be that the generation of potassium graphite and its reaction with elemental sulphur is the most critical step. This procedure should be further investigated.

Finally, since there was no appreciable yield of 2, 5-dimethylthiophene during the entire synthetic procedure via sulphur on C_8K , this project thesis should pave the way for further research work where appropriate experimental conditions could be discovered that could help in the improvement of the yield.

CHAPTER 5

EXPERIMENTAL

5.1 Materials and Instruments

5.1.1 Materials

The glassware for the experiment was dried in an oven (100 °C) overnight. All the reactions were carried out in an atmosphere of argon. An argon cylinder was equipped with a dried flexible tube and a syringe for the gas inlet to reaction flask. The source of heat was derived from silicone oil, in which the reaction flask is immersed. The flask was fitted with thermometer and the oil bath was heated with an adjustable dual-purpose laboratory electric heater and magnetic stirrer.

Solvents

n-Heptanes, n-hexane was dried over KOH pellets for 1hr and filtered. Dried THF and diethyl ether was collected directly from the integrated dry solvent dispenser. The chloroform was used directly as collected from the bottle.

Reagents.

The reagents were used as delivered.

2, 5-hexanedione (97%) was obtained from ALFA AESAR.

Elemental sulphur (99.9%), graphite powder, 48% BF₃ Borontrifluoride etherate, 99% Cl tin (IV) chloride, 99% Aluminum Chloride(anhydrous) were obtained from FLUKA CHEMIKA.

Tetralin (99%) was obtained from SIGMA ALDRICH.

Potassium metal (cylindrical pieces in paraffin oil) was obtained from SEELZE-HANNOVER

5.1.2 Substance Identification Instruments

Gas-Liquid Chromatography (GC)

The GC analyses were made using Varian 3400 instrument equipped with an unpolar Supelco (spB-5, 0.35mm * 30mm) column and a flame ionization detector. The initial oven temperature is 60 °C.

NMR Spectroscopy

NMR spectra were recorded on a Mercury-Varian plus instrument (400MHz for ^1H , 100MHz for ^{13}C) at room temperature. Chemical shifts are reported in parts per million (ppm). ^1H shifts are referenced to residual chloroform-d ($\delta=7.26$). ^{13}C shifts are referenced to chloroform-d ($\delta=77.16$).

Splitting patterns were represented as follows: s for singlet; d for doublet; t for triplet; q for quartet and m for multiplet.

Infrared (IR) Spectroscopy:

The IR spectra of the liquid substances were run on a Varian 7000e FT-IT spectrometer powered by a high wattage water-cooled infrared source.

Mass Spectroscopy (GC/MS):

These were recorded at the pharmacy department with a Quattro micron $^{\text{tm}}$ GC 689N by Agilent technologies. The column is equipped with an unpolar DB-5, 30m * 0.25mm. EI, 70eV was used for ionization with an initial oven temperature of 50 °C.

5.2 General Procedure (Synthesis of 2, 5-Dimethylthiophene)

Formation of 2, 5-Dimethylthiophene, from K_2S , is a multi-step procedure. The first part involves melting potassium over graphite powder to generate C_8K and its subsequent reaction with elemental sulphur to form potassium sulphide. This is followed by the nucleophilic attack by the sulphide at the two carbonyl carbon of the ketone and subsequent dehydration to form the desired product — thiophene.

5.2.1 Formation of K_2S on C_8K .

An oven dried round bottom flask was charged with 0.46g, (0.0048 mol), of graphite and magnetic stirrer. The flask was air-tightened and closed with a flexible rubber stopper. It was heated in an oil bath to 150 °C to 200 °C, for 30 minutes, under a constant flow of argon. The graphite powder was stirred in a way by placing the heating flask on the edge

of the magnetic stirring/heating plate so that there is a random movement of the stirring bar in order to facilitate better and even stirring. Potassium metal 0.023g (0.0059 mol) was introduced into the flask with continued stirring and high rate of argon flow. The potassium melted on the heated graphite powder and reaction occurred which was seen by the colourisation of the black powder to bronze colour. After the formation of this bronze-coloured C_8K , it was allowed to stir for 30 min. Then the temperature was reduced to 125 °C—140 °C (a little above the melting point of sulphur-112.8 °C). Flowers sulphur (2.0g, 0.063 moles) was then added and the gold coloured powder changed to a black semi-solid (slurry).

5.2.2 Formation of 2, 5-Dimethylthiophene from K_2S .

This reaction is an immediate continuation of experimental section 3.1 in the same pot. After the formation of the black slurry, the flask was cooled to room temperature with argon still flowing. Heptane 20 ml was added to the black substance in the flask with stirring. The flask was fitted with a reflux condenser and the heat was restored and heated to 120 °C. Then 2.00 g, (0.018 mol) of 2, 5-hexanedione was added dropwise. The reaction was allowed to proceed for 30 minutes. Then 2.23 g, (0.0085 mol), boron trifluoride etherate was added two times at one hour interval. The reaction was continued for 4hrs after which the reaction was stopped.

WORK-UP: When the refluxing in the reaction flask had subsided, the reaction was stopped by quenching with ice water. A total amount of 25 ml of water was added. The mixture was isolated by steam distillation; extracted with ether and washed several times with saturated NaCl solution. The organic layers were combined and dried over anhydrous $MgSO_4$. After drying, the solvent was removed in a rotary evaporator.

A yield of 0.30g, 15% of light yellow liquid was collected.

MS(EI, 70eV) m/z (relative intensity): 115.1 (0%), 113.1 (11%), 112.1 (87%, M^+), 111.1 (100%), 109.1 (2%), 97.1 (56%), 77.1 (16%), 71.01 (6.5%), 69.0 (8%), 59.0 (26%), 53.1 (12.5%), 51.1 (18%), 45.0 (20%).

There were no peaks in the NMR spectrum indicating the presence of 2,5-dimethylthiophene. Only the recovered ketone was detectable in the spectrum. The GC/MS shows some trace of the product because of the 112.12 present in the spectrum corresponds to molecular ion is equivalent of 2,5-dimethylthiophene.

5.3 Testing Different Solvent and Lewis Acid

5.3.1 Hexane as the Solvent with Boron Trifluoride Etherate

The experimental procedure given in 5.2.1 and 5.2.2 above was used with hexane as the solvent. Upon work-up, trace amount of 2,5-dimethylthiophene (1.6%) was detected by the GC. The starting ketone was recovered in 98.4%.

5.3.2 Ether as the Solvent with Boron Trifluoride Etherate

The experimental condition (section 5.2.1, 5.2.2) was use with diethyl ether as solvent. However, no or only trace amounts (<2%) of the thiophene was found after work-up.

5.3.3 Heptane, Hexane, Ether with Either Aluminum Chloride or Tin (IV) Chloride

Also, when the experimental condition in 5.2.1 and 5.2.2 were used with hexane, ether heptane as solvent and with either aluminum chloride or tin (IV) chloride as the drying agent, no improvements in the formation of the thiophene were observed.

5.3.4 Chloroform with Boron Trifluoride Etherate

When the experiment was carried out with chloroform as the solvent and boron trifluoride etherate, no thiophene was detected at the end of the reaction.

5.3.5 THF with Boron Trifluoride Etherate

The experimental conditions describe in section 5.2.1 and 5.2.2 was used. When THF (solvent) and boron trifluoride etherate (drying agent) was used, the yield of the target product was better compare to when heptane, hexane and ether was used. After work-up, a yield of 0.27g, 13.50%, light yellow liquid was obtained. The GC analysis shows 49.7% of the 2,5-dimethyl thiophene 44.5% of the unreacted ketone. The NMR spectrum showed the presence of the desired product and the unreacted ketone.

^1H NMR (CDCl_3): 2,5-dimethylthiophene: δ 6.5 (CH), 2.4 (CH_3);
2,5-hexanedione: δ 2.7 (CH), 2.1 (CH_3);

^{13}C NMR (CDCl_3): 2,5-dimethylthiophene: δ 137.5 (C (CH_3) (S)); 125.0 (CH); 15.4 (CH_3);
2,5-hexanedione: δ 207.4 (C=O), 37.1 (CH_2), 30.1 (CH_3);

GC/MS (EI, 70eV) m/z (relative intensity): 115.1 (0%), 113.1 (11%), 112.1 (87%, M⁺), 111.1 (100%), 109.1 (2%), 97.1 (57%), 77.10 (16%, 7%), 69.0 (8%), 59.0 (30%), 58.0 (11%), 53.1(15%), 51.1 (20%), 45.0 (23%).

5.3.6 THF with Tin (IV) Chloride

The experimental condition in 5.2.1 and 5.2.2 were used with THF (solvent) and Tin (IV) chloride (drying agent). This procedure gave the best result so far where the GC shows 78.27% of 2,5-dimethylthiophene in the crude product. After work-up, a yield 0.33g, 16.5% of a light yellow liquid was collected. NMR analysis showed the spectrum of the 2,5-dimethylthiophene. The MS and the GC however, showed some trace of unreacted ketone.

¹H NMR (CDCl₃): δ 6.6 (CH); 2.5 (CH₃)

¹³C NMR (CDCl₃): δ 137.7 (C (CH₃) (S)); 125.0 (CH); 15.5 (CH₃)

GC/MS (EI, 70eV) {m/z (% relative intensity)}: 115.1 (0%), 113.1 (15%), 112.1 (96%, M⁺), 111.1 (100%), 97.1 (73%), 78.1, 80.0, (11%) 69.0 (11.05%), 77.0(26%), 69.0 (11.05%), 59.0 (43%), 58.0 (14%), 51.1 (22%), 45.0 (26%).

This procedure was repeated and the result obtained was the same. The procedure and combination of materials was now selected for the screening (factorial) experiment.

5.4 FID Response Factor Determination.

Due to the difficulties in isolating pure 2,5-dimethylthiophene from the reaction mixture and that there is always some loss during work-up, it was decided to determine the yield directly from the crude product using GC through internal standard technique. Tetralin was found to be a suitable internal standard since it is chemically inert under the reaction condition used. For this internal standard technique, it is necessary to calibrate the FID response. This was done as follows:

Four different samples of 2,5-dimethylthiophene collected from experimental section 5.3.6 were weighed (0.056 g, 0.112 g, 0.224 g, 0.448 g). To each of these samples, a constant and accurately weighed amount of tetralin (0.132 g) and diluted with 10 ml of THF (solvent). Then, 0.1 microlitres was injected into the GC instrument.

The concentration ratios were calculated. The peak area ratios were determined from the GC chromatogram. The data are shown in Table 7.

SAMPLE NUMBER	AMOUNT OF TETRALIN (moles)	AMOUNT OF 2,5-DIMETHYLTHIOPHENE (moles)	AREA RATIO	CONCENTRATION RATIO
1	1.028×10^{-3}	0	0	0
2	1.021×10^{-3}	0.516×10^{-3}	0.275	0.505
3	1.028×10^{-3}	1.016×10^{-3}	0.525	0.988
4	1.021×10^{-3}	2.011×10^{-3}	1.008	1.972
5	0.998×10^{-3}	4.011×10^{-3}	2.072	4.019

Table 7: The Amount in moles of Tetralin, Amount in moles of 2, 5-dimethylthiophene, Peak Area ratio and the Concentration Ratio.

The plot of the area ratio versus the concentration ratio gives the calibration curve in Figure 12. The gradient (0.512) of this linear graph is equal to the instrumental response factor (F) in relation to the compound.

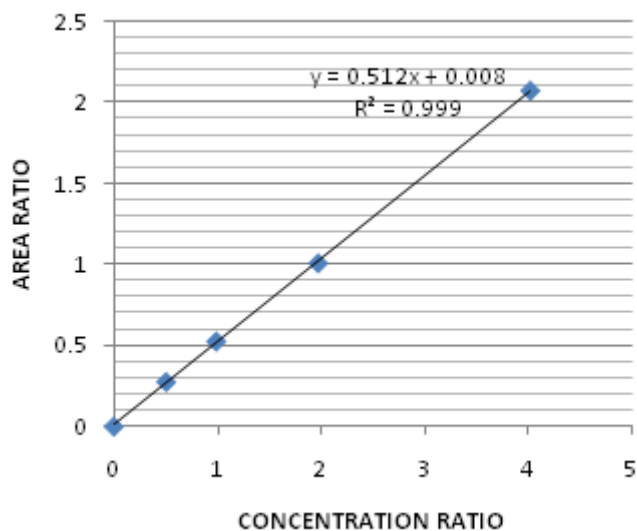


Figure 5.0: FID CALIBRATION CURVE

This calibration was then used to determine the yield of 2,5-dimethylthiophene, in the screening experiment. The yield was compared according to this mathematical relation below:

$$\frac{A_X}{A_S} = F \left(\frac{X}{S} \right)$$

Where,

A_x/A_s = area ratio determined from the chromatogram,

A_x = the area of the thiophene peak,

A_s = the area of the tetralin peak.

F = the response factor determined from the FID curve (0.512).

S = amount of internal standard (mol)

X = unknown amount of analyte (mol)

The percentage yield was then calculated from:

$$\text{yield (\%)} = \frac{X}{\text{amount (mol) of starting ketone}} \times \frac{100}{1}$$

Experimental

5.5 Experimental Procedure for the Screening (Factorial) Experiment.

An oven dried round bottom flask was charged with 0.46g, (0.0048 mol) of graphite and a magnetic stirring bar. The flask was air-tighten and closed with a flexible rubber septum. It was heated in an oil bath to 150 °C to 200 °C, for 30 min, under a constant flow of argon. The graphite powder was stirred in a way by placing the heating flask on the edge of the magnetic stirring/heating plate so that there is a random movement of the stirring bar in order to facilitate better stirring of the powder. Potassium metal, 0.023 g (0.00059 mol) was introduced to the flask with continued stirring and high rate of argon flow. The potassium melted on the heated graphite powder and the intercalation reaction occurs which was seen by the colourisation of the black powder to bronze colour. After the formation of this bronze-coloured C_8K , it was allowed to stir for 30 min. Then the temperature was reduced to 125 °C—140 °C (a little above the melting point of sulphur). Flowers of sulphur, according to the experimental domain (−1 and +1)

in table 2, was then added and the bronze coloured powder changes to black semi-solid (slurry). The flask was cooled to room temperature with argon still flowing. THF 20 ml was added to the black substance in the flask with stirring. The flask was fitted with a reflux condenser and the heat was restored to 120°C. Then 2,5-hexanedione, 1.50 g, (0.0128 mol) was added dropwise. An accurately weighed, 1.309 g, (0.009905 mol) of tetralin (internal standard) was added. After 30 minutes, tin (IV) chloride, according to their experimental domain (-1 and +1) in table 2, was added twice at 90mins interval. After complete addition of the Lewis acid, the reaction was allowed to proceed for 4 hrs further.

To monitor the reaction, (0.1 ml) samples of the reaction mixture were withdrawn after 2, 3, and 4hrs respectively. The samples were diluted with 1 ml of THF and analyse by GC.

The yields obtained were determined as described in above (section 5.4).

5.6 Experimental Procedure Using Optimum Conditions

An oven dried round bottom flask was charged with 0.46g, (0.0048 mol), of graphite and magnetic stirrer. The flask was air-tighten and closed with a flexible rubber septum. It was heated in an oil bath to 150 °C to 200 °C, for 30 min, under a constant flow of argon. The graphite powder was stirred in a way by placing the heating flask on the edge of the magnetic stirring/heating plate so that there is a random movement of the stirring bar in order to facilitate better stirring of the powder. 0.023g (0.00059 mol) of potassium metal was introduced into the flask with continued stirring and high rate of

Experimental

argon flow. The potassium melted on the heated graphite powder and intercalation reaction occurs which was seen by the colourisation of the black powder to bronze colour. After the formation of this bronze-coloured C_8K , it was allowed to stir for 30 min. Then the temperature was reduced to 125°C—140°C (a little above the melting point of sulphur). Sulphur 1.0 g, (0.063 mol) was then added and the bronze coloured powder changes to black semi-solid (slurry).

After the formation of the black slurry, the flask was cooled to room temperature with argon still flowing. THF 20 ml was added to the black substance in the flask with stirring. The flask was fitted with a reflux condenser and the heat was restored to 120°C. Then 1.5 g, (0.00059 mol) of 2, 5-haxanedione was added in dropwise. It was allowed to react

for 30 minutes. Then 2.23 g, (0.0085 mol), of tin (IV) chloride was added twice at 90 min interval. After Lewis acid addition, it was allowed to react 4 hours further after which the reaction was discontinued.

WORK-UP: When the refluxing in the reaction flask had subsided (after 4 hours), the reaction was stopped by pouring ice water into the flask. Steam distillation was used to collect the product from the mixture. The distillate was extracted with diethyl ether and the combined organic layers were washed several times with saturated NaCl solution. The organic layer was collected and dried over anhydrous MgSO_4 . After drying and filtered, the solvent was removed in a rotary evaporator. A yield of 0.27 g, 18.1% of 2,5-dimethylthiophene was collected.

When this reaction was repeated using 5.47 g, (0.021 mol), of tin (IV) chloride (higher amount), a yield of 0.33 g, 22% of 2, 5-dimethylthiophene was collected.

^1H NMR (CDCl_3): δ 6.59 (CH); 2.48 (CH_3)

^{13}C NMR (CDCl_3): δ 137.67 (C (CH_3) (S)); 125.05 (CH); 15.52 (CH_3)

GC/MS {m/z (% relative intensity)}: 115.0 (0.3%), 114.0 (3%), 113.1 (9%), 112.1 (79.50%, M^+), 111.1 (100%), 98.0 (4%), 97.0 (74%), 78.0 (12%), 7.0 (28%), 58.9 (33%), 44.9 (19%)

IR {wave number (cm^{-1})}: 2919.23(C—H stretch in CH_3); 3066.31(C—H aromatic); 790.76 (aromatic C—H bending); 670.99(C-S stretching); 1600—1400 (C=C stretching)

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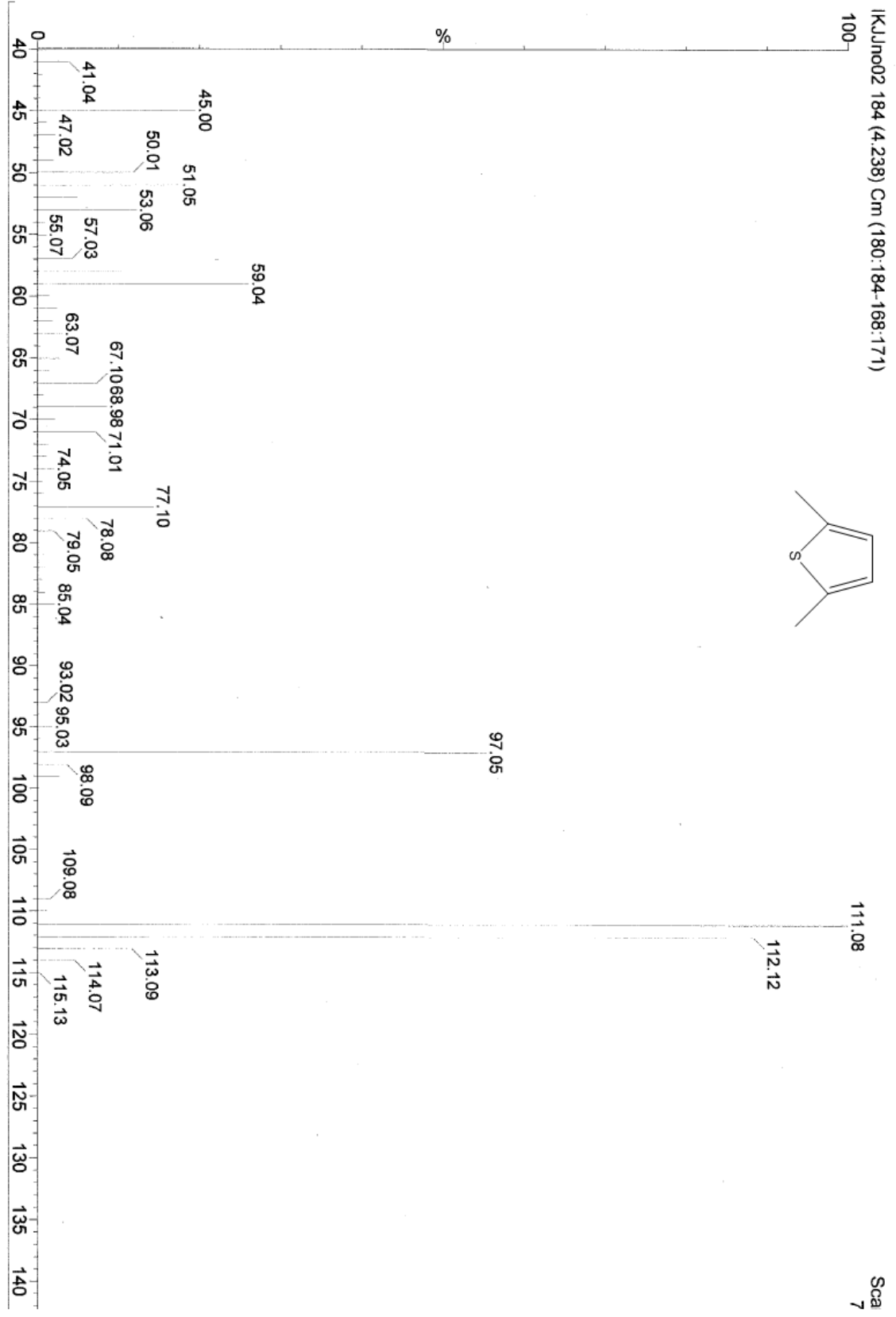
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APPENDICES

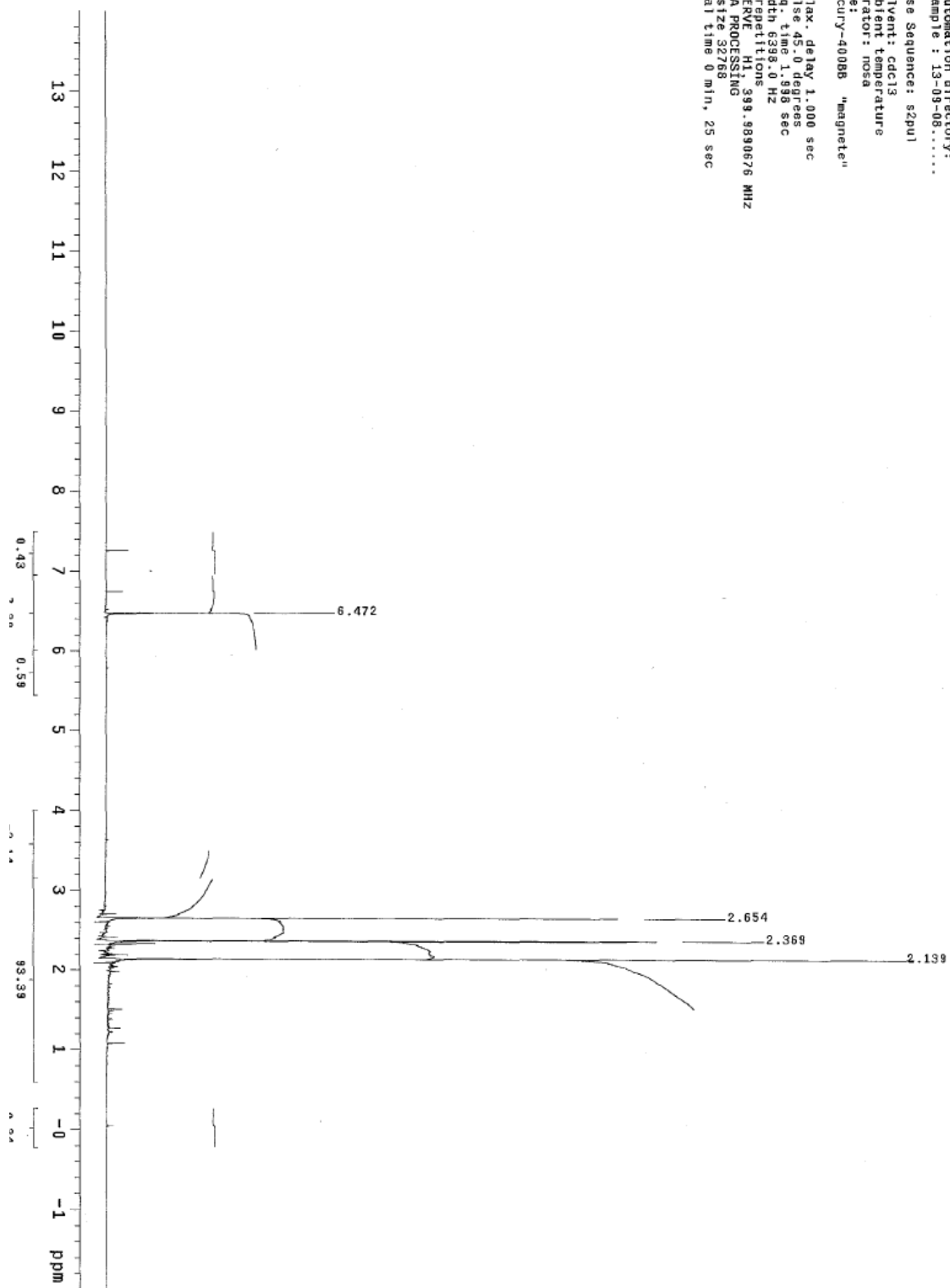
¹H NMR, ¹³C NMR, GC-MS, IR SPECTRA AND GC CHROMATOGRAM OF THIOPHENE COMPOUNDS:

GC-MS result when heptane (solvent) and Boron trifluoride etherate was used

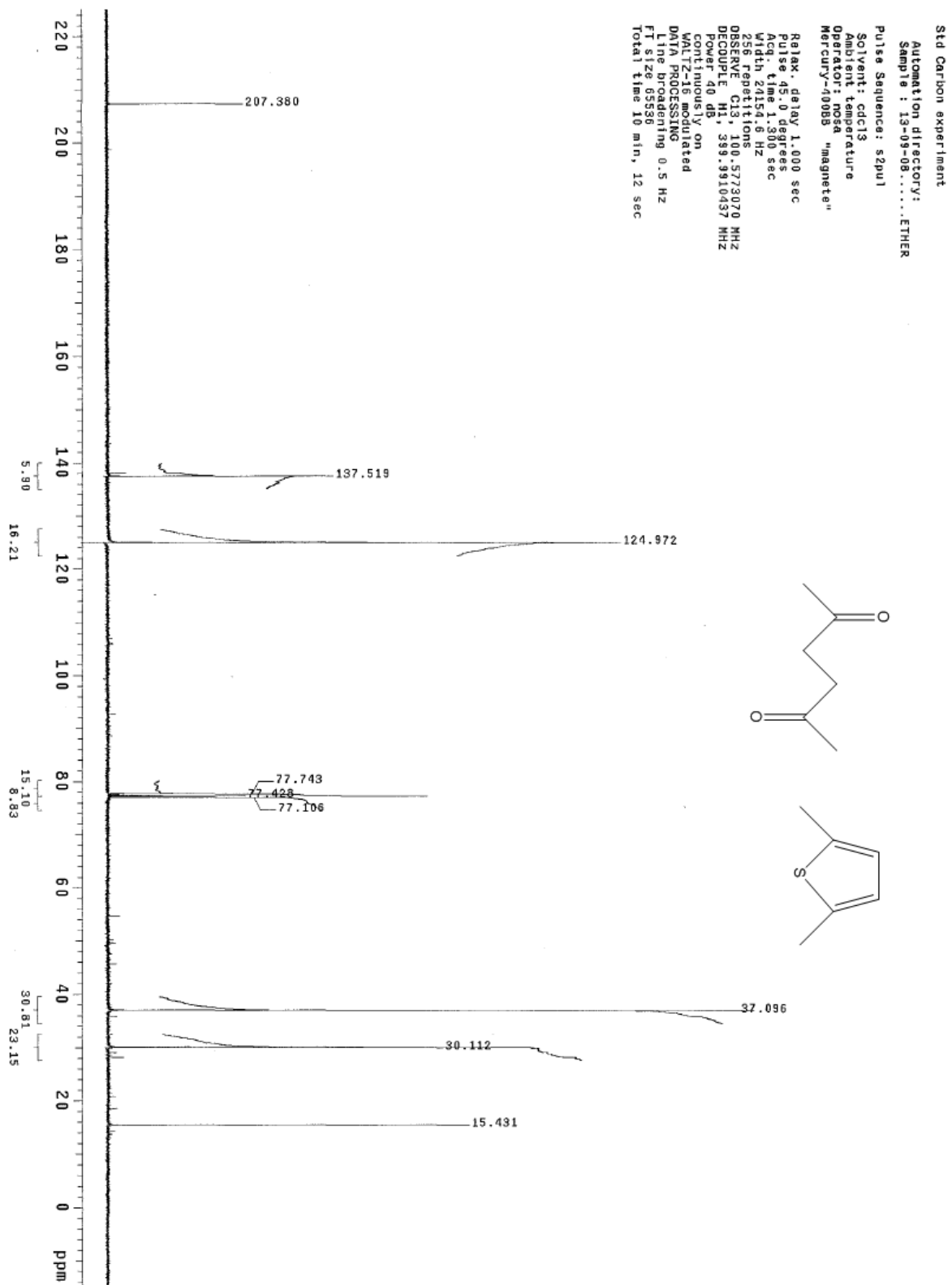


Proton NMR when THF (solvent) and Boron Trifluoride Etherate (drying agent) was tried.

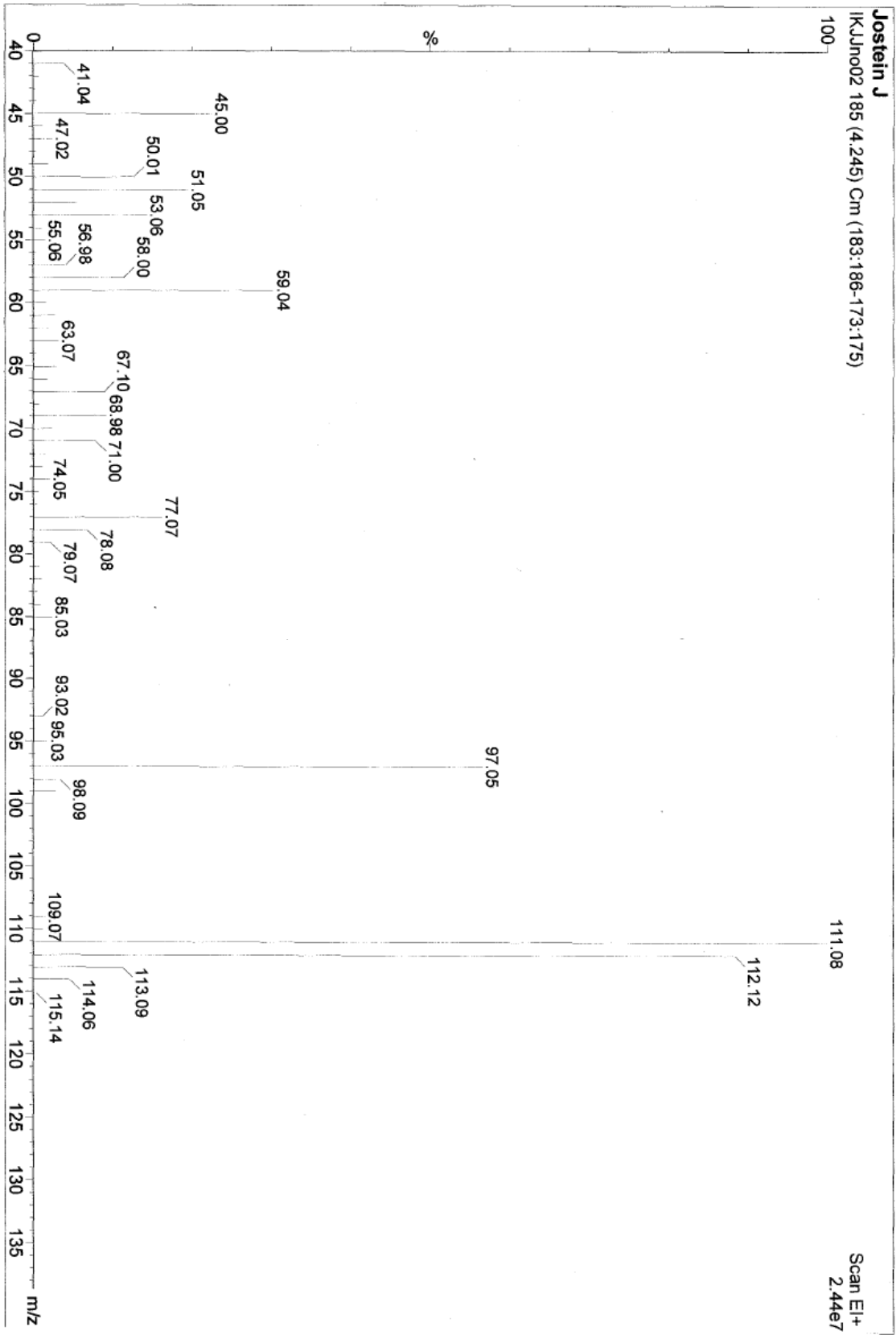
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File:
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Pulse 45.0 degrees
Acq. time 1.998 sec
Width 6398.0 Hz
& repetitions
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DATA PROCESSING
F1 size 32768
Total time 0 min, 25 sec



Carbon-13 NMR when THF (solvent) and Boron trifluoride etherate was tried



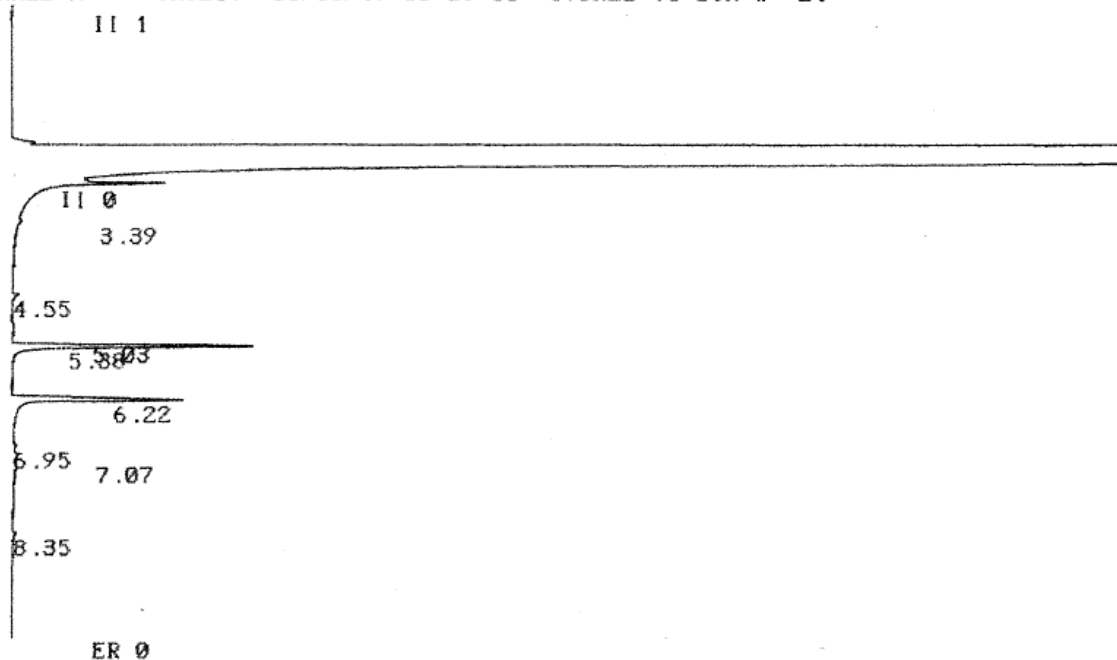
GC-MS result when THF (solvent) and Boron trifluoride etherate was tried



GC result when THF (solvent) and Boron trifluoride etherate was used.

LOW BATTERY

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DATA SAVED TO BIN # 24

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4	49.686	5.38	10214 03
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6	0.389	6.95	80 01
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8	0.851	8.35	175 01

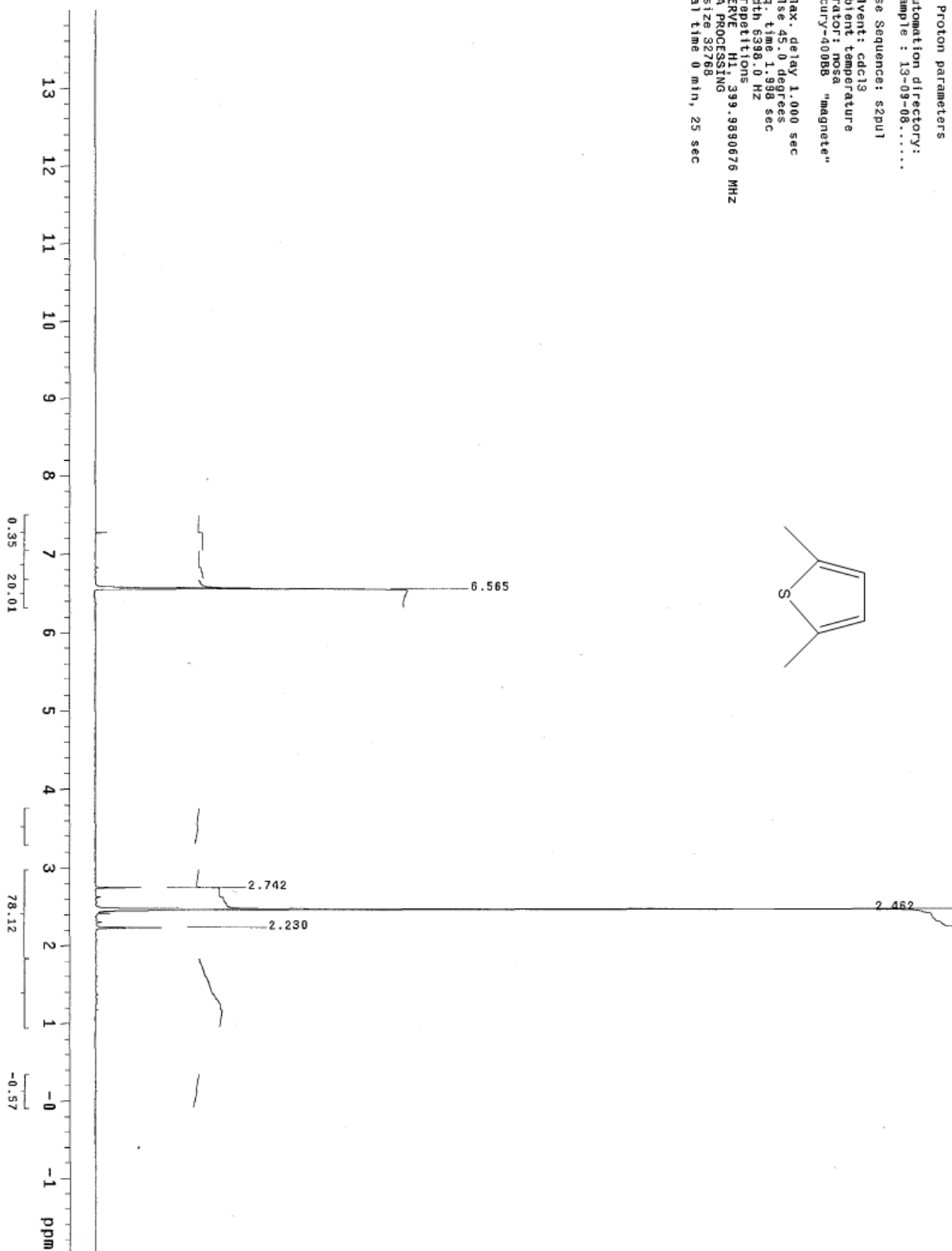
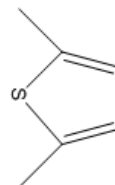
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WARNING - MEMORY AT 2. K - UNPROTECTED CHROMATOGRAMS WILL BE REPLACED

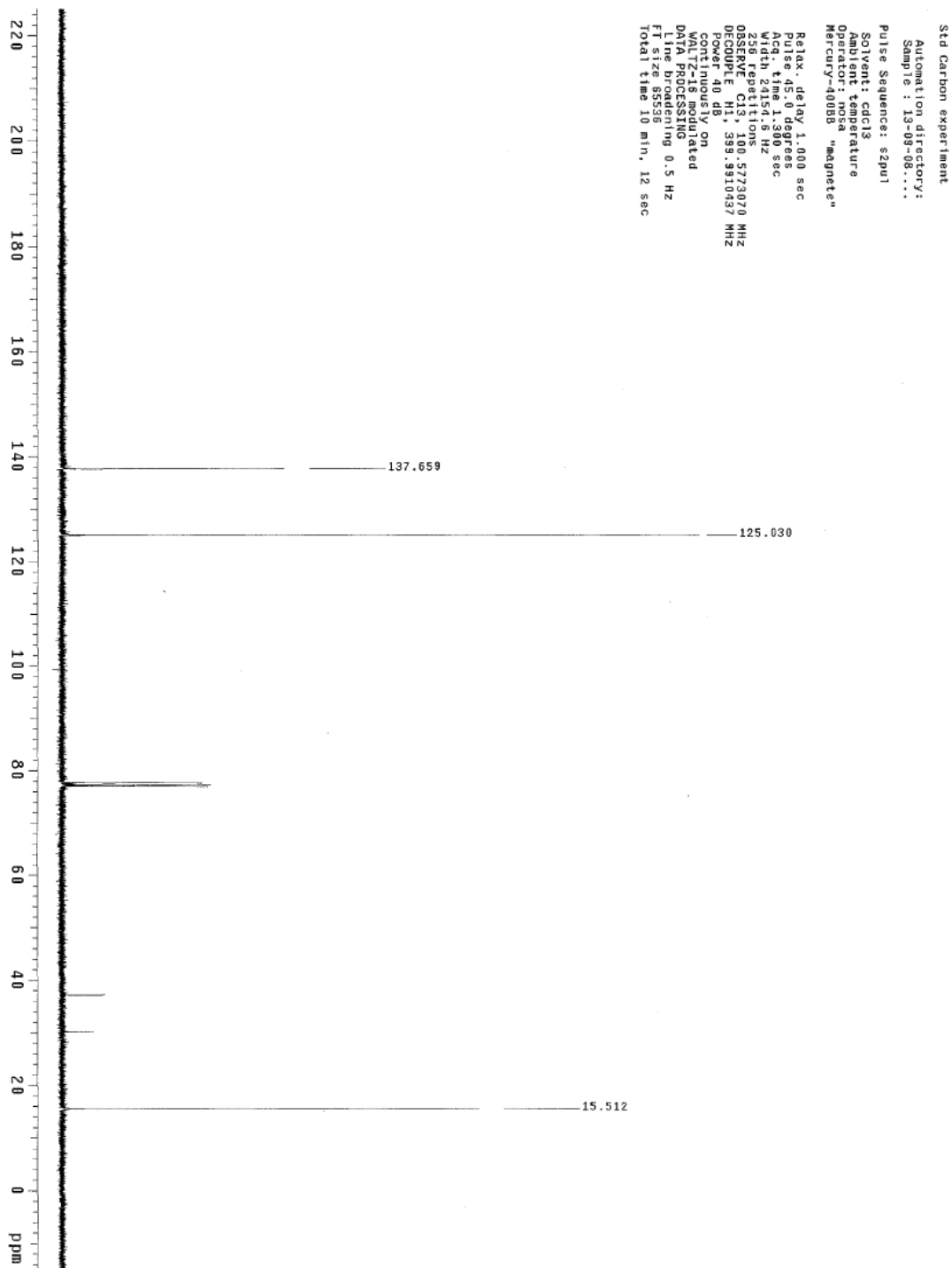
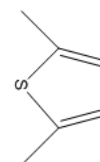
INK LOW - CHANGE PRINT CARTRIDGE AND PRESS [CTRL-SHIFT-C]

Proton NMR when THF (solvent) and Tin (IV) tetrachloride was tried/used.

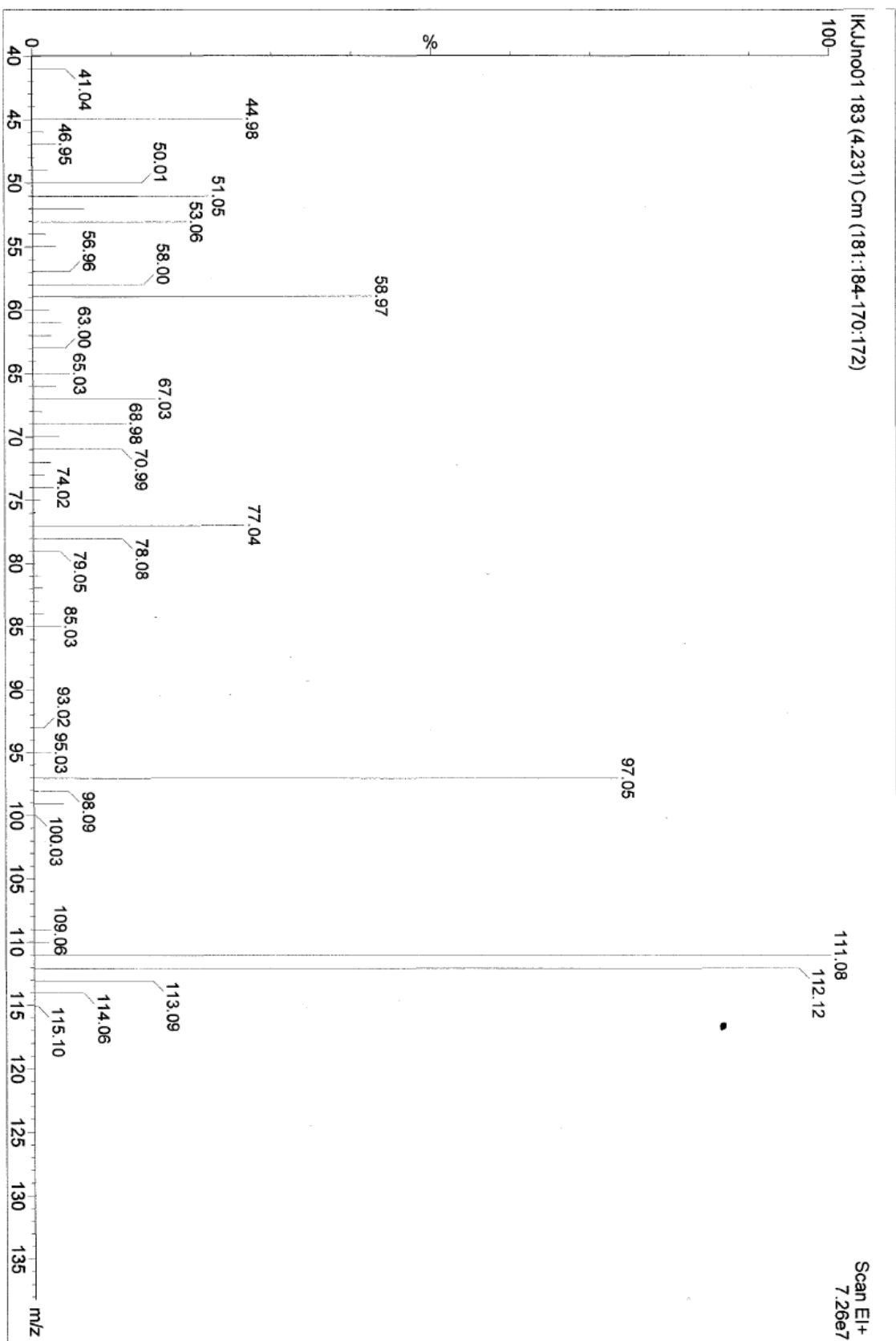
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DATA PROCESSING
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Total time: 0 min, 25 sec



Carbon-13 NMR when THF (solvent) and Tin (IV) tetrachloride

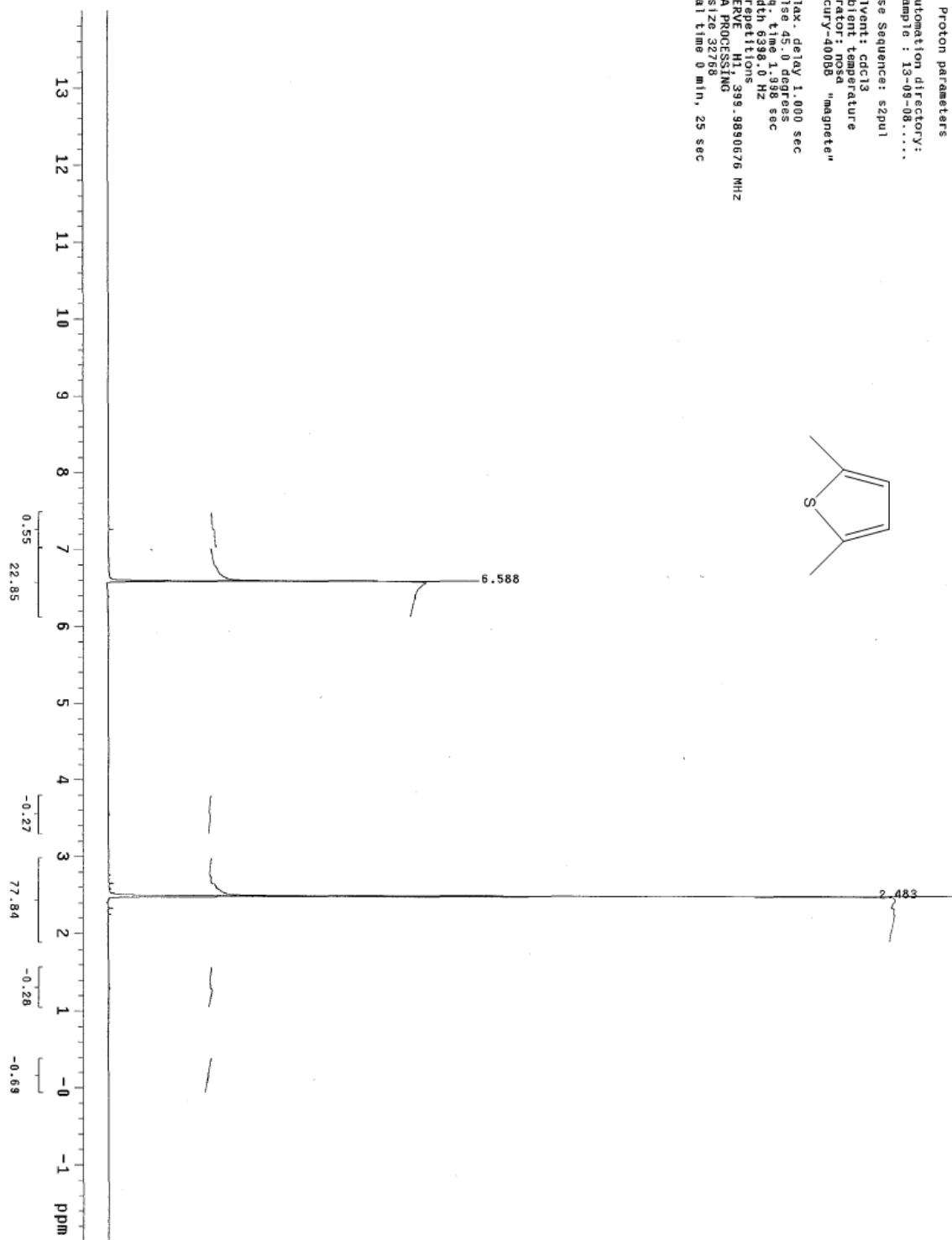
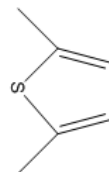


GC-MS when THF (solvent) and Tin (IV) Tetrachloride was used/ tried

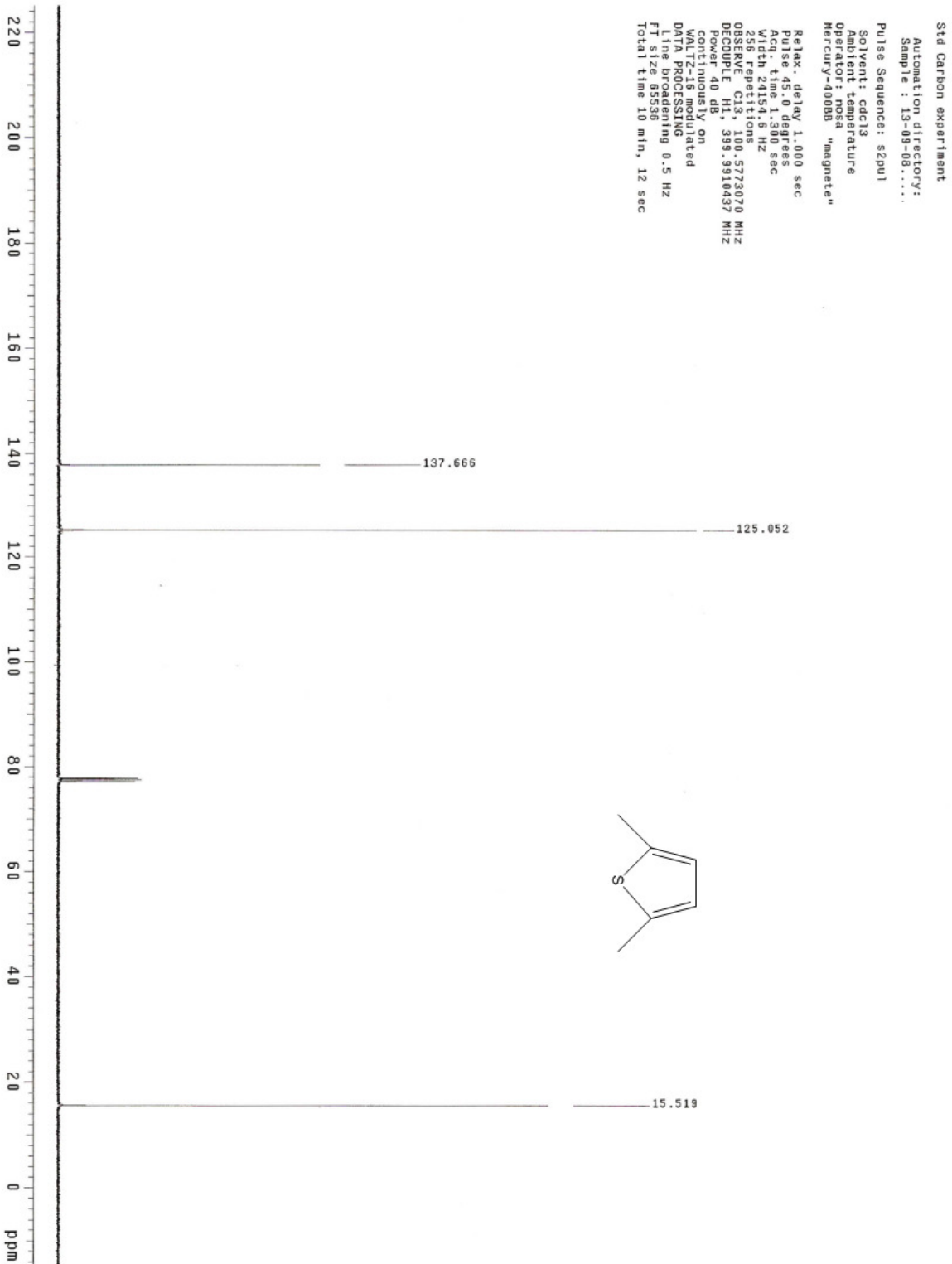


Proton NMR results from optimum experiments

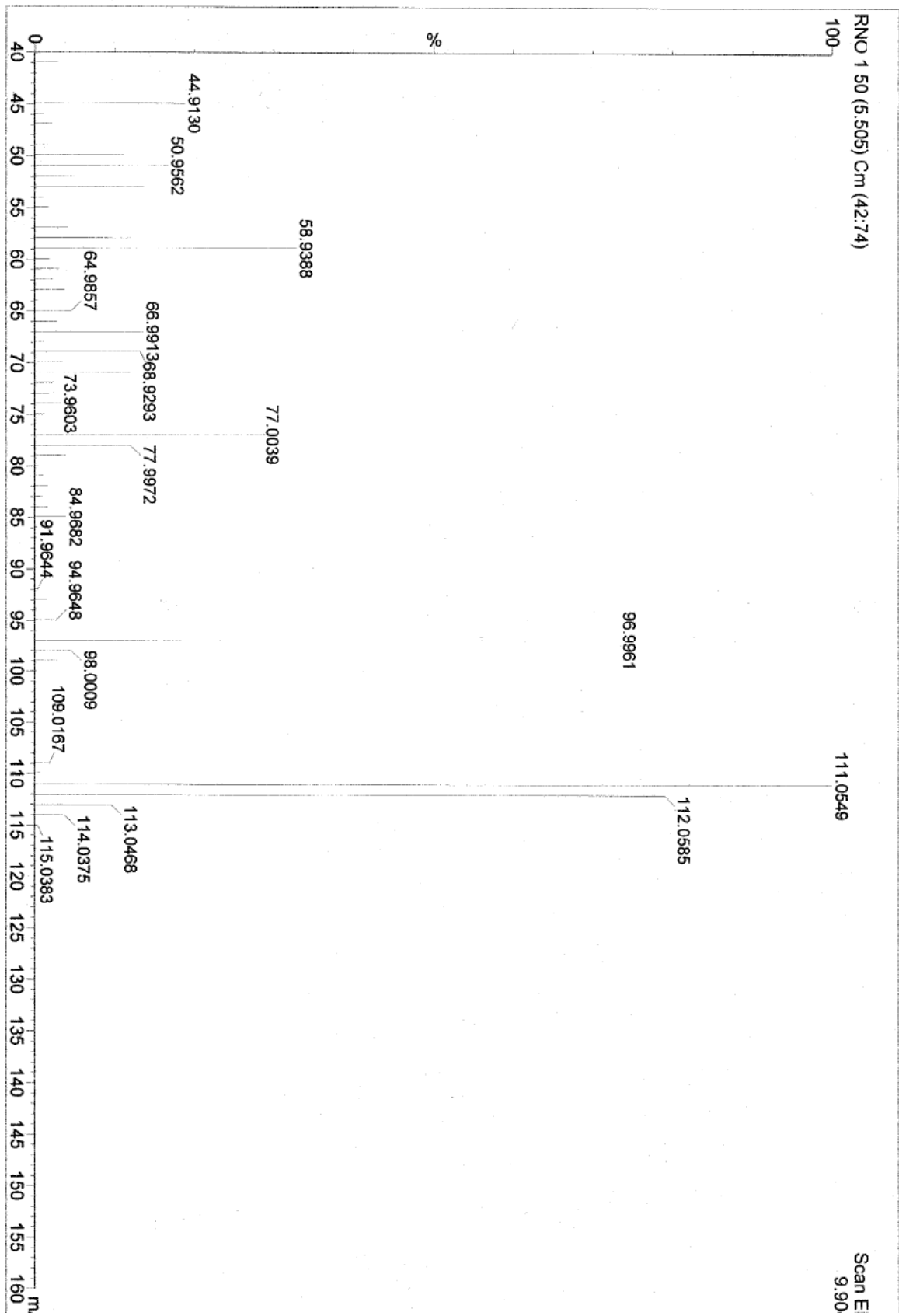
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DATA PROCESSING
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Total time 0 min, 25 sec



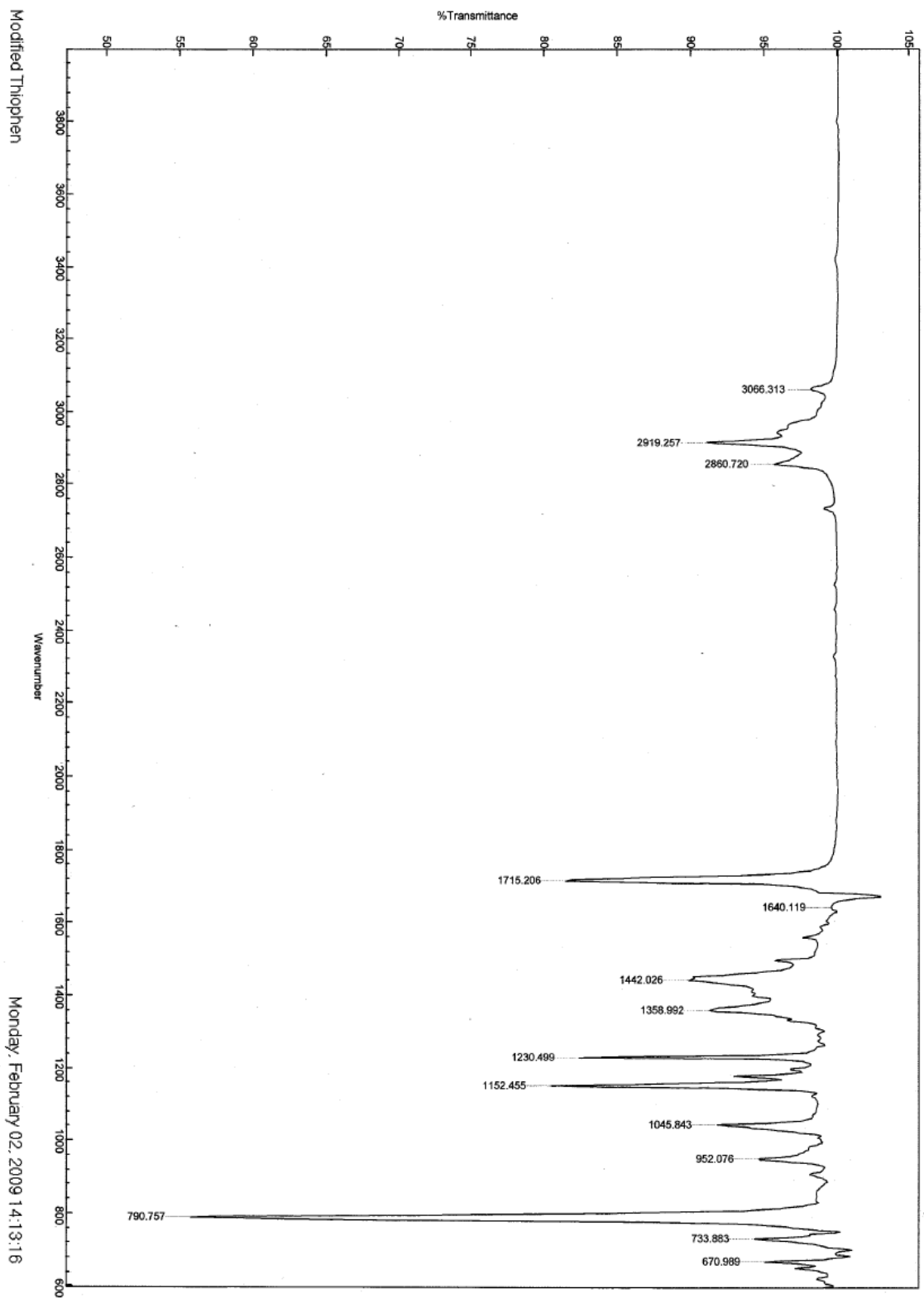
Carbon-13 NMR results from optimum reaction experiment



GC-MS results from optimum reaction experiment



IR results from optimum reaction experiment



Print Composition3

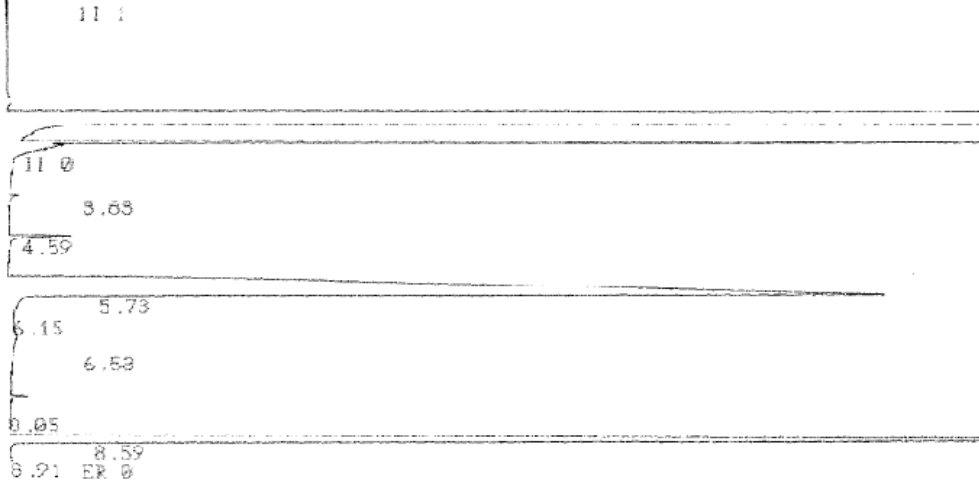
Monday, February 02, 2009 14:13:16

GC results from screening experiments

Experiment 1

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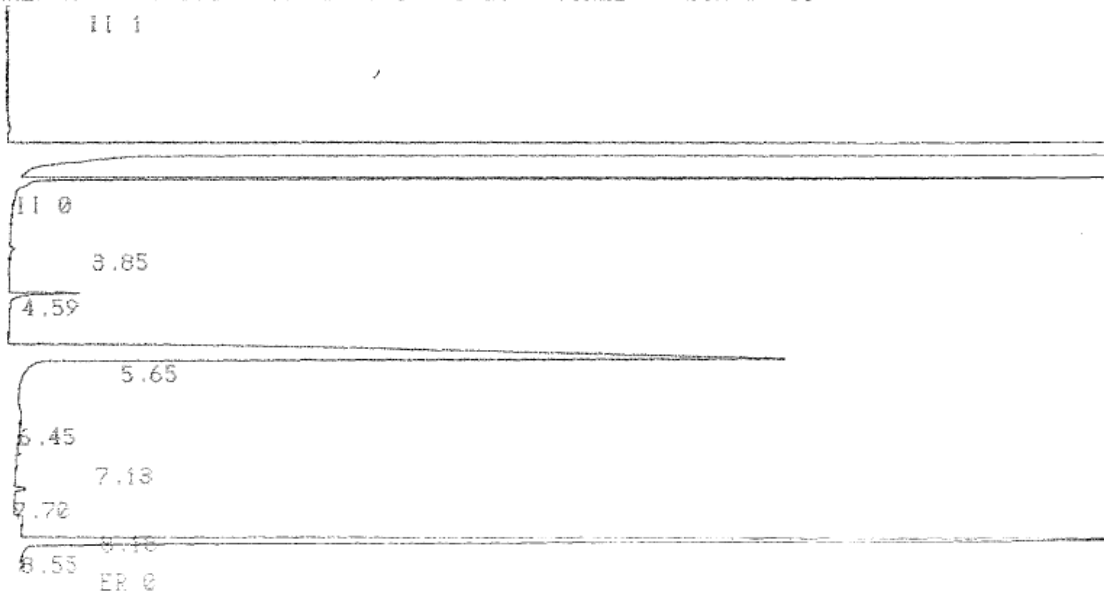


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Experiment 2

LOW BATTERY

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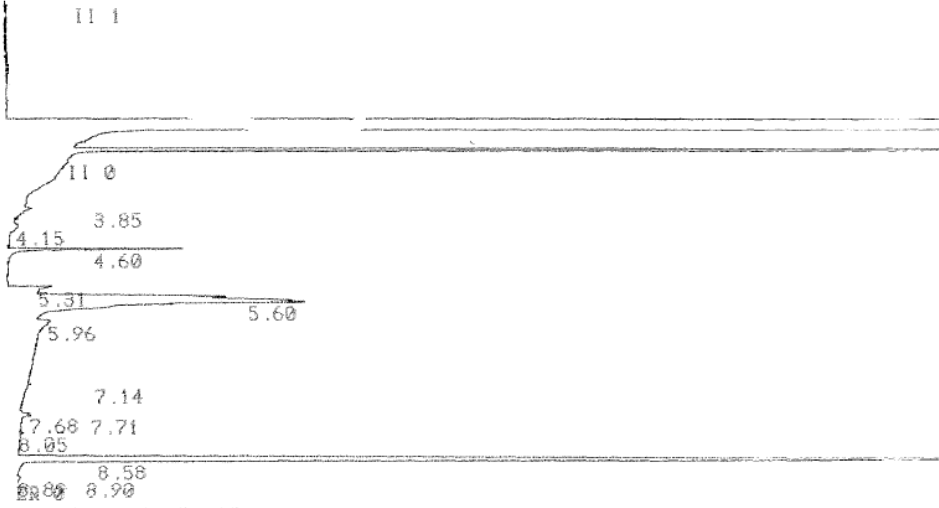


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Experiment 3

LOW BATTERY

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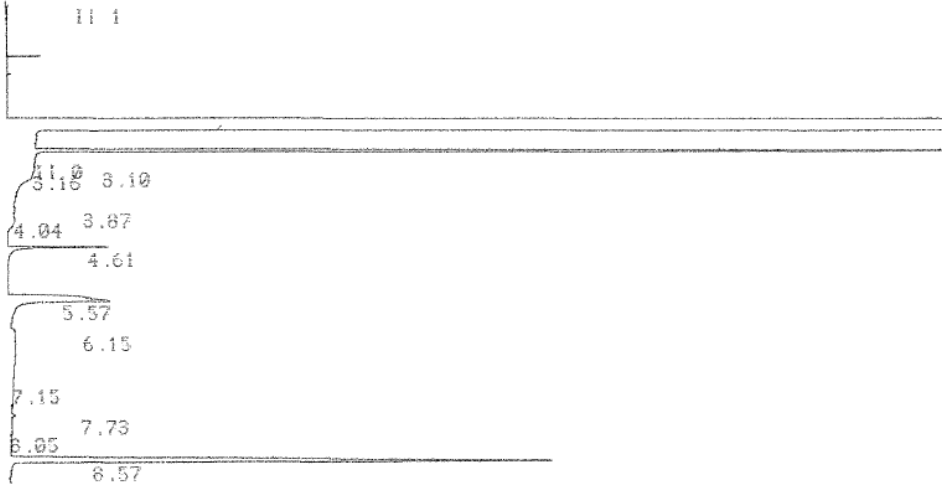
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Experiment 4

LOW BATTERY

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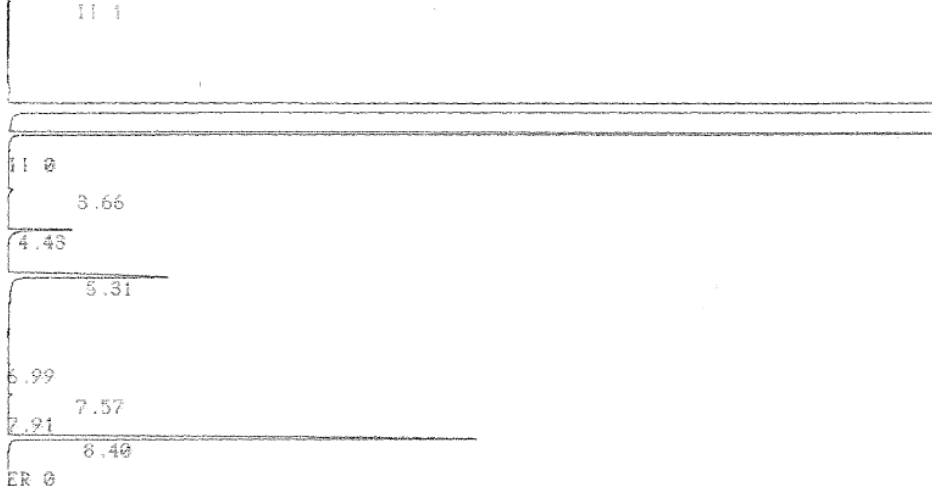
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Experiment 5

END OF DIALOG
LOW BATTERY

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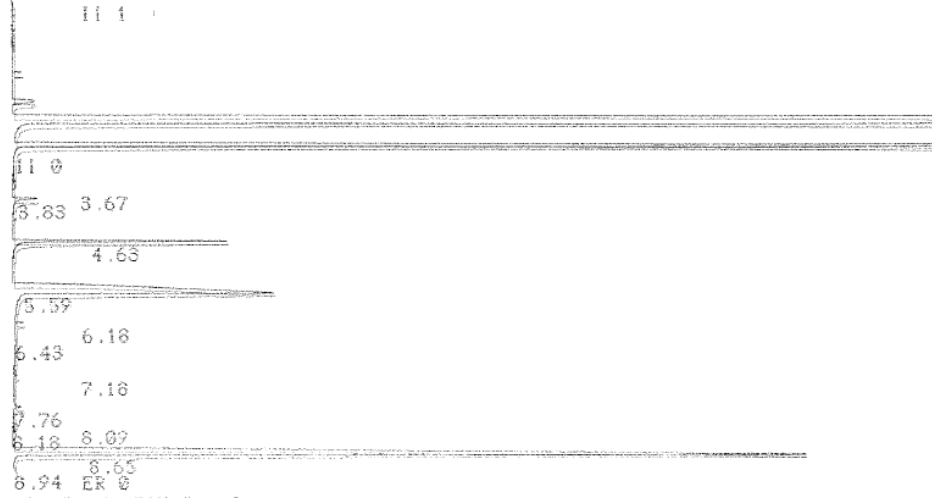
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Experiment 6

LOW BATTERY

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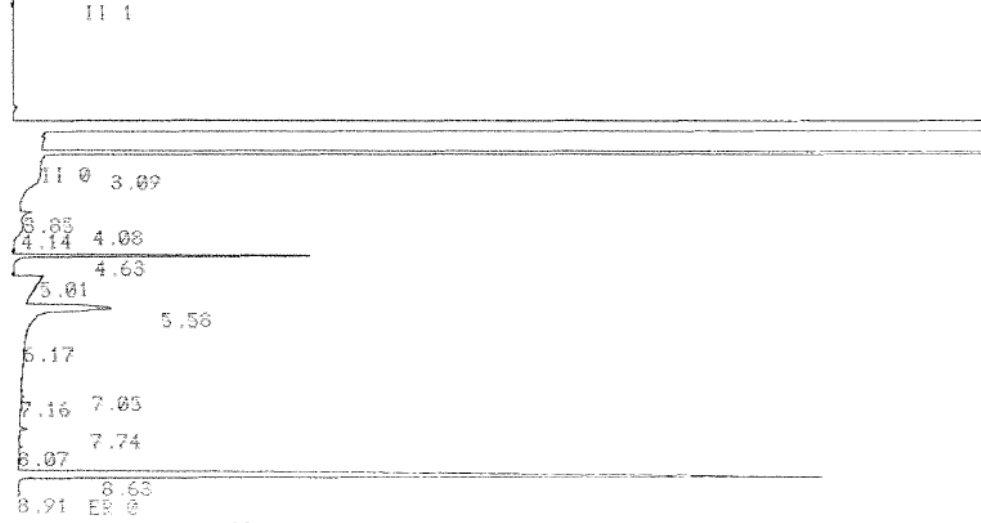
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DATA SAVED TO BIN # 8

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Experiment 7

LOW BATTERY

CHANNEL A INJECT 06/01/47 08:01:41 STORED TO BIN # 01



DATA SAVED TO BIN # 01

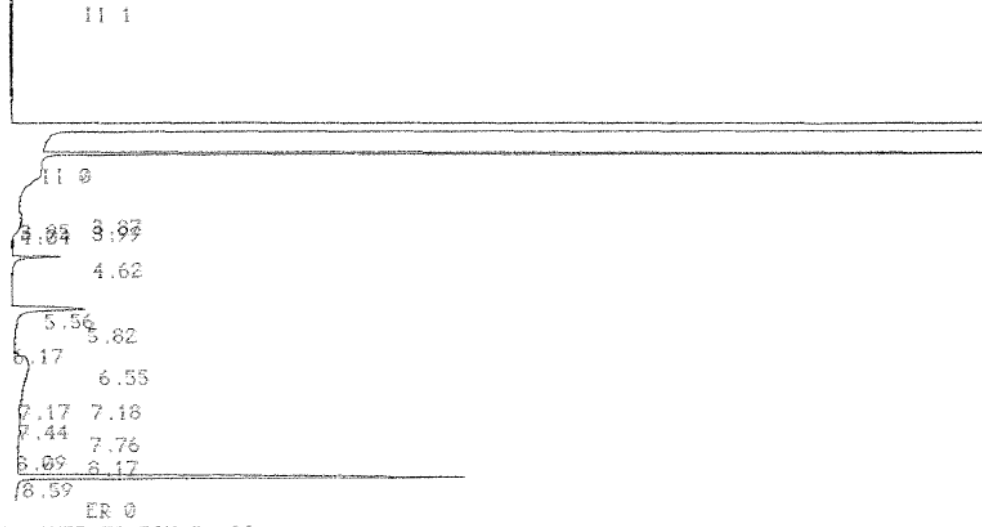
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Experiment 8

LOW BATTERY

CHANNEL A INJECT 05/30/47 11:14:37 STORED TO BIN # 22



DATA SAVED TO BIN # 22

RCH

05/30/47 11:14:37 CH= "A" PS= 1.