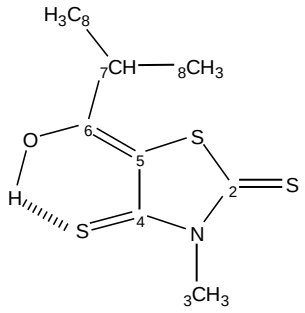
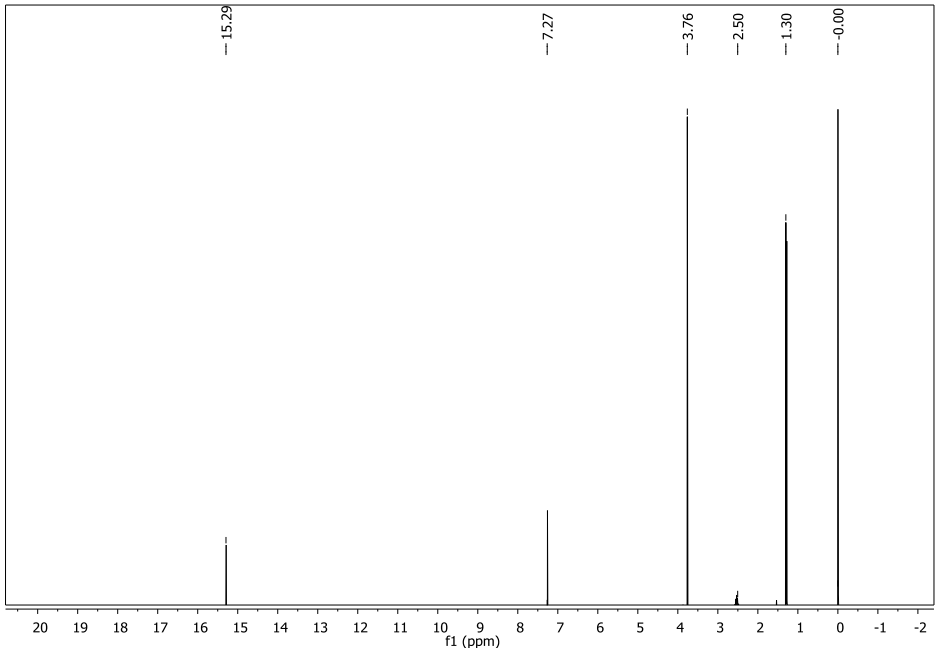
Synthesis, acylation and structural characterization of 3-methyl-1,3-thiazolane-2,4-dithiones.



5-(1-hydroxy-2-methylpropylidene)-3-methyl-1,3thiazolane-2,4-dithione



^{1}H NMR of 5-(-1-hydroxy-2-methylpropylidene)-3-methyl-1,3-thiazolane-2,4-dithione

Written by:

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Roskilde University. Autumn 2010-2011

ABSTRACT

The aim of the project is to investigate the influence of different aliphatic substituents on enol protons and the nature of hydrogen bond formed, when 3-methyl-4-thiorhodanine (3-methyl-1, 3-thiazolane-2, 4-dithione) is acylated with different aliphatic substituents. Which are CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, cyclopropyl, cyclohexyl, $C_6H_5CH_2$, $CH_2C(CH_3)_3$, $C(CH_3)_3$, $CH_3CHCH_2CH_3$, $CH(CH_2CH_3)_2$, 1-adamantane. NaOH was used as base and this resulted in successfully acylating the first nine products which contain an enol proton which takes part in hydrogen bonding and for the last four substituents mixed C- and S- acylated products were obtained. When the base was changed to pyridine only S-acylated products were obtained for the substituents which had mixed products while using NaOH. Therefore leading to the conclusion that steric effects could have played a role in which reaction pathway to follow as the last four substituents have large negative steric effect constants.

The correlation of the inductive effect (σ*) values was made by plotting the ^{13}C chemical shift of the substituents and ^{1}H NMR chemical shifts of the enol protons as a function of the σ* values. The results showed that there was no linear correlation. The influence of the steric effect was also analysed and neither was there a linear correlation.

The ^{1}H NMR of the enol protons had a high chemical shift value which ranged from 15.08-15.32 ppm which shows that the sulphur formed strong hydrogen bond.

Future studies would include studying the influence of both steric and inductive effects of the substituents maybe this could give a clear correlation if both parameters are considered together.

PREFACE

This report is part of my master project in chemistry in the autumn semester 2010-2011. All the experiments were carried out in the organic synthesis laboratory at the Department of Science, Systems and Models, Roskilde University.

I would like to thank my supervisor Associate Professor Fritz Duus, for his engagement and enormously useful discussions, guidance and supervision.

I would also like to thank Rita Buch and Annette Christiansen, laboratory technicians for all the help and good discussions offered during the process of this project.

Contents

1 INTRODUCTION

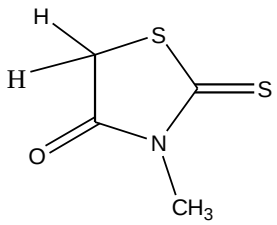
The attractive interaction of a hydrogen atom with an electronegative atom such as nitrogen, oxygen or fluorine is known as hydrogen bonding. The hydrogen is covalently bonded to another electronegative atom to create the bond. When these bonds occur between molecules they are known as intermolecular or when they are within different parts of a molecule they are known as intramolecular. Hydrogen bonding occurs in both organic molecules such as DNA, proteins and in inorganic molecules such as water. Intermolecular hydrogen bonding is responsible for the high boiling point of water while intramolecular hydrogen bonding is partly responsible for the secondary structures of proteins and nucleic acids [1].

Since hydrogen bonding plays an important role both in biology and chemistry it is interesting to study if it is possible to acylate 3-methyl-4-thiorhiodanine with different aliphatic substituents. And thereby obtain compounds that will give an insight on the hydrogen bond and how it is affected with respect to the various substituents.

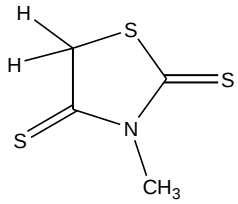
1.1 Purpose

Michel et al [2] succeeded in acylating 3-methylrhodanine (figure.1.1) with five aliphatic substituents. It was found that the products contained an enol proton involved in intramolecular hydrogen bonding.

Therefore the purpose of this project is to synthesize the thio derivative 3-methyl-4-thiorhodanine (figure 1.1) and acylate with aliphatic substituents and thereafter investigate the influence of these substituents on the hydrogen bond. The acylation is possible to take place on the carbon with methylene group on position five.



3-methylrhodanine



3-methyl-4-thiorhodanine

Figure 1.1: 3 methylrhodanine and 3-methyl-4-thiorhodanine

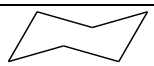
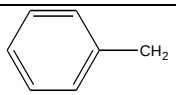
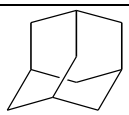
1.2 Substituent constants

To study the effect of substituents, two parameters are used; that is the polar constants and the steric constants. The polar substituent constants are used to describe the way a substituent will influence a reaction through polar (inductive, field and resonance) effects. The steric substituent constants are considered to also influence the reaction mechanism due to the size of the molecule.

In his pioneering studies, Taft [3] made distinct advances in understanding both polar and steric effects in aliphatic systems and his inductive and steric constants are supposed to be the most reliable substituent parameters.

The thirteen aliphatic substituents used for the acylation are shown in table 1 also shown are the inductive (σ*) values and steric effect (E_S) values. The values are obtained from refs [3] the value for cyclopropyl is obtained from ref [4]

Table 1: Sustituents used for the acylation including the σ* and E_S values

Substituent	σ*	E_S
CH_3	0.000	0.00
CH_2CH_3	-0.100	-0.07
$CH_2CH_2CH_3$	-0.115	-0.36
$CH(CH_3)_2$	-0.190	-0.47
$CH_2CH(CH_3)_2$	-0.125	-0.93
$CH_2C(CH_3)_3$	-0.165	-1.74
$CH(CH_2CH_3)_2$	-0.225	-1.98
$CH_3CHCH_2CH_3$	-0.210	-1.13
$C(CH_3)_3$	-0.300	-1.54
	-0.08	
	-0.15	
	+0.215	-0.38
		

1.3 Structure properties of thiorhodanine

3-methyl-4-thiorhodanine may possibly exhibit thione-thiol (thioketo-thioenol) tautomerism between the C4 and C5 (see Figure 1.2). The ketone tautomer of 3-methylrhodanine is 23 kcal/mol more stable than the enol tautomer [5].

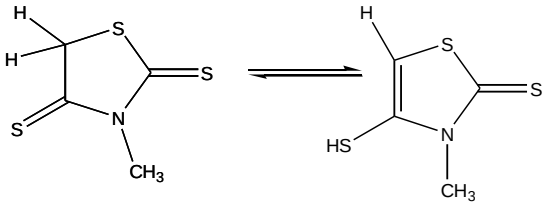


Figure 1.2: The tautomeric forms of 3-methyl-4-thiorhodanine

Tahmassebi [6] studied the tautomerism of thiorhodanine and concluded that the thioketone tautomer was the most stable in the gas phase as well as in two different solvents DMSO and cyclohexane and that the thione form was planar.

Different resonance structures of the 3-methyl-4-thiorhodanine can be described by using the lone pairs of nitrogen and/or sulfur in the thiazolane ring to form double bonds. (See figure 1.3).

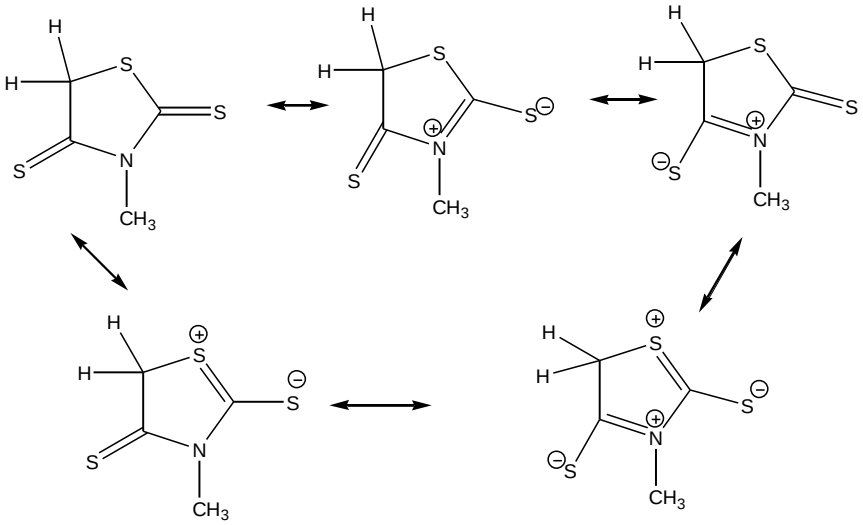
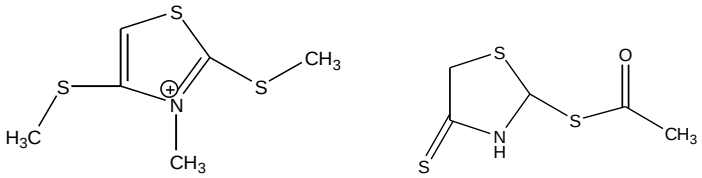


Figure 1.3: Resonance structures of 3-methyl-4-thiorhodanine

1.4 Thiorhodanine and its derivatives

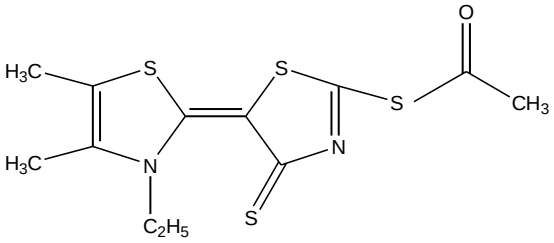
Thiorhodanine (1, 3-thiazolane-2, 4-dithione) and its derivates are used in coordination chemistry for the determination and detection of certain metal ions [7].

Sych et al [8] have reacted thiorhodanine with several electrophilic reagents which resulted in the methylation of sulfur in the 2 and 4 positions respectively. When dimethyl sulfate was reacted with thiorhodanine the reaction was accompanied by the formation of a quaternary thiazolium salt (see figure 1.4 structure I). When reacted with acetyl chloride the reaction took place only in position 2 and lead to 2-acetylthiothiazolidine-4-thione as shown in figure 1.4 structure II. Since structure 2 contains an active methylene group on position 5 it was reacted with quaternary salts of 2-methyl derivatives of nitrogen hetercycles which gave 2-acetythio-5-(3-ethyl-4,5-dimethylthiazolin-2-ylidene) thiazolidine-4-thione (structure III in figure 1.4)



I

II



III

Figure 1.4: Derivatives of thiorhodanine synthesized by Sych et al. [8]

Cohen [9] synthesized 3-methyl-4-thiorhodanine and acylated it with different kinds of para-substituted aromatic acid chlorides. Using $Ca(OH)_2$ as a base two isomers were obtained with C acylation on position 5 or S acylation on position 4 as shown in figure 1.5.

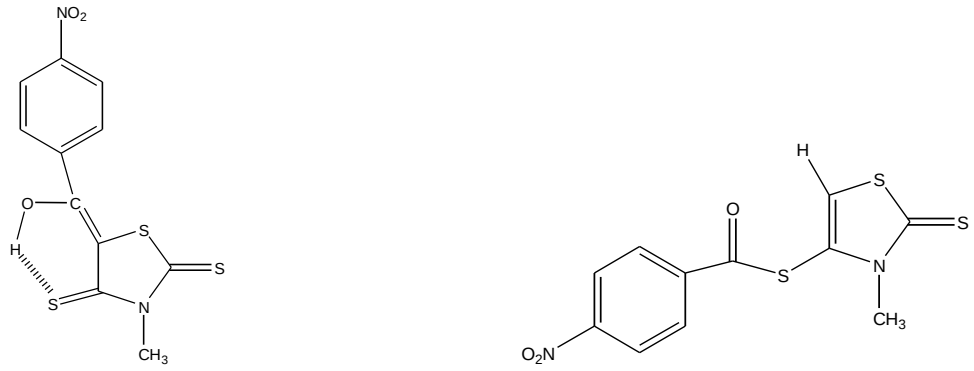


Figure 1.5: Examples of products obtained by Cohen [9] when 3-methyl-4-thiorhodanine was acylated with para-substituted aromatic acid chlorides.

2 EXPERIMENTS

In this chapter the methods and materials used for the synthesis of the starting material 3-methyl-4-thiorhodanine are described. Also described are the methods and materials used for the ayclation of 3-methyl-4-thiorhodanine. Two methods of acylation are described in one the base used is sodium hydroxide (NaOH) and dioxane as solvent while in the other pyridine is used as base and dichloromethane as solvent. The experimental procedures were modified from Cohen [9].

All the chemicals used in the experiments were obtained from Sigma Aldrich and did not require any purification prior to use.

2.1 Synthesis of 3-methyl-4-thiorhodanine

In a 3-necked round-bottomed flask with nitrogen inlet, and outlet through condenser is added 0.30 mol (66.68 g) diphosphorous pentasulphide (P_2S_5) in 150 mL anhydrous 1,4-dioxane, while using a mechanical stirrer. The solution which is in a paraffin oil bath is heated to 80-90^{o}C. Thereafter 0.10 mol (14.72 g) 3-methylrhodanine in 150 mL anhydrous 1,4-dioxane is added drop wise while refluxing. The reaction mixture is kept at this temperature with continuous stirring for 1.5 hours during which the solution turns red. To prevent oxidation 2 g active charcoal and 4 g zinc dust is added to the solution while slowly cooling for about 30 minutes. The reaction mixture is thereafter filtered through a 2 cm silica gel layer. The solvent is evaporated off and the crude product is recrystallized in preheated 99.9% ethanol as fast as possible to prevent decomposition.

Ozturk et al [10] have proposed a reaction mechanism for thionation using P_2S_5 as shown below. The mechanism possibly involves dissociation equilibriums which yield 3 (figure 2.1) and these decomposition products can then react with carbonyl functional groups.

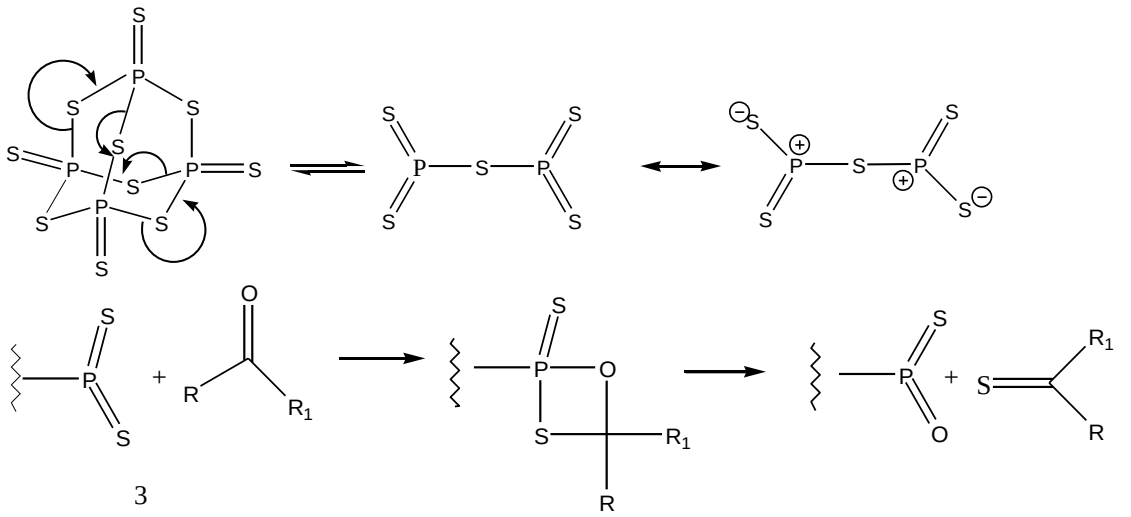


Figure 2.1: Reaction mechanism for the thionation using P_2S_5 [Ozturk et al [10]

2.2 Acylation of 3-methyl-4-thiorhodanine with aliphatic acid chlorides using sodium hydroxide (NaOH)

0.02 mol (0.8 g) sodium hydroxide (NaOH) in 30 mL dioxane is added to a 3-necked round-bottomed flask with nitrogen inlet and outlet through condenser in a paraffin oil bath. The solution is stirred at room temperature for about 10 minutes. Thereafter, 0.005 mol (0.815 g) 3-methyl-4-thiorhodanine in 10mL dioxane is dropped in to the reaction mixture. The colour changes from white to yellow as the light red 3-methyl-4-thiorhodanine is dropped in. This solution is stirred for another 10 minutes after all the 3-methyl-4-thiorhodanine has dropped in. 0.01 mol of the appropriate aliphatic acid chloride is dropped in while raising the temperature to 80-90^{o}C. The reaction mixture is stirred for 1 hour 30 minutes at this temperature under reflux. Afterwards the solution is poured into 40 mL 2M HCl while stirring. A precipitate will form immediately or after standing for a while. This precipitate is isolated by vacuum filtration and recrystallized in different mixtures of 99.9% ethanol and chloroform.

A suggested reaction mechanism for the acylation of 3-methyl-4-thiorhodanine is shown in figure 2.2.

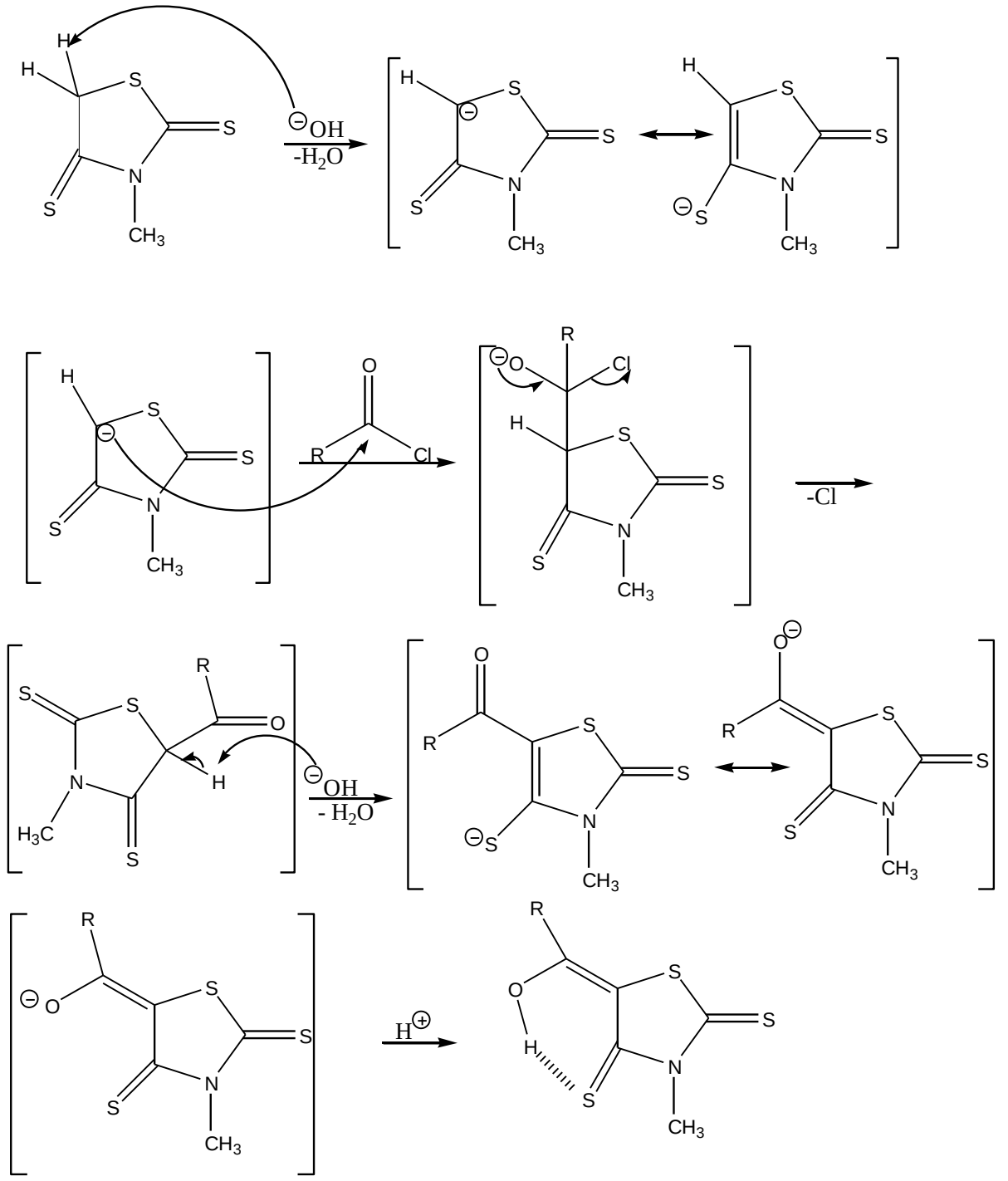


Figure 2.2: Suggested reaction mechanism for the acylation of 3-methyl-4-thiorhodanine with the aliphatic acid chlorides using NaOH.

2.3 Acylation of 3-methyl-4-thiorhodanine with aliphatic acid chlorides using pyridine.

In a 3-necked round –bottomed flask with nitrogen inlet, and out let through condenser is added 0.005 mol (0.815 g) 3-methyl-4-thiorhodanine in 20 mL dichloromethane (CH_2Cl_2). Subsequently 0.005 mol (0.395 g) pyridine in 10mL CH_2Cl_2 is dropped into the solution while stirring and cooling in an ice bath. Let the reaction stir for about 10 minutes then drop in 0.005 mol of the appropriate acid chloride while still cooling in an ice bath. When everything is dropped in, remove the ice water bath and stir the reaction mixture at room temperature for 1 hour. Thereafter the solution is poured into 50 mL ice water while stirring this result in two layers which are separated in a separatory funnel by washing the H_2O layer with 100 mL CH_2Cl_2 three times. The CH_2Cl_2 extracts are collected and washed with H_2O until a neutral pH is obtained (usually 3 washes). Anhydrous sodium sulphite (Na_2SO_4) is used to dry the CH_2Cl_2 phase. The solvent is evaporated off and the crude product is recystallized in different mixtures of hot 99.9% ethanol and chloroform. A reaction mechanism is suggested in figure 2.3.

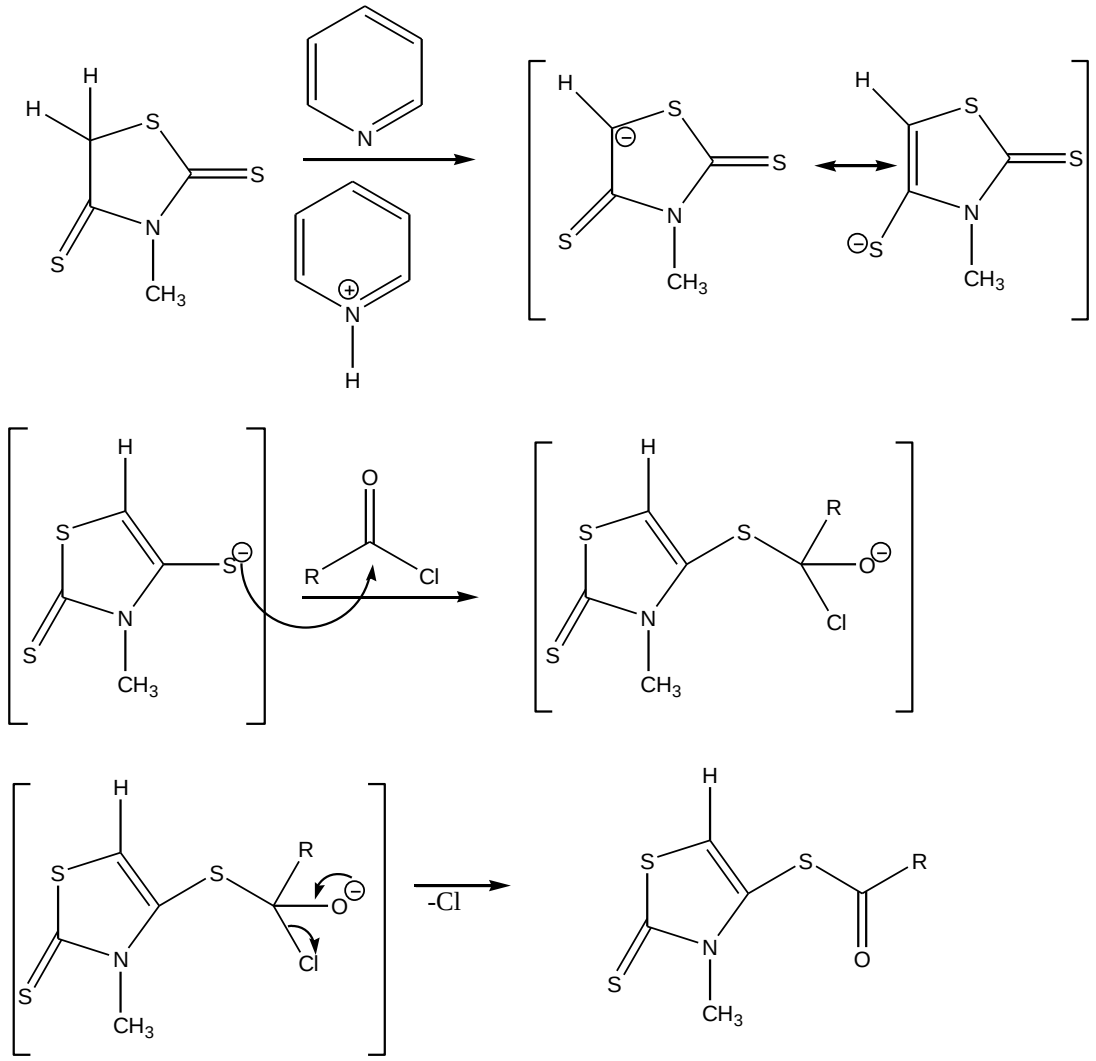


Figure 2.3: Proposed reaction mechanism for the acylation of 3-methyl-4-thiorhodanine with aliphatic acid chlorides using pyridine.

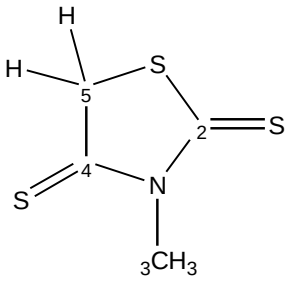
3 RESULTS

This chapter contains the results obtained from the synthesis, ^{13}C and ^{1}H NMR spectra of the products as well as correlation plots of carbon chemical shifts as a function of σ* values.

For the determination of the ^{1}H and ^{13}C NMR chemical shifts the following references were used Kalinowski et al [11] and Pavia et al [12].

N.B the numbers in the structure denote the numbering of carbons.

3.1 3-methyl-4-thiorhodanine.



MW=163g/mol

3-methyl-1,3-thiazolane-2,4-dithione

Synthesis of 3-methyl-4-thiorhodanine	
Chemicals	0.30 mol (66.68 g) P_2S_5 0.10 mol (14.72 g) rhodanine 2.0 g active charcoal 4.0 g zinc dust EtOH (recrystalliztion)
Product	3-methyl-1,3-thiazolane-2,4-dithione
Yield	5.3-3.0 g (32.0-18.4%) Golden yellow crystals
Melting Point	101.7-104.4 ^{o}C
^{1}H-NMR (ppm)	δ = 4.44 (2H, s) CH2 δ = 3.72 (3H, s) N-CH3
^{13}C-NMR (ppm)	C2: 203.54; C3: 35.69; C4: 203.32; C5: 46.20

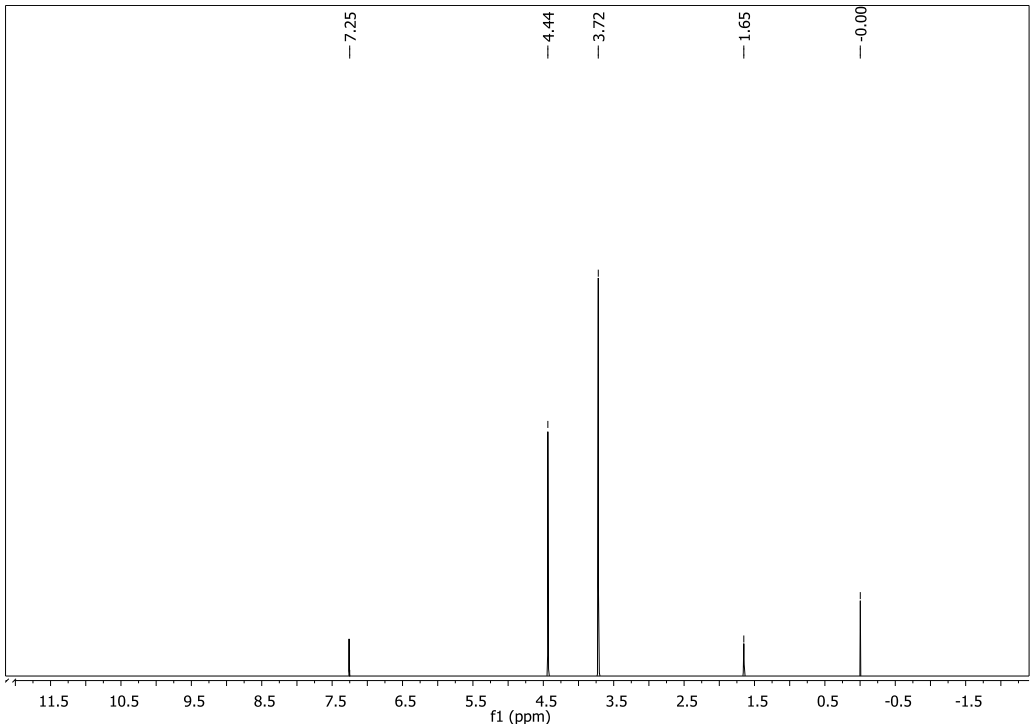


Figure 3.1.1: ^{1}H NMR spectrum of 3-methyl-1,3-thiazolane-2,4-dithione in CDCl3 at 300 MHz

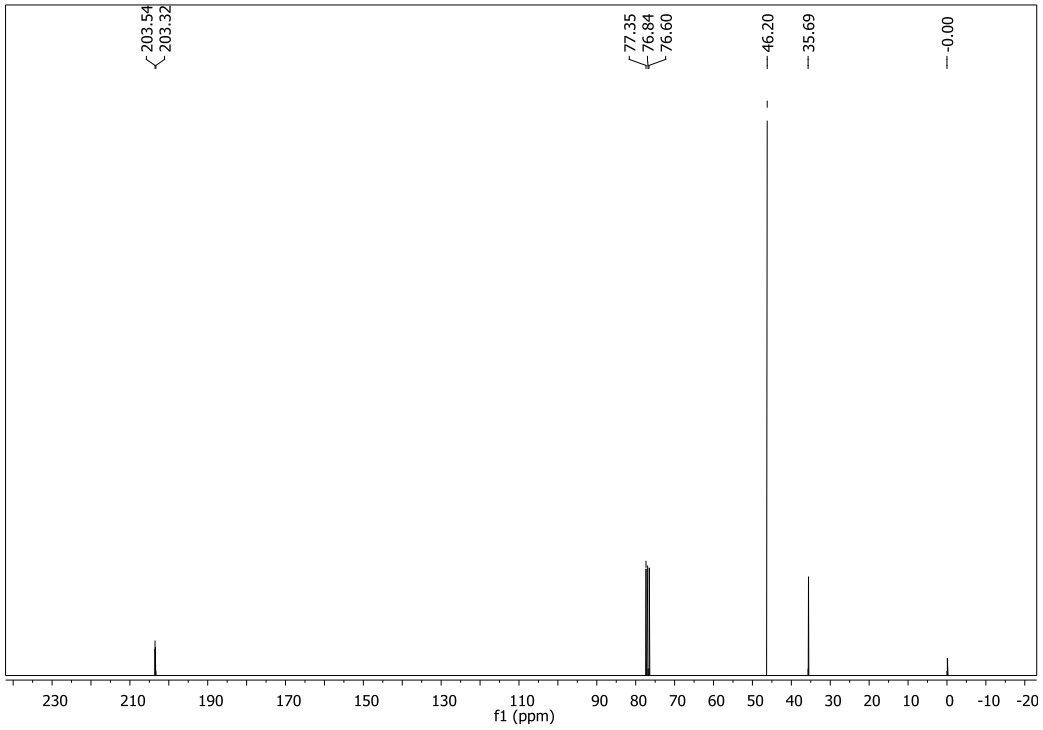
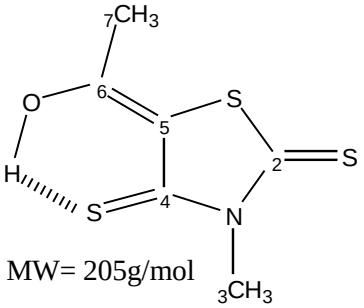


Figure 3.1.2: ^{13}C-NMR spectrum of 3-methyl-1,3 thiazolane-2,4-dithione in $CDCl_3$ at 75 MHz

3.2 Acylations in dioxane using NaOH as base

3.2.1 with acetyl chloride



MW= 205g/mol

5-(1-hydroxyethylidene)-3-methyl-1,3-thiazolane-2,4-dithione

Acylation with acetyl chloride	
Chemicals	0.02 mol (0.8 g) NaOH 0.005 mol (0.815 g)-3-methyl-4-thiorhodanine 0.01 mol (acetyl chloride) 1:1 $CHCl_3$:EtOH (recrystallization)
Product	5-(1-hydroxyethylidene)-3-methyl-1,3-thiazolane-2,4-dithione
Yield	0.200-0.600 g (19.5-58.5%) Dark green crystals
Melting Point	109.0-110.4 ^{o}C
^{1}H-NMR (ppm)	δ = 15.08 (1H) OH δ = 2.25 (3H,s) CH_3 δ = 3.76 (3H,s) N-CH_3
^{13}C-NMR (ppm)	C2: 192.55; C3: 34.54; C4: 185.70; C5:110.96; C6: 171.52; C7: 22.91

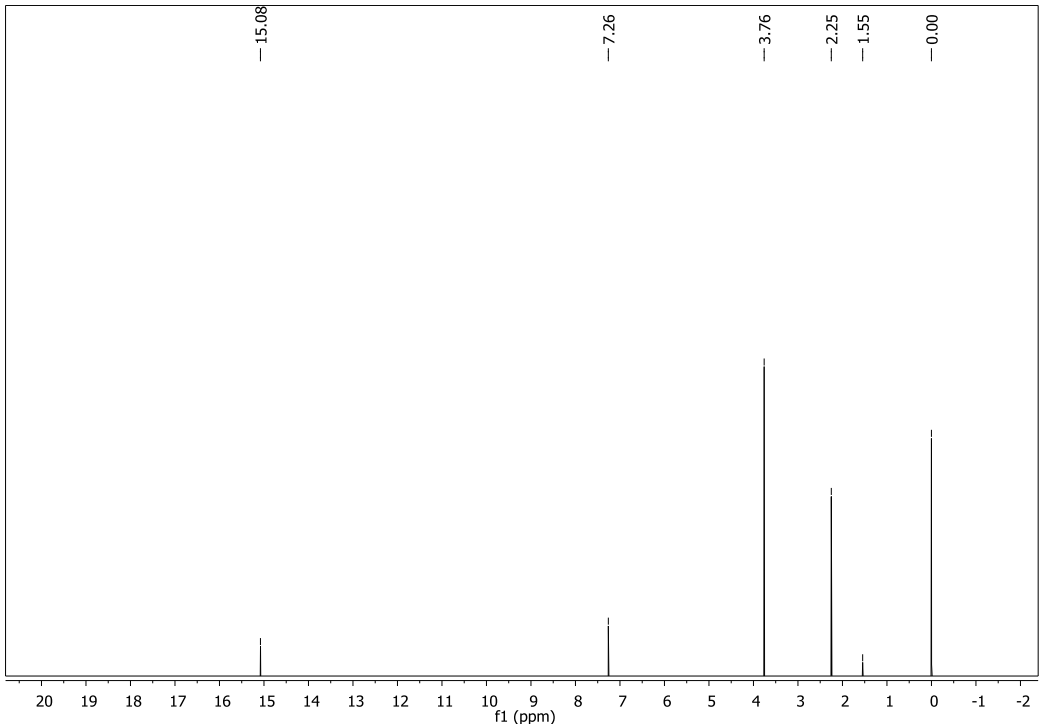


Figure 3.2.1: ^{1}H-NMR spectrum of 5-(1-hydroxyethylidene)3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

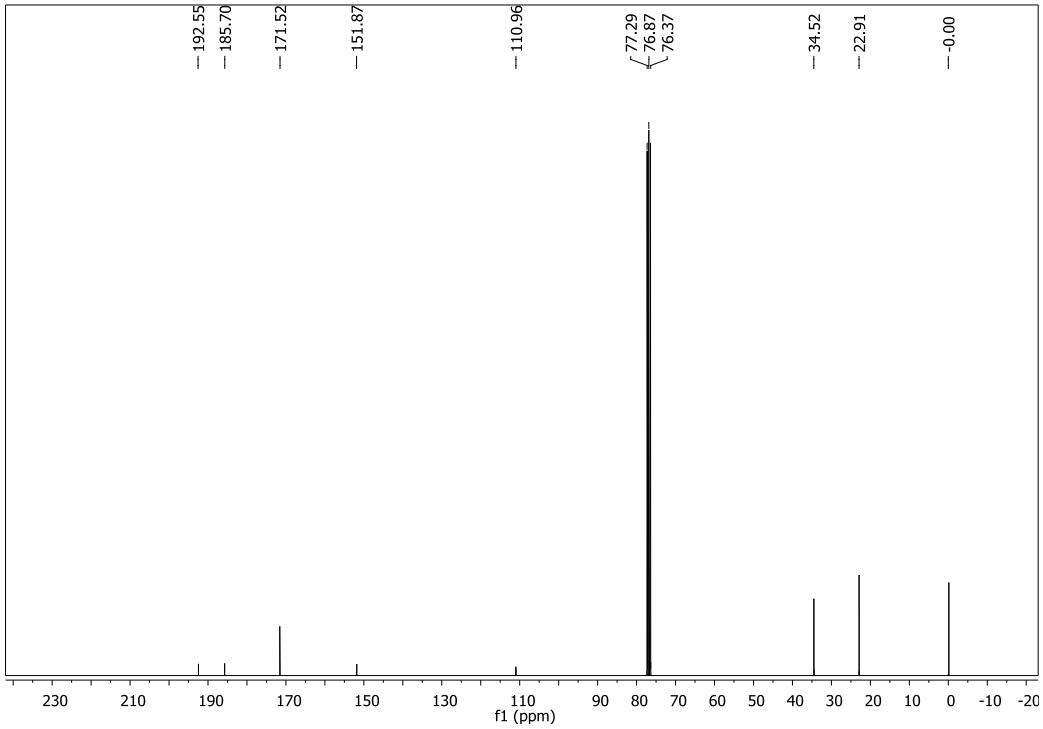
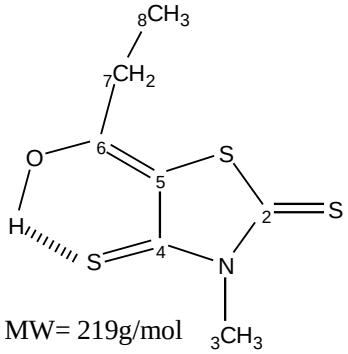


Figure 3.2.2: ^{13}C-NMR spectrum of 5-(1-hydroxyethylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75 MHz

3.2.2 with propionyl chloride



MW= 219g/mol

5-(1-hydroxypropylidene)-3-methyl-1,3-thiazolane-2,4-dithione

Acylation with propionyl chloride	
Chemicals	0.02 mol (0.8 g) 0.005 mol (0.815 g) 3-methyl-4-thiorhodanine 0.01 mol (0.92 g) propionyl chloride 1:1 $CHCl_3$: EtOH (recrystallization)
Product	5-(1-hydroxypropylidene)-3-methyl-1,3-thiazolane-2,4-dithione
Yield	0.240-0.260 g (23.7-21.9%) Light green crystals
Melting Point	88.0-89.0 ^{o}C
^{1}H-NMR (ppm)	δ = 15.20 (1H,t) OH δ = 3.75 (3H,s) N-CH_3 δ = 2.47 (2H,q) CH_2 δ = 1.30 (3H,t) CH_3
^{13}C-NMR (ppm)	C2: 192.32 ; C3: 34.52; C4:185.70; C5: 110.26; C6: 176.11; C7: 30.38 C8: 9.82

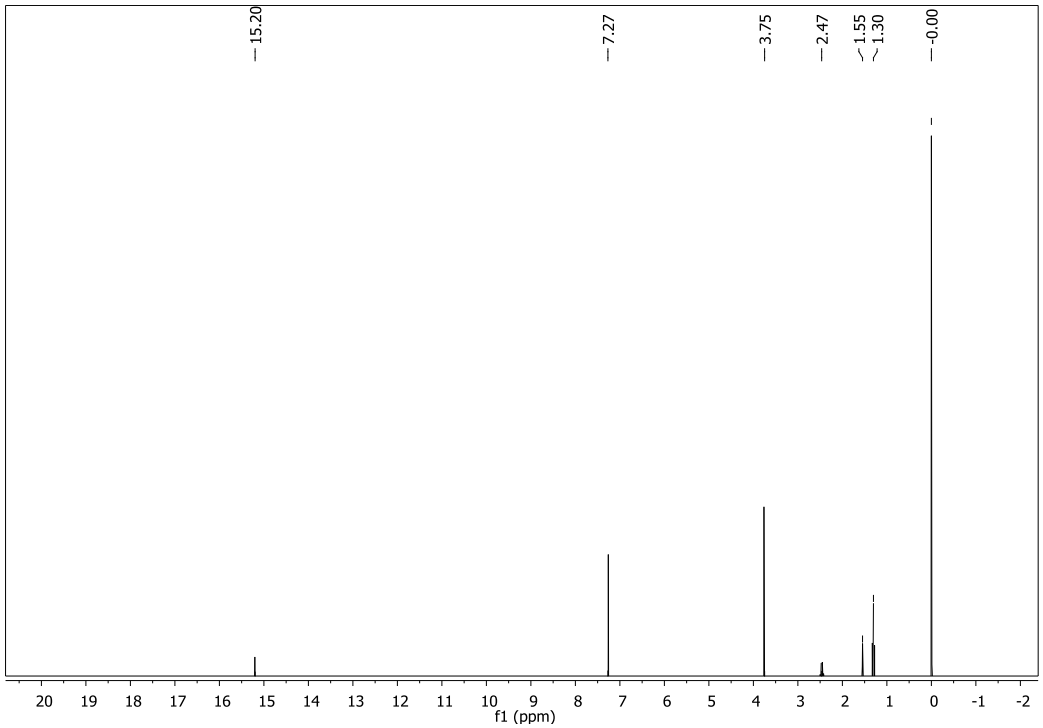


Figure 3.2.3: ^{1}-H-NMR spectrum of 5-(1-hydroxypropylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

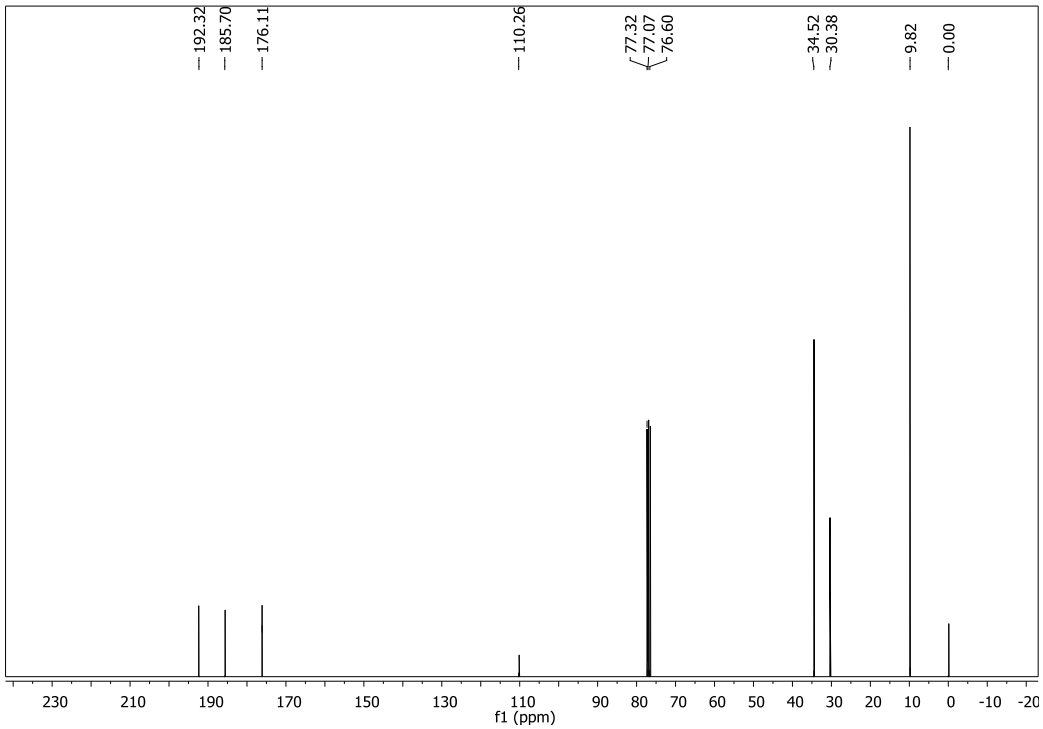


Figure 3.2.4: ^{13}C-NMR spectrum of 5-(1-hydroxypropylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75 MH

3.2.3 with butyryl chloride

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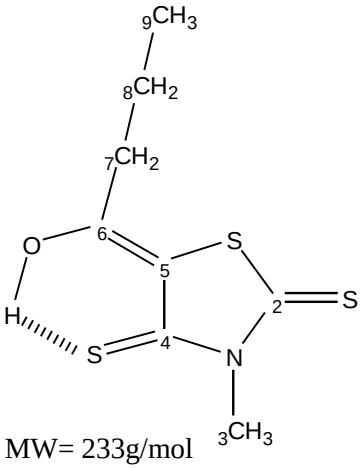
<tr><td rowspan="8"> 

MW= 233g/mol

5-(1-hydroxybutylidene)-3-methyl-1,3-thiazolane-2,4-dithione</td><td colspan="2">Acylation with butyryl chloride</td></tr>
<tr><td>Chemicals</td><td>0.02 mol (0.8 g) NaOH

0.005 mol (0.815 g) 3-methyl-4-thiorhodanine

0.01 mol (1.06 g) butyryl chloride

1:1 $CHCl_3$: EtOH (recrystallization)</td></tr>
<tr><td>Product</td><td>5-(1-hydroxybutylidene)-3-methyl-1,3-thiazolane-2,4-dithione</td></tr>
<tr><td>Yield</td><td>0.238-0.330 g (28.3-20.4%) Light yellow crystals</td></tr>
<tr><td>Melting Point</td><td>110.5-111.9 ^{o}C</td></tr>
<tr><td>^{1}H-NMR (ppm)</td><td>δ = 15.18 (1 H, t) OH

δ = 3.77 (3 H, s) N-CH_3

δ = 2.38 (2H, m) CH_2

δ = 1.77 (2 H, sextet) CH_2

δ = 1.02 (3H, t) CH_3</td></tr>
<tr><td>^{13}C-NMR (ppm)</td><td>C2: 192.79; C3: 34.69; C4: 185.70

C5: 111.20; C6: 175.65; C7: 39.11

C8:19.76; C9: 13.72</td></tr>
</table>

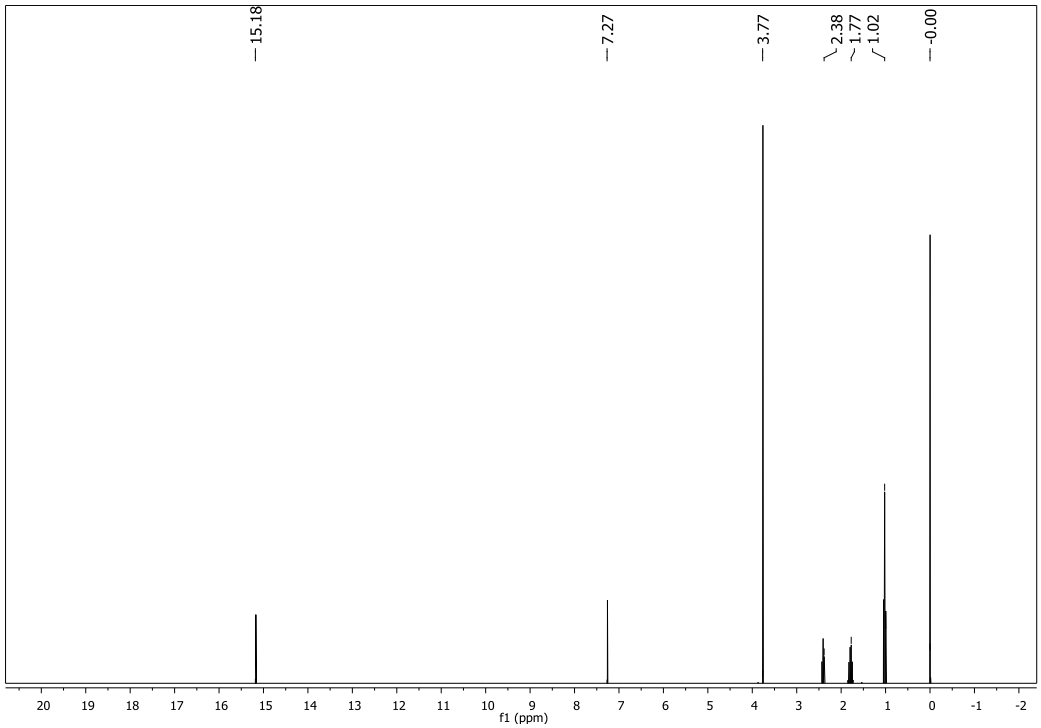


Figure 3.2.5: ^{1}H-NMR spectrum of 5-(1-hydroxybutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in CDCl3 at 300MHz

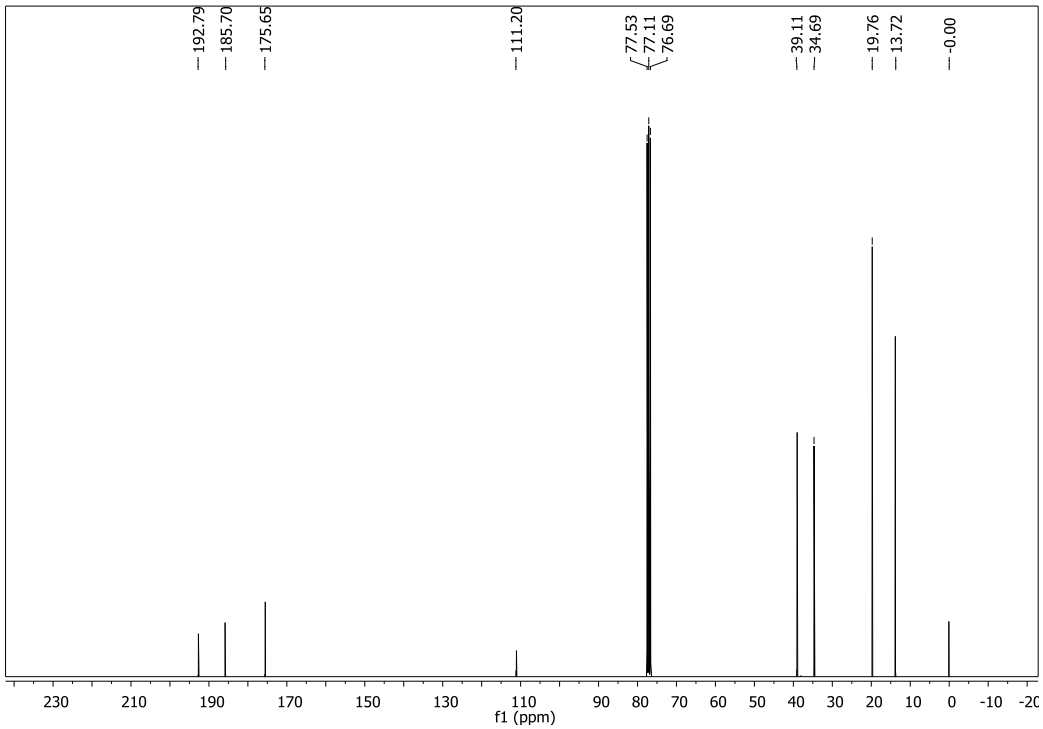
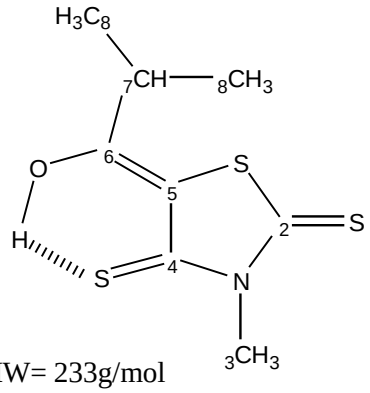


Figure 3.2.6: ^{13}C-NMR spectrum of 5-(1-hydroxybutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75 MHz

3.2.4 with isobutyryl chloride

<table>
<tr><td rowspan="8"> 
MW= 233g/mol

5-(1-hydroxy-2-methylpropylidene)-3-methyl-1,3thiazolane-2,4-dithione</td><td colspan="2">Acylation with isobutyryl chloride</td></tr>
<tr><td>Chemicals</td><td>0.02 mol (0.8 g) NaOH

0.005 mol (0.815 g) 3-methyl-4-thiorhodanine

0.01 mol (1.06 g) isobutyryl chloride

1:1 $CHCl_3$: EtOH (recrystallization)</td></tr>
<tr><td>Product</td><td>5-(1-hydroxy-2-methylpropylidene)3-methyl-1,3-thiazolane-2,4-dithione</td></tr>
<tr><td>Yield</td><td>0.150-0.192 g (12.8-16.5%) dark green crystals</td></tr>
<tr><td>Melting Point</td><td>71.8- 72.7 ^{o}C</td></tr>
<tr><td>^{1}H-NMR (ppm)</td><td>δ = 15.29 (1H, d) OH

δ = 3.76 (3H, s) N-CH_3

δ = 2.50 (1H, m) CH

δ = 1.30 (6H,d) CH_3, CH_3</td></tr>
<tr><td>^{13}C-NMR (ppm)</td><td>C2: 192.32; C3: 34.52; C4: 185.70;

C5: 109.33; C6: 179.54; C7: 36.62;

C8: 19.01</td></tr>
</table>

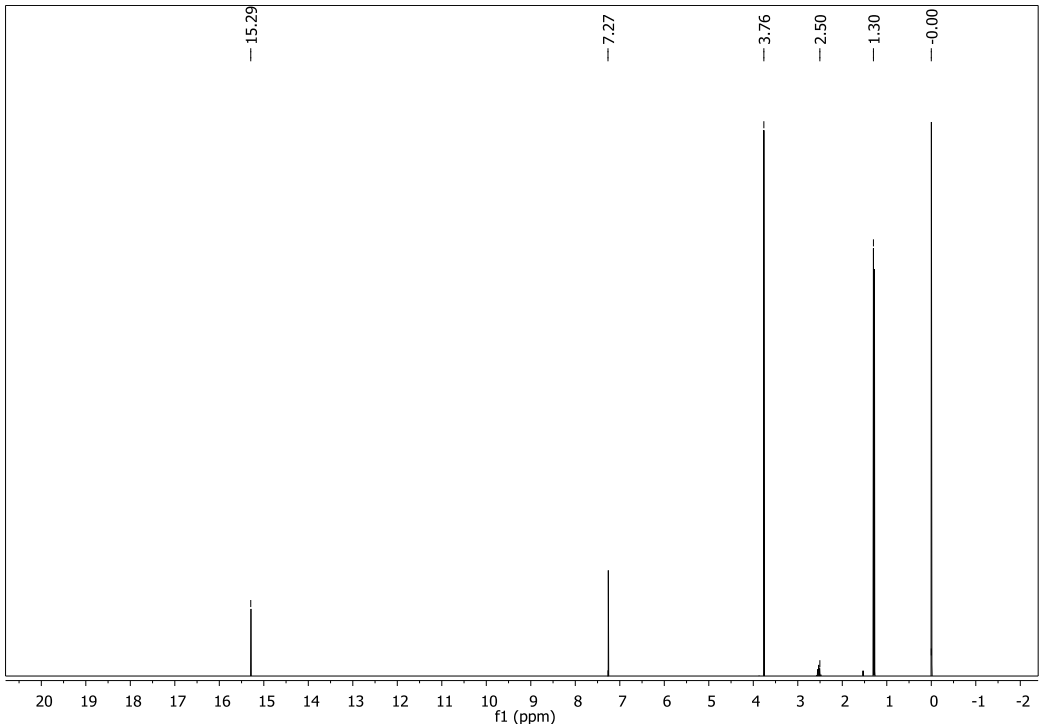


Figure 3.2.7: ^{1}H-NMR spectrum of 5-(1-hydroxy-2-methylpropylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

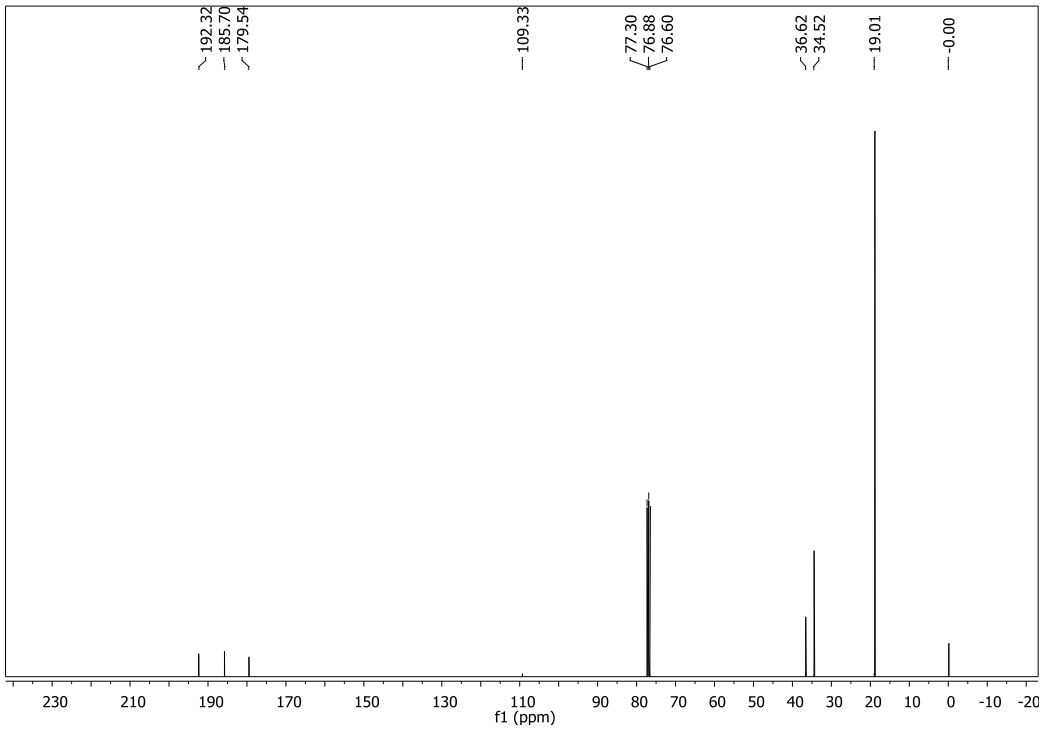
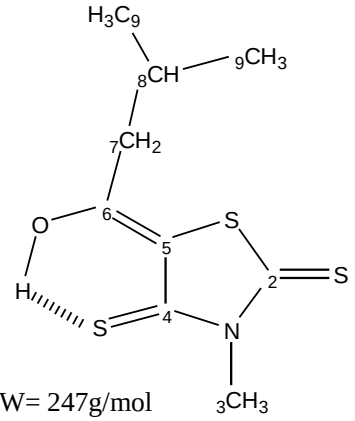


Figure 3.2.8: ^{13}C-NMR spectrum of 5-(1-hdroxy-2-methylpropylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75 MHz

3.2.5 with Isovaleryl chloride (3-methylbutyryl chloride)



MW= 247g/mol

5-(1-hydroxy-3-methylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione

Acylation with Isovaleryl chloride	
Chemicals	0.02 mol (0.8 g) NaOH 0.005 mol (0.815 g) 0.01 mol (1.2 g) isovaleryl chloride 1:1 $CHCl_3$: EtOH (recrystallization)
Product	5-(1-hydroxy-3-methylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione
Yield	0.100-0.365 g (8.1-29.5%) Light green crystals
Melting Point	77.8-79 ^{o}C
^{1}H-NMR (ppm)	δ = 15.18 (1H, t) OH δ = 3.76 (3H,s) N-CH_3 δ = 2.32 (1H,m) CH δ = 2.25 (2H,m) CH_2 δ = 1.03 (6H,d) CH_3, CH_3
^{13}C-NMR (ppm)	C2: 192.55; C3: 34.46; C4: 185.69; C5: 111.35; C6: 174.94; C7: 45.95; C8: 27.22; C9: 22.39

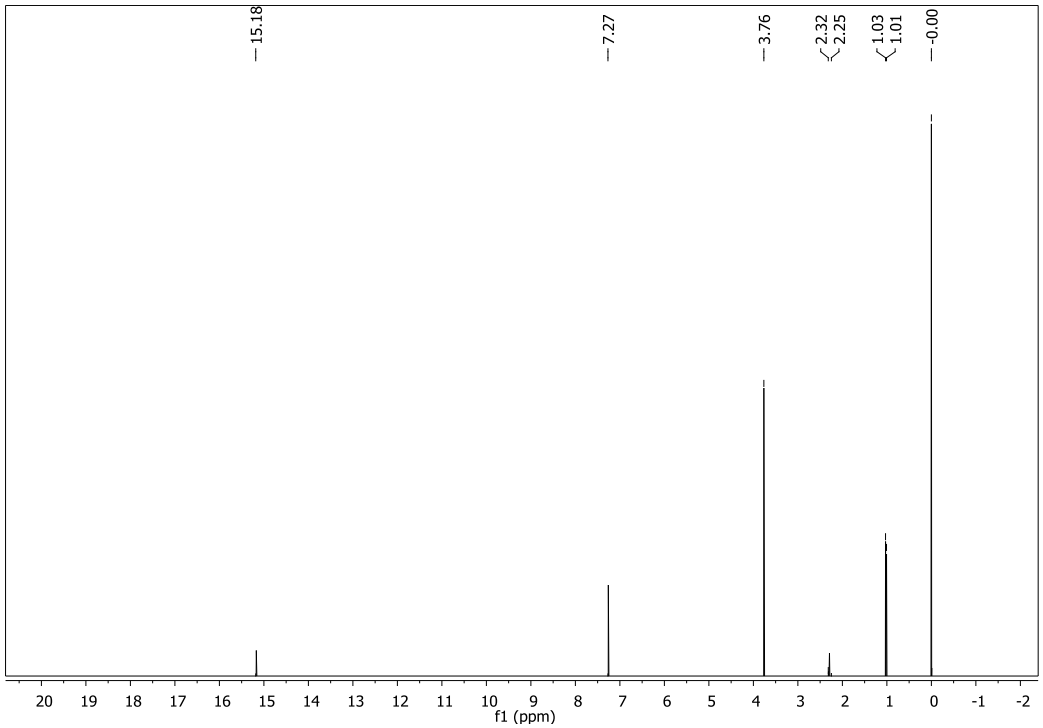


Figure 3.2.9: ^{1}H-NMR spectrum of 5-(1-hydroxy-3-methylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in CDCl3 at 300 MHz

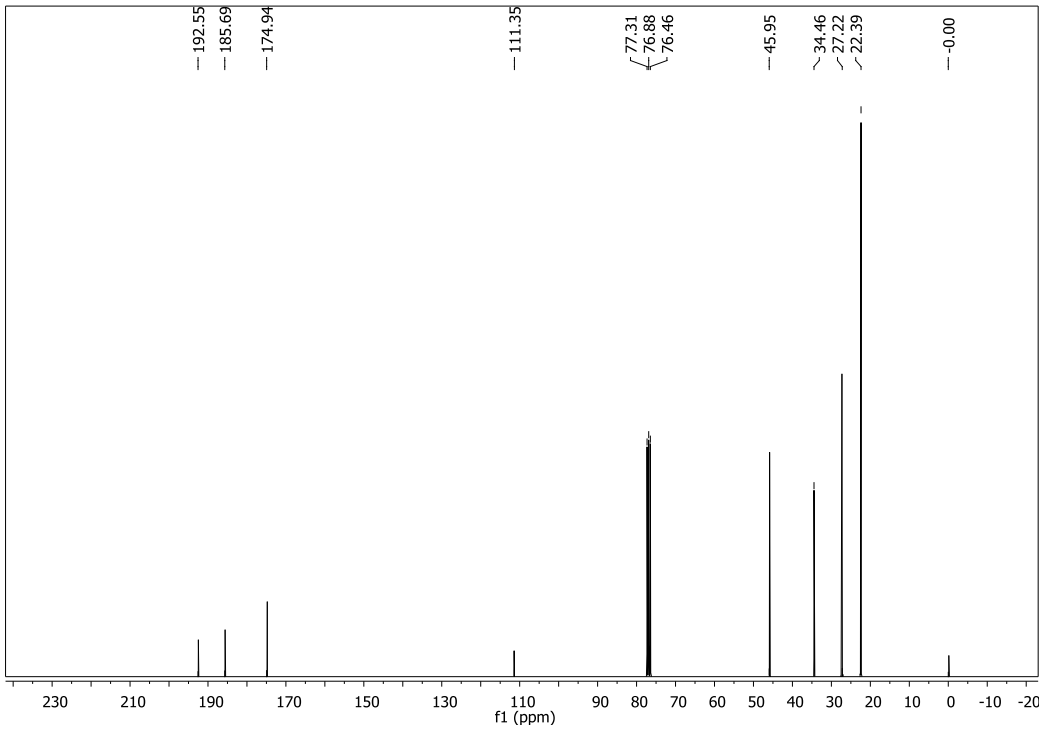


Figure 3.2.10: ^{13}C-NMR spectrum of 5-(1-hydroxy-3-methylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in CDCl3 at 75 MHz

3.2.6 with cyclopropane carbonyl chloride

<table>
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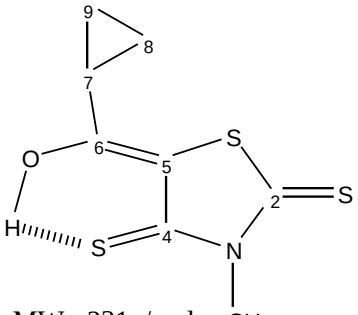
<td rowspan="8"> 
MW= 231g/mol
5-(1-hydroxy-1-cyclopropylmethylene)-3-methyl-1,3-thiazole-2,4-dithione</td>
<td colspan="2">Acylation with cyclopropane carbonyl chloride</td>
</tr>
<tr>
<td>Chemicals</td>
<td>0.02 mol (0.8 g) NaOH

0.005 mol (0.815 g) 3-methyl-4-thiorhodanine

0.01 mol (1.04 g) cyclopropane carbonyl chloride

1:1 $CHCl_3$: EtOH (recrystallization)</td>
</tr>
<tr>
<td>Product</td>
<td>5-(1-hydroxy-1-cyclopropymethylene)-3-methyl-1,3-thiazolane-2,4-dithione</td>
</tr>
<tr>
<td>Yield</td>
<td>0.495-0.590 g (42.8-51.0%) Dark yellow crystals</td>
</tr>
<tr>
<td>Melting Point</td>
<td>123.0-124.0 ^{o}C</td>
</tr>
<tr>
<td>^{1}H-NMR (ppm)</td>
<td>δ = 15.32 (1H,d) OH

δ = 3.77 (3H,s) N-CH_3

δ = 1.48-1.30 (4H,m) CH_2,CH_2

δ = 1.28-1.26 (1H,m) CH</td>
</tr>
<tr>
<td>^{13}C-NMR (ppm)</td>
<td>C2: 192.56; C3: 34.76; C4: 183.49;

C5: 110.50; C6: 177.49; C7: 17.89;

C8-C9 : 12.65</td>
</tr>
</table>

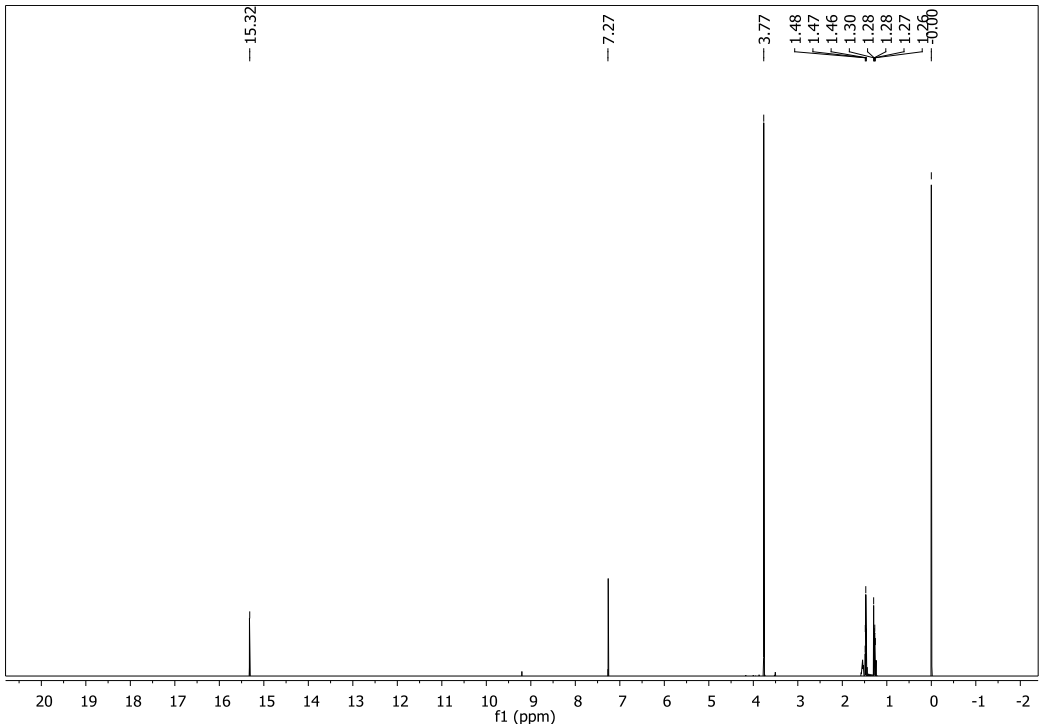


Figure 3.2.11: ^{1}H-NMR spectrum of 5-(1-hydroxy-1-cyclopropylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

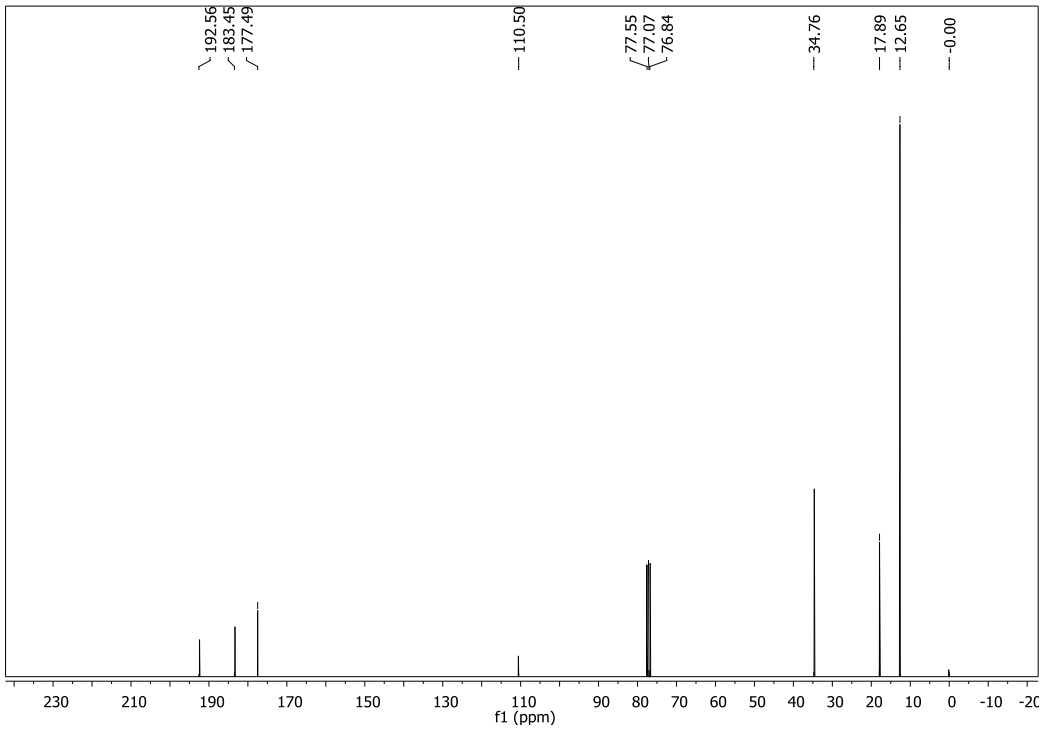
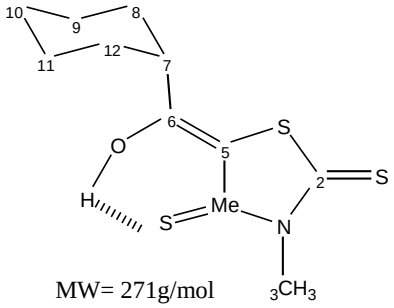


Figure 3.2.12: ^{13}C-NMR spectrum of 5-(1-hydroxy-1-cyclopropylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione in CDCl3 at 75 MHz

3.2.7 with cyclohexane carbonyl chloride



MW= 271g/mol

5-(1-hydroxy-1-cyclohexylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione

Acylation with cyclohexane carbonyl chloride	
Chemicals	0.02 mol (0.8 g) NaOH 0.005 mol (0.815 g) 3-methyl-4-thiorhodanine 0.01 mol (1.46 g) cyclohexane carbonyl chloride 1:1 $CHCl_3$: EtOH (recrystallization)
Product	5-(1-hydroxy-1-cyclohexylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione
Yield	0.125-0.307 g (9.2-22.6%) Dark yellow crystals
Melting Point	127.2-128.9 ^{o}C
^{1}H-NMR (ppm)	δ = 15.28 (1H,d) OH δ = 3.75 (3H, s) N-CH_3 δ = 2.18 (1H,m) CH δ = 1.88-1.25 (10,m) CH_2
^{13}C-NMR (ppm)	C2: 192.09; C3: 34.52; C4: 185.47; C5: 109.57; C6: 178.83; C7: 46.68; C8,C12: 28.60; C9,C10,C11: 25.64-25.40;

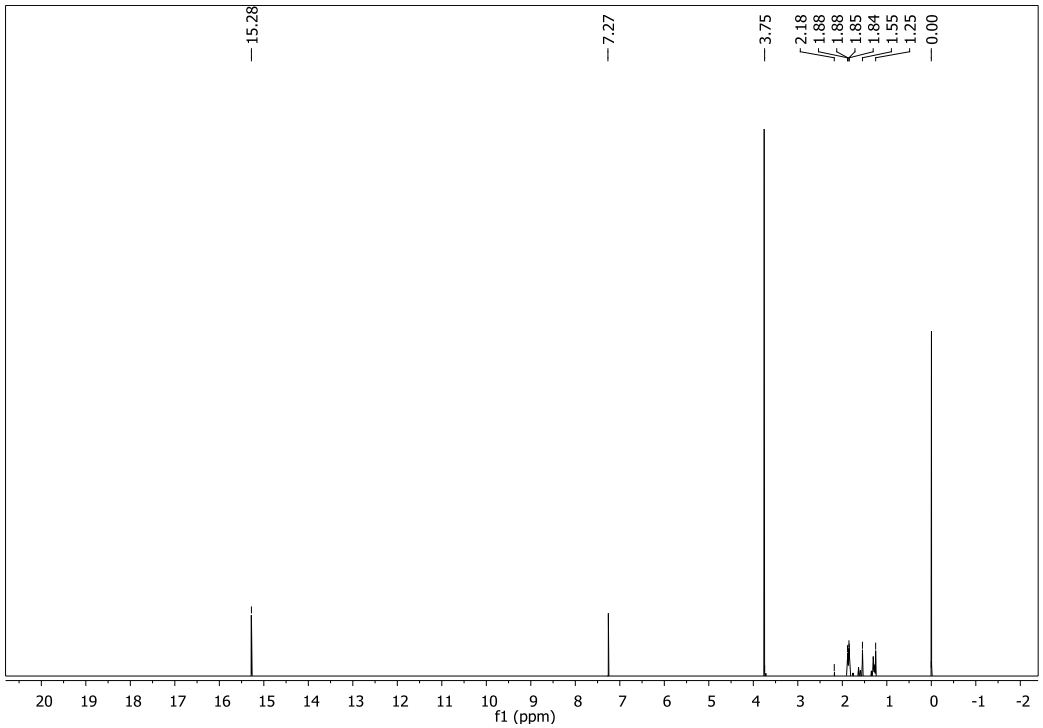


Figure 3.2.13:^{1}H-NMR spectrum of 5-(1-hydroxy-1-cyclohexylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

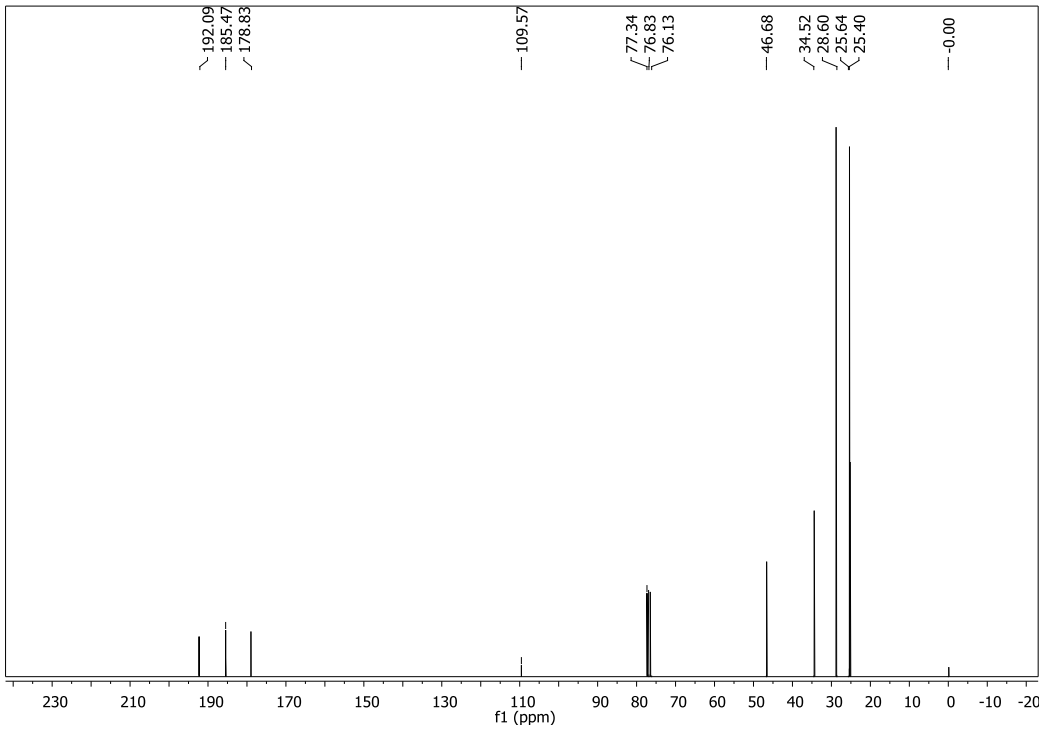
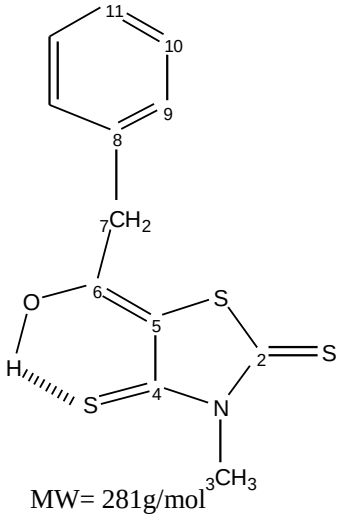


Figure 3.2.14:^{13}C-NMR spectrum of 5-(1-hydroxy-1-cyclohexylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75 MHz

3.2.8 with phenylacetyl chloride



MW= 281g/mol

5-(1-hydroxy-2-phenylethylidene)-3-methyl-1,3-thiazolane-2,4-dithione

Acylation with phenylacetyl chloride	
Chemicals	0.02 mol (0.8 g) NaOH 0.005 mol (0.815 g) 3-methyl-4-thiorhodanine 0.01 mol (1.54 g) phenylacetyl chloride 1:1 $CHCl_3$: EtOH (recrystallization)
Product	5-(1-hydroxy-2-phenylethylidene)-3-methyl-1,3-thiazolane-2,4-dithione
Yield	0.122-0.520 g (10.5-37.0%)Light yellow crystals
Melting Point	97.7-97.9 ^{o}C
^{1}H-NMR (ppm)	δ = 15.16 (1H,t) OH δ = 3.75 (3H,s) N-CH_3 δ = 3.70 (2H,s) CH_2 δ = 7.37-7.27 (5H) aromatic region
^{13}C-NMR (ppm)	C2: 192.55; C3: 34.48; C4: 186.40; C5: 110.96; C6: 172.20; C7: 43.02; C8: 133.09; C9: 129.43; C10: 129.20; C11: 128.95

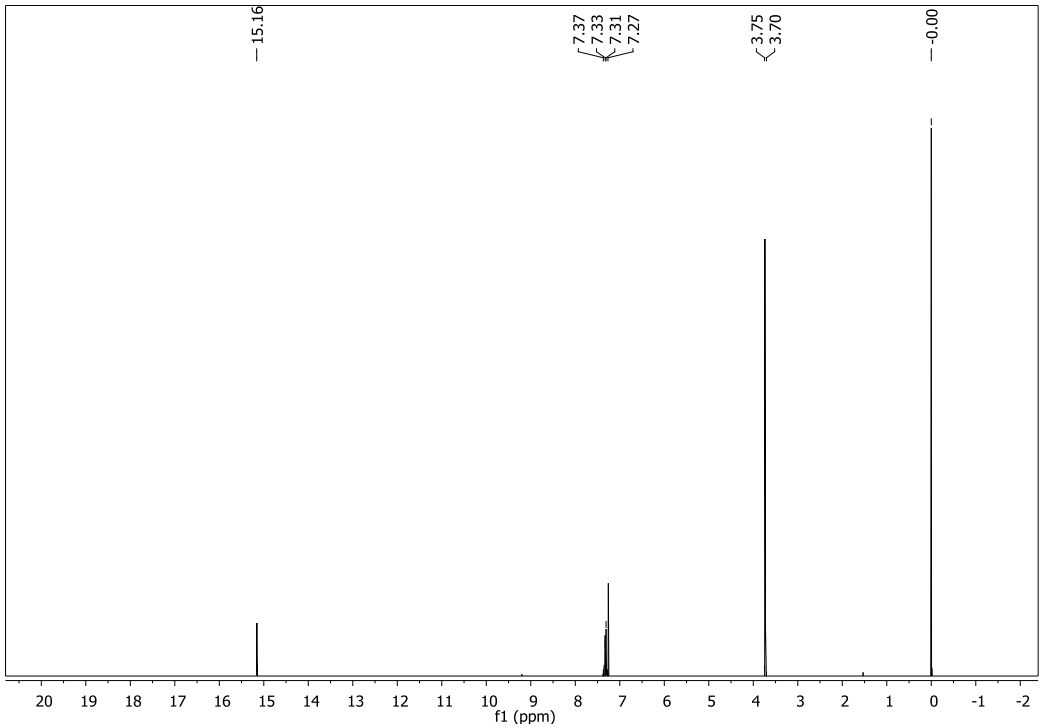


Figure 3.2.15: ^{1}H-NMR spectrum of 5-(1-hydroxy-2-phenylethylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

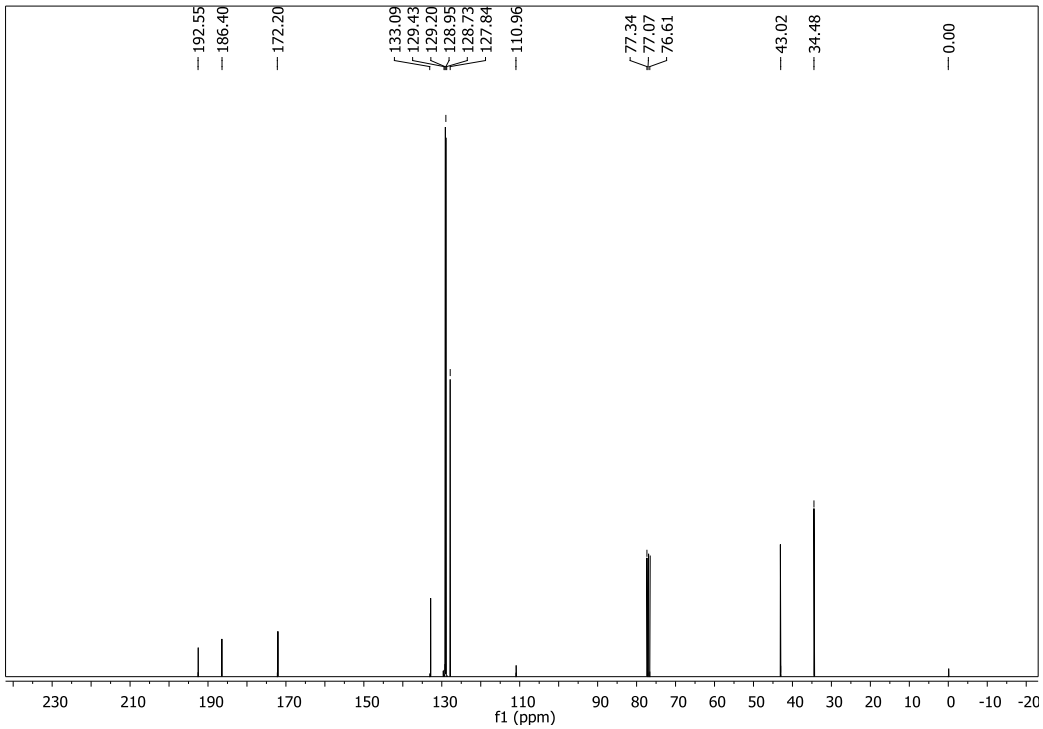
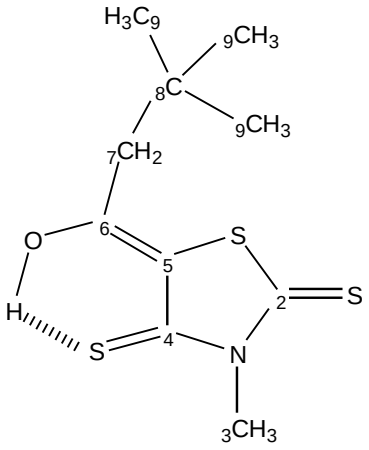


Figure 3.2.16: ^{13}C-NMR spectrum of 5-(1-hydroxy-2-phenylethylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75MHz

3.2.9 with tert-butylacetyl chloride



MW= 261g/mol

5-(1-hydroxy-3,3-dimethylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione

Acylation with tert-butylacetyl chloride	
Chemicals	0.02 mol (0.8 g) NaOH 0.005 mol (0.815 g) 3-methyl-4-thiorhodanine 0.01 mol (1.34 g) tert-butylacetyl chloride 2:1 $CHCl_3$: EtOH (recrystallization)
Product	5-(1-hdroxy-3,3-dimethylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione
Yield	0.359-0.450 g (27.5-34.5%) Dark green crystals
Melting Point	106.6-107.9 ^{o}C
^{1}H-NMR (ppm)	δ = 15.24 (1H,t) OH δ = 3.76 (3H,s) N-CH_3 δ = 2.32 (2H,d) CH_2 δ = 1.09 (9H,s) CH_3
^{13}C-NMR (ppm)	C2: 192.56; C3: 34.53; C4: 185.70; C5: 112.53; C6: 174.48; C7: 33.87; C8: 50.37; C9: 30.07

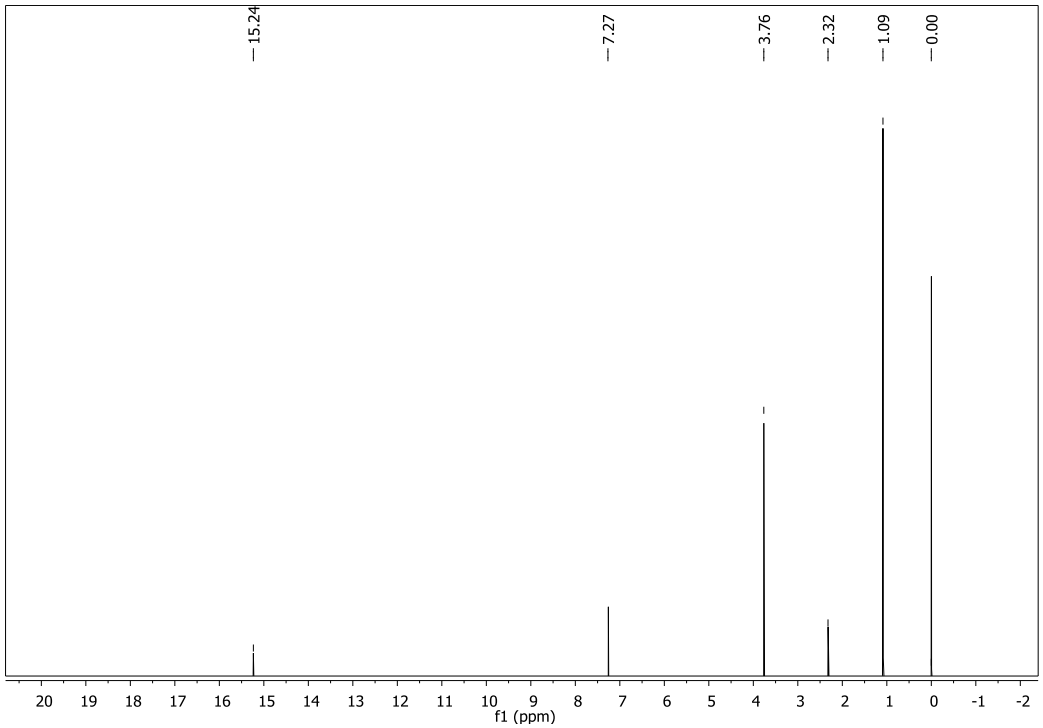


Figure 3.2.17: ^{1}H-NMR spectrum of 5-(1-hydroxy-3,3-dimethylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

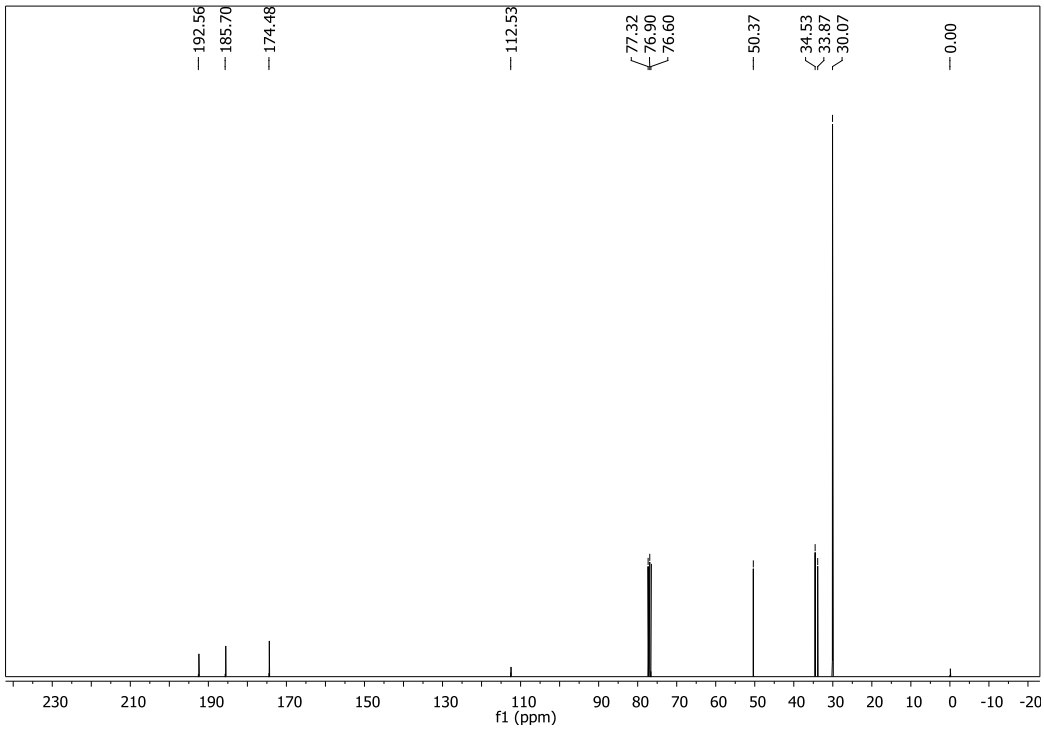
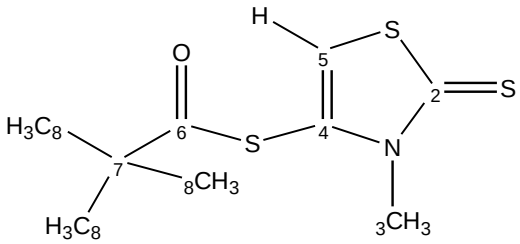


Figure 3.2.18: ^{13}C-NMR spectrum of 5-(1-hydroxy-3,3-dimethylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 75 MHz

3.3 Acylations in dichloromethane using pyridine as base

3.3.1 with trimethylacetyl chloride



MW= 247g/mol

4-(trimethylacetylthio)-3-methyl-1,3-thiazol-4-ene-2-thione

Acylation with trimethylacetyl chloride	
Chemicals	0.005 mol (0.815 g) 3-methyl-4-thorhodanine 0.005 mol (0.395 g) pyridine 0.005 mol (0.6 g) trimethylacetyl chloride 5:2 EtOH : $CHC1_3$ (recrystallization)
Product	4-(trimethylacetylthio)-3-methyl-1,3-thiazol-4-ene-2-thione
Yield	0.562 g (45.5%) Dark green crystals
Melting Point	116.5-118.0 ^oC
^{1}H-NMR (ppm)	δ = 6.90 (1H) CH δ = 3.56 (3H) N-CH_3 δ = 1.32 (9H) CH_3
^{13}C-NMR (ppm)	C2: 187.80; C3: 34.52; C4: 127.90; C5: 120.06; C6: 201.76; C7: 47.38; C8: 26.79

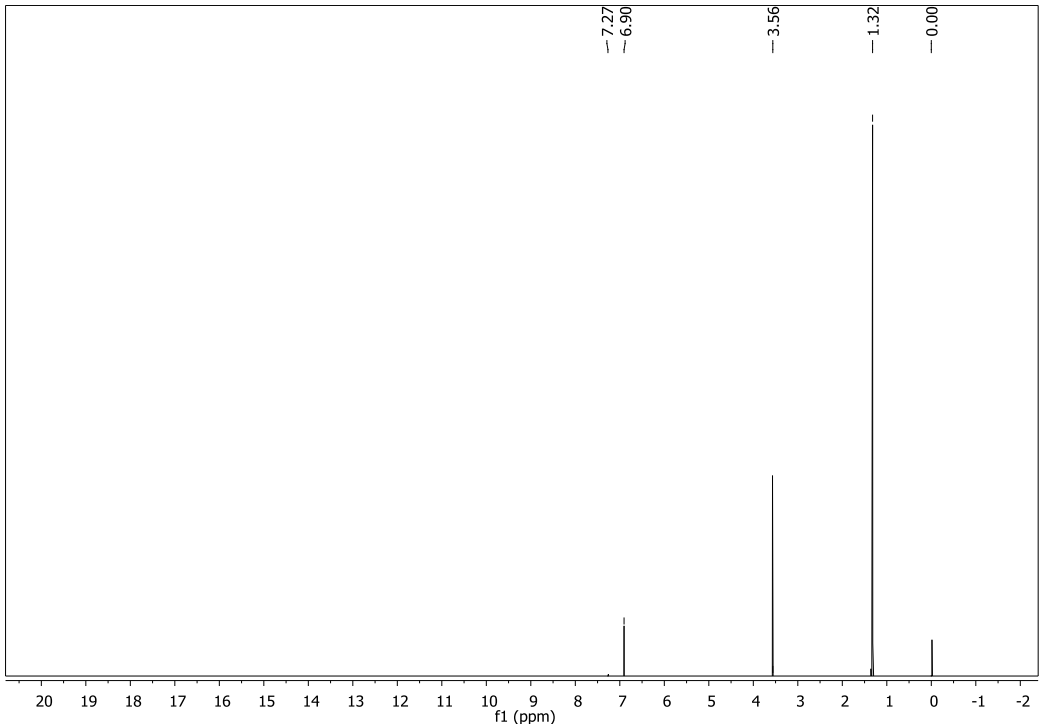


Figure 3.3.1: ^{1}H NMR spectrum of 4-(trimethylacetylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 300 MHz

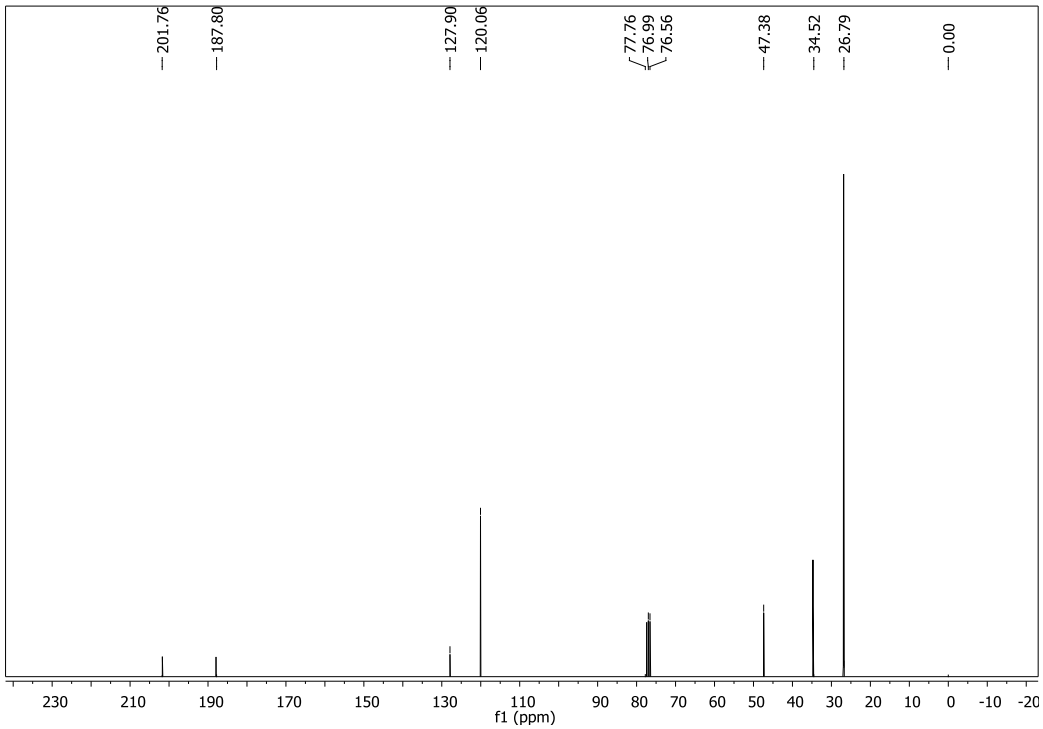
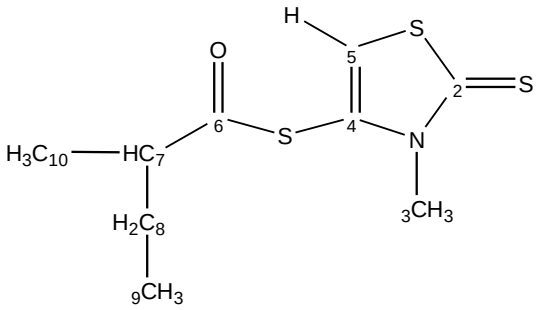


Figure 3.3.2: ^{13}C-NMR spectrum of 4-(trimethylacetylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 75 MH

3.3.2 with 2-methylbutyryl chloride



MW= 247g/mol

4-(2-methylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione

Acylation with 2-methylbutyryl chloride	
Chemicals	0.005 mol (0.815 g) 3-methyl-4-thiorhodanine 0.005 mol (0.395 g) pyridine 0.005 mol (0.6 g) 2-methylbutyryl chloride 5:2 EtOH: $CHCl_3$ (recrystallization)
Product	4-(2-methylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione
Yield	0.866g (70.1%) Dark green crystals
Melting Point	67.6-68.0 ^oC
^{1}H-NMR (ppm)	δ = 6.92 (1H) CH δ = 3.62 (3H) N-CH_3 δ = 2.73 (1H) CH δ = 1.80 (3H) CH_3 δ = 1.28 (2H) CH_2 δ = 0.99 (3H) CH_3
^{13}C-NMR (ppm)	C2: 188.04; C3: 34.86; C4: 127.90; C5: 119.89; C6: 198.77; C7: 49.91; C8: 16.60; C9: 11.24; C10: 26.72

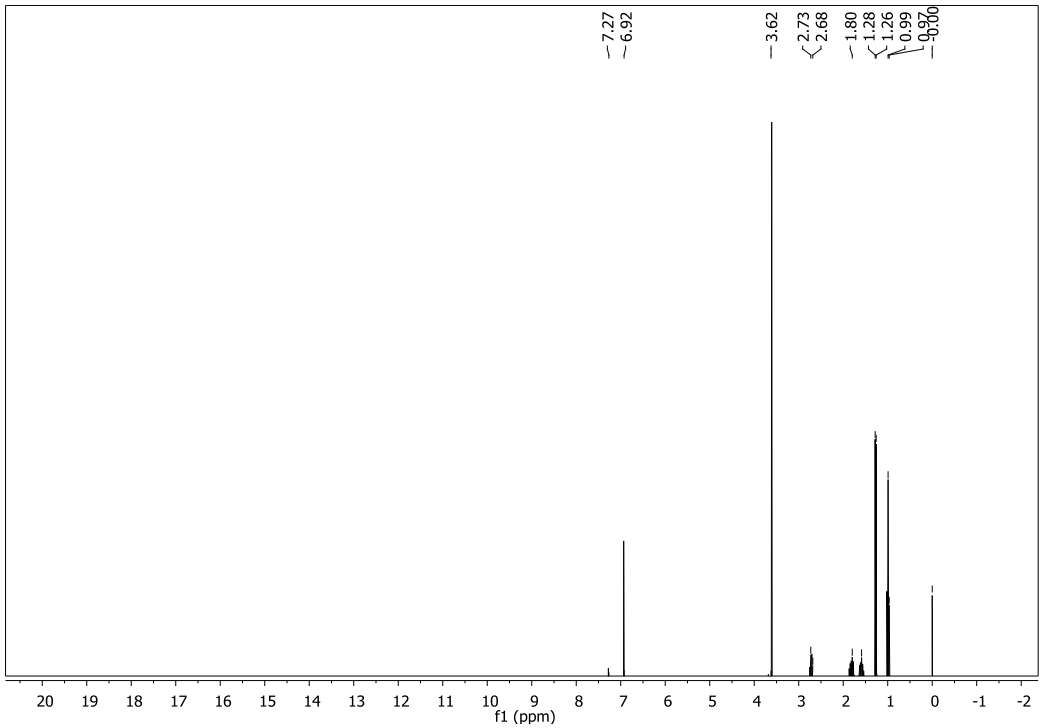


Figure 3.3.3: ^{1}H-NMR spectrum of 4-(2-methylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 300 MHz

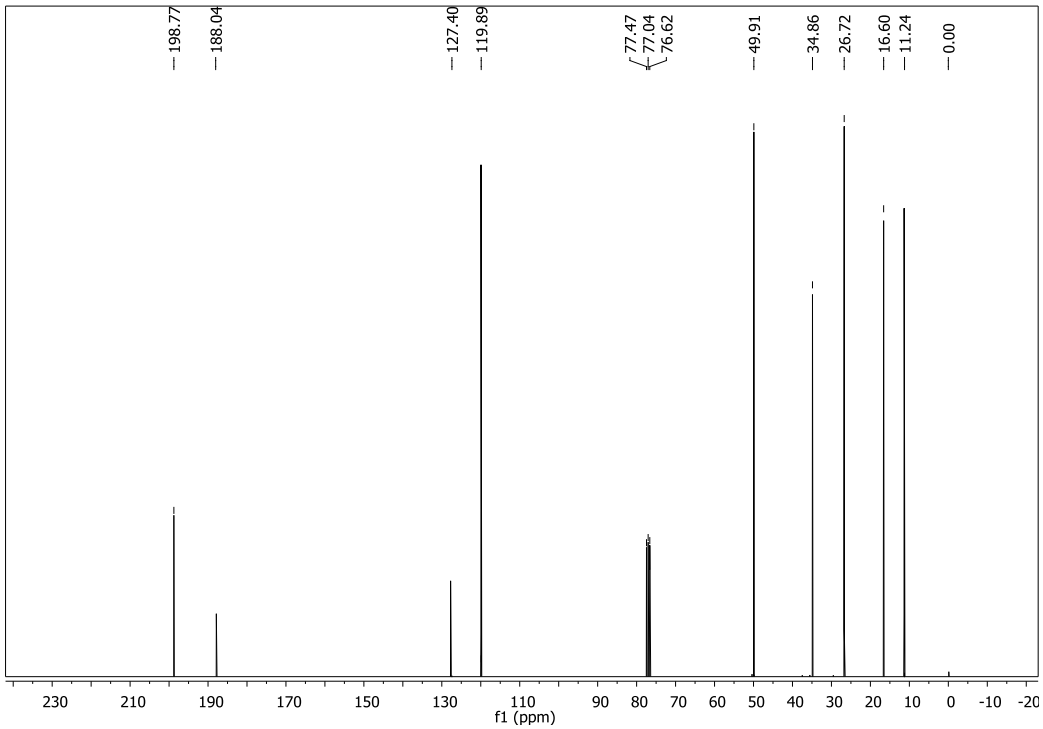
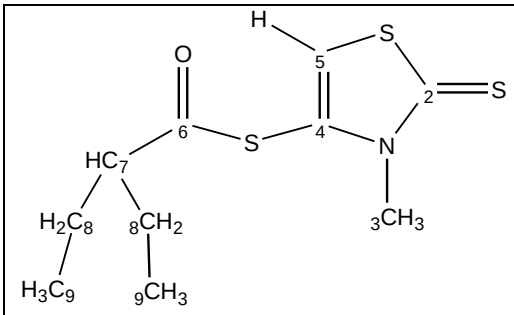


Figure 3.3.4: ^{13}C-NMR spectrum of 4-(2-methylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 75 MHz

3.3.3 with 2-ethylbutyryl chloride



MW= 261g/mol

4-(2-ethylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione

Acylation with 2-ethylbutyryl chloride	
Chemicals	0.005 mol (0.815 g) NaOH 0.005 mol (0.395 g) pyridine 0.005 mol (0.67 g) 2-ethylbutyryl chloride 5:2 EtOH: $CHCl_3$ (recrystallization)
Product	4-(2-ethylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione
Yield	0.820 g (62.8%) Reddish brown crystals
Melting Point	69.0-70.0 ^{o}C
^{1}H-NMR (ppm)	δ = 6.93 (1H) CH δ = 3.62 (3H) N-CH_3 δ = 2.57 (1H) CH δ = 1.79 (4H) CH_2 δ = 0.99 (6H) CH_3
^{13}C-NMR (ppm)	C2: 187.84; C3: 35.00; C4: 127.87; C5: 119.84; C6: 198.56; C7: 57.42; C8: 25.03; C9: 11.54

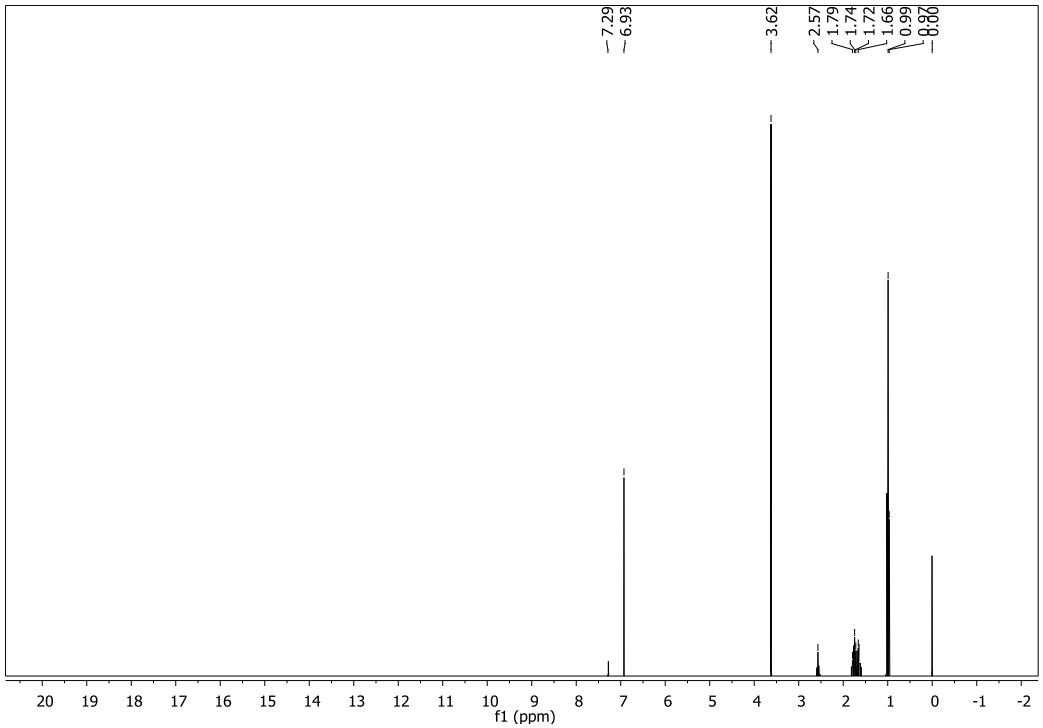


Figure 3.3.5: ^{1}H-NMR spectrum of 4-(2-ethylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 300 MHz

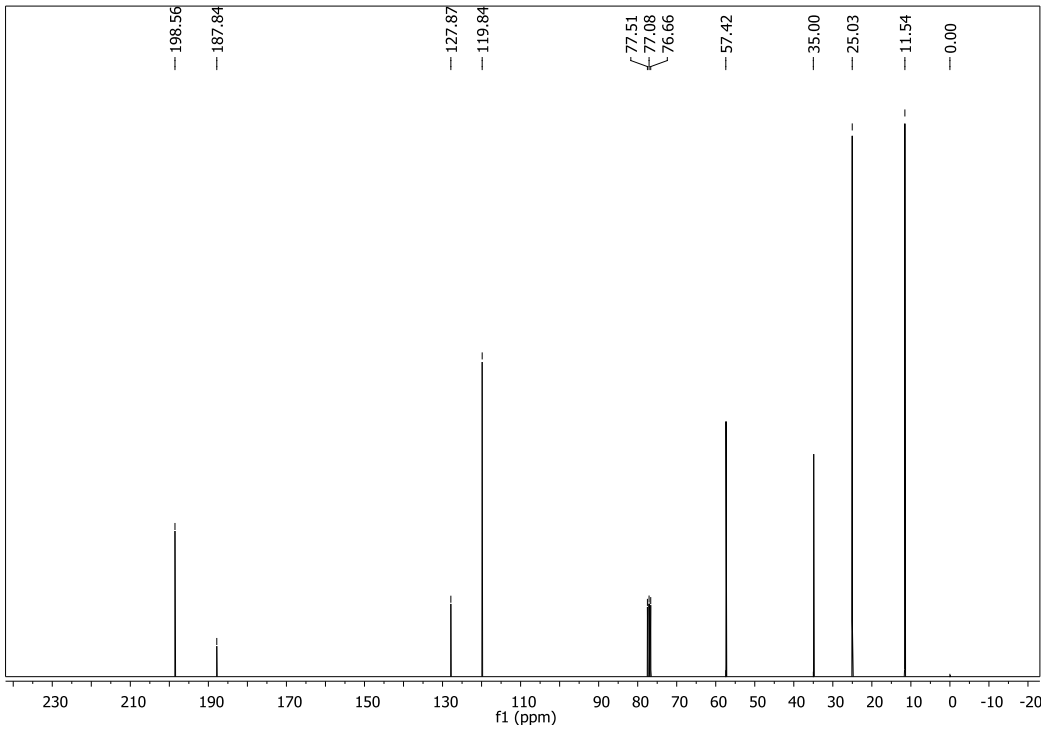
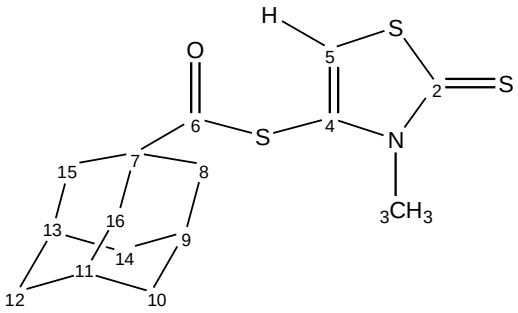


Figure 3.3.6: ^{13}C-NMR spectrum of 4-(2-ethylbutyrylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 75 MHz

3.3.4 with 1-adamantanecarbonyl chloride



MW= 325g/mol

4-(1-adamantanecarbonylthio)-3-methyl-1,3-thiazol-4-ene-2-thione

Acylation with 1-adamantanecarbonyl chloride	
Chemicals	0.005 mol (0.815 g) 3-methyl-4-thiorhodanine 0.005 mol (0.395 g) pyridine 0.005 mol (0.99 g) 1-admantane carbonyl chloride 5:2 EtOH: $CHCl_3$ (recrystallization)
Product	4-(1-adamantanecarbonylthio)-3-methyl-1,3-thiazol-4-ene-2-thione
Yield	0.806 g (49.6%) Brown crystals
Melting Point	157.8-160.0 ^{o}C
^{1}H-NMR (ppm)	δ = 6.91 (1H) CH δ = 3.54 (3H) N-CH_3 δ = 2.11 (7H) δ = 1.97 (7H) δ = 1.77 (4H)
^{13}C-NMR (ppm)	C2: 187.80; C3: 35.92; C4: 127.88; C5: 119.85; C6: 201.28; C7: 49.64; C8, 12, 15: 38.65; C9, 10, 13, 14: 28.37; C11,16: 27.66

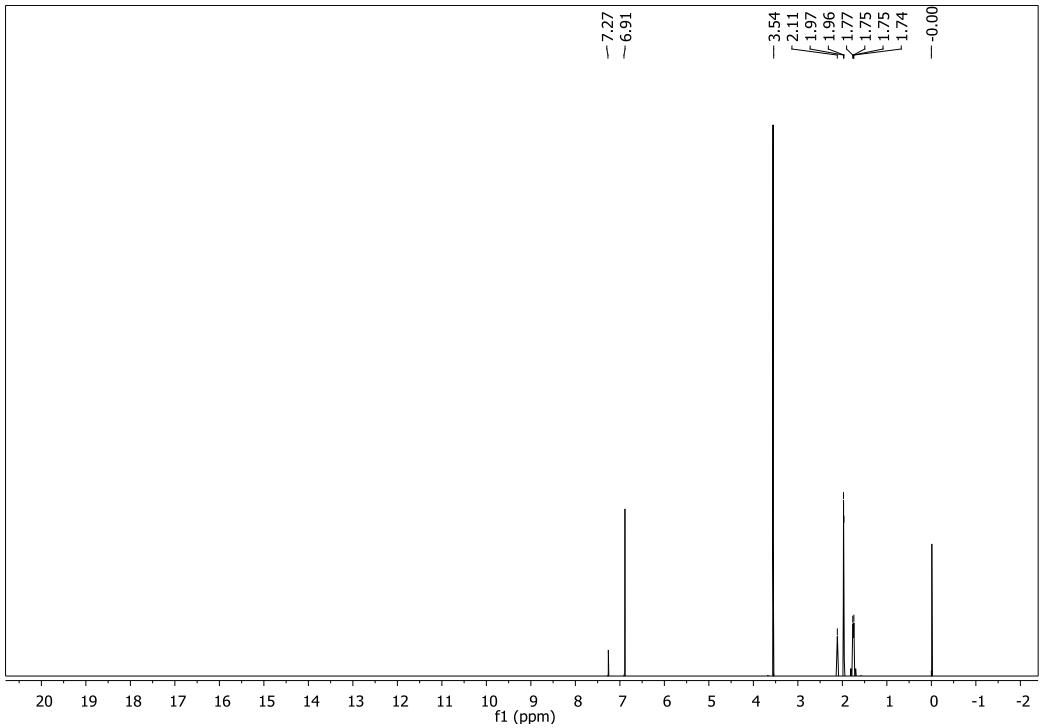


Figure 3.3.7: **^{1}H-NMR spectrum of 4-(1-admantanecarbonylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 300 MHz**

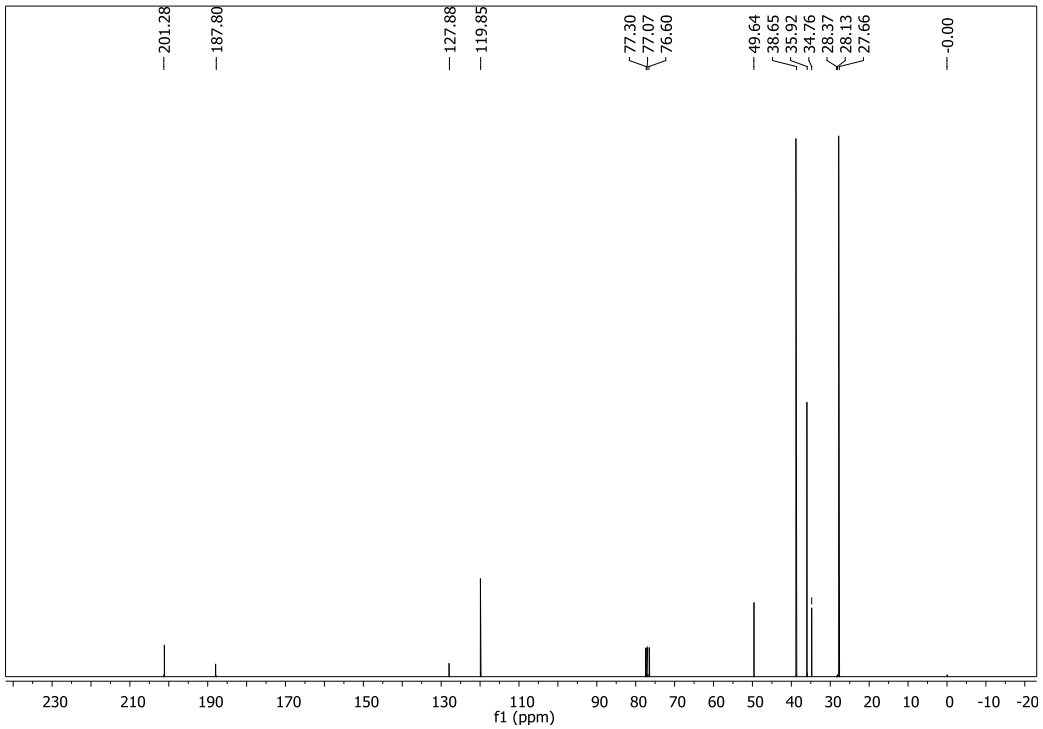


Figure 3.3.8:**^{13}C-NMR spectrum of 4-(1-admantanecarbonylthio)-3-methyl-1,3-thiazol-4-ene-2-thione in $CDCl_3$ at 75 MHz**

3.4 Summary of chemical shifts

Tables 3.4.1 and 3.4.2 present the chemical shifts of all obtained C- and S-acylation products.

The basic structure of the products is shown in figure 3.4.1

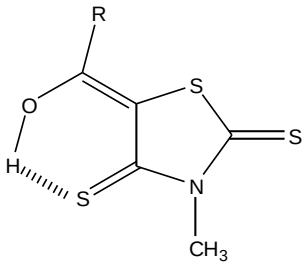


Figure 3.4.1 basic structure of the C-acylated products

Table 3.4.1: Summary of ^{13}C NMR and ^{1}H NMR chemical shifts for the C-acylation products in $CDCl_3$, the shifts are in ppm.

R=	CH_3	CH_2CH_3	$(CH_2)_2CH_3$	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	$*C_3H_5$	$*C_6H_{11}$	$C_6H_5CH_2$	$CH_2C(CH_3)_3$
C2	192.55	192.32	192.79	192.32	192.55	192.56	192.09	192.55	192.56
C3	34.54	34.52	34.69	34.52	34.46	34.76	34.52	34.48	34.53
C4	185.70	185.70	185.70	185.70	185.69	183.49	185.47	186.40	185.70
C5	110.96	110.26	111.20	109.33	111.35	110.50	109.57	110.96	112.53
C6	171.52	176.11	175.65	179.54	174.94	177.49	178.83	172.20	174.48
C7	22.91	30.38	39.11	36.62	45.95	17.89	46.68	43.02	33.87
C8			19.76	19.01	27.22	12.65	28.60	133.09	50.37
C9			13.72		22.39	12.65	25.64	129.43	30.07
C10							25.64	129.20	
C11							25.64	128.95	
C12							28.60		
OH	15.08	15.20	15.18	15.29	15.18	15.32	15.28	15.16	15.24
$N\text{-}CH_3$	3.76	3.75	3.77	3.76	3.76	3.77	3.75	3.75	3.76
H7	2.25	2.47	2.38	2.32	2.32	1.48	2.18	3.70	2.32
H8		1.30	1.77	2.25	2.25	1.28	1.88	7.37	1.09
H9			1.02	1.03	1.03	1.28	1.88	7.33	
H10							1.88	7.27	

Note: * C_3H_5 is cyclopropyl, while * C_6H_{11} is cyclohexyl

The basic structure of the S-acylated products is shown in figure 3.4.2

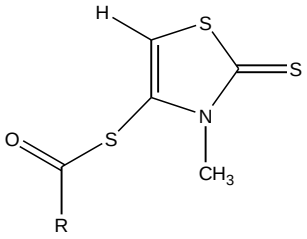


Figure 3.4.2 basic structure of S-acylated products.

Table 3.4.2: Summary of ^{13}C NMR and ^{1}H NMR chemical shifts for the S-acylation products in $CDCl_3$, the shifts are in ppm.

R=	$C(CH_3)_3$	$CH_3CHCH_2CH_3$	$CH(CH_2CH_3)_2$	*1-adamantanecarbonyl
C2	187.80	188.04	187.84	187.80
C3	34.52	34.86	35.00	35.92
C4	127.90	127.90	127.87	127.88
C5	120.06	119.89	119.84	119.85
C6	201.76	198.77	198.56	201.28
C7	47.38	49.91	57.42	49.64
C8	26.79	16.60	25.03	38.65
C9		11.24	11.54	28.37
C10		26.72		28.37
C11				27.66
C12				38.75
=CH	6.90	6.92	6.93	6.91
N-CH3	3.56	3.62	3.62	3.54
H7	1.32	2.73	2.57	2.11
H8		1.28	1.79	1.97
H9		0.99	0.99	1.77
H10		1.80		

Note * 1-adamantanecarbonyl the full structure can be seen in 3.3.4.

3.5 Correlation between σ* values and NMR chemical shifts.

To analyse the effect of different substituents the chemical shift of carbon numbers 2-7 and the enol protons are plotted as a function of σ* values for the products. Plotting of the chemical shifts as a function of σ* values gives an insight to the relative charge distribution in the molecule, a higher chemical shift relative to another means that the atom in question will be more deshielded and thus more positively charged.

The plots are fitted to make the best straight line and the correlation coefficient, R^2 is determined. The σ*values used are shown in table 3.1 and the NMR chemical shifts used are shown in tables 3.4.1 and 3.4.2 respectively.

Table 3.1: Substituents used for the acylation including the σ* and E_S values

Substituent number used in the graphs	Substituent	σ*	E_S
1	CH_3	0.000	0.00
2	CH_2CH_3	-0.100	-0.07
3	$CH_2CH_2CH_3$	-0.115	-0.36
4	$CH(CH_3)_2$	-0.190	-0.47
5	$CH_2CH(CH_3)_2$	-0.125	-0.93
6	Cyclopropyl (C_3H_5)	-0.08	
7	Cyclohexyl (C_6H_{11})	-0.15	-0.79
8	$C_6H_5CH_2$	+0.215	-0.38
9	$CH_2C(CH_3)_3$	-0.165	-1.74
10	$C(CH_3)_3$	-0.300	-1.54
11	$CH_3CHCH_2CH_3$	-0.210	-1.13
12	$CH(CH_2CH_3)_2$	-0.225	-1.98
13	1-adamantylcarbonyl		

3.5.1 C-acylated carbon shifts

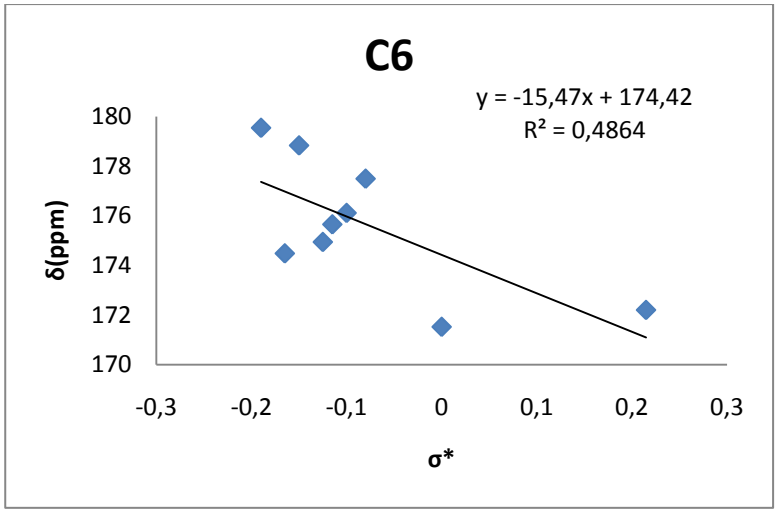


Figure 3.5.1: The chemical shifts of C6 as a function of the σ* values of the substituents for the C-acylated products (contains all substituents)

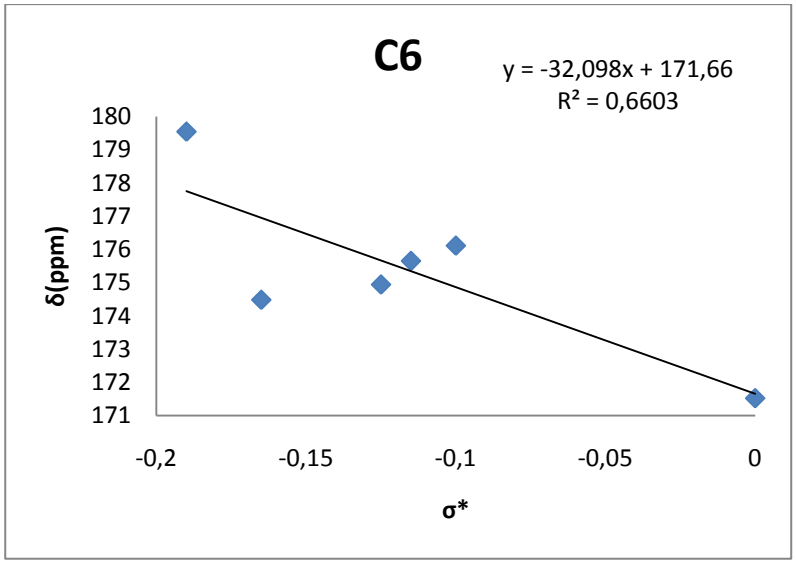


Figure 3.5.2: The chemical shifts of C6 as a function of the σ* values of the substituents for the C-acylated products (does not contain values for cyclopropyl, cyclohexyl and $C_6H_5CH_2$)

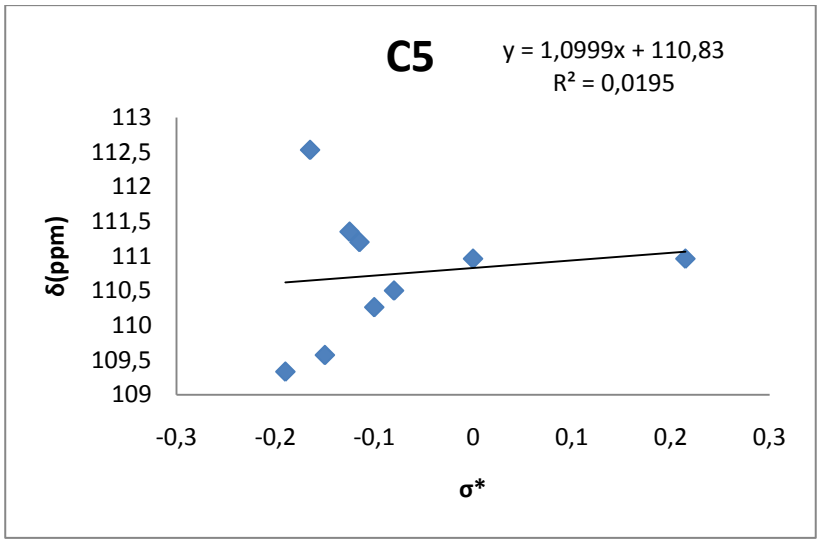


Figure 3.5.3: The chemical shifts of C5 as a function of the σ* values of the substituents for the C-acylated products (contains all substituents)

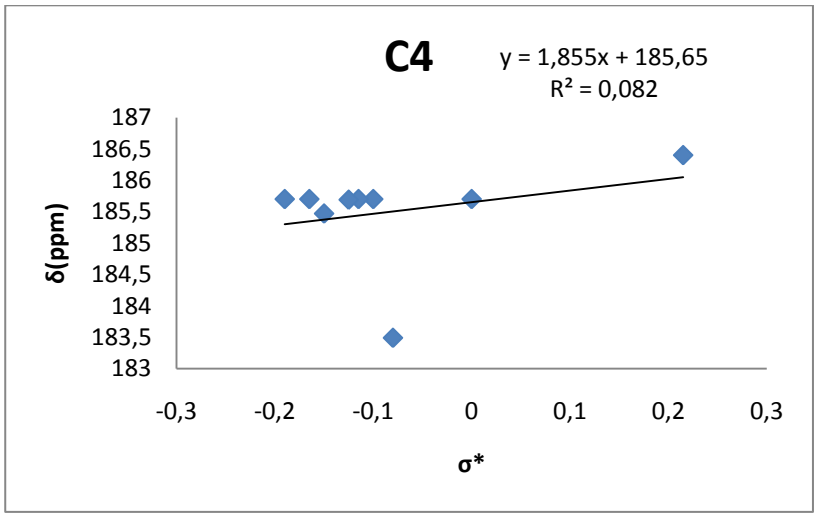


Figure 3.5.4: The chemical shifts of C4 as a function of the σ* values of the substituents for the C-acylated products (contains all substituents)

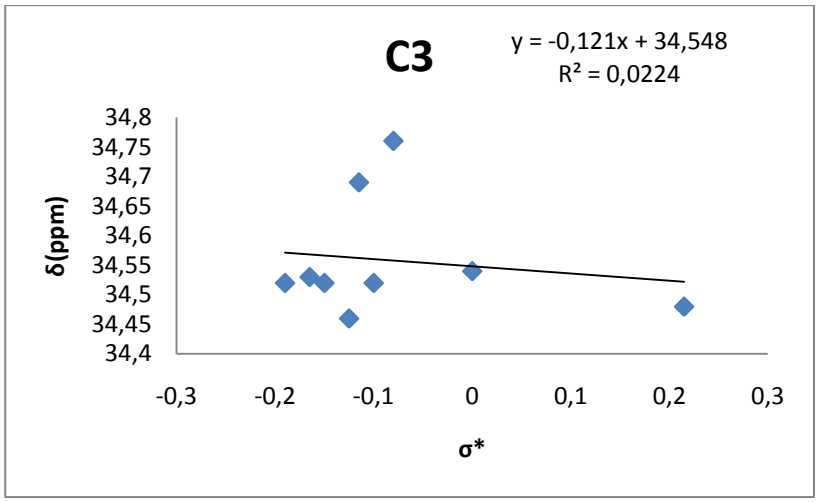


Figure 3.5.5: The chemical shifts of C3 as a function of the σ* values of the substituents for the C-acylated products (contains all substituents)

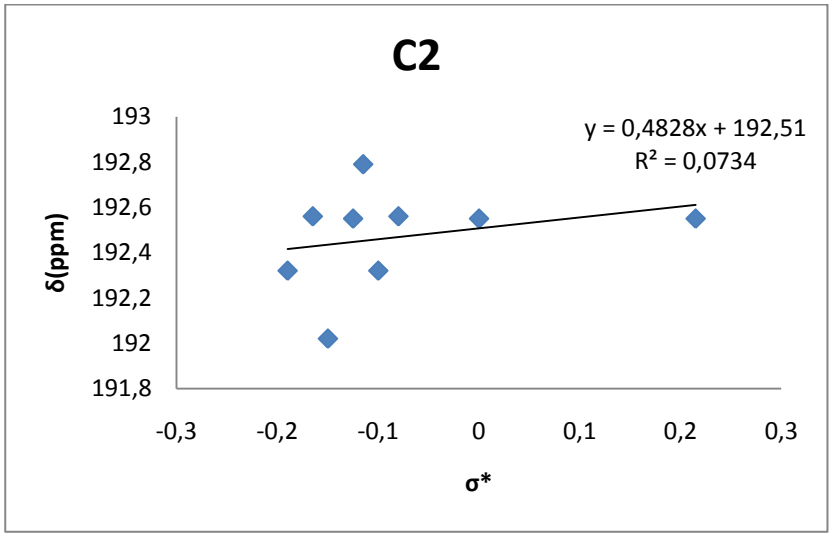


Figure 3.5.6: The chemical shifts of C2 as a function of the σ* values of the substituents for the C-acylated products (contains all substituents)

3.5.2 Enol protons

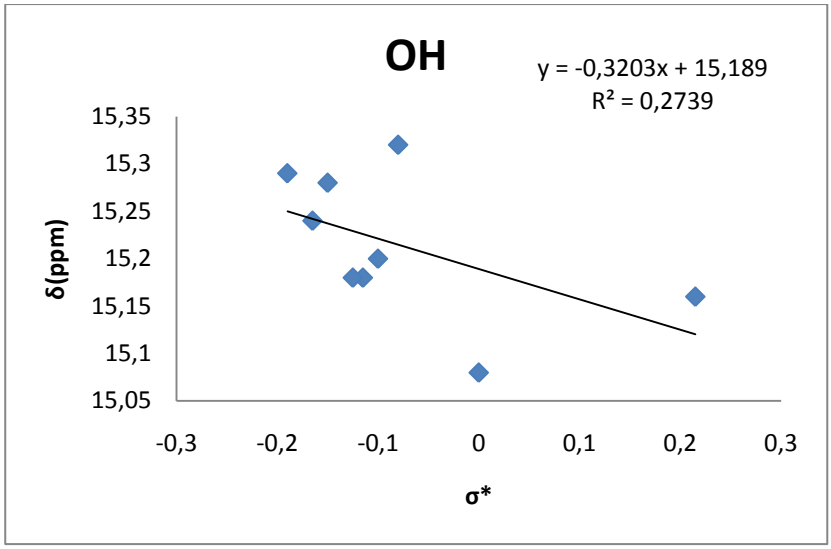


Figure 3.5.7: The chemical shift of the enol protons in C-acylated products as a function of the σ* values of the substituents (contains all substituents)

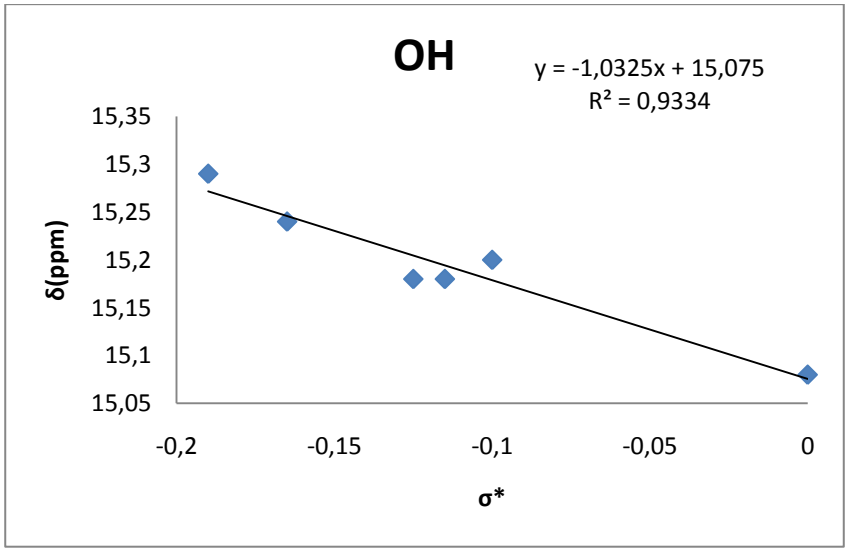


Figure 3.5.8: The chemical shift of the enol protons in C-acylated products as a function of the σ* values of the substituents (does not contain values for cyclopropyl, cyclohexyl and $C_6H_5CH_2$)

3.5.3 S-acylated products

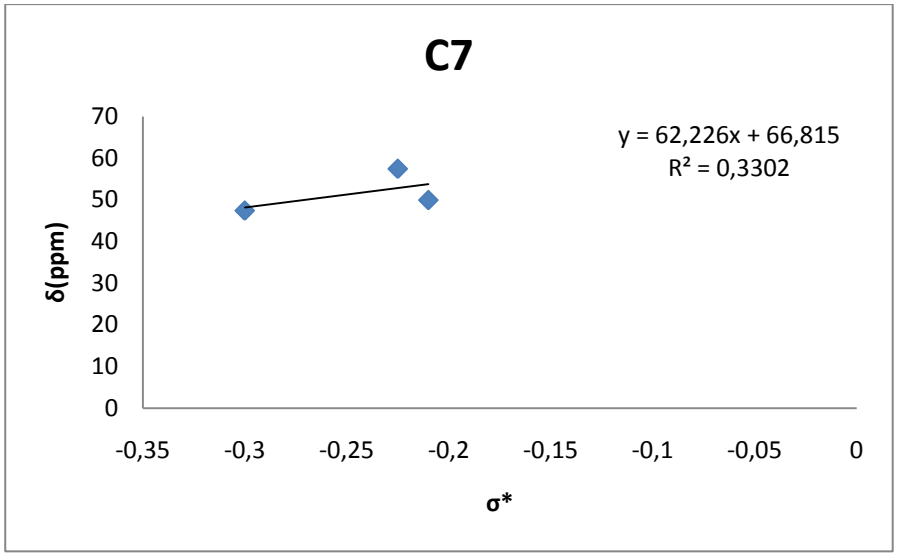


Figure 3.5.9: The chemical shifts of C7 as a function of the σ* values of the substituents for the S-acylated products (substituents analysed are from 10-12)

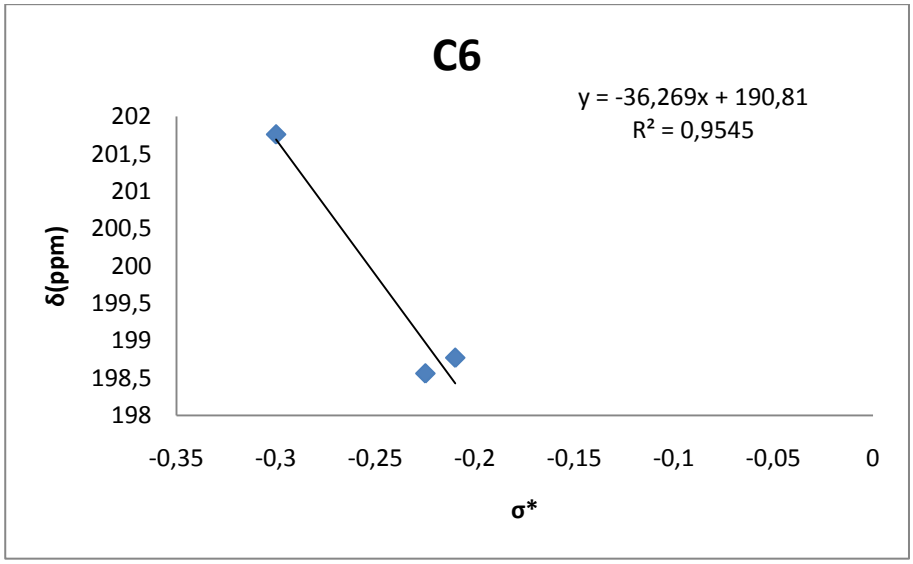


Figure 3.5.10: The chemical shifts of C6 as a function of the σ* values of the substituents for the S-acylated products (substituents analysed are from 10-12)

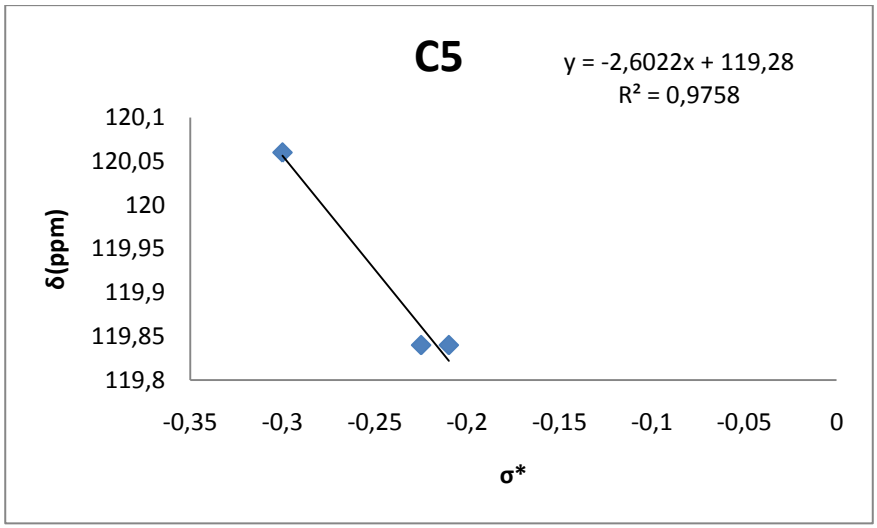


Figure 3.5.11: The chemical shifts of C5 as a function of the σ* values of the substituents for the S-acylated products (substituents analysed are from 10-12)

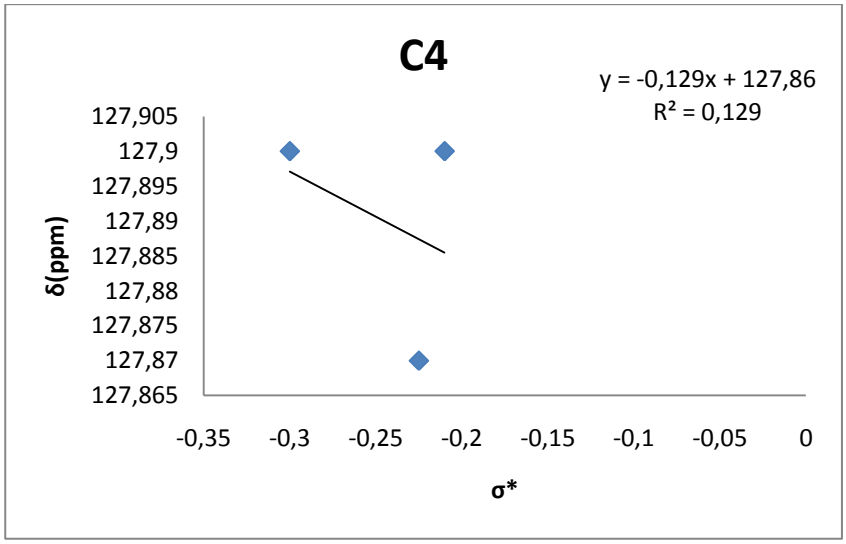


Figure 3.5.12: The chemical shifts of C4 as a function of the σ* values of the substituents for the S-acylated products (substituents analysed are from 10-12)

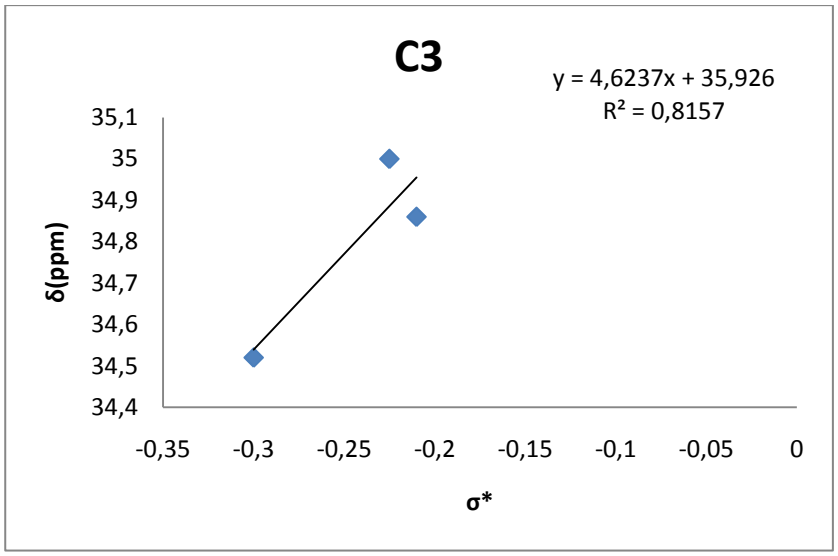


Figure 3.5.13: The chemical shifts of C3 as a function of the σ* values of the substituents for the S-acylated products (substituents analysed are from 10-12)

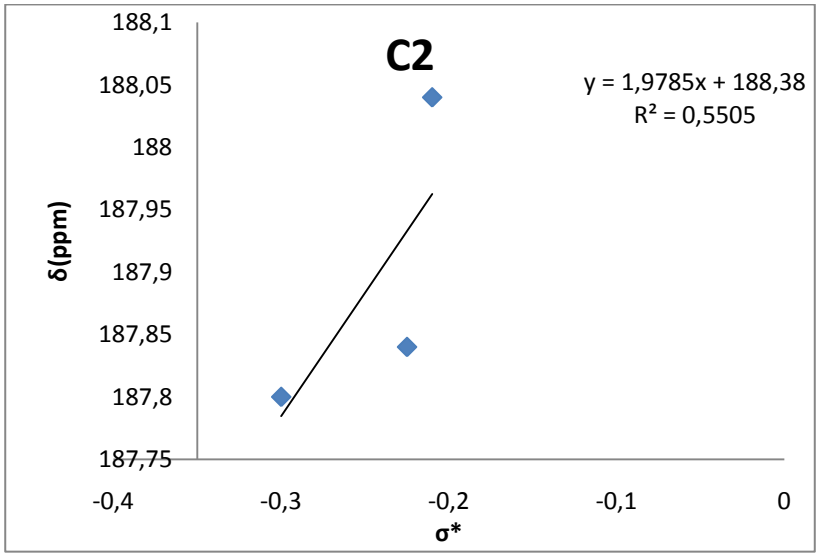


Figure 3.5.14: The chemical shifts of C2 as a function of the σ* values of the substituents for the S-acylated products (substituents analysed are from 10-12)

3.5.4 Vinyl Protons

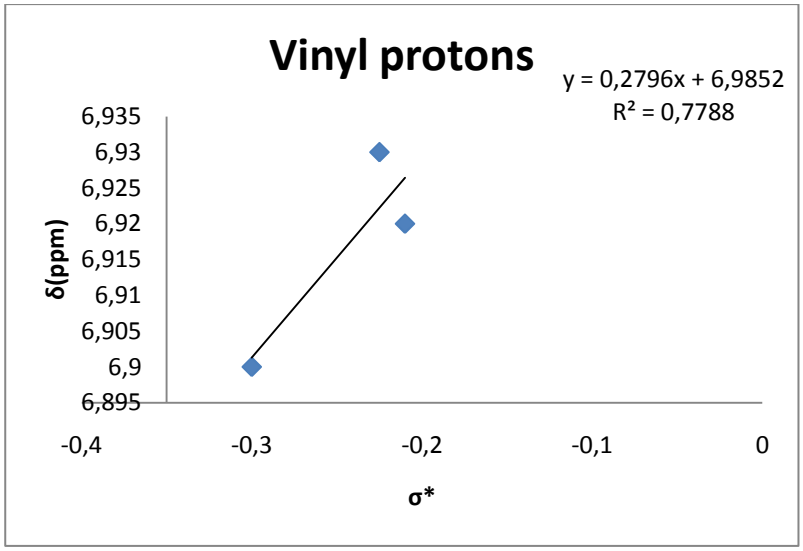


Figure 3.5.15: The chemical shift of the vinyl protons in S-acylated products as a function of the σ* values of the substituents (substituents analysed are from 10-12)

4. DISCUSSION

4.1. Experiments

4.1.1 Synthesis of 3-methyl-4-thiorhodanine

The synthesis of 3-methyl-4-thiorhodanine was carried out as described in the experimental section. If during recrystallization the filtration was not done immediately the product partly decomposed to a black looking substance. Investigations to find out what this black substance was were not carried out. Grischuck [13] also obtained a black substance which he believes that this could be a dimerization of thiorhodanine. During the thionation of rhodanine Grischuck also obtained a dark reddish violet dye which results when thiorhodanine oxidizes.

The crystals obtained were golden yellow in colour and the melting point corresponds well with what Cohen [9] obtained.

4.1.2 Acylation of 3-methyl-4-thiorhodanine.

The purpose of this project was to acylate 3-methyl-4-thiorhodanine with 13 aliphatic substituents and thereby analyse the effect of these substituents on the intramolecular hydrogen bond. For this to be possible all the products should be acylated on carbon 5 (C5). Only nine of the aliphatic substituents could be acylated on C5 the results can be seen in the result section. To make sure the C-acylated products could be repeated, a second synthesis was carried out and it was also possible to improve the yield the second time. The melting points were corresponding on both occasions so were the colours of the crystals.

Before finally deciding to synthesize the four products using pyridine as base several attempts were tried with NaOH as base. For the acyaltion with 2-methylbutyryl chloride using NaOH the product was always an oil layer but fortunately it was possible to do a ^{1}H NMR of the crude product and the spectra showed that it was a C acylation the spectrum is shown in appendix figure A.1 but since every time this acylation was carried out the product was an oil and very little product was formed it was decided to use pyridine as base and the result was an S-acylation and the yield was good as shown in the results section.

For the acylations with trimethy acetyl chloride, 2-ethylbutyryl chloride and 1-adamantanecarbonyl the ^{1}H NMR crude products as well as recystallized products showed that the products were a

mixture of S and C ayclation the spectra are shown in appendix figures A2, A3, A4 respectively. But when pyridine was used as base the products were all S-acylated with good yields.

4.1.3 Effect of base on acylation.

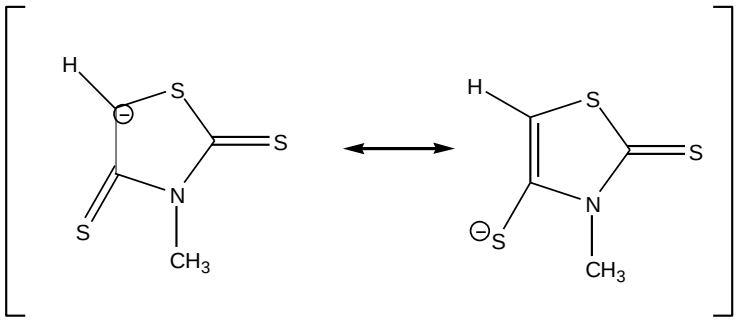


Figure 4.1: The conjugate intermediate in the mechanism of acyaltion of 3-methyl-4-thiorhodanine.

When using NaOH as base, the acylations were all C-acylated except for those where mixed products were obtained and when using pyridine as base, the acylations were all S-acylated. It is possible that when using NaOH as base, the Na^+ cation formed a strong ion pair with the carbanion thereby preventing the conjugation into S^-, thus only C-acylation occurs. In the acylation mechanism, there are two conjugated forms as shown in figure 4.1 in which the second form has a negative charge on sulphur and this makes the sulphur to be more nucleophilic. So when a weak base such as pyridine is used, the second form is easier to react with respective acid chlorides.

Size of the groups (steric effect) and the polarities (inductive effect) affect the reactivity of substituents and it is possible that in the acylations these factors had an effect on which conjugate form to favour. As shown in table 3.1 the products which were obtained as mixed C-acylated and S-acylated have large negative σ* values as well as Es values and become bulkier compared to the ones which were successful to be obtained only as C-acylated.

4.2 Correlation between σ* values and NMR chemical shifts

The inductive (σ*) and steric (Es) constants are known to be reliable and widely used substituent parameters and therefore there should be a correlation between the chemical shift and the constants. And also the relative charge distributions in the molecules could also be investigated by plotting the chemical shift as a function of the σ* values. The purpose of investigating the relative charge distribution is that a higher chemical shift relative to another means that the atom in question will be more deshielded, and therefore more positively charged. The points are fitted to make the best straight line and the correlation coefficient, R^2 is determined.

In the analysis only the σ* values were plotted and thereby overlooking the steric effects. Graphs correlating the chemical shift as a function of Es have been plotted and are found in the appendix A.3. The correlations coefficients are very weak. Therefore only graphs correlating the chemical shift as a function of σ* are analysed here.

4.2.1 Carbon shifts for the C-acylated products.

For the C-acylated only C-6 (figure 3.5.1) had variations in the chemical shift and a slightly stronger correlation, $R^2 = 0.4864$ compared to other carbons. Carbon C-5 had a correlation coefficient $R^2 = 00195$, while C-4 had a correlation coefficient $R^2 = 0{,}082$, C-3: $R^2 = 0,\ 0224$ and C-2: $R^2 = 0,\ 0732$, the respective graphs are shown in figures 3.5.3, 3.5.4, 3.5.5, 3.5.6.

From the carbon chemical shifts of the different substituents it is not possible to observe a tendency of whether there is an increase or decrease in the chemical shift as the σ* values decrease. The substituent which has a high chemical shift in C-6 is $CH(CH_3)_2$ being 179.54 ppm and it also has a more negative σ* value and this could indicate a stronger positive charge on the C-6. Since $CH(CH_3)_2$ has a more negative δ* value it is possible that it will stabilize the positive charge on C-6 and thus lead to a stable structure.

To try and make the best fitting line for C-6 only σ* values for six substituents were plotted in figure 3.5.2 and a correlation coefficient $R^2 = 0,\ 6603$ was obtained. The reason for removing the σ* values of cyclopropyl, cyclohexyl and phenylacetyl is that maybe the analysis of non-cyclic alkyl substituents will give a good correlation. The removal of the three sustituents leads to a better correlation coefficient.

4.2.2 Enol protons.

To analyse the correlation between the chemical shifts and σ* values, the chemical shifts of the enol protons as a function of σ* were plotted as shown in figure 3.5.7 and a correlation coefficient R^2 = 0, 2739. This is a very weak correlation. To make the best fit, the σ* values of cyclopropyl, cyclohexyl, phenyl acetyl were not used and this gave a strong correlation coefficient R^2 = 0.993.

The chemical shifts of the enol protons also don't show any tendency of increase or reduction in the chemical shift as the σ* values decrease. For the enol protons the substituent which had the next high chemical shift is $CH(CH_3)_2$ at 15.29 ppm and also has a more negative σ*.

The chemical shifts of the enol protons are in the range of 15.08-15.32 ppm and this indicates that the hydrogen bond to sulphur is strong. The enol protons of 3-methylrhodanine in which the hydrogen bonds to oxygen were found to be in the range of 11.91-13.78 ppm by Michel et al [2]. The high chemical shift observed here for the enol protons could also be that the sulphur is closer to the enol proton.

To find out if there could have been a correlation if all the products contained an enol proton, the chemical shifts of the enol protons from the mixed products are also plotted as a function of σ*. The graph is shown in appendix A.2. It appears that there is no correlation even if all the products were C acylated with R^2 = 0.2911.

4.2.3 Carbon shifts for the S-acylated products.

Four S-acylated products were obtained and correlation graphs were plotted, the chemical shift as a function of σ* values. Since only values for three substituents were available only these were analysed.

It is not possible either to say that the chemical shift is increasing as the σ* values get more negative as the number of sustituents is very small. C6, C5, C3 had strong correlations with R^2 coefficients being 0, 9545, 0,975, 0,817 respectively while C7, C4, C2 had weak correlations with R^2 coefficients being 0, 3302, 0,129, 0, 5503. The graphs are shown in figures, 3.5.9-3.5.14.

The chemical shifts as a function of steric effects (Es) were also considered, the graphs are found in appendix A11-A17. As observed from the graph C4 has a strong correlation R^2 = 0, 7674 in respect to steric effects, this is clear because the substitution is taking place on the sulphur that is bound to C4 and these substituents are bulky.

4.2.4 Vinyl Protons

Only three substitutents were analysed and the graph shown in figure 3.5.15 have a correlation coefficient R^2 = 0, 7788 and this indicates that there is a slightly stronger correlation, the chemical shifts are high and this means the protons are deshielded.

CONCLUSION

3-methyl-4-thiorhodanine has been synthesized and acylated with thirteen aliphatic acid chlorides, the substituent groups were CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, cyclopropyl, cyclohexyl, $C_6H_5CH_2$, $CH_2C(CH_3)_3$, $C(CH_3)_3$, $CH_3CHCH_2CH_3$, $CH(CH_2CH_3)_2$, 1-adamantanecarbnyl. Of these it was only possible to successful obtain C-acylated products with the first nine aliphatic acid chlorides. The yields of the C-acylated products ranged from 8.1-58.5%, some of the products had to be recrystallized twice in order to get a pure compound.

When using NaOH as base, it was straightforward to obtain C-acylated products for the first nine aliphatic acid chlorides while the remaining four substituents were obtained as containing both C- and S-acylated products. Therefore pyridine was used as base for the acylation of the other four substituents and only S-acylated products were obtained. It is assumed that this could have been due to the increasing bulkiness of these substituents as can also be seen by the increasing negative steric effect constants of the substituents that could have favoured this pathway.

To study if there is a correlation between the inductive effects (σ*) and the substituents, the chemical shifts were plotted as a function of the σ* values. It was found that there was a weak correlation between the ^{13}C chemical shifts and the σ*, it was also found carbon 6 in the C-acylated compounds was mostly affected by the different substituents with the correlation coefficient $R^2 = 0,4864$. Correlations were also made between ^1H NMR chemical shifts for the enol protons and it was found that there was no linear correlation with $R^2 = 0,2739$.

With these low correlation coefficients it is not possible to conclude that there is a linear correlation between the different substituents and the inductive effect (σ*) and neither is it possible to conclude that there is a correlation between the different substituents and the steric effect. But maybe both inductive and steric effects should have been considered simultaneously.

PERSPECTIVE

Linear regressioin was used to analyse the effects of the different substituents chemical shift and inductive (σ*) values and there seems to be no correlation. Maybe multiple regression should have been used were both steric and inductive effects are included. Pavelich et al [14] have proposed an equation that includes both steric and inductive effects.

$\text{Log } (k/ko) = \sigma^* \rho^* + \delta Es,$

Where σ* and Es are steric and polar substituents constants respectively, ρ* and δ are reaction constants that measure the susceptibility of the reaction series to polar and steric effects respectively.

The above equation can be rewritten in relation to chemical shifts as

$\delta^{obs} = \delta^{ref} + \rho\, \sigma^* + \gamma Es$ [15]

where ρ and γ are sensitivity constants.

It will therefore be interesting to investigate these sensitivity parameters so that a solid conclusion can be made because it is possible that both steric and inductive effects play a role in these reactions.

REFERENCES

1. Marye Anne-Fox and James K. Whitesell

   "Organic Chemistry"

   Third Edition. [2004] Jones and Bartlett Publishers

2. Dana Michel and Samira Tavin

   "Synthesis and analysis of 5-acyl-N-methylrhodanines with aliphatic substituents.

   Chemistry module II Project.[2010] Roskilde University

3. Steric Effects in Organic Chemistry.

   Edited by Melvin S.Newman. [1956] John Wiley and Sons.

4. Pews.R.G and N.D Ojha.

   "The electronic properties of three-membered rings. The transmission of conjugation by

   the cyclopropane ring".

   Journal of the American Chemical Society[1969] **91**:21

5. Lars B. Smith. "Syntese og NMR specktrokemometrisk strukturanalyse af 5-acyl-3-methylrhodaniner".

   Speciale i organisk kemi.[2004] Roskilde universitetscenter

6. Tahmassebi Daryoush.

   "Theoretical studies of the tautomerism in oxalidine and thiazolidine heterocyclic systems".

   Journal of Molecular Structure (Theochem)[2003] **638**:11-20

7. Qiufen Hu, Xiangjun Yang, Zhangjie Huang, Jing Chen, Guangyu Y.

   "Simultaneous determination of palladium, platinum,rhodium and gold by the on-line solid phase

   extraction and high performance liquid chromatography with 5-(2-hydroxy-5-

   nitrophenyaazo)thiorhodanine as pre-column derivatization reagents".

   Journal of chromatography A, [2005] Vol.**1094**:77-82

8. Sych E.D and Mikitenko E.K.

   "Condensation of thiorhodanine with electrophillic reagents".

   Chemistry of Heterocyclic Compounds [1978] **14**, 464

9. Malene Cohen.
"Synthesis and structural characterization of S-acylated and C-acylated 3-methyl-1,3-thiazolane-2,4-dithiones"
Master project in Chemistry. [2009] Roskilde University

10. Turan Ozturk, Erdal Ertas and Olcay Mert.
"Use of Lawesson's reagent in organic syntheses."
Chem. Rev [2007]**107 (**11): 5210-5278.

11. Han-Otto Kalinowski,Stefen Berger and Siegmar Braun.
"Carbon-13 NMR Spectroscopy"
[1988] John Wiley and sons limited.

12. Donald L. Pavia, Gary M. Lampman, George S. Kriz.
"Introduction to spectroscopy.A guide for students of organic chemistry".
Third edition [2001] Thomson Brooks/Cole.

13. A.P. Grischuck.
"Azolidine-4-thiones, their derivatives and analogs. Synthesis and reactions of Thiorhodanine".
Khimiya Geterosiklicheskikh Soedinenii [1966]. **2,** 2: 372-375

14. William A. Pavelich and Robert W.Taft Jr.
"The Evaluation of Inductive and Steric Effects on Reactivity.
The Methoxide Ion-Catalyzed Rates of Methanolysis of L-Methyl Esters in Methanol."
Journal of the American Chemical Society [1957] **79**: 4935-4940.

15. Fritz Duus. Personal communications

APPENDIX

A.1 ^{1}H-NMR of mixed products

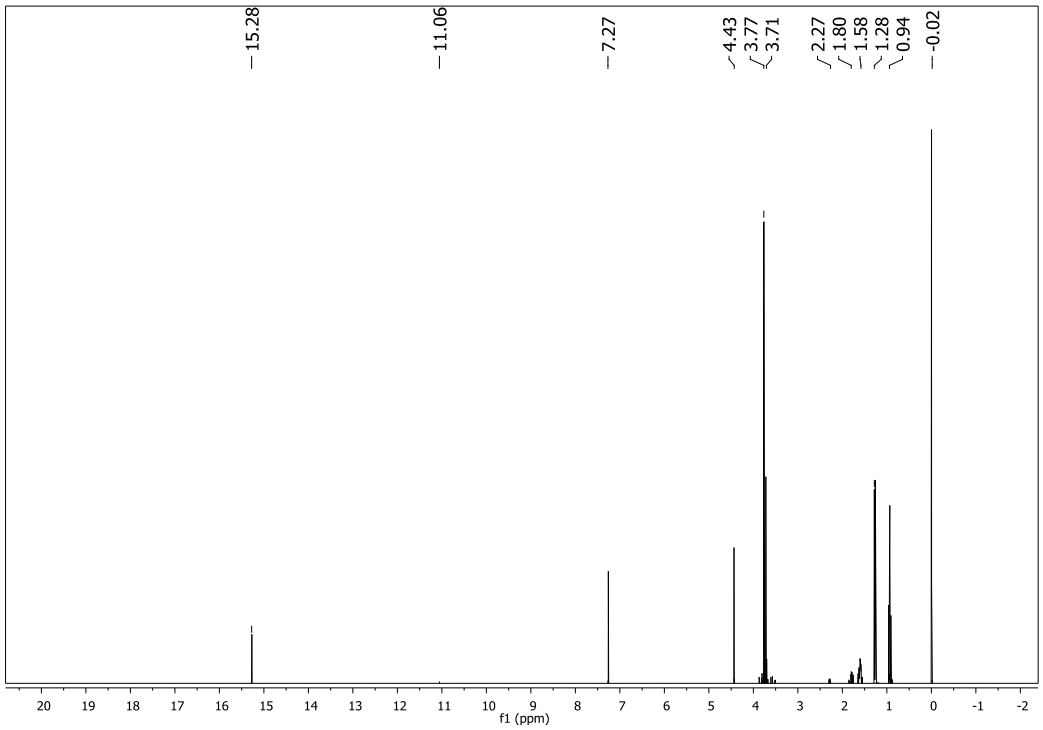


Figure A.1: ^{1}H-NMR spectrum of the crude product of 5-(1-hydroxy-2-methylbutylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

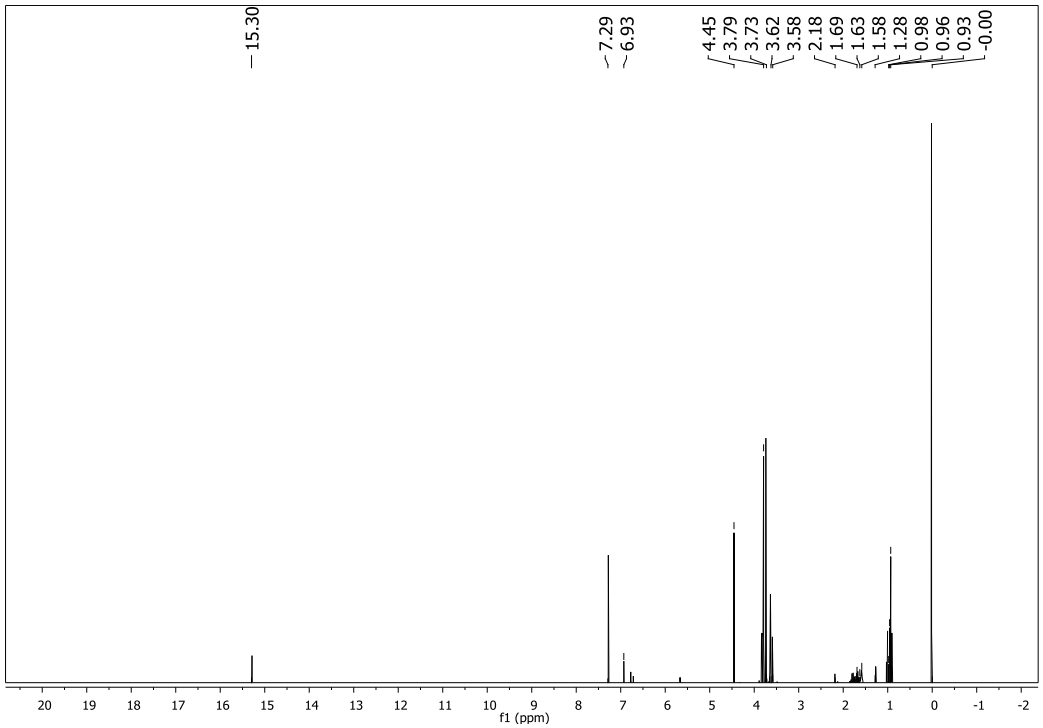


Figure A.2: ^{1}H-NMR spectrum of the crude product of 5-(1-hdroxy-2-ethylbutyrylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

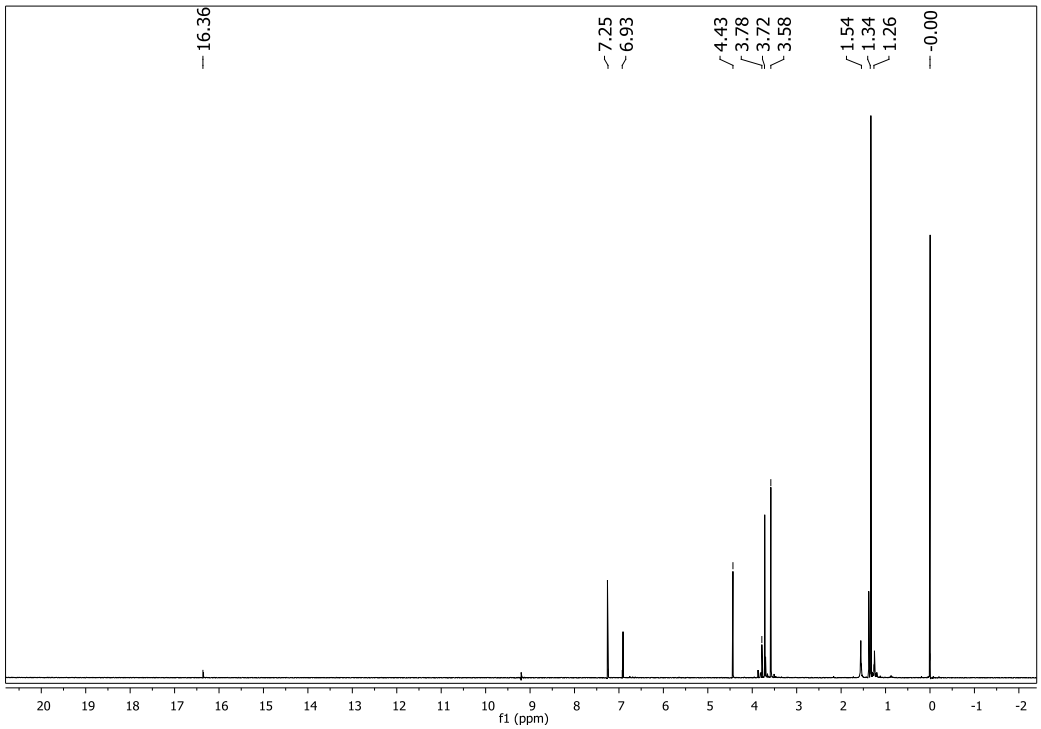


Figure A.3: ^{1}H-NMR spectrum of the crude product of 5-(1-hdroxy-2,2-dimethylpropylidene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

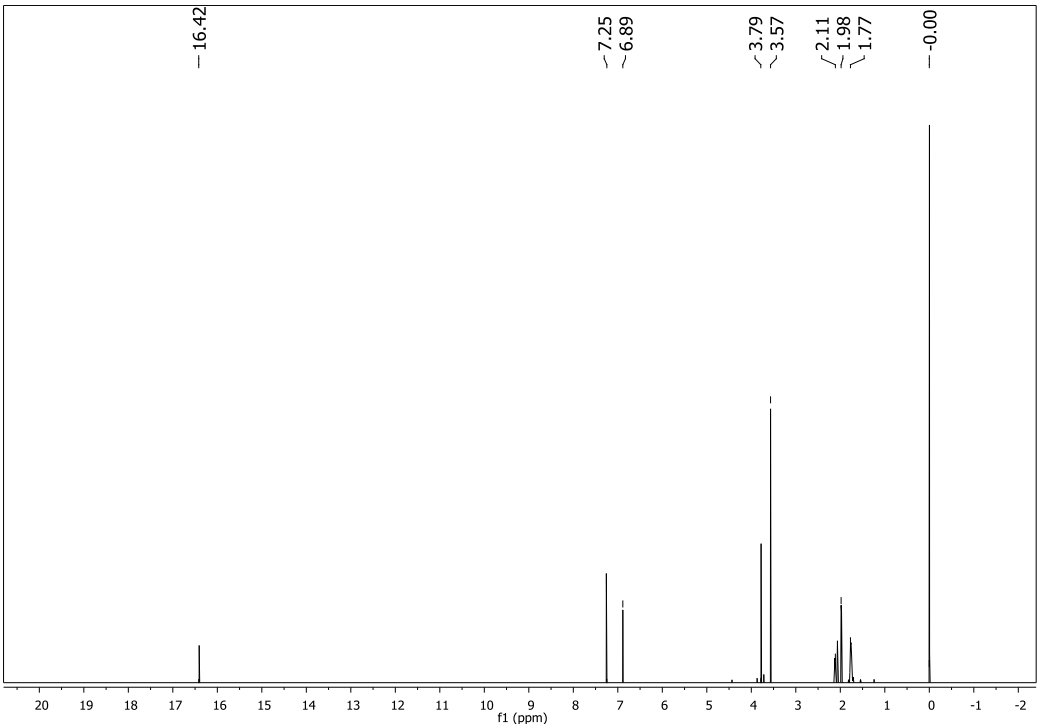


Figure A.4: ^{1}H-NMR spectrum of 5-(1-hydroxy-1-adamantylmethylene)-3-methyl-1,3-thiazolane-2,4-dithione in $CDCl_3$ at 300 MHz

A.2: Correlation between σ* and enol protons including the OH of the mixed products

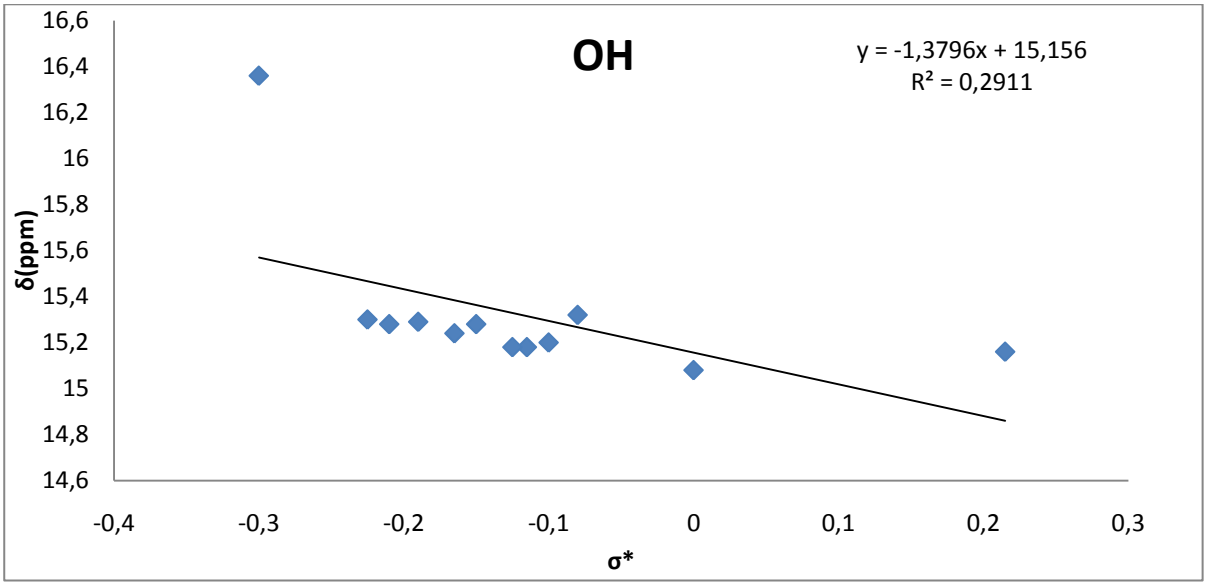


Figure A.5: The chemical shift of the enol protons including the OH of the mixed products as a function of the σ* values of the substituents (contains all substituents)

A.3: Correlation between Es and NMR chemical shifts for C-acylated products.

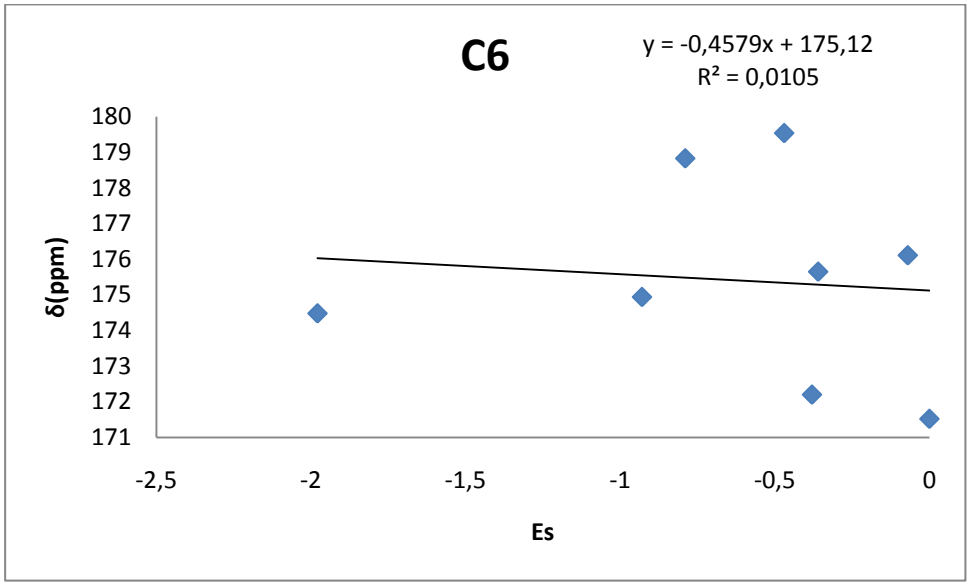


Figure A.6: The chemical shifts of C6 as a function of the Es values of the substituents for the C-acylated products

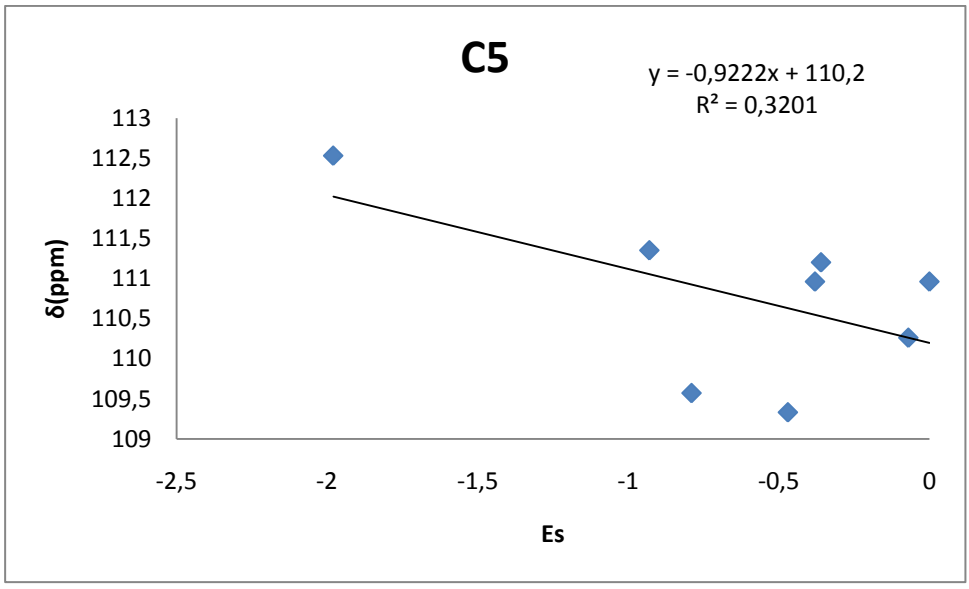


Figure A.7: The chemical shifts of C5 as a function of the Es values of the substituents for the C-acylated products

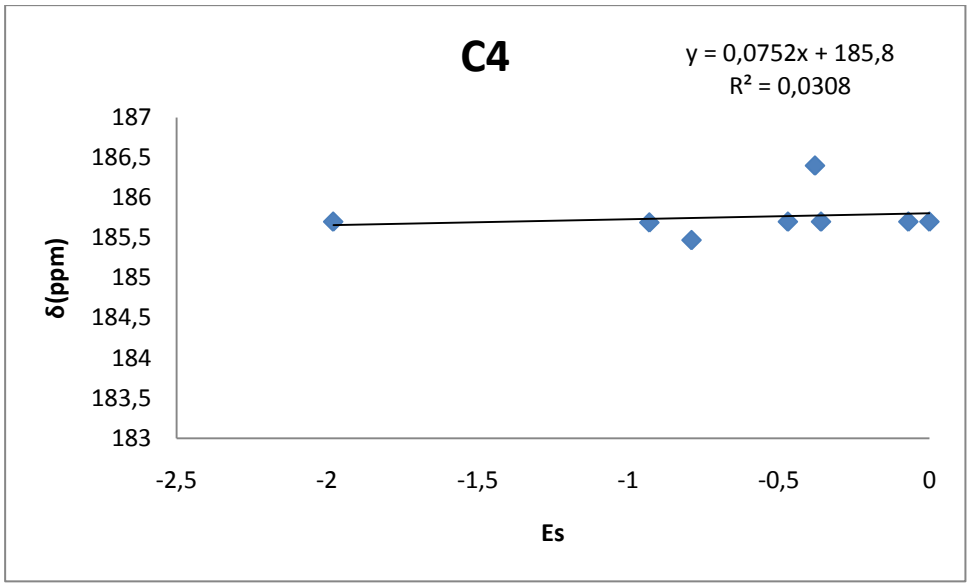


Figure A.8: The chemical shifts of C4 as a function of the Es values of the substituents for the C-acylated products

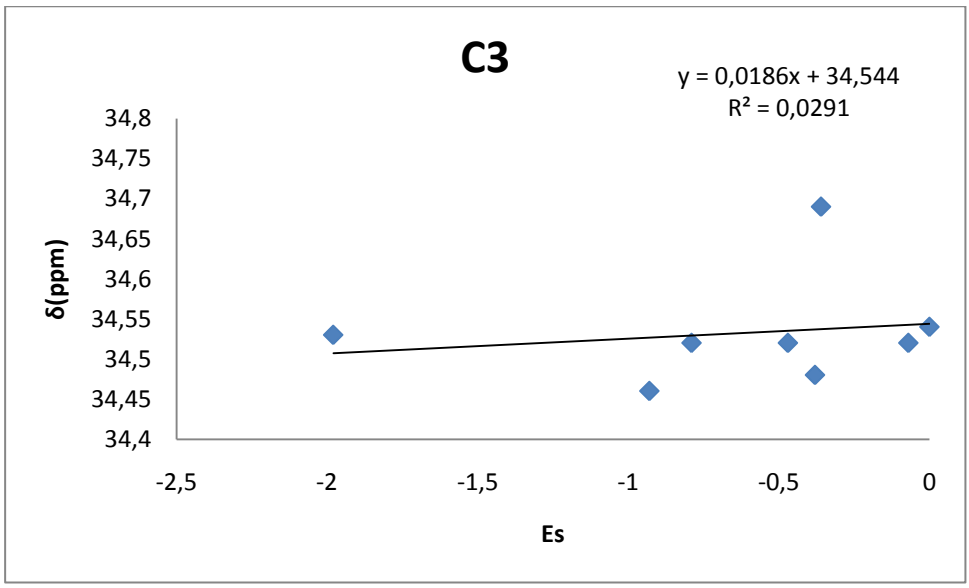


Figure A.9: The chemical shifts of C3 as a function of the Es values of the substituents for the C-acylated products

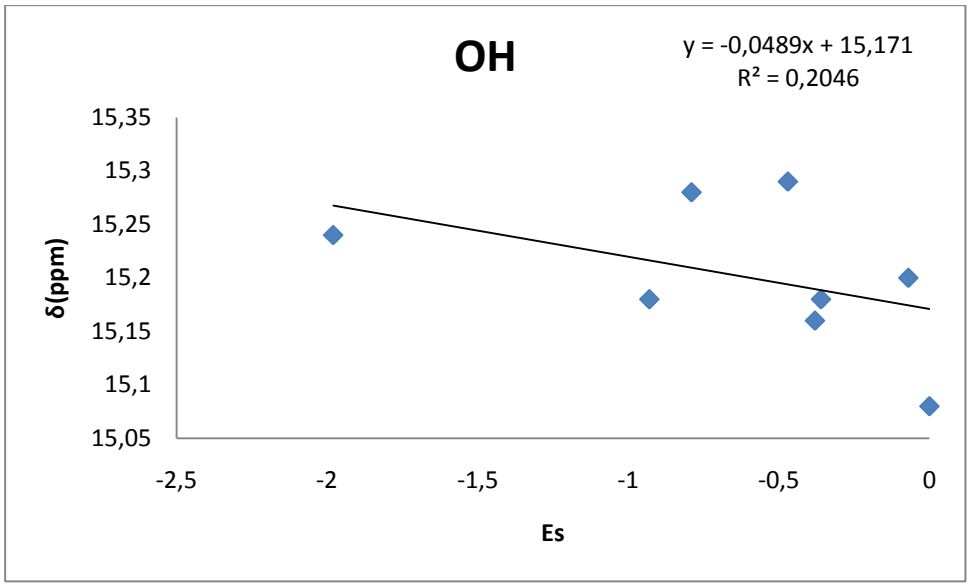


Figure A.10: The chemical shift of the enol protons in C-acylated products as a function of the Es values of the substituents.

A.4 :Correlation between Es and NMR chemical shifts for S-acylated products.

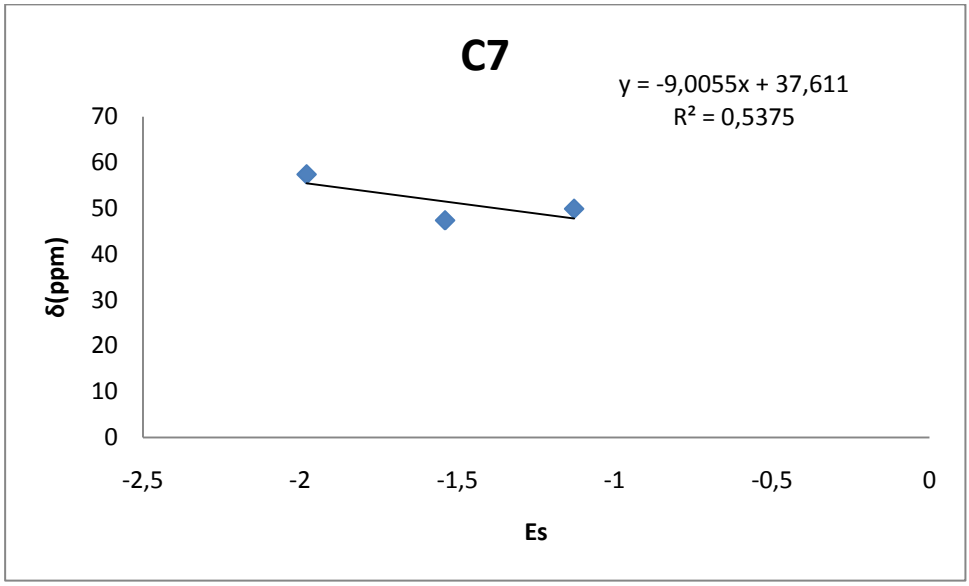


Figure A.11: The chemical shifts of C7 as a function of the Es values of the substituents for the S-acylated products

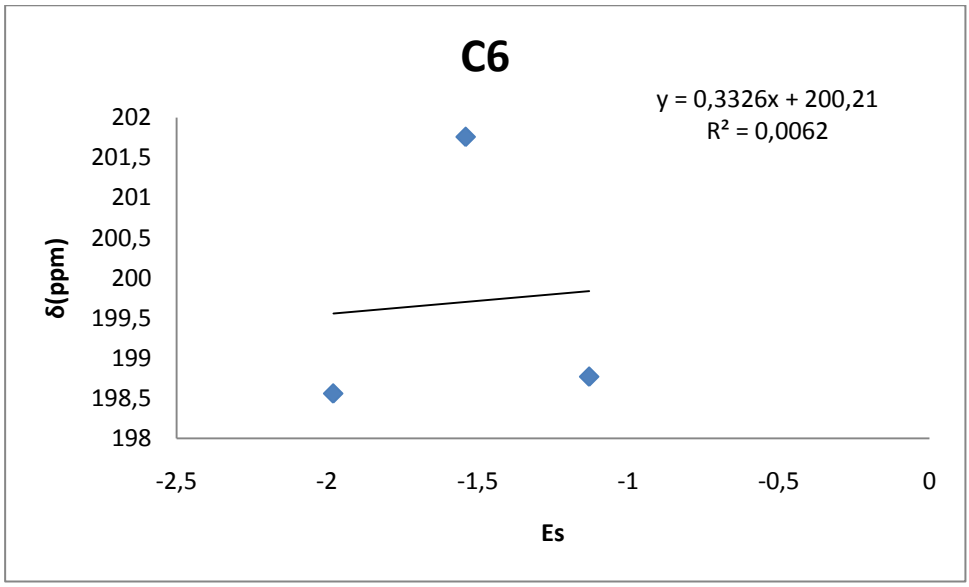


Figure A.12: The chemical shifts of C6 as a function of the Es values of the substituents for the S-acylated products

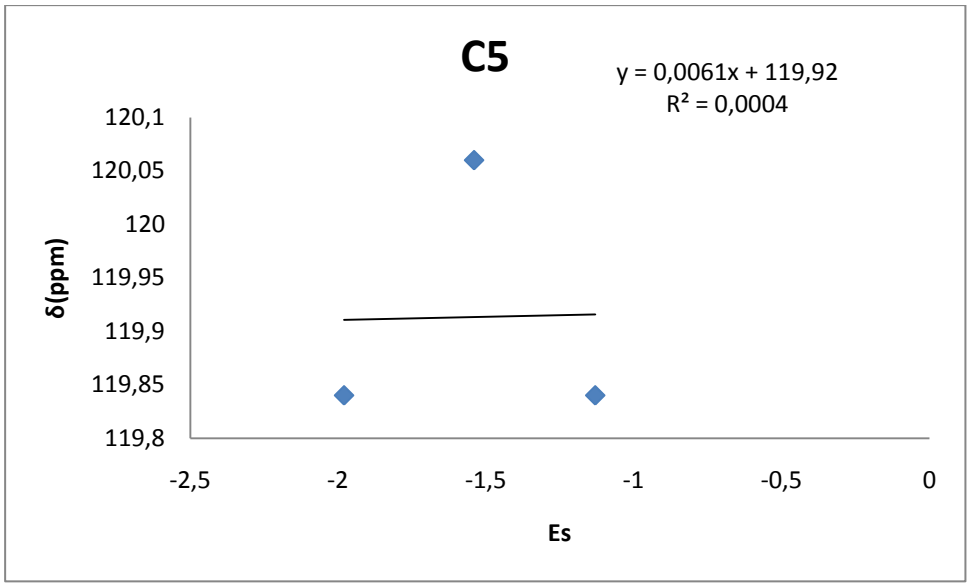


Figure A.13: The chemical shifts of C5 as a function of the Es values of the substituents for the S-acylated products

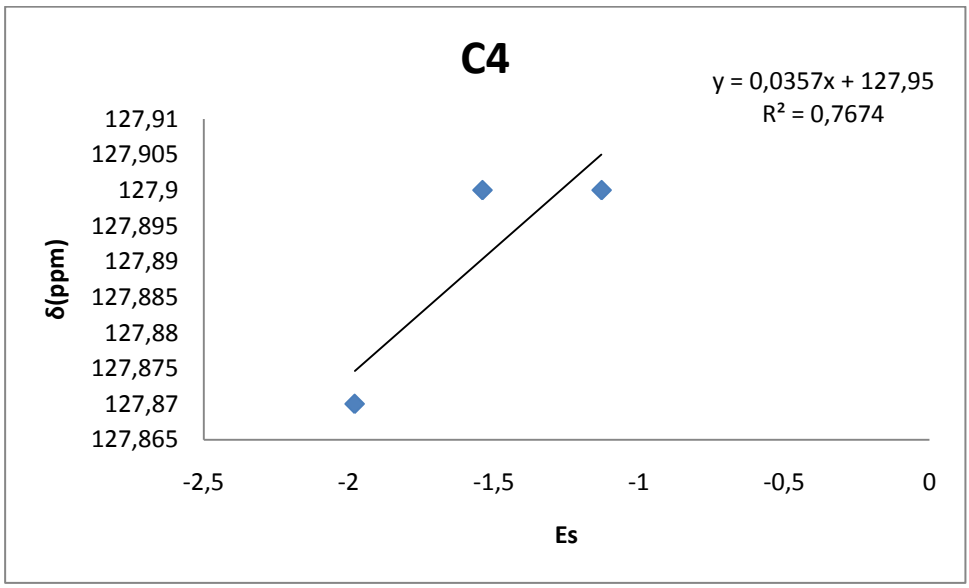


Figure A.14: The chemical shifts of C4 as a function of the Es values of the substituents for the S-acylated products

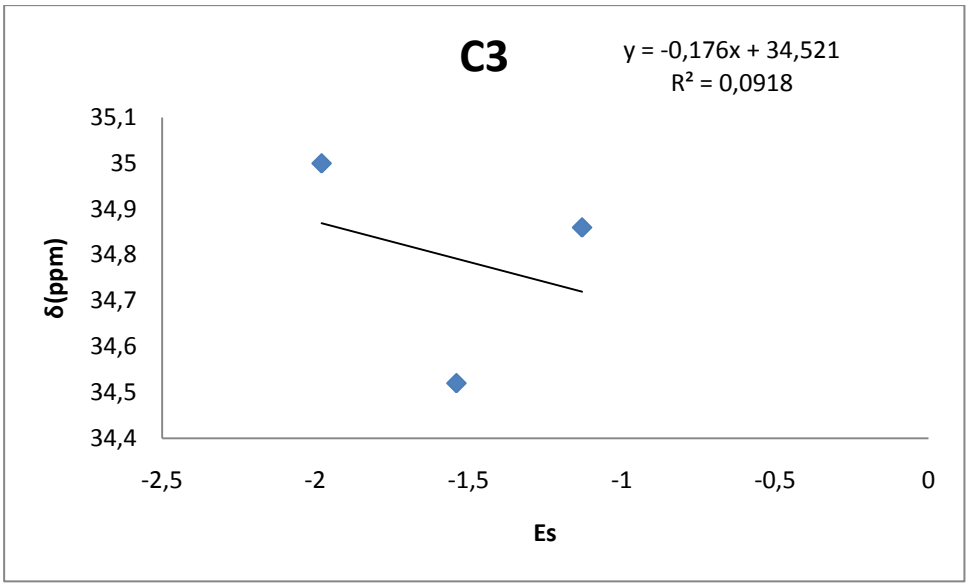


Figure A.15: The chemical shifts of C3 as a function of the Es values of the substituents for the S-acylated products

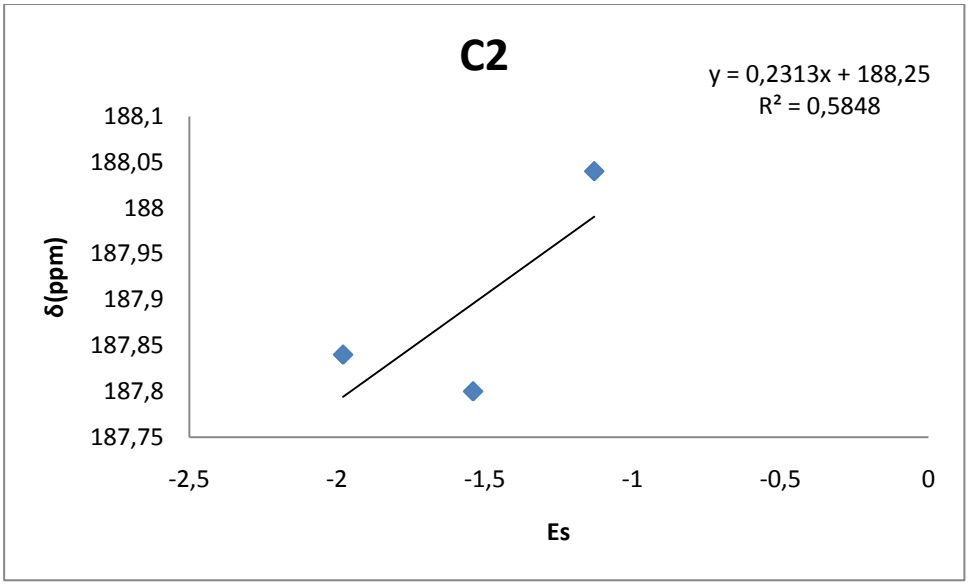


Figure A.16: The chemical shifts of C2 as a function of the Es values of the substituents for the S-acylated products

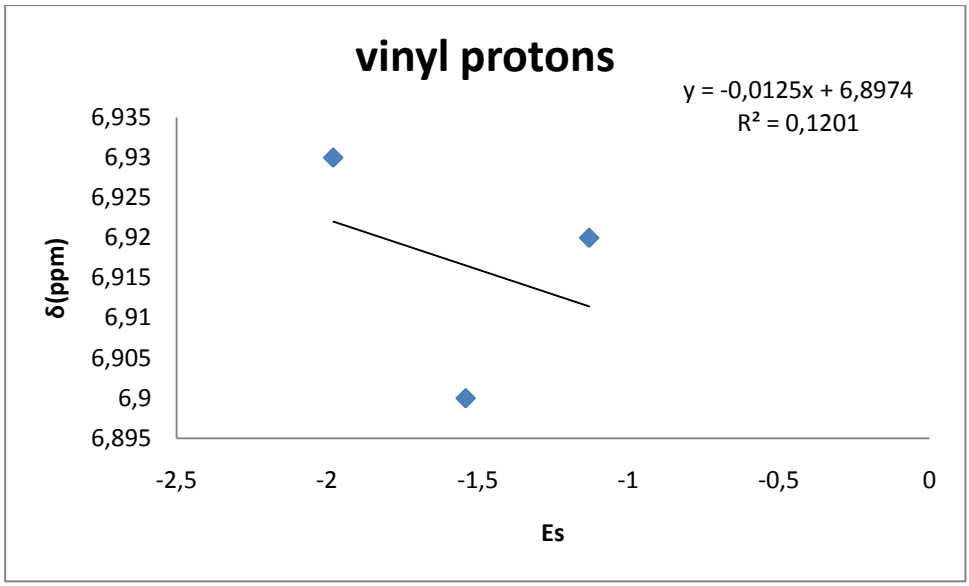


Figure A.17: The chemical shift of the vinyl protons in S-acylated products as a function of the Es values of the substituents.