SYNTHESIS OF 2,3-DISUBSTITUTED THIOPHENES FROM KETOALKYNES

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SYNTHESIS OF 2,3-DISUBSTITUTED THIOPHENES FROM KETOALKYNES

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ABSTRACT

SYNTHESIS OF 2,3-DISUBSTITUTED THIOPHENES FROM KETOALKYNES

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December 2013, 88 pages

Synthesis of thiophene containing compounds are of particular interest in synthetic organic chemistry. Besides the importance for synthetic organic chemistry, thiophene derivatives are used in applied research such as drug synthesis and study of functional materials. In this thesis, a new methodology for developing of 2,3-disubstituted thiophenes was developed. This methodology utilizes readily available compounds in a two-step synthesis to provide a facile access to the 2,3-disubstituted thiophenes. In the first step, ketoalkynes were prepared by Sonogashira coupling of readily available acyl chlorides and terminal alkynes. Then they were reacted with 2,5-dihydroxy-1,4-dithiane in the presence of triethylamine to yield alcohol intermediates. Finally, alcohol intermediates were dehydrated by treatment with silica gel to yield 2,3-disubstituted thiophenes.

Keywords: Acyl-chloride, terminal alkyne, 2,3-disubstituted thiophene, ketoalkyne, Sonogashira coupling

ÖZ

2,3-DİSÜBSİTÜTE TİYOFENLERİN KETOALKİNLER ÜZERİNDEN SENTEZLENMESİ

Vatansever, Erol Can

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Aralık 2013, 88 sayfa

Tiyofen içeren moleküllerin sentezi, sentetik organik kimyada önemli bir yere sahiptir. Sentetik organik kimyanın yanı sıra, tiyofen içeren bileşikler, ilaç sentezi ve diğer farklı malzemeler içinde kullanılmaktadır. Bu çalışmada, 2,3-disübsitüte tiyofen bileşiklerinin sentezi için yeni bir yöntem geliştirildi. Bu yöntemde, kolayca temin edilebilen başlangıç maddeleri kullanılarak, iki basamaklı sentez sonunda 2,3-disübsitüte tiyofen bileşikleri sentezlendi. İlk basamakta açil klorür ve alkin bileşiklerinden Sonogashira kenetlenmesi yöntemi ile ketoalkin bileşikleri elde edildi. Daha sonra bu bileşiklerin, trietil amin varlığında 2,5-dihydroxy-1,4-dithiane ile tepkimesinden dihidrotiyofen ara ürünleri elde edildi. Son kademede, bu ürünlerin silika jel ile muamele edilmesi sonucunda su eliminasyonu sağlanarak, 2,3-disübsitüte tiyofen bileşikleri elde edildi.

Anahtar kelimeler: Açil klorür, alkin, 2,3-disübsitüe tiyofen, ketoalkin, Sonogashira kenetlenmesi

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CHAPTER 1

INTRODUCTION

1.1 Heteroaromaticity

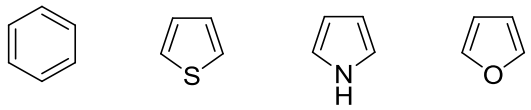
The term heteroaromaticity is used for the heterocyclic compounds having aromatic structure. Due to their structural features, heteroaromatic compounds are highly abundant in nature. In a review article published in 2000, it is stated that among the chemical compounds identified to that time, about half of the known compounds had heteroaromatic structure.[1]

Although presence of a heteroatom in a ring structure is sufficient to denote a compound as heterocyclic, the situation is far more complex for designation of a compound as aromatic. Basically, four criteria that are known as Hückel's rules should be met.

Furthermore, aromatic compounds that obey all Hückel's rules also differ in their degree of aromaticities due to unique electronic nature of these compounds.

To determine the degree of aromaticity, both theoretical and experimental methods are developed. The results of a qualitative experimental determination based on hydrogenation enthalpies of the aromatic compounds are shown below.[1]

Table 1 Dewar resonance energy values for benzene, thiophene and furan



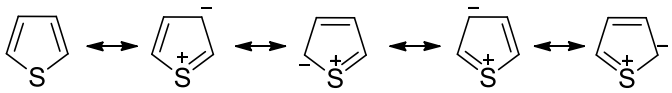
DRE(kcal/mol)	22.6	6.5	5.3	4.3

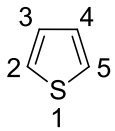
The Table 1 illustrates the relative aromaticities of benzene and three common five-membered heterocyclic compounds. Dewar Resonance Energy (DRE) values indicate the stabilization gained by the aromatic structure with respect to the compounds unsaturated analogs. Therefore larger DRE values indicate greater stability gained by aromaticity.

1.2 Thiophene

Thiophene (**1**) is an aromatic five-membered heterocyclic compound. Although there are both some computational[2,3] and experimental results[3] suggesting pyrrole is more aromatic than thiophene, the generally accepted order for the aromaticity of thiophene is being between the aromaticites of benzene and pyrrole.[1,2,4]

Scheme 1 depicts resonance structures of unsubstituted thiophene. According to theoretical calculations, the electron density on carbons 2 and 5 are more intense than carbons 3 and 4 of thiophene.[5] That result is in agreement with the reactivity profile of thiophene towards nucleophiles. This phenomenon can be rationalized by considering stability gained by the proximity of counterions.

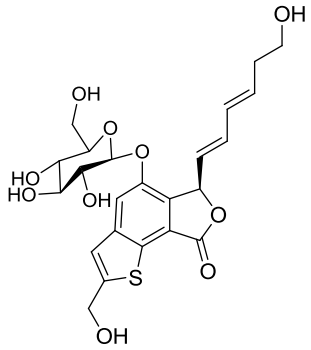




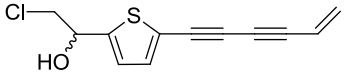
Thiophene (**1**)

Scheme 1 Resonance structures of thiophene

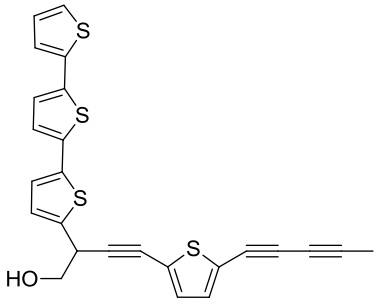
Thiophene moieties are encountered in natural products. Echinothiophene (**2**), isolated from the roots of *Echinops grijissii*, has benzothiophene moiety in its structure.[6] Moreover, Xanthopappins A (**3**) isolated from *Xanthopappus subacaulis* has a thiophene acetylene structure.[7] Another thiophene polyacetylene example is Echinopsacetylenes A (**4**) that is isolated from the roots of *Echinops Transiliensis.*[8]



Echinothiophene (**2**)

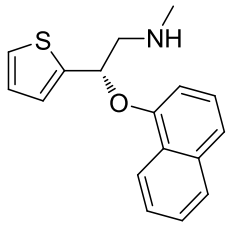


Xanthopappins A (**3**)

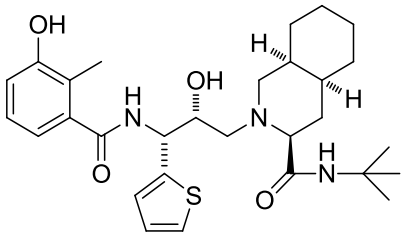


Echinopsacetylenes A (**4**)

Thiophene containing molecular structures are also used in medicinal chemistry. For example; Duloxetine (**5**), a drug marketed by Eli Lilly that is used as an anti-depressant agent,[9] has thiophene moiety in its molecular structure. Moreover compound **6** has shown inhibition of the catalytic activity of HIV PR.[10] Compound **7** was found to be effective in acute hypoxia-induced pulmonary hypertension in rats.[11]



Duloxetine (**5**)



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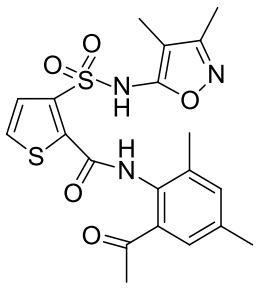

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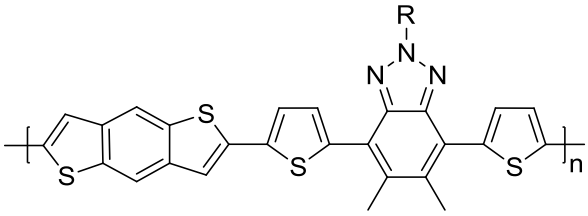
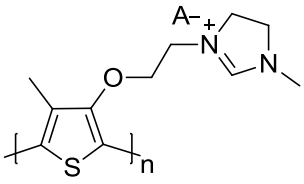
Moreover, thiophene containing polymers are extensively used in materials chemistry. Compund **8** is designed as a medium band-gap photovoltaic device[12] and compound **9** is a fluorescent biosensors that is used for selective detection of nucleic acids.[13]



R= 2-butyloctyl

8



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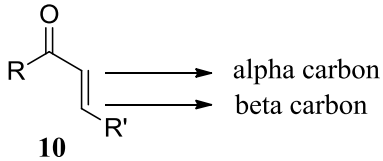
1.3 Addition of thiol/thiolate nucleophiles to α,β-unsaturated carbonyl compounds

Thiols are highly nucleophilic compounds owing to their great tendency for polarization. For instance, according to experimental studies conducted based on rate constants, n-propyl thiolate anion is found to be even more nucleophilic than compounds showing α-effect like hydroxylamine.[14]

Moreover, both thiols and thiolates can be classified as soft bases due to their high polarizability and relatively low electronegativity. At the same time having high nucleophilicity and soft base nature, alkyl thiols are good nucleophiles for Michael Addition reactions. Due to the their soft base nature thiols and thiolates prefer to attack an α,β-unsaturated carbonyl compound **10** from β-position (Scheme 2).

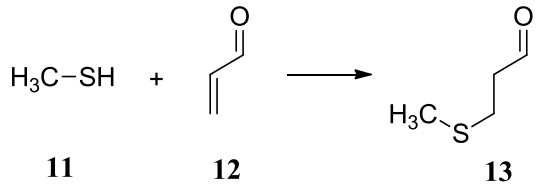


10

Scheme 2 α (alpha) and β (beta) positions of an unsaturated carbonyl compound

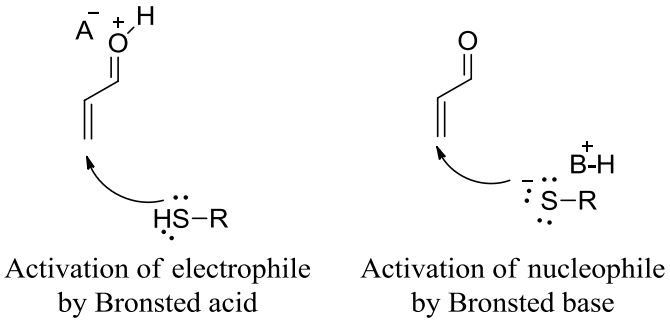
Addition of alkyl and aryl thiols/thiolates to α,β-unsaturated carbonyl compounds is extensively studied in the literature.

For example, the compound **13** was formed by addition of methanethiol (**11**) to acrolein (**12**) at 0 ^{o}C in 41% yield. Compound **13** is important because; it is the precursor of amino acid methionine (Scheme 3).[15]



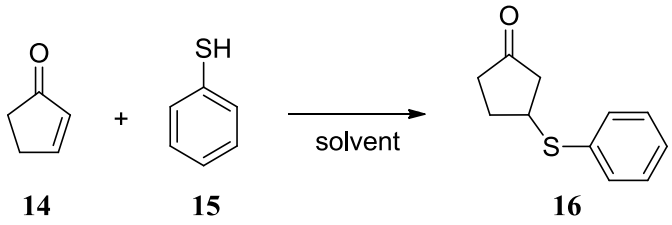
Scheme 3 Addition reaction of methanethiol (**11**) to acrolein (**12**)

Brønsted acids[16] and Brønsted bases[17,18] are frequently used as catalysts in Michael addition of alkyl or aryl thiol compounds to α,β-unsaturated carbonyl compounds. Brønsted acids increase the rate of reaction via activation of the electrophile whereas; Brønsted bases operate by activating the nucleophile. Scheme 4 depicts how these activation modes are achieved.



Scheme 4 Two activation modes of Michael addition reaction

The studies done with the aromatic thiols as nucleophiles are shown to be highly solvent dependent. The reaction between 2-cyclopenten-1-one (**14**) and benzene thiol (**15**) afforded product **16** in 6% yield in dichloromethane after 2 days (Scheme 5).[19]



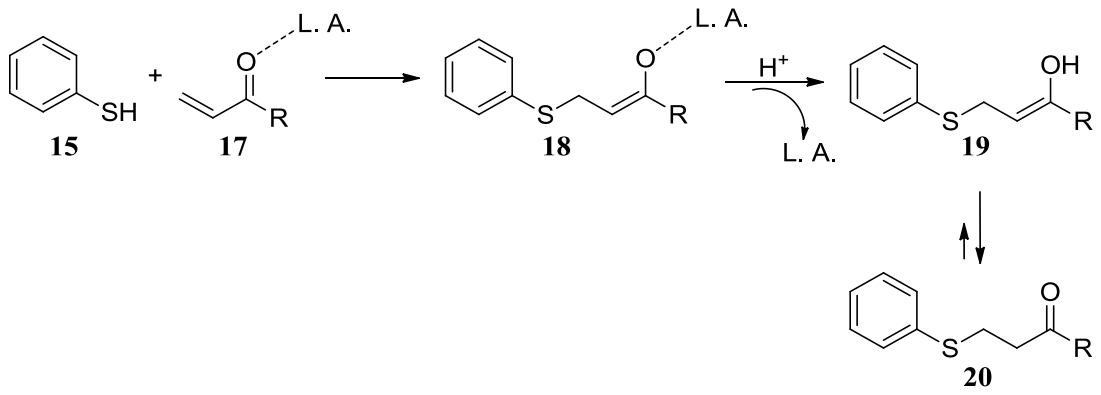
14 **15** **16**

Scheme 5 Addition of benzene thiol (**15**) to 2-cyclopenten-1-one (**14**)

In another study, same reaction was carried out in water as the solvent. Interestingly, the reaction was completed in 5 min. with 90% yield at room temperature. The authors proposed, that the role of water may be the activation of both electrophile and nucleophile. Hydrogen of a water molecule may form a hydrogen bond with oxygen present in the 2-cyclopenten-1-one (**14**). So, this will withdraw the electrons of 2-cyclopenten-1-one (**14**) towards water molecule and will activate the electrophile.

Moreover, the oxygen of the same water molecule may form hydrogen bonding via accepting hydrogen from the acidic proton of benzenethiol (**15**) therefore, activating the nucleophile. As a result, the rate of the reaction was accelerated.[20]

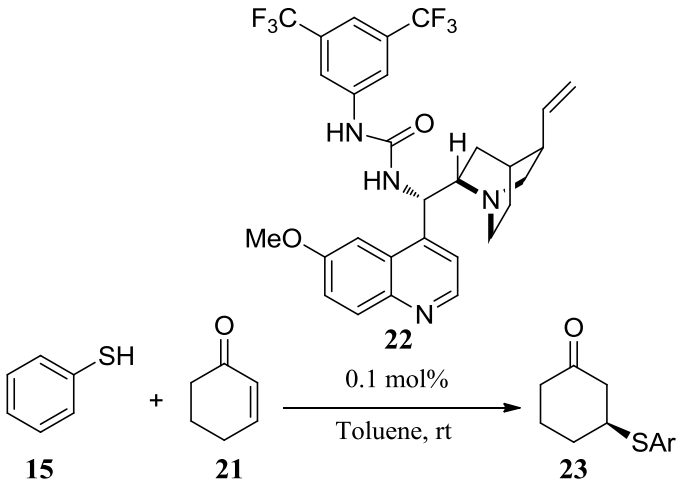
Furthermore it is shown that, also in the presence of Lewis acids like $Cu(OAc)_2$,[21] $InBr_3$,[19] $FeCl_3$,[22] ceric ammonium nitrate,[23] iodine[24] the addition of thiol groups to α,β-unsaturated carbonyl compounds was also studied. General mechanism for Lewis acid catalyzed reactions begin with activation of compound **17** with Lewis acid. Then, benzenethiol (**15**) attacks the β-carbon atom of compound **17**. After proton transfer, enol structure **19** is formed. Then, by tautomerisation the keto structure **20** is formed (Scheme 6).



Scheme 6 General mechanism for Lewis acid catalyzed Michael addition reactions

Enantioselective synthesis with chiral catalysts was also studied.[25,26] When a chiral cinchona alkaloid-derived urea **22** was used as a base the product **23** was formed in quantitative yield and in 99% ee.[26]

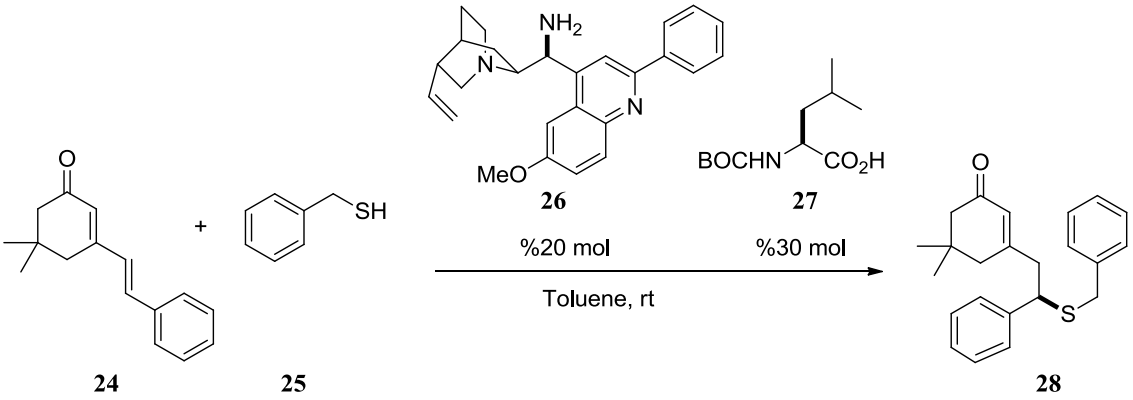
The bifunctional catalyst **22** was used to activate both benzene thiol (**15**) and 2-cyclohexen-1-one (**21**). The catalyst activates **21** by forming hydrogen bonds between the hydrogen atoms present in urea moiety of **22** and carbonyl compound **21**. Activation of benzene thiol (**15)** done by abstraction of the proton of **15** by tertiary amine functionality of **22**. Furthermore, enantioselectivity is achieved by the chirality of the bifunctional catalyst **22** (Scheme 7).



Scheme 7 Enantioselective benzene thiol (**15**) addition to 2-cyclohexen-1-one (**21**)

Another interesting Michael addition reaction was observed with α,β,γ-unsaturated carbonyl compound **24** as an electrophile.[27] In this application, benzyl-thiol (**25**) was used as the nucleophile, quinine derived amine compound **26** served as the catalyst, besides BOC protected amino acid **27** as the co-catalyst.

Amine functionality present in the quinine derived amine catalyst **26** forms highly reactive imminium intermediate with compound **24.** Afterwards**,** addition of benzylthiol (**25**) gives the desired compound **26** with 91% conversion and 91% ee (Scheme 8).



Scheme 8 Enantioselective benzyl thiol (**25**) addition to α,β,γ-unsaturated carbonyl compound (**24**)

1.4 Cascade reactions of α-thiolated carbonyl compounds with α,β-unsaturated carbonyl compounds for accessing di/tetrahydrothiophene structures

2,5-Dihydrotihophene (**29**) and tetrahydrothiophene (**30**) structures are saturated analogues of thiophene. They differ from each other in their degree of unsaturation.

Thiophene (**1**)

2,5-Dihydrothiophene **(29)**

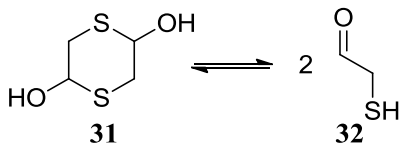
Tetrahydrothiophene **(30)**

Synthesis of 2,5-dihydrothiophene (**29**) and tetrahydrothiophene (**30**) molecular structures are also studied in the literature.[28-33] The reactions listed in this part can be

called as cascade reactions because; in each case there are two consecutive reactions taking place to form the final product.

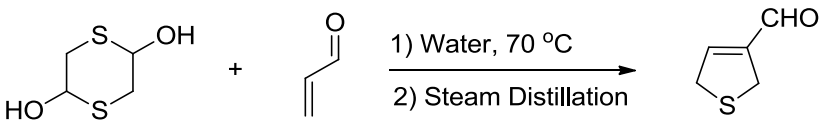
1.4.a. Construction of dihydrothiophene/tetrahydrothiophene ring through reaction between α-thiolated carbonyl compounds and α,β-unsaturated carbonyl compounds

A convenient method for the synthesis of dihydrothiophene (**29**) analogues is to use 2,5-dihydroxy-1,4-dithiane (**31**) as a precursor of 2-mercaptoacetaldehyde (**32**) (Scheme 9). The reaction between 2,5-dihydroxy-1,4-dithiane (**31**) and acrolein (**12**) forms compound **33** in 64% yield (Scheme 10).[28]



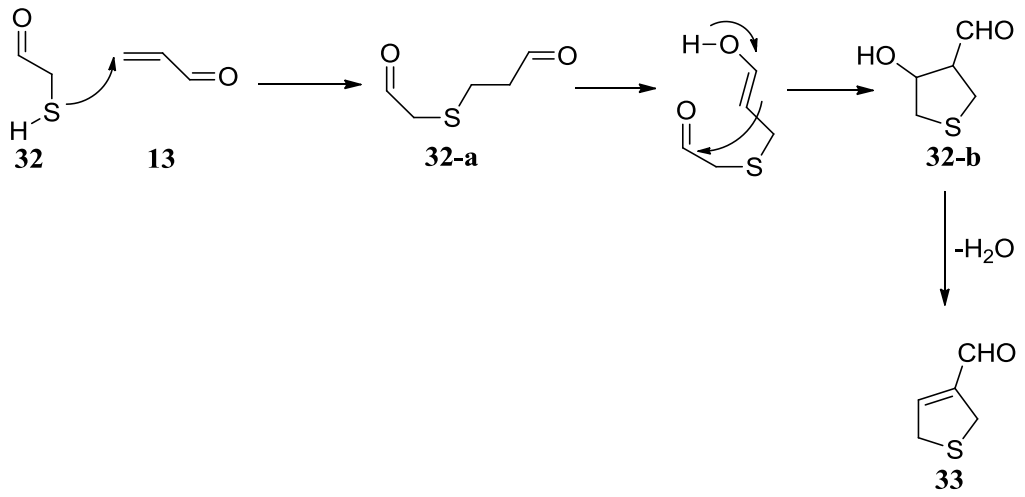
31 **32**

Scheme 9 2,5-Dihydroxy-1,4-dithiane (**31**) is a dimer form of 2-mercaptoacetaldehyde (**32**)



31 **12** **33**

Scheme 10 Reaction of 2,5-dihydroxy-1,4-dithiane (**31)** and acrolein (**12**)



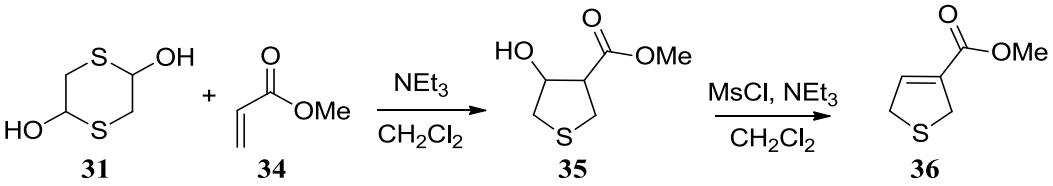
Scheme 11 Mechanism for reaction between 2-mercaptoacetaldehyde (**32**) and acrolein (**12**)

Mechanism of this reaction begins with addition of 2-mercaptoacetaldehyde (**32**) to acrolein (**12**). After the proton transfer, acyclic compound **32-a** is formed (Scheme 11). Then, the intramolecular aldol reaction gives cyclic compound **32-b**. Finally, spontaneous loss of water yields dihydrothiophene structure **33**.

Furthermore, the substrate scope of electrophile is not limited with aldehydes, α,β-unsaturated esters,[29-30] nitro olefins,[31,33] α,β-unsaturated ketones[32] are also found to work well as electrophiles.

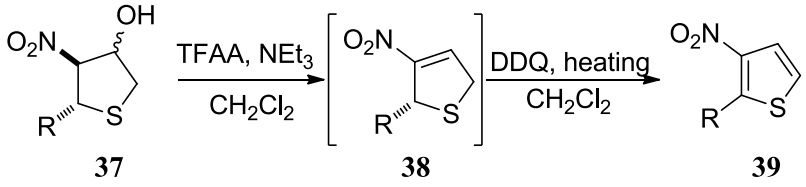
However, in some cases under different reaction coniditions and with different electrophiles, the spontaneous loss of water was not observed and product having tetrahydrothiophene skeleton was isolated at the end of the reaction.[30-33]

For example; the alcohol **35** was isolated from the reaction of 2,5-dihydroxy-1,4-dithiane (**31**) and methyl acrylate (**34**). Furthermore, the product was resistant to dehydration so, Bishop and coworkers reacted the compound **35** with mesyl chloride to eliminate water and obtain compound **36** (Scheme 12).[30] In general, water can be easily removed from system such as **35** or **37** by treatmant either with mesyl chloride or TFAA.



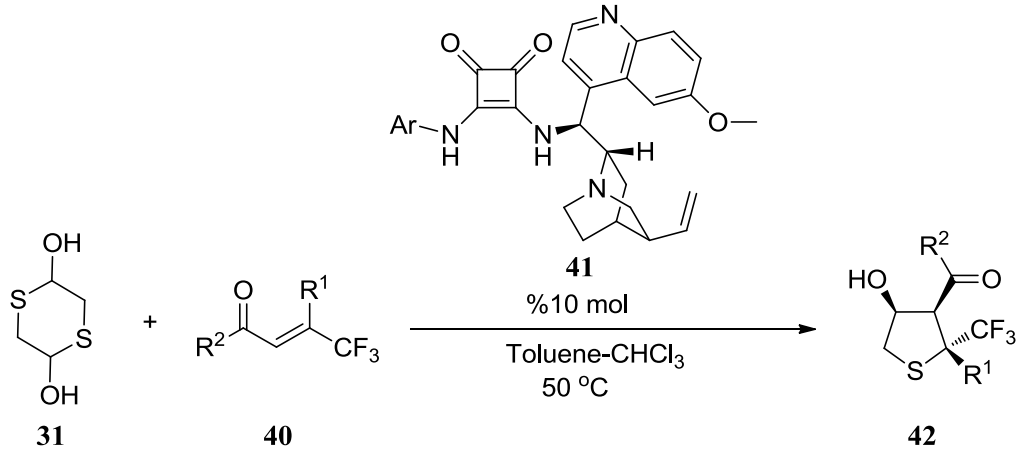
Scheme 12 Formation route of the dihydrothiophene **36** structure

For example, if a nitro olefin is used as an electrophile, the resultant structure at the end of the reaction will be compound **37**. Treatment of compound **37** with trifluoroacetic anhydride gave compound **38**. Furthermore, an oxidizing agent like DDQ[31] provided further oxidation to thiophene structure **39**. An example is illustrated in Scheme 13.[31]



Scheme 13 Formation of compound **39** from **37**

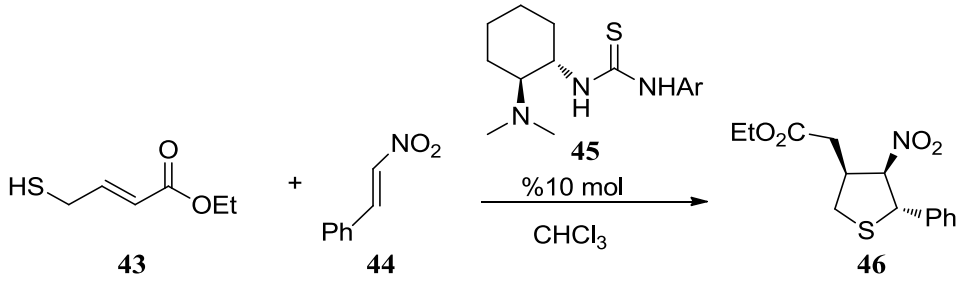
Moreover, enantioselective synthesis of tetrahydrothiophene ring was also published recently.[32] In this article; α,β-unsaturated carbonyl compounds bearing tirfluoromethyl moieties were used as electrophiles due to the biological importance of trifluoromethyl moiety.



Scheme 14 Enantioselective synthesis of tetrahydrothiophene structure **42**

The chiral catalyst **41** used in this study is a bifunctional catalyst that activates the electrophile **40** by donating hydrogen bonds and activates in-situ formed 2-mercaptoacetaldehyde (**32**) molecule by abstracting the hydrogen bonded to sulfur. Finally, the tetrahydrothiophene structure **42** containing three chiral centers was formed (Scheme 14).

All the examples given above present tetrahydrothiophene structures that are susceptible to dehydration however; there is also another study in which a modified thiol **43** and trans-β-nitro styrene (**44**) were used, which resulted in a more stable tetrahydrothiophene structure **46** (Scheme 15).[33] The trick here was the usage of α,β-unsaturated carbonyl compound as electron withdrawing group instead of carbonyl group.



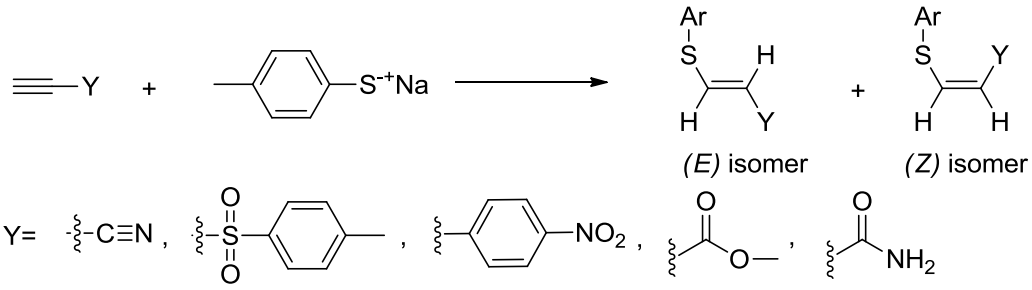
Scheme 15 Enantioselective synthesis of nitro group containing tetrahydrothiophene structure **46**

1.5 Michael addition of thiol compounds to α,β-alkynyl carbonyl compounds

It is also well-known that both aromatic and alkyl thiols can undergo Michael addition reactions with α,β-alkynyl carbonyl compounds without any catalyst. Although, thiolate anions are also capable of giving nucleophilic addition reaction with alkynes with no adjacent electron withdrawing moiety,[34] alkynes with electron withdrawing groups undergo reactions at milder conditions.[35-40]

Michael addition of thiols to α,β-alkynyl carbonyl compounds also meet with the criterias of click chemistry like high yield, regioselectivity, stereoselectivity, no by-products so, therefore, this reaction is also called as a click reaction.[36,40]
Because of these merits, Michael addition of thiols to α,β-alkynyl carbonyl compounds are used in materials chemistry applications.[36]

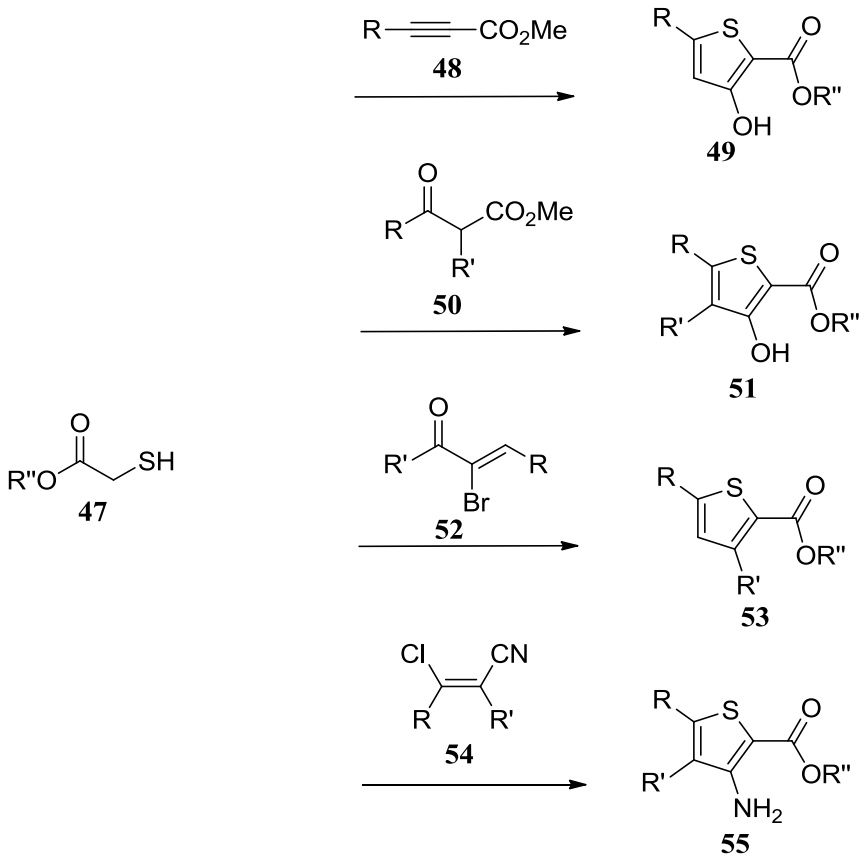
A study published by Truce *et al.*[38] showed the wide scope of this reaction with various electron withdrawing group moieties adjacent to alkynes (Scheme 16). Moreover, Truce *et al*. also studied *E*/*Z* isomer ratios and found that *Z* isomer is formed preferentially.



Scheme 16 Study by Truce *et al*. indicating the substrate scope of the reaction

1.6 Fiesselmann Thiophene Synthesis

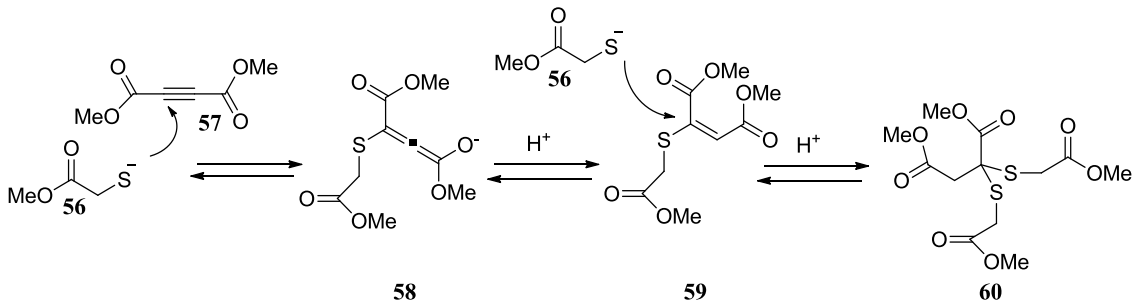
Fiesselmann thiophene synthesis is a method for thiophene ring construction by condensation reaction between alkyl thioglycolate **47** and α,β-alkynyl carbonyl compounds. Scheme 17 summarizes the work done with alkyl thioglycolate **47** and electrophiles **48, 50, 52, 54** for the synthesis of thiophene derivatives **49**, **51, 53, 55**.[41]



Scheme 17 Brief examples for substrate scope of Fiesselmann synthesis

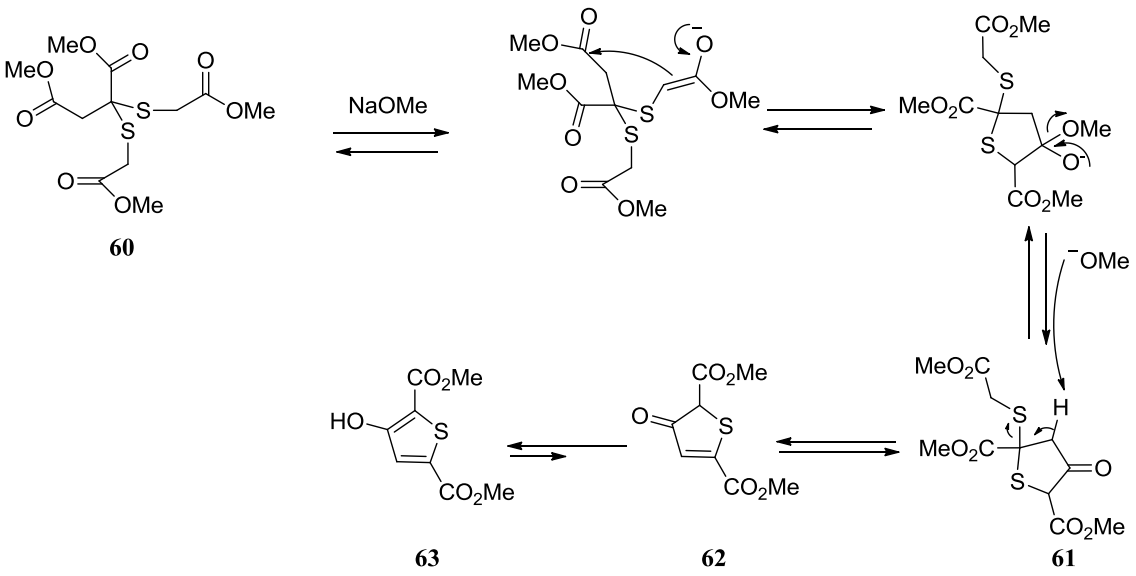
1.6.1 Mechanism of the reaction between thioglycolic acid α,β-alkynyl carbonyl compounds:

The generally accepted mechanism for this reaction begins with the addition of methyl thioglycolate anion **56** to the alkyne carbon atom of dimethyl acetylene dicarboxylate (**57**). Following this, the allenic enolate **58** is formed. After the proton transfer, another methyl thioglycolate anion **56** attacks at the sulfur-bonded carbon atom of the α,β-unsaturated carbonyl compound **59** and forms the dithioacetal compound **60** (Scheme 18).



Scheme 18 First part of the mechanism of Fiesselmann synthesis

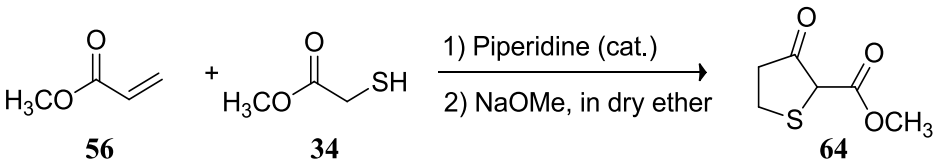
After two consecutive Michael addition reactions, NaOMe abstracts one of the methylenic protons bonded to sulfur atom of compound **60**. Then Dieckmann condensation reaction takes place and methanol elimination occurs and compound **61** is formed. Since thiolate aninos are good leaving groups and NaOMe is a base that is strong enough to facilitate E2 elimination, double bond is formed on the cyclic compound **62** by E2 elimination. Lastly, following keto-enol tautomerization yields the thiophene ring **63** (Scheme 19). It is important to note that all the steps here are expected to be reversible since thiolate anion is both a good nucleophile and a good leaving group. Details of this mechanism will be discussed in results & discussion part.



Scheme 19 Second part of the mechanism of Fiesselmann synthesis

1.6.2 Histroical view of Fiesselmann thiophene synthesis:

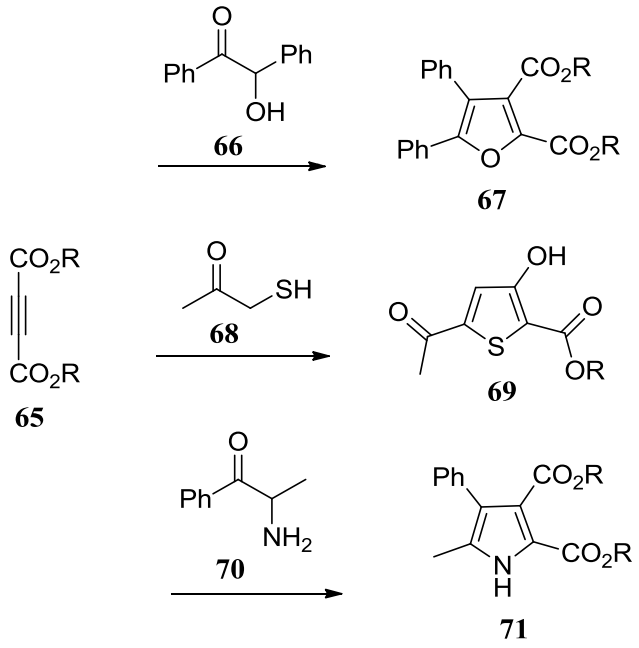
Along the way of the discovery of Fiesselmann reaction, the chemical structure of biotin was newly elucidated so, synthesis of tetrahydrothiophene skeleton had started to gain importance. R. B. Woodward published the synthesis of **64** which utilizes methyl thioglycolate (**34**) and methyl acrylate (**56**) in the presence of base to access tetrahydrothiophene structure **64** (Scheme 20). [42]



Scheme 20 Woodward's synthesis of tetrahydrothiophene ring **64**

After eight years of Woodward's publication, Fiesselmann adopted this system to synthesis of 2,3,5 trisubstituted thiophenes.[43] In the following years, Fiesselmann and co-workers, other researchers[46] applied this system for synthesis of various thiophene structures.[44,45,48] Later, a similar methodology was published for pyrrole, furan and

thiophene synthesis by Hendrickson *et al*.[47] In this article the synthesis of furan **67**, thiophene **69** and pyrrole **71** derivatives were described by using dialkyl acetylene dicarboxylate **65** as electrophile and α-heteroatom carbonyl compounds **66**, **68**, **70** as nucleophiles (Scheme 21).



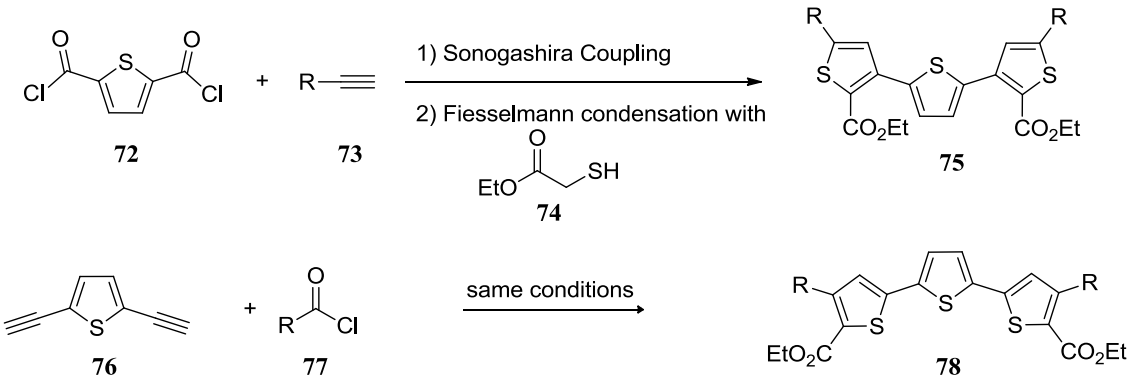
Scheme 21 Hendrickson's general synthesis for heterocyclic ring construction

However; Fiesselmann published his works mostly as patents and doctoral theses so that, scientific community was not truly aware of his studies. Obrecht *et al.*[48] published a work in 1997, where the work of Fiesselmann was rediscovered without giving citation to Fiesselmann's previous works.[41]

1.6.3 New applications of Fiesselmann synthesis:

Nowadays Fiesselmann thiophene synthesis is recognized and still being studied. For instance, Müller and co-workers first utilized thiophene diacyl chloride **72** for Sonogashira coupling with **73** (Scheme 22). Then ethyl thioglycolate (**74**) was added to the reaction mixture. This multi-component reaction yielded compound **75**.[49] In

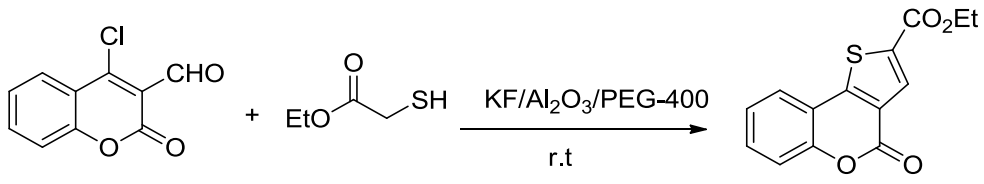
another study they prepared unstable compound **76** and applied Sonogashira coupling with **77.** After, adding ethyl thioglycolate (**74**) yielded **78** which is a constitutional isomer of **75**.[50] Both oligothiophenes **75** and **78** were found to be useful molecules for materials chemistry applications.[49,50]



72 **73** **74** **75** **76** **77** **78**

Scheme 22 Two alternative methods for accessing oligothiophenes **75**, **78** by Fiesselmann synthesis

Finally, an alternative method for a variation of Fiesselmann reaction was also developed by using KF/Al_2O_3 as an inorganic base and PEG-400 (polyethylene glycol) as a green solvent.[51] Conversion of **79** into **80** was achieved in 80% yield (Scheme 23).



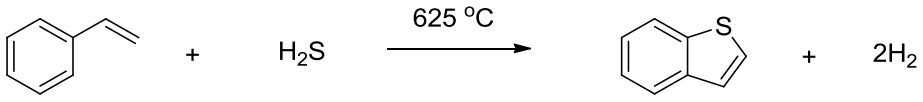
79 **74** **80**

Scheme 23 Fiesselmann synthesis of **80** from **79** with an inorganic base

1.7 Synthesis of 2,3-disubstituted thiophenes by cyclization reactions

Compounds containing thiophene moiety are particularly of interest in materials chemistry, medicinal chemistry and natural product total synthesis. Therefore, synthesis of 2,3-disubstituted thiophenes was also studied widely in the literature. Due to the large number of methods for synthesis of 2,3-disubstituted thiophenes, the reactions described in this part are limited to the synthesis of 2,3-disubstituted thiophenes by cyclization reactions.

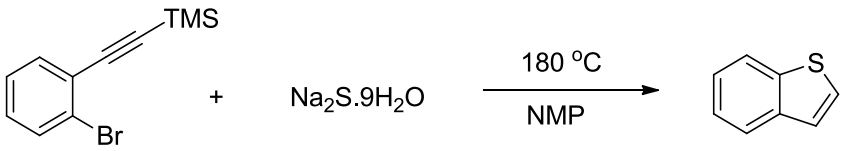
A classical example for the formation of 2,3-disubstituted thiophenes by cyclization is the synthesis of benzothiophene (**83)**. An early example utilized styrene (**81**) and H_2S (**82**) at high temperatures for the synthesis of benzothiophene (**83**) (Scheme 24).[52]



81 **82** **83**

Scheme 24 Synthesis of benzothiophene (**83**) under harsh conditions

According to a recenty published method, benzothiophene (**83**) was obtained in 70% yield by reaction of ((2-bromophenyl)ethynyl)silane (**84**) with $Na_2S.9H_2O$ (**85**) at a relatively lower temperature. (Scheme 25).[53]

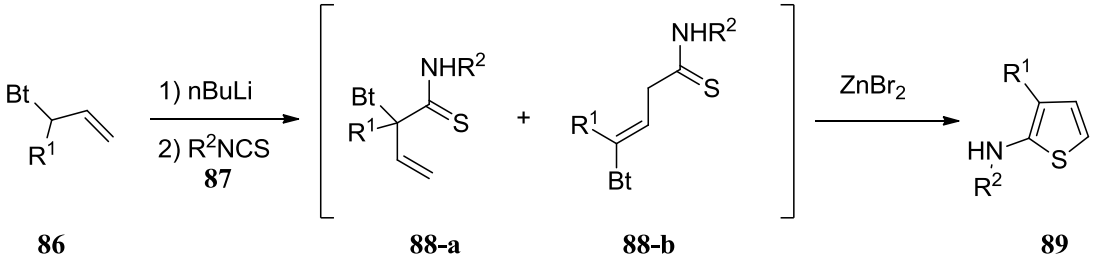


84 **85** **83**

Scheme 25 Synthesis of benzothiophene (**83**) under milder conditions

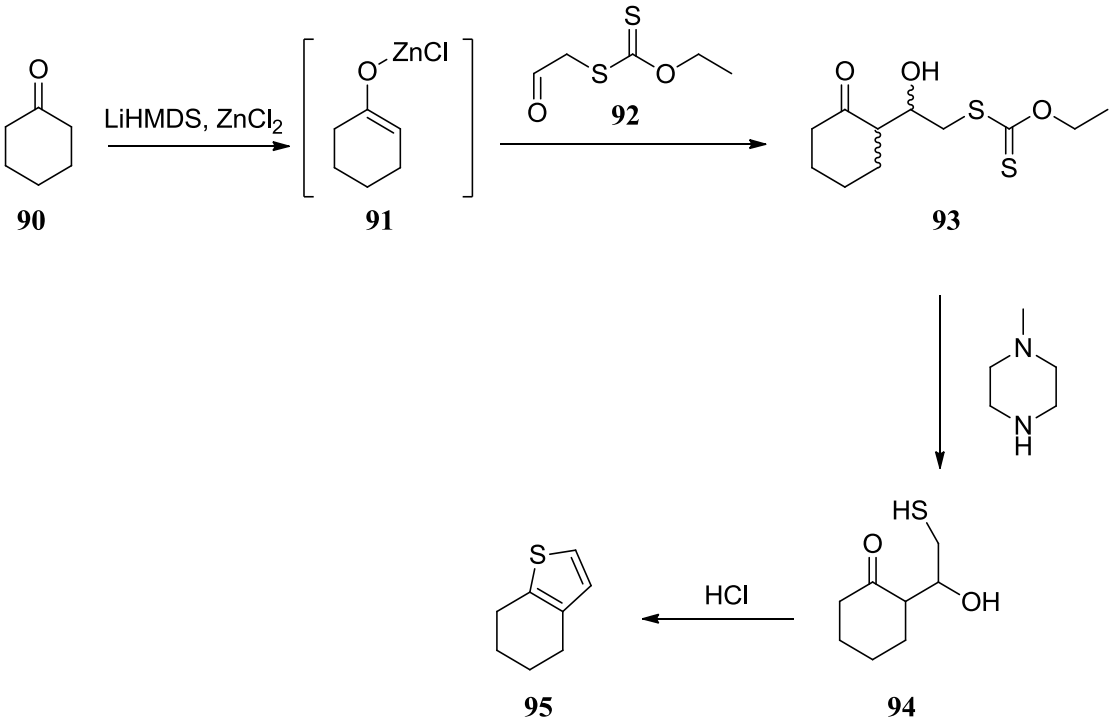
A different approach was developed by Katritzky and co-workers, for the synthesis of 3-substituted 2-aminothiophene **89**. Treatment of vinyl compound **86** with nBuLi,

followed by the reaction with isothiocyanate **87** gave a mixture of thioamides **88-a, 88-b**. Then, the mixture of thioamides **88-a, 88-b** were used without purification and treated with $ZnBr_2$ to yield 3-substituted 2-aminothiophenes **89** (Scheme 26).[54]



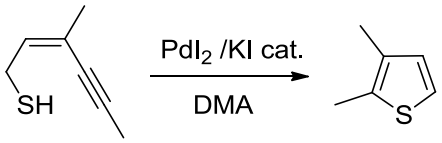
Scheme 26 Synthesis of 3-substituted 2-aminothiophene **89**

In another study, *O*-ethyl *S*-(2-oxoethyl)carbonodithinote (**92)** was utilized as sulfur source. The enolate **91** was formed by treatment of cyclohexanone (**90**) with LiHMDS and $ZnCl_2$. Then the enolate **91** was reacted with *O*-ethyl *S*-(2-oxoethyl)carbonodithinote (**92)**. Afterwards, the aldol product **93** was treated with 1-methylpiperazine to form compound **94**. Then treatment of **94** with HCl yielded thiophene derivative **95** (Scheme 27).[55]



Scheme 27 Synthesis of thiophene **95**

Moreover, there is also a metal induced strategy developed by Gabriele and co-workers. By this methodology, 2,3-dimethyl thiophene (**97**) was prepared by palladium catalyzed cycloisomerisation of (Z)-2-en-4-yne-1-thiol (**96**) Authors claimed that alkyne was activated by coordination of palladium to the alkyne moiety. Then nucleophilic attack of thiol yields the corresponding thiophene **97** (Scheme 28).[56]

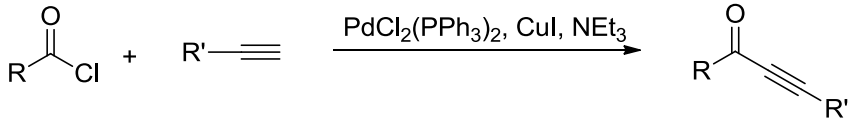


96 **97**

Scheme 28 Synthesis of 2,3-dimethyl thiophene (**97**)

1.8 Aim of the thesis

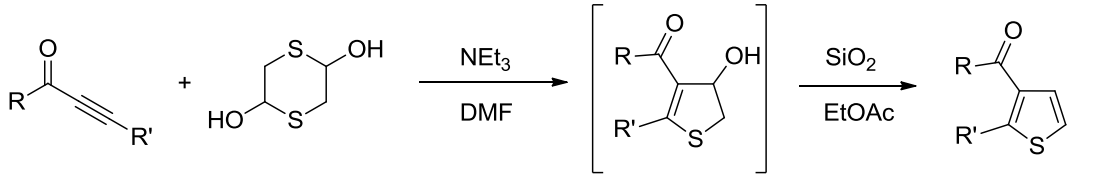
The aim was to develop a new and efficient methodology to synthesize 2,3-disubstituted thiopenes. To achieve this goal, first ketoalkynes will be synthesized from readily available acyl chlorides and alkynes by Sonogashira coupling (Scheme 29).



98-100 **101-103** **104-109**

Scheme 29 Synthesis of ketoalkynes

Then, the ketoalkynes will be reacted with 2,5-dihydroxy-1,4-dithiane (**31**) to form alcohol intermediates. For formation of desired thiophene derivatives, alcohols will be submitted to water elimination (Scheme 30).



104-109 **31** **122** **110-115**

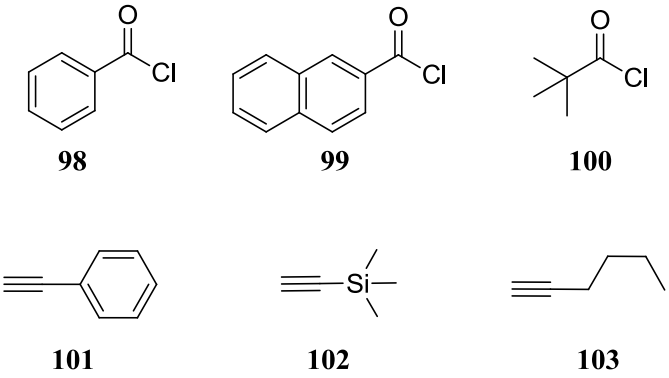
Scheme 30 Synthesis of 2,3-disubstituted thiophenes from ketoalkynes

CHAPTER 2

RESULTS AND DISCUSSION

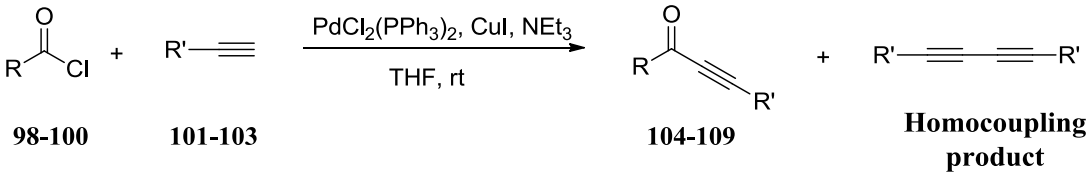
2.1 Synthesis of starting materials

Ketoalkynes were used as the starting materials for the synthesis of 2,3-disubstituted thiophene derivatives. For the synthesis of ketoalkynes, readily available acyl chlorides **98-100** and terminal acetylene derivatives **101-103** were utilized (Scheme 31).



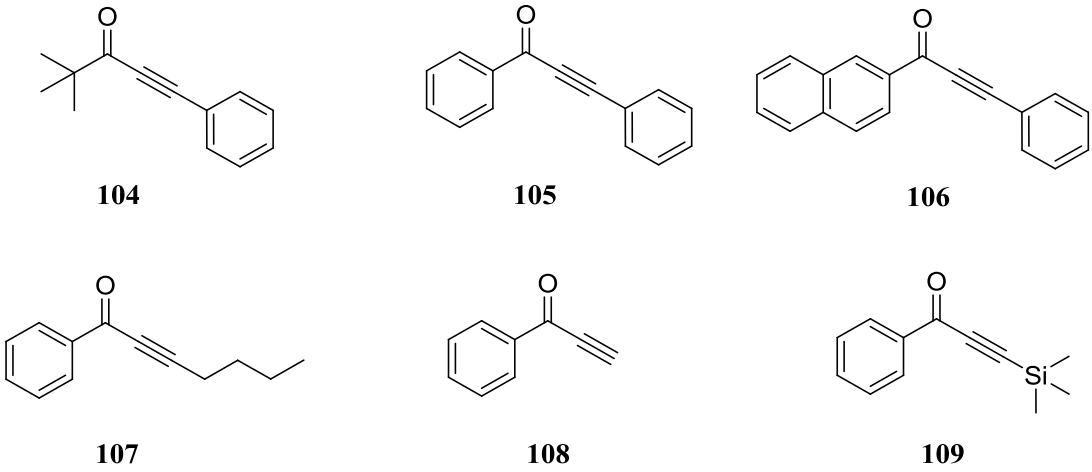
Scheme 31 Readily available starting compounds

Ketoalkynes were synthesized by Sonogashira coupling of acyl chlorides **98-100** and terminal alkynes **101-103** according to a literature procedure (Scheme 32).[62] Homocoupling product was also formed as a minor product.



Scheme 32 Synthesis of ketoalkynes by Sonogashira coupling

The synthesized ketoalkynes (**104**-**109**) (Scheme 33) are known in the literature.[62-68]

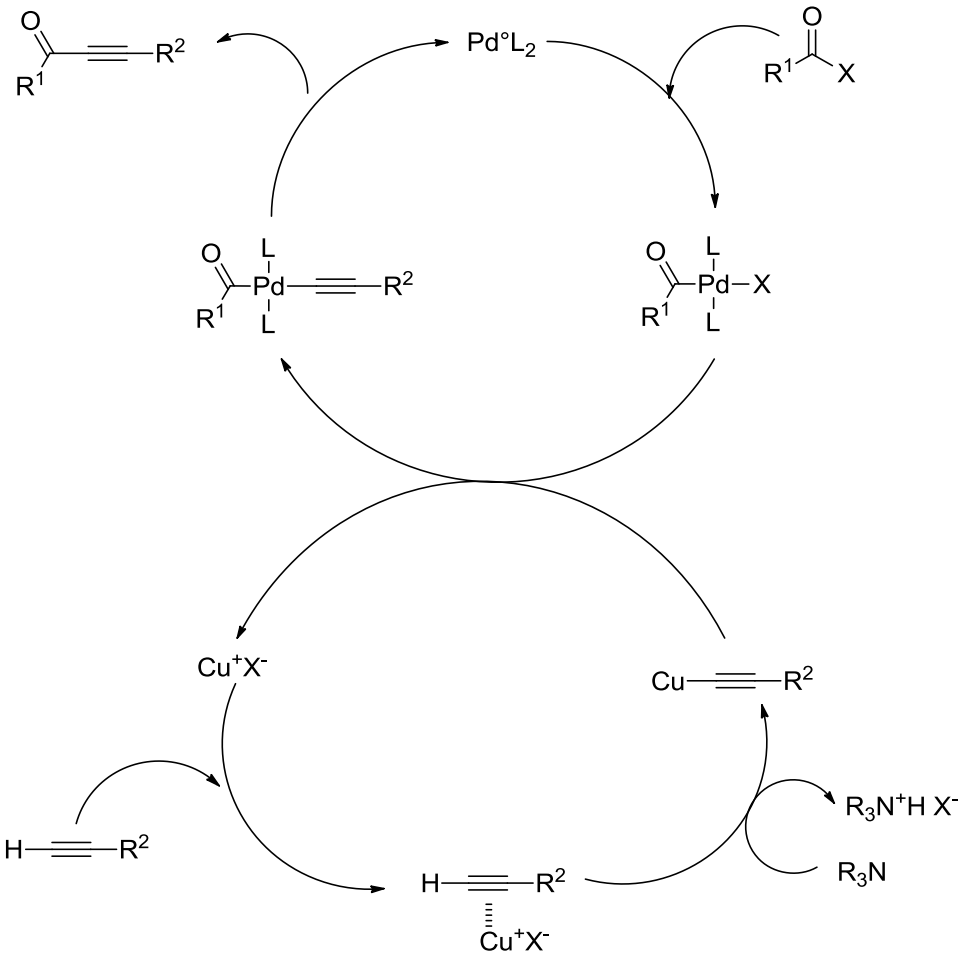


Scheme 33 Sythesized ketoalkynes

2.1.1 Mechanism for Sonogashira coupling

Although the mechanism of Sonogashira coupling is not entirely understood, the generally accepted catalytic cycle is shown in Scheme 34. The catalytic cycle begins with the reduction of Pd(II) species to Pd(0). Then oxidative addition of Pd(0) species to acyl halide occurs. A tetra coordinated palladium species is formed at the end of this step. Then transmetallation of this tetracoordinated palladium species with copper acetylide complex forms the palladium acetylide complex. Finally reductive elimination of this palladium acetylide complex gives the final product and regenerates the catalyst.

The second cycle begins with the coordination of copper to the triple bond. Coordination of the copper increases the acidity of acetylenic proton. Then this acetylenic proton is abstracted by the nitrogenous base and copper acetylide complex is formed which is then used in the transmetallation step (Scheme 34).[57]



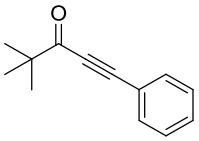
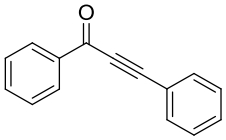
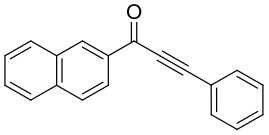
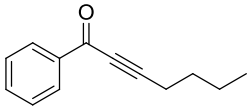
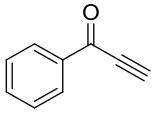
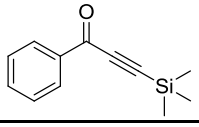
Scheme 34 Catalytic cycle for Sonogashira coupling

2.1.2 Interpretation of polarization of alknyl carbon atoms by ^{13}C NMR chemical shift differences

An important feature of the ketoalkyes, that are synthesized as starting materials for this synthesis, is the electron withdrawing moiety adjacent to alkyne that is crucial for the reactivity. The experiments carried out with nonpolarized symmetrical triple bonds didn't give any reaction. Therefore, we turned our attention to the synthesis of alkynes that are bearing an electron withdrawing moiety. So, it is well known that due to the conjugation of π bonds, the β-carbon atom is expected to be more electrophilic than the α-carbon atom with respect to the carbonyl group. This phenomenon is also expected to be observed in the ^{13}C NMR spectra. The more

polarized triple bonds would show more difference in their chemical shift values. The absolute values of ^{13}C NMR chemical shift differences of α- and β-carbon atoms in ketoalkynes **104-109** are shown in Table 2.

Table 2 ^{13}C NMR data for ketoalkynes **104-109**

Compound		**^{13}C NMR (101 MHz, $CDCl_3$) Chemical Shifts (ppm) |Δ [(δ β-carbon) – (δ α-carbon)]|**
104		6.2
105		6.2
106		6.0
107		17.2
108		0.5
109		0.3

This observed chemical shift differences is highly subsituent dependent. For instance, in case of compounds **108** and **109** the difference in chemical shifts are even less than 1 ppm whereas, for compound **107** the Δδ value is 17.2 ppm.

If Δδ ppm values of **105**, **107**, **108**, **109** are considered it would provide a concise result on effect of β-substitution on polarization. Because, all these compounds contain benzoyl moiety and differ only in their β-position.

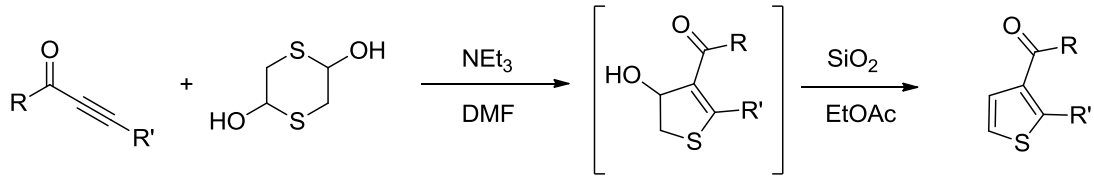
For instance, compound **109** has the lowest Δδ ppm value. This trend is reasonable considering the electron releasing effect of trimethyl silyl group. Second lowest Δδ ppm value belongs to hydrogen atom substituted compound **108**. When the

electropositive nature of hydrogen atom is considered again it is not surprising that the Δδ ppm value is low compared to **105** and **107**.

The comparison of compounds **105** and **107** clearly indicates the effect of delocalization. Due to enhanced electron-releasing effect caused by conjugation present in **105**, this structure has less polarized alkyne moiety compared to **107**.

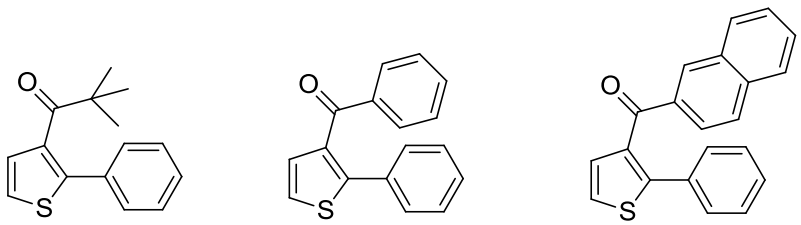
2.2 Synthesis of the 2,3-disubstituted thiophenes from ketoalkynes

Reaction of 2,5-dihydroxy-1,4-dithiane (**31**) with corresponding ketoalkynes **104-109** in the presence of NEt_3 as the base followed by treatmeant with silica gel yielded 2,3-disubstituted thiophenes **110-115** in good to excellent yields (Scheme 35). Formation of 2,3-disubstituted thiophene ring was easily detected by measuring the coupling constant *J* between the thiphene protons which has a characteristic value of 5.3 Hz. Synthesized 2,3-disubstituted thiophenes are shown in Scheme 36.

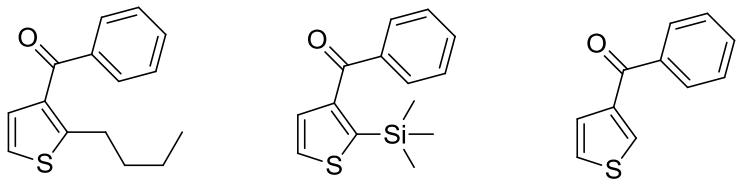


104-109 **31** **122** **110-115**

Scheme 35 Synthesis of 2,3-disubstituted thiophenes



110 **111** **112**



113 **114** **115**

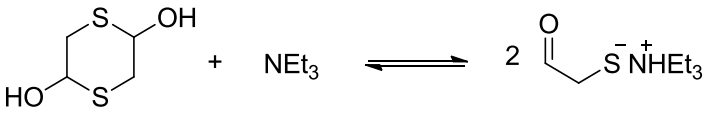
Scheme 36 Synthesized 2,3-disubstituted thiophenes

2.3 Mechanistic considerations on the reaction between 2,5-dihydroxy-1,4-dithiane and ketoalkyne

In this part two of the plausible mechanisms for the formation of alcohol product **122** is discussed with an emphasis on the first pathway.

2.3.1 First pathway

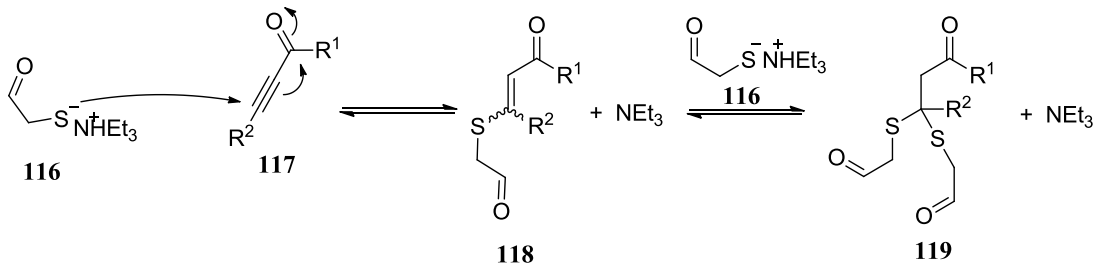
The suggested mechanism for this reaction begins with the base induced cleavage of 2,5-dihydroxy-1,4-dithiane (**31)** that forms the corresponding thiolate salt **116** (Scheme 37).



31 **116**

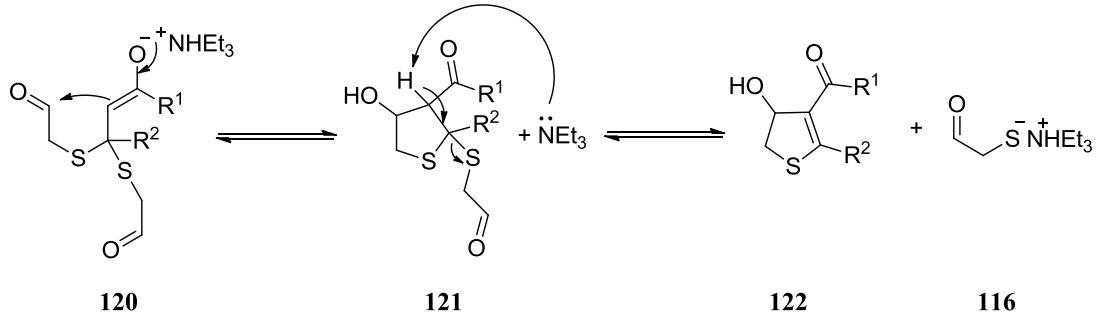
Scheme 37 Base induced fragmentation of 2,5-dihydroxy-1,4-dithiane

Then, the highly nucleophilic thiolate anion **116** attacks the β-carbon atom of the ketoalkyne **117**. After the proton transfer from trimethyl hydrogen cation to vinyl anion, thioenol ether **118** is formed and NEt_3 is regenerated. Next step is the attack of another thiolate salt **116** on β-carbon atom of thioenol ether **118** to form thioacetal **119**. This step produces two acidic hydrogen atoms at the α-position of carbonyl moiety of thio acetal **119** (Scheme 38).



Scheme 38 Formation of thioacetal **119** as an intermediate

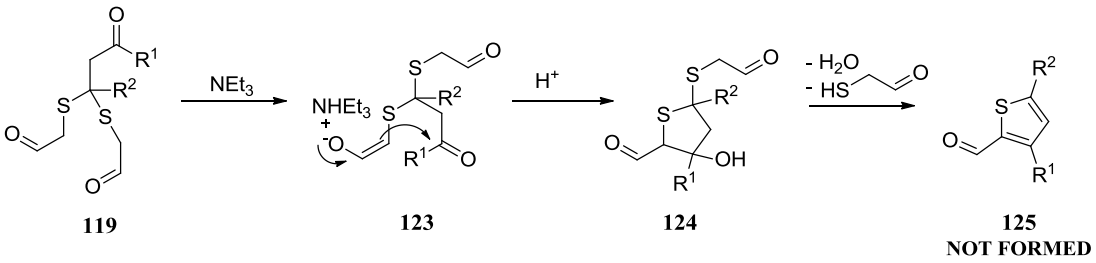
Abstraction of this hydrogen atom by NEt_3 forms the enolate **120**. Then attack of the enolate **120** to aldehyde carbon atom, forms the tetrahydrothiophene intermediate **121** and regenerates NEt_3 after proton transfer step. Since thiolate groups are excellent leaving groups, NEt_3 induced elimination yields relatively stable alcohol intermediate **122** and regenerates thiolate anion **116** (Scheme 39).



Scheme 39 Formation of alcohol **122** intermediate

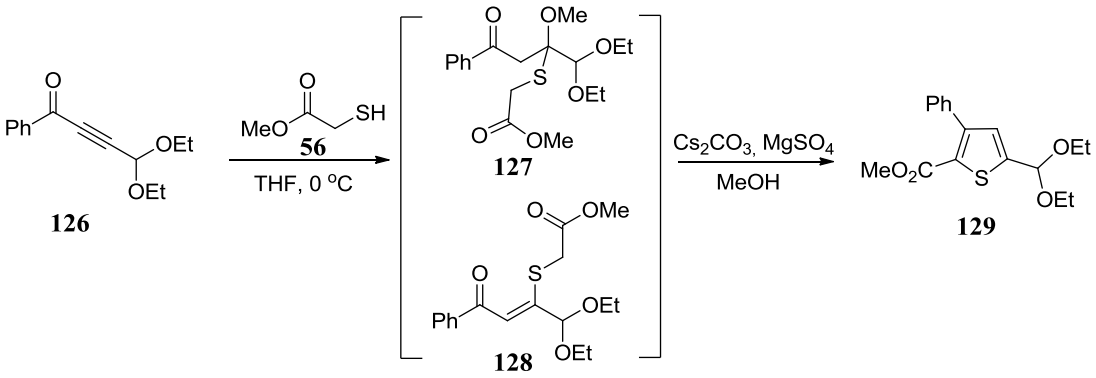
Effect of the selective enolization on the product formation

The thioacetal intermediate **119** contains 2 different carbonyl goups. First one is the two equivalent aldehyde groups, second one is the ketone group. It is known from the literature that, if there are two enolizable carbonyl groups, the enol form of the less electrophilic carbonyl group attacks the more electrophilic carbonyl group. The thioacetal intermediate **119** shown in Scheme 40 follows this general trend. The enol form of the keto group attacks the aldehyde group (Scheme 40). If the reaction was proceeded over enolization of aldehyde and the attack to the ketone, the trisubstituted thiophene **125** would be formed. Formation of the product **125** was not detected in any reaction (Scheme 40).



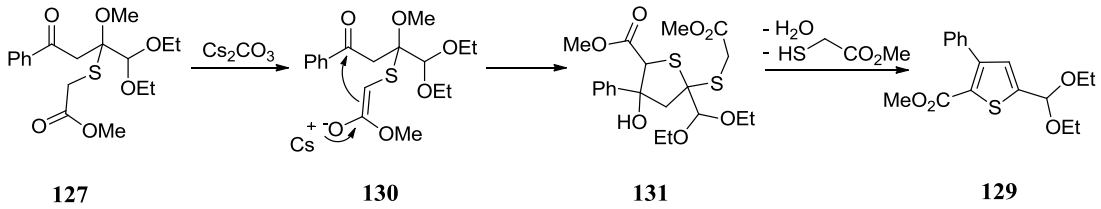
Scheme 40 An inoperative mechanism for enolization of **119**

However, when Obrecht and co-workers reacted ketoalkyne **126** with methyl thioglycolate (**56**) in the presence of Cs_2CO_3 and $MgSO_4$, the product was a trisubstituted thiophene **129** (Scheme 41).[48] Authors claimed that intermediates **127** and **128** were formed at the end of the first reaction. Then Cs_2CO_3, $MgSO_4$ and MeOH were added and a trisubstituted thiophene **128** was formed. For this example, formation of trisubstituted thiophene can be explained by the same trend also. Enol is formed at the ester group and attack occurs to the keto group which is more electrophilic. It is important to note that, the authors did not provide any spectroscopic data showing the formation of **127** and **128**.



Scheme 41 Reaction of **126** with **56**

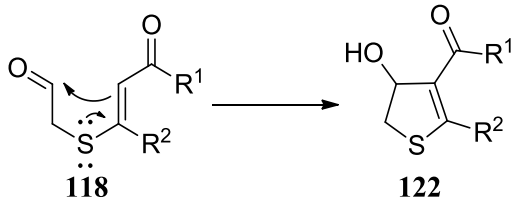
The authors did not suggest a mechanism for this reaction. Our suggestion for the formation of trisubstituted thiophene **129** is depicted in Scheme 42.



Scheme 42 Suggested mechanism for formation of **129**

2.3.2 Second Pathway

There is also another pathway that is worth to be discussed. This pathway is the intermolecular attack of thiol enol ether moeity to the aldehyde group in compound **118** (Scheme 43). This pathway also seems to be plausible when several factors are taken into account. First of all, the nucleophilicty of the α-carbon atom with respect to carbonyl group. This carbon atom is expected to show nucleophilic character because, this carbon atom is at the β-position with respect to sulfur atom of thio vinyl structure at the same time. Moreover the electrophile is an alkyl aldehyde carbon atom which is expected to show high electrophilicty. Furthermore, this pathway operates through intermolecular attack.



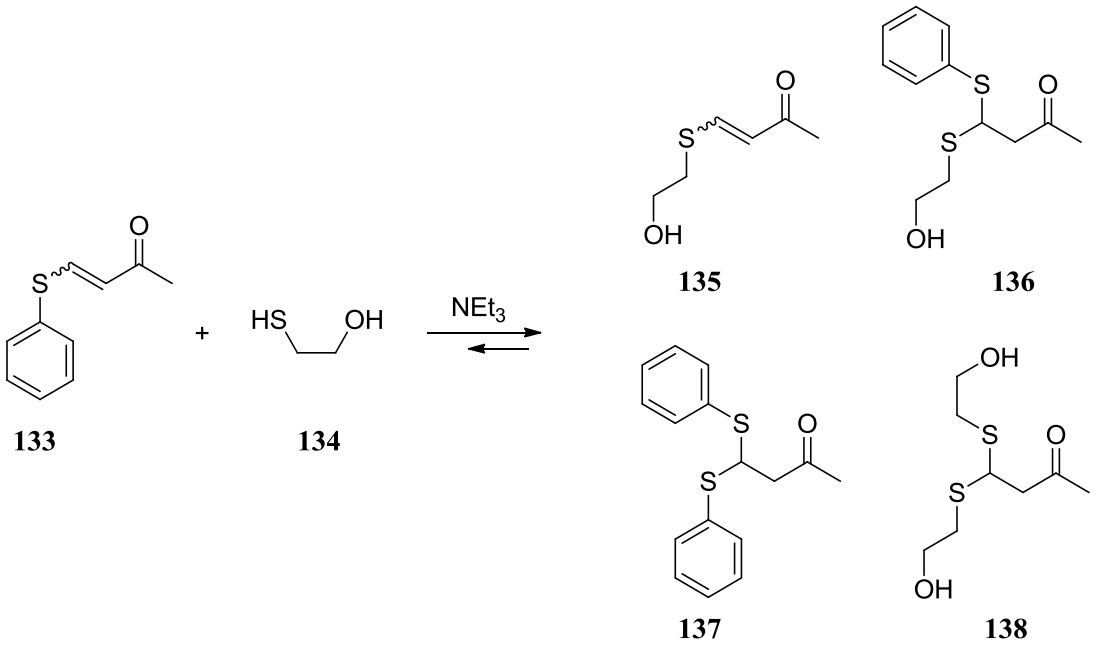
Scheme 43 Second pathway for formation of alcohol intermediates **122**

2.3.3 Evaluation of the two pathways

However, an investigation of the literature showed that first pathway seems to be more plausible than second pathway.

For instance, Fiesselmann synthesis[42] that is depicted in introduction part scheme 18, operates through the attack of sceond thiolate group on the β-carbon atom of thioenol ether **59** to form thioacetal **60**. Moreover in an article[58] the equilibrium between the

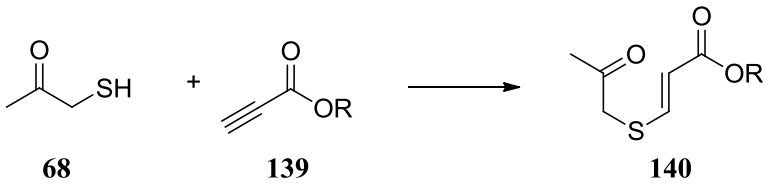
β-sulfido-α,β-unsaturated ketones and thioacetals are studied. In this study authors found that the reaction between compound **133** and **134** in the presence of NEt_3 produced 6 compounds (**133** + **134** ⇌ **135**, **136**, **137, 138**) which were found to be in equilibrium (Scheme 44).



Scheme 44 The equilibrum reaction of **133** and **134**

From that information, a similar equilibrium would also be expected in the reaction of **116** and **117** in the presence of NEt_3 also.

On the other hand in an article[59] published by Fevig *et al.* compound **140** was isolated from reaction of **68** with **139**. Fevig *et al.* reported that reaction did not proceed further after the formation of **140**. However, it was important to note that the electrophile in this reaction was a ketone which is less reactive than aldehyde. Furthermore, there is no base in the reaction medium (Scheme 45).

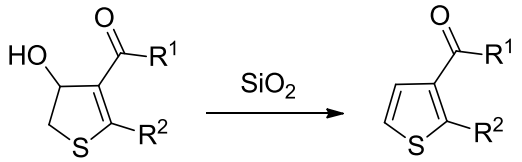


68 **139** **140**

Scheme 45 Reaction between **68** and **139**

2.4 Stability of the alcohol intermediates

The alcohol intermediates **122** formed were treated with SiO_2 to eliminate water and form the thiophene **141** (Scheme 46).



122 **141**

Scheme 46 Formation of thiophene **141** from alcohol derivatives **122**

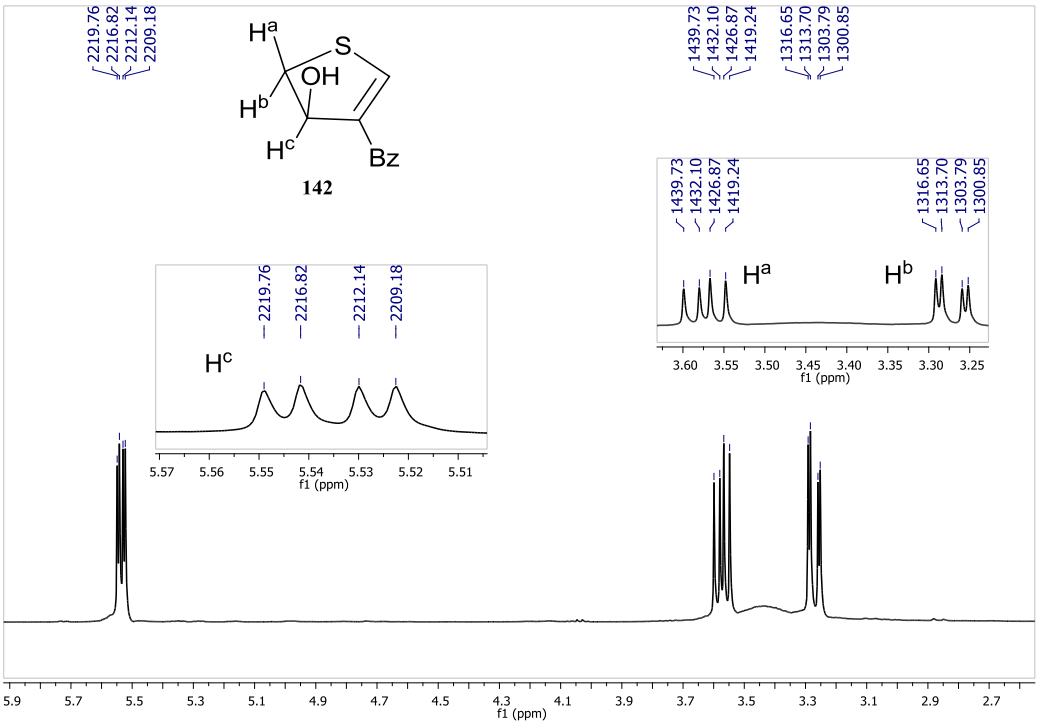
The alcohol intermediates **122** underwent a slow dehydration which led to the prolonged reaction times. They were also not stable in $CDCl_3$ solvent.

In addition to silica gel induced dehydration of alcohol intermediates **122**, washing the alcohol intermediates **122** with acidic water solution also caused dehydration.

The tendency for the dehydration of alcohol intermediates **122** was to generate aromatic thiophene ring **141**. However, the dehydration process needs at least a solvent to proceed rather than occuring spontaneously.

Due to the instability of alcohol intermediates **122** on silica gel, full characterization of these compounds were not studied and the alcohols **141** were detected in all crude NMR spectra.

Figure 1 ^{1}H NMR spectrum of the alcohol **142**



In Figure 1, the ^{1}H NMR spectrum of the alcohol **142** is presented. In addition to the broad alcohol signal resonating between H_a and H_b resonance signals, the chemical shifts and splitting patterns of H_a, H_b and H_c also support the proposed structure. The geminal methylene protons resonate as an AB-system. Both parts of the AB-systems are further split into doublets due to the coupling with the adjacent H_c proton. The coupling constants and the chemical shifts of these protons are presented in the Table 3.

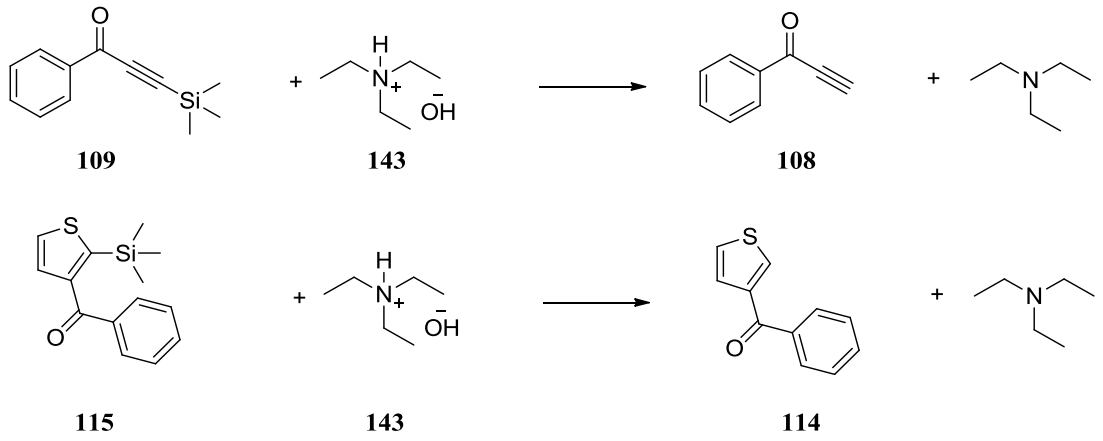
Table 3 Spectral data for alcohol **142**

Proton	**^{1}H NMR (400 MHz, $CDCl_3$) Chemical Shifts (ppm) and Coupling Constants (Hz)**
H_a	3,57 ppm
H_b	3,27 ppm
H_c	5,53 ppm
	$J_{a,c}$ = 7.6 Hz $J_{b,c}$ = 2.9 Hz $J_{a,b}$ = 12.9 Hz

It should be also noted that trans and geminal coupling constants reported in the Table 3 are in well agreement with the literature values of tetrahydrothiophene ring, however; the cis coupling which is 2.9 Hz is remarkably lower with respect to the reported literature value which is 5.4 Hz.[60]

2.5 Hydrolysis of trimethyl silyl group

The two compounds **109** and **115** that were bearing trimethyl silyl groups in their structures were found to be partially hydrolyzed in the reaction medium. It is known from the literature, that trimethyl silyl groups are sensitive to mildly basic conditions.[61] Therefore, the presence of triethyl amine in the reaction medium may have triggered the decomposition of both compounds **109** and **115**. Especially, the presence of triethylammonium hydroxide (**143**) as impurity in triethyl amine may be responsible for hydrolysis of trimethylsilyl group (Scheme 47).



Scheme 47 Possible hydrolysis pathway for compounds **109** and **115**

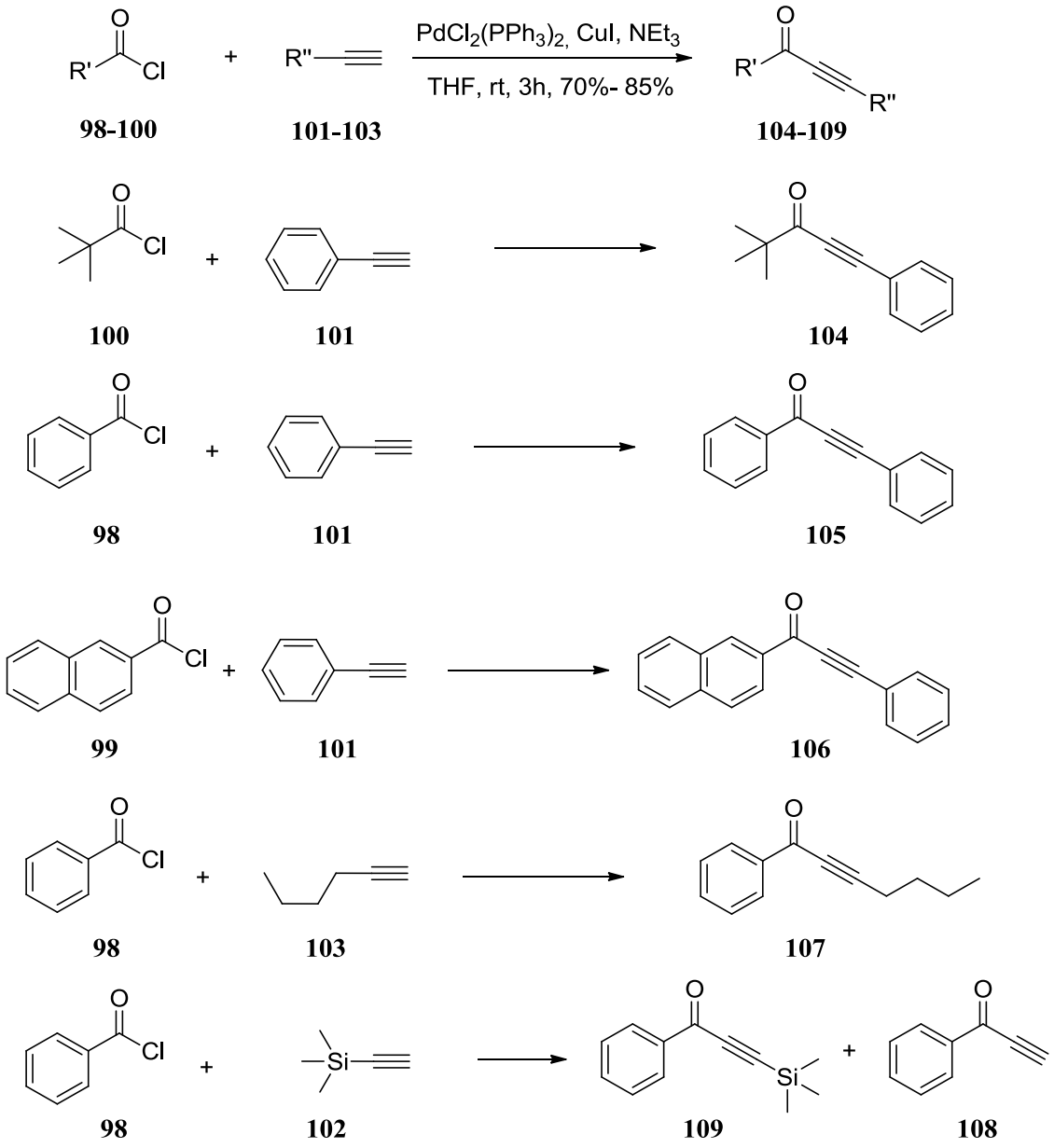
CHAPTER 3

CONCLUSION

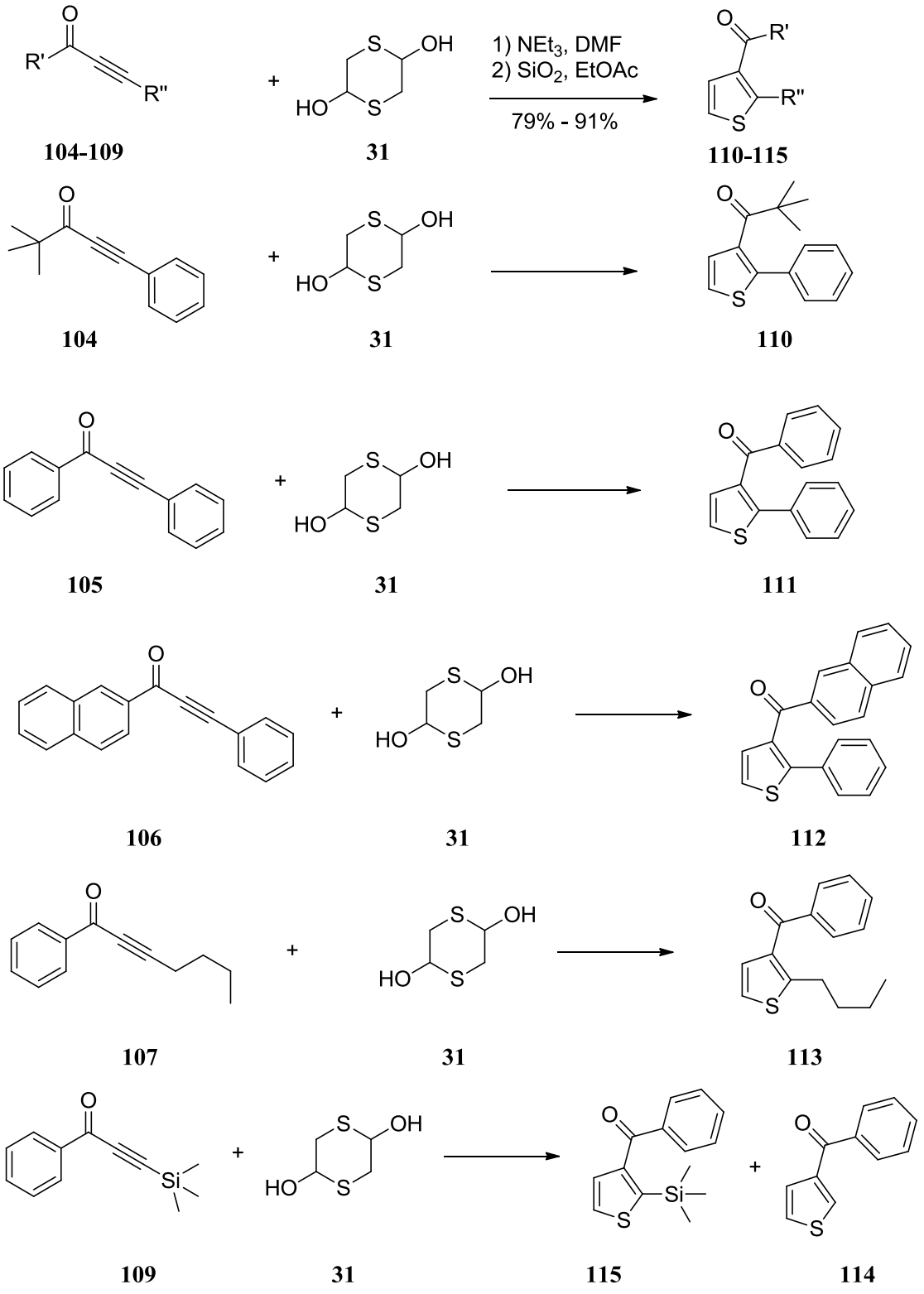
Since, the importance of thiophene derivatives not only for synthetic organic chemistry but also for medicinal chemistry and materials chemistry is noteworthy, we aimed to develope a new facile methodology to access 2,3-disubstituted thiophenes.

In the first step ketoalkyne derivatives were synthesized by Sonogashira coupling of acyl chlorides and terminal alkynes in good yields (Scheme 48).

In the second step, the 2,3-disubstituted thiophene ring was formed by cyclization reaction of 2,5-dihydroxy-1,4-dithiane (**31**) and corresponding ketoalkynes in the presence of base followed by dehydration by silica (Scheme 49).



Scheme 48 Synthetic scheme for synthesis of ketoalkynes **104-109**



Scheme 49 Synthesis of **110 – 114**

As a conclusion, a new two-step methodology was developed for a facile synthesis of 2,3-disubstituted thiophene derivatives starting from readily available compounds. The yields were good to excellent for both steps.

CHAPTER 4

EXPERIMENTAL

4.1 General

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quintet (quint), hextet (h), multiplet (m), broad doublet (bd), broad triplet (bt) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Thermo Smart Nicolet iS10 FT-IR spectrometer equipped with ATR accessory. Band positions were reported in reciprocal of centimeters (cm^{-1}).

High resolution Mass spectra were recorded by Agilent 1200/6210 LC-MS TOF with electrospray ionization detector.

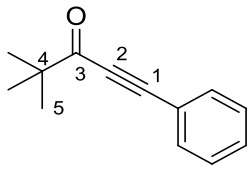
Column chromatographic separations were performed by using Fluka silica gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Naming of the compounds were done by ACD NMR (Name generator).

4.2 General procedure for the synthesis of ketoalkyne derivatives 104-109

Ketoalkynes were prepared according to a literature method with slight modifications.[62] $Pd(PPh_3)_2Cl_2$ (19 mg, 0.028 mmol) and CuI (11 mg, 0.056 mmol) in THF (5 mL) were stirred under N_2 atomsphere for 30 min. Then 0.2 mL (1.42 mmol) of triethylamine, 1.42 mmol of acyl chloride, and alkyne (1.7 mmol) were added respectively. The reaction was stirred for 3 h at room temperature. After the reaction was completed, the solvent was evaporated, and the residue was treated with 25 mL of diethyl ether. Then, the diethyl ether solution is passed through a pad of celite. The celite was washed with diethyl ether (3 × 50 mL). Then, the filtrate and diethyl ether solutions were combined and was washed with water (3 × 50 mL). Afterwards, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the crude residue was subjected to column chromatography. Gradient elution starting from hexane to hexane/ EtOAc (3:1) was employed for the purification of desired ketoalkynes.

4.2.1 4,4-Dimethyl-1-phenylpent-1-yn-3-one (104): (Yellow oil, 82%, 217 mg) . This compound is known in the literature and the spectroscopic data are consistent with the literature values.[63]

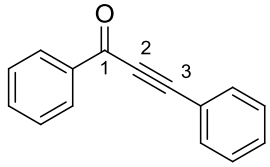


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bd, *J* = 6.9 Hz, 2H), 7.43 (bt, *J* = 7.4 Hz 1H), 7.36 (bt, *J* = 7.4 2H), 1.19 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 133.0, 130.6, 128.7, 120.3, 92.3, 86.1, 44.9, 26.2.

IR (ATR, cm^{-1}) 2969, 2196, 1660, 1284, 1070, 1011, 757, 688.

4.2.2 1,3-Diphenylprop-2-yn-1-one (105): (Yellow oil, 85%, 247 mg) This compound is known in the literature and the spectroscopic data are consistent with the literature values.[62]

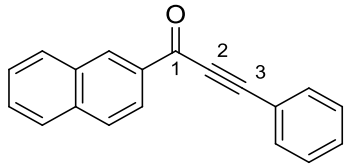


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (bd, *J* = 7.1 Hz, 2H), 7.72 -7.67 (m, 1H), 7.64 (bt, *J* = 7.4 Hz 2H), 7.55 -7.53 (m, 2H), 7.51 - 7.46 (m, 1H), 7.43 (bt, *J* = 7.3 Hz 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 136.9, 134.2, 133.2, 130.9, 129.7, 128.8, 128.7, 120.2, 93.2, 87.0.

IR (ATR, cm^{-1}) 2196, 1637, 1284, 1028, 1011, 994 731, 688.

4.2.3 1-(Naphthalen-2-yl)-3-phenylprop-2-yn-1-one (106): (Pale yellow solid, 74%, 268 mg, mp: 91-93 ºC) This compound is known in the literature and the spectroscopic data and melting point data are consistent with the literature values.[62,67]

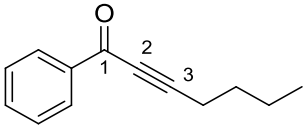


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.21 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.89 (t, *J* = 8.8 Hz, 2H), 7.74 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.65 - 7.54 (m, 2H), 7.53 - 7.40 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 136.2, 134.4, 133.1, 132.7, 132.4, 130.9, 129.9, 129.1, 128.8, 128.6, 128.0, 127.0, 124.0, 120.2, 93.1, 87.1.

IR (ATR, cm^{-1}) 2201, 1622, 1303, 1285, 1166, 1125, 756, 724, 688.

4.2.4 1-Phenylhept-2-yn-1-one (107): (Yellow oil, 78%, 206 mg) This compound is known in the literature and the spectroscopic data are consistent with the literature values.[63]

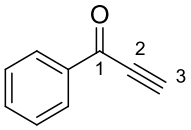


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (bd, *J* = 8.5 Hz, 2H), 7.59 (bt, *J* = 7.4 Hz 1H), 7.47 (bt, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 1.66 (quint, *J* = 7.3 Hz, 2H), 1.51 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 137.1, 134.0, 129.7, 128.6, 97.0, 79.8, 30.0, 22.2, 19.0, 13.6.

IR (ATR, cm^{-1}) 2958, 2932, 2200, 1641, 1262, 698.

4.2.5 1-Phenylprop-2-yn-1-one (108): (Obtained as the side product from reaction of trimethyl silyl acetylene and benzoyl chloride. Brown solid, 19%, 80 mg, from reaction with 3.2 mmol acyl chloride, mp 48-50 ^{o}C). This compound is known in the literature and the spectroscopic data and melting point data are consistent with the literature values.[65,66]

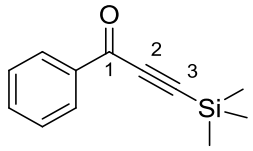


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (bt, *J* = 8.5 Hz, 2H), 7.64 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 3.45 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 136.3, 134.7, 129.8, 128.8, 80.9, 80.4.

IR (ATR, cm^{-1}) 3233, 2092, 1635, 1594, 1579, 1451, 1314, 1245, 1174, 1001, 733, 713, 691.

4.2.6 1-Phenyl-3-(trimethylsilyl)prop-2-yn-1-one (109): (Obtained as the major product from reaction of trimethyl sillyl acetylene and benzoyl chloride. Yellow oil, 70%, 450 mg, from reaction with 3.2 mmol acyl chloride) This compound is known in the literature and the spectroscopic data are consistent with the literature values.[64]



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.0 Hz 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), - 0.15 (s, 9H).

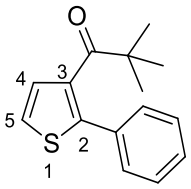
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 136.6, 134.3, 129.8, 128.7, 101.0, 100.7, -0.6.

IR (ATR, cm^{-1}) 2962, 2153, 1625, 1244, 1035, 1016, 760, 699, 662.

4.3 General procedure for the synthesis of 2,3-disubstituted thiophene derivatives 110-115

Ketoalkyne (0.5 mmol) was dissolved in 2 mL of DMF. Then 2,5-dihydroxy-1,4-dithiane (0.25 mmol, 38 mg) and triethylamine (0.5 mmol, 70 μL) were added respectively. After the addition of triethyl amine, the colour of the solution rapidly turned into black and may get warm. After 15 min., the reaction was completed. The reaction mixture was diluted with 20 mL of water and extracted with dietyl ether (3 × 20 mL). Then, the combined organic layers were washed with water (3 × 50 mL) to remove residual DMF. The organic layer is seperated and dried over Na_2SO_4, the crude residue was concentrated under reduced pressure. Then, the residue was diluted with 10 mL of ethyl acetate and about 250 mg silica gel is added. The heterogenous mixture was stirred overnight. After the reaction was stopped, the heterogeous mixture was filtrated. The solid was washed with ethyl acetate (3 × 10 mL). Finally, the combined ethyl acetate portions were dried over Na_2SO_4 and concentrated at reduced pressure to yield the desired compounds.

4.3.1 2,2-Dimethyl-1-(2-phenylthiophen-3-yl)propan-1-one (110): (Yellow oil, 79%, 96 mg)



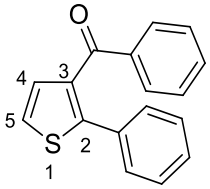
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.39 (m, 2H), 7.39 - 7.31 (m, 3H), 7.28 (d, $J_{5,4}$ = 5.3 Hz, 1H, H-5), 7.02 (d, $J_{4,5}$ = 5.3 Hz, 1H, H-4), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 142.3, 137.8, 134.1, 128.9, 128.8, 128.3, 127.2, 124.7, 45.4, 27.0.

IR (ATR, cm^{-1}) 2966, 2868, 1684, 1272, 1047, 1006, 867, 722, 695, 665.

HRMS analysis: m/z $(M+H)^+$ for $C_{15}H_{16}OS$ calculated: 245.0995, detected: 245.1058.

4.3.2 Phenyl(2-phenylthiophen-3-yl)methanone (111): (Brown oil, 91%, 120 mg)



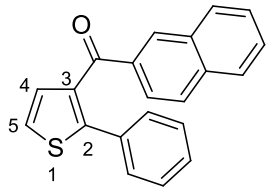
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (bd, J = 8.4 Hz, 2H), 7.34 (bt, J = 7.4 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.25 (d, $J_{5,4}$ = 5.3 Hz, 1H, H-5), 7.21 (d, $J_{4,5}$ = 5.3 Hz, 1H, H-4), 7.21 (t, J = 7.7 Hz, 1H), 7.15 - 7.09 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 147.8, 137.6, 136.6, 133.1, 132.8, 130.2, 129.9, 129.2, 128.4, 128.3, 128.2, 124.6.

IR (ATR, cm^{-1})1650, 1596, 1276, 858, 761, 691, 674.

HRMS analysis: m/z $(M+H)^+$ for $C_{17}H_{12}OS$ calculated: 265.0682, detected: 265.0684.

4.3.3 2-Naphtyl(2-phenylthiophen-3-yl)methanone (112): (Brown oil, 89%, 139 mg)



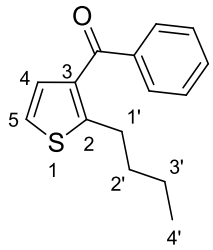
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.92 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.84 - 7.76 (m, 3H), 7.58 - 7.52 (m, 1H), 7.48 (t, *J* = 7.3 Hz, 1H) 7.41 - 7.36 (m, 3H), 7.34 (d, *J* = 5.2 Hz, 1H,), 7.21 -7.09 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 147.7, 136.9, 135.5, 135.0, 133.3, 132.5, 132.3, 130.3, 129.6, 129.2, 128.6, 128.5, 128.3, 128.3, 127.8, 126.7, 125.2, 124.7.

IR (ATR, cm^{-1})1650, 1624, 1371, 1283, 1122, 755, 727, 693.

HRMS analysis: m/z $(M+H)^+$ for $C_{21}H_{14}OS$ calculated: 315.0838, detected: 315.0844.

4.3.4 (2-Butylthiophen-3-yl)(phenyl)methanone (113): (Yellow oil, 91%, 111 mg)



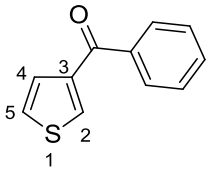
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (bd, *J* = 8.4, 2H), 7.56 (bt, *J* = 7.4 Hz 1H), 7.46 (bt, *J* = 7.5 Hz 2H), 7.10 (d, $J_{5,4}$ = 5.3 Hz, 1H, H-5), 7.08 (d, $J_{4,5}$ = 5.3 Hz, 1H, H-4), 3.07 (t, *J* = 7.8 Hz, 2H), 1.69 (quint, *J* = 7.7 Hz, 2H), 1.38 (h, *J* = 7.4, Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 139.4, 135.8, 132.5, 130.0, 129.6, 128.4, 121.3, 34.2, 31.0, 29.1, 22.5, 13.9.

IR (ATR, cm^{-1})2956, 2927, 1649, 1514, 1444, 1266, 853, 694, 670.

HRMS analysis: m/z $(M+H)^+$ for $C_{15}H_{16}OS$ calculated: 245.1011, detected: 245.0995.

4.3.5 Phenyl(thiophen-3-yl)methanone (114): (Obtained as the side product from the reaction of **109** with 2,5-diydroxy-1,4-ditihane after 5 h) (Dark brown oil, 7 mg, 8%) This compound is known in the literature and the spectroscopic data are consistent with the literature values.[68]

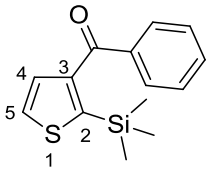


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, $J_{2.5}$ = 2.9, $J_{2.4}$ = 1.2 Hz, 1H, H-2), 7.84 (d J = 7.0 Hz, 2H), 7.60 (dd, $J_{4,5}$ = 5.0, $J_{4,2}$ = 1.1 Hz, 1H, H-4), 7.57 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.38 (dd, $J_{5,4}$ = 5.1, $J_{5,2}$ = 2.9 Hz, 1H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) 190.1, 141.4, 138.7, 134.1, 132.4, 129.5, 128.7, 128.5, 126.3.

IR (ATR, cm^{-1}) 1646, 1509, 1408, 1274, 1137, 856, 820, 781, 695, 671.

4.3.6 Phenyl(2-(trimethylsilyl)thiophen-3-yl)methanone (115): (Obtained as the major product from the reaction of **109** with 2,5-diydroxy 1,4-ditihane after 5 h. Brown oil, 80%, 104 mg)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.0 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.53 (d, $J_{5,4}$ = 4.8 Hz, 1H, H-5), 7.47 (t, J = 7.5 Hz, 2H), 7.37 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 0.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 150.0, 146.8, 139.3, 132.4, 131.9, 129.7, 129.5, 128.4, 0.0.

IR (ATR, cm^{-1}) 2952, 1650, 1393, 1247, 1017, 837, 709, 694, 619.

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APPENDIX A

SPECTRAL DATA

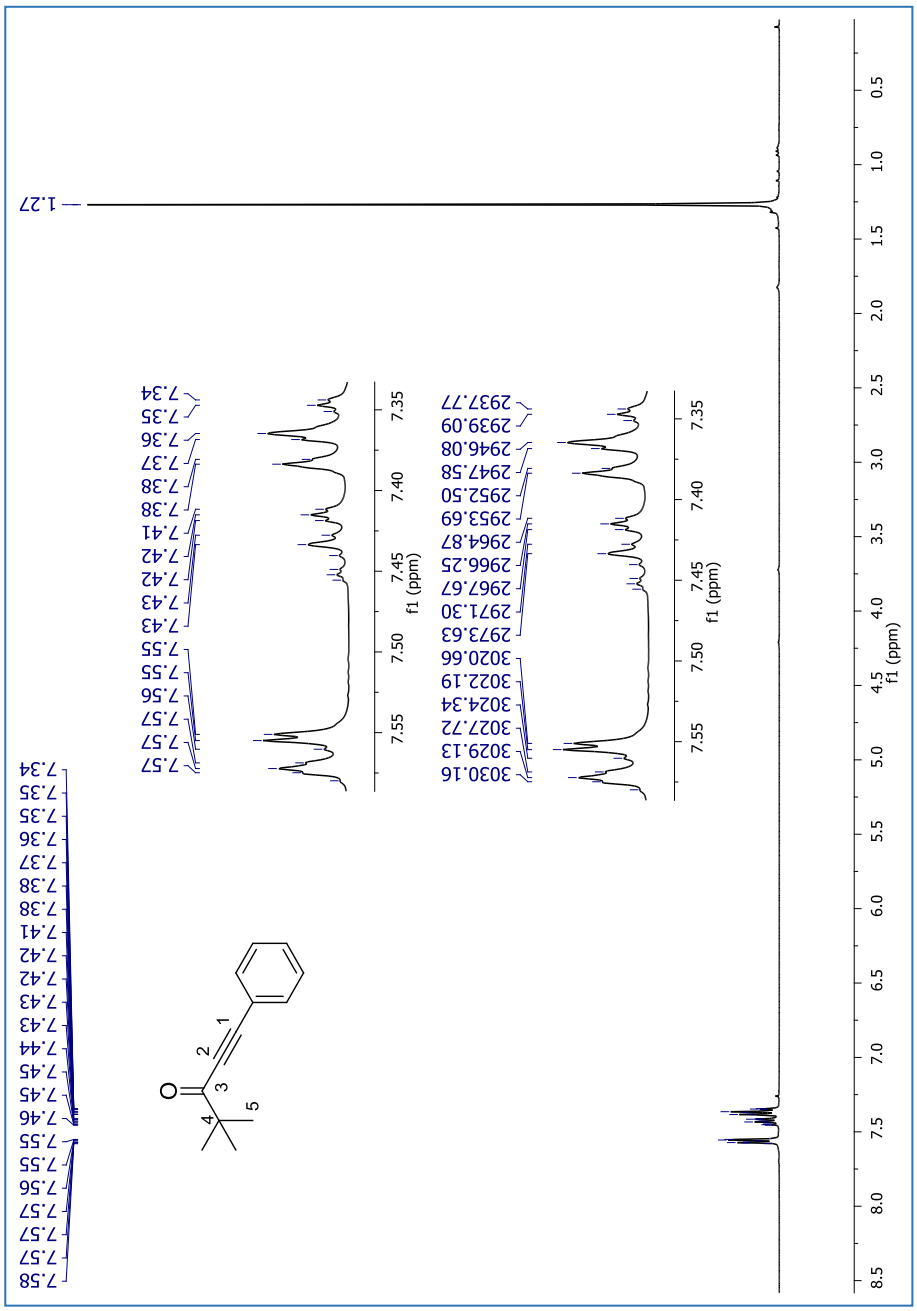

Figure A1 ^{1}H NMR spectrum of compound **104**

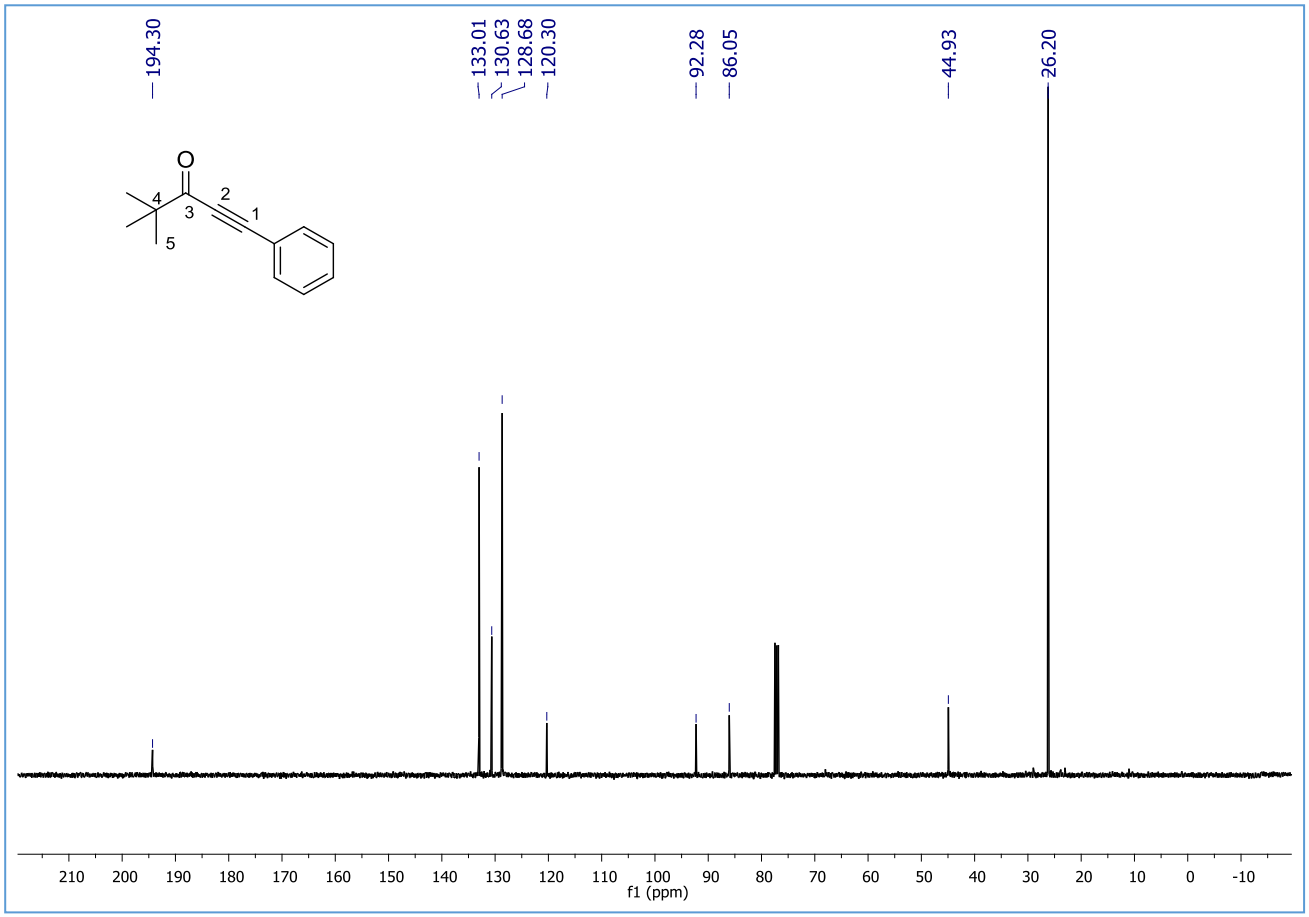

Figure A2 ^{13}C NMR spectrum of compound **104**

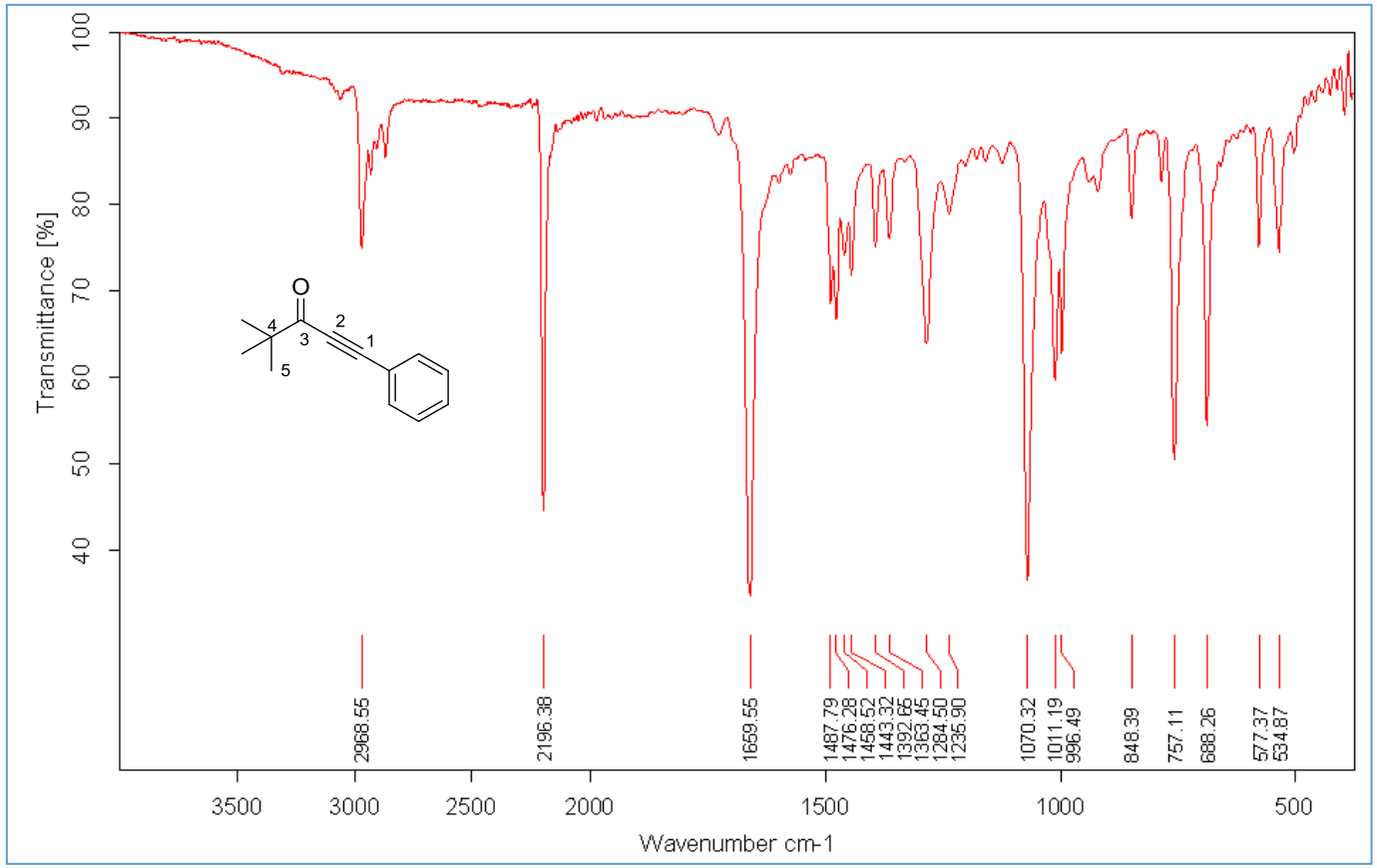

Figure A3 IR spectrum of compound **104**

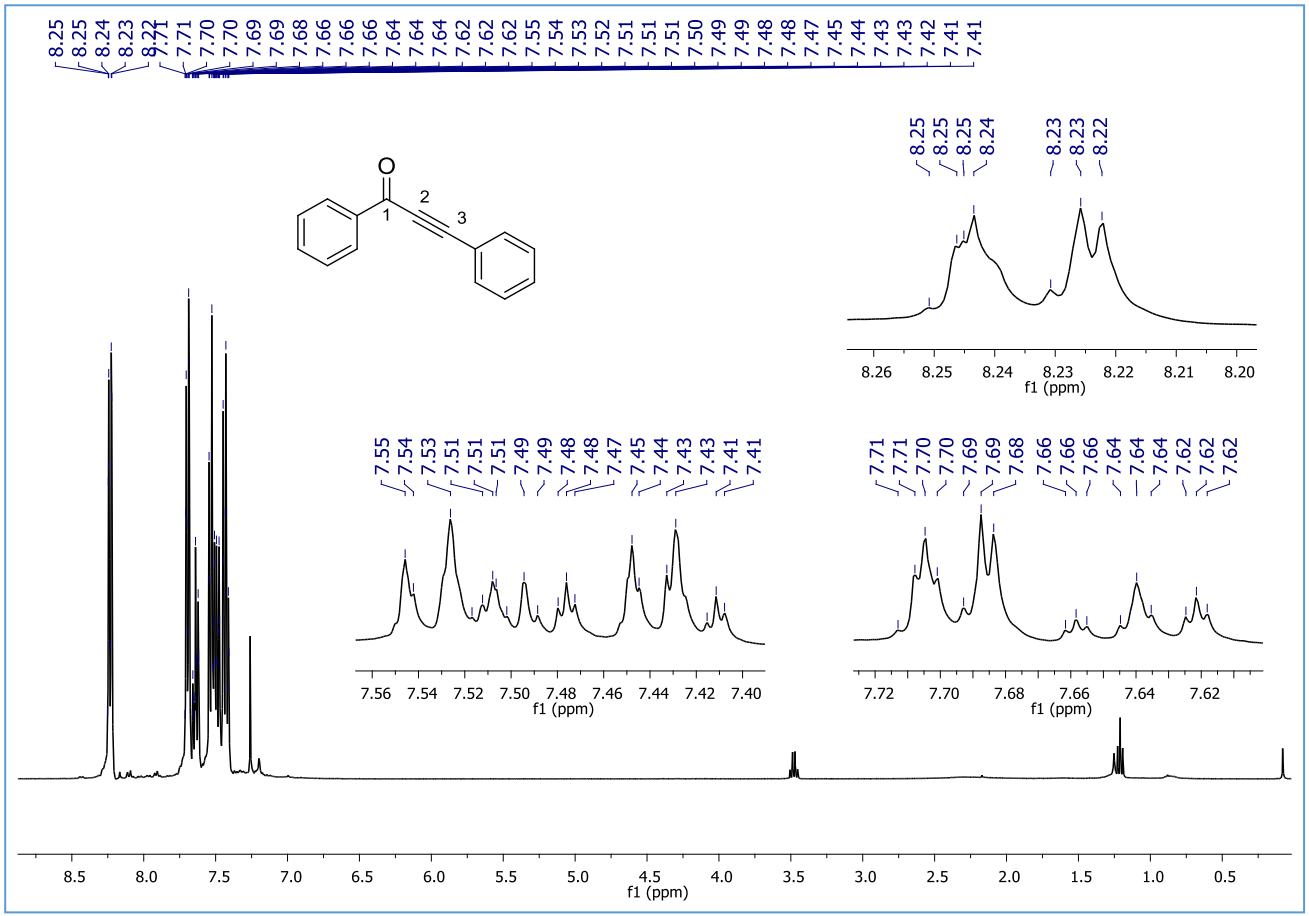

Figure A4 ^{1}H NMR spectrum of compound

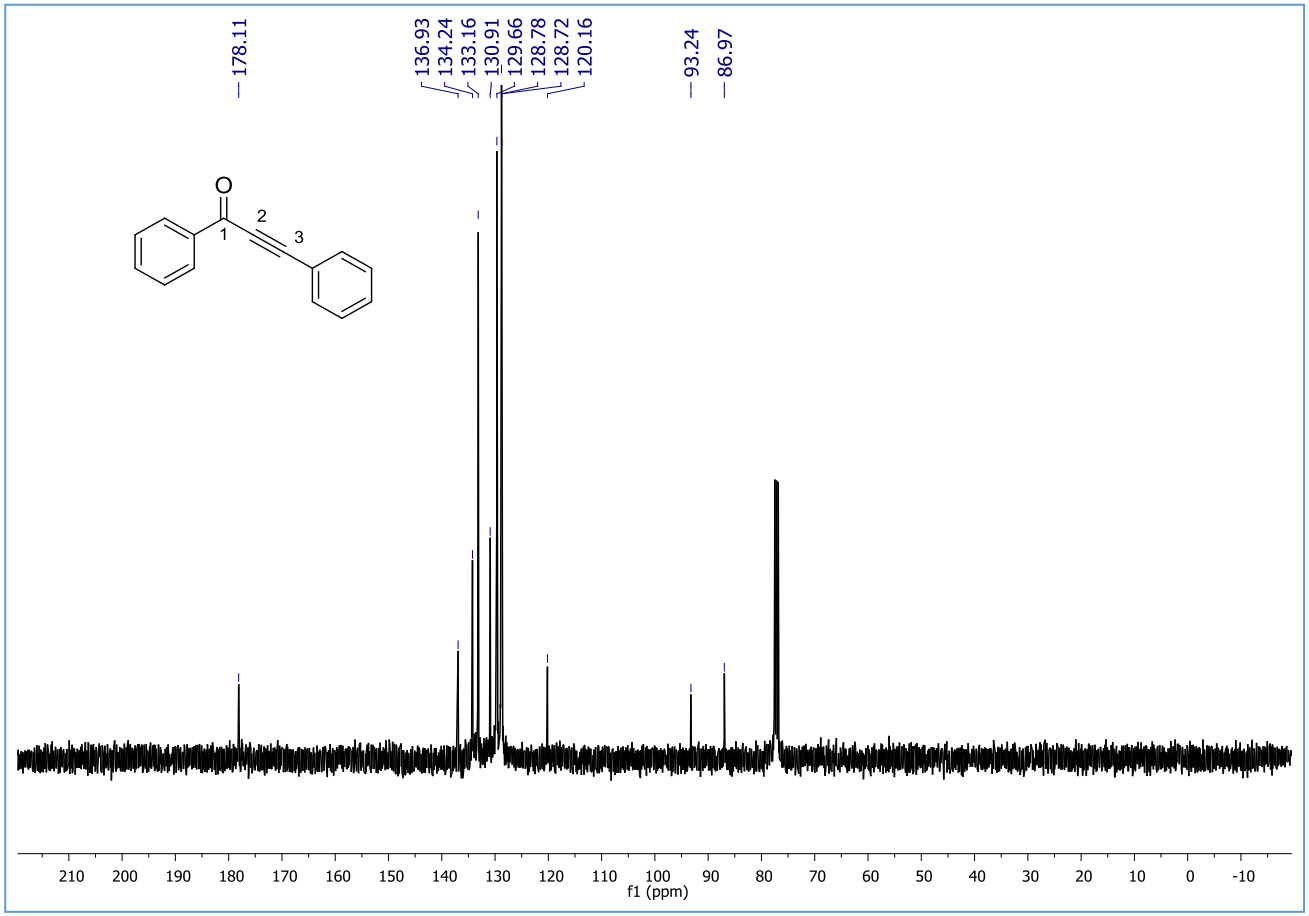

Figure A5 ^{13}C NMR spectrum of compound **105**

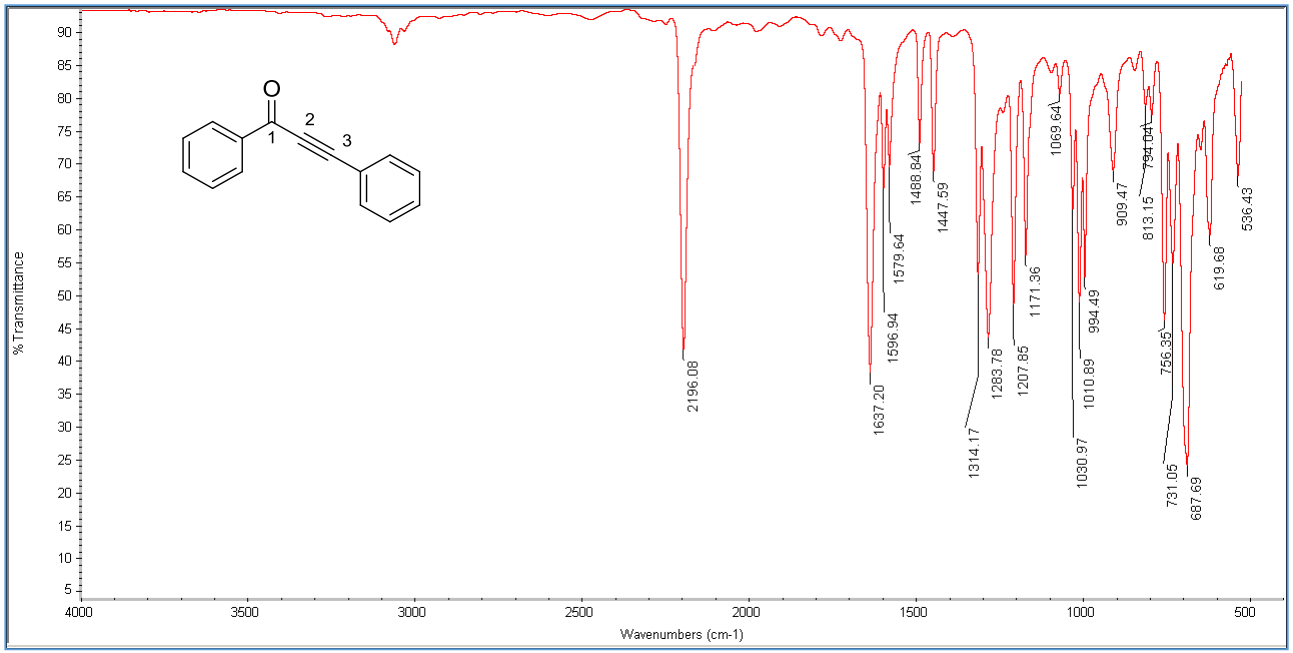

Figure A6 IR spectrum of compound **105**

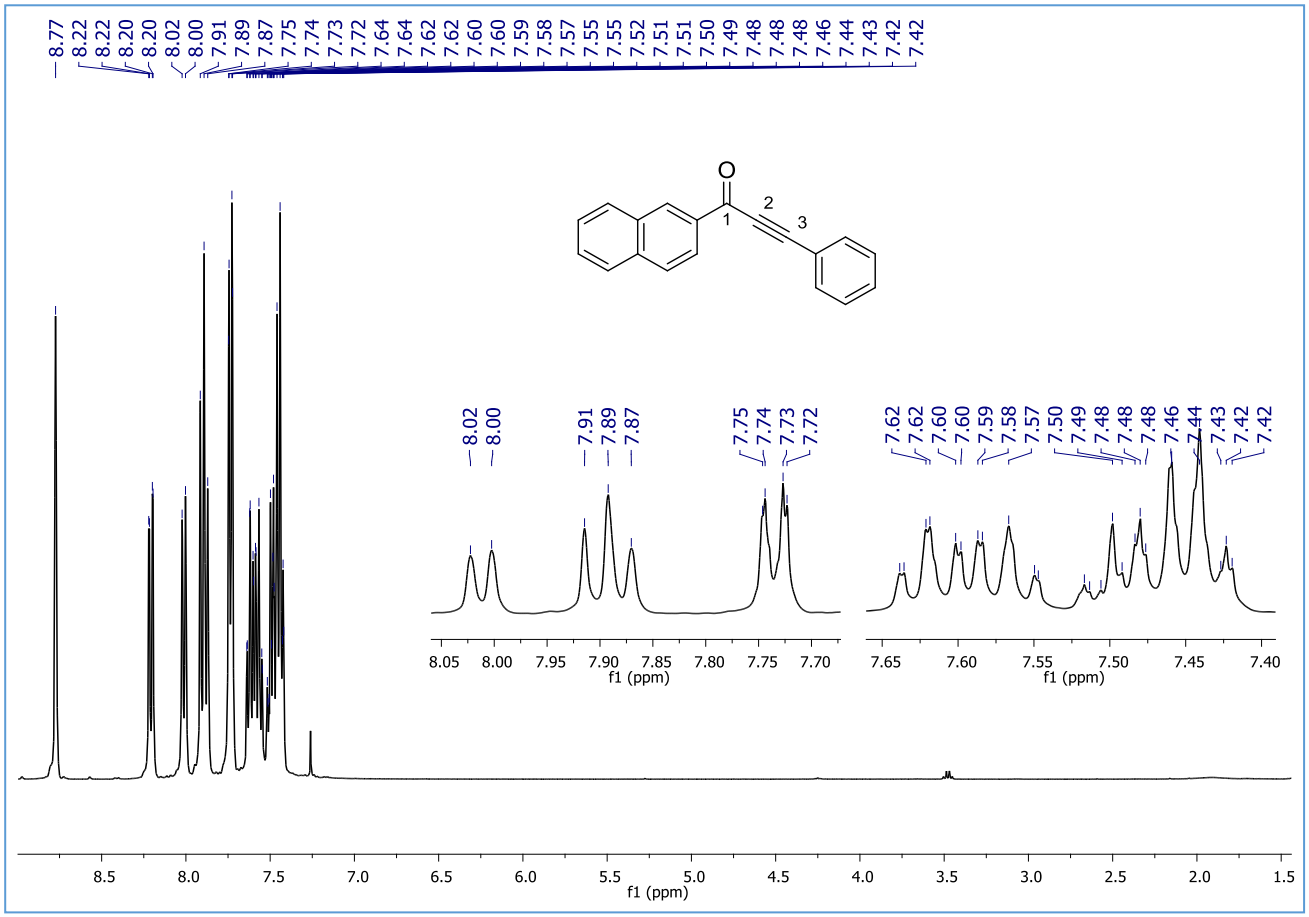

Figure A7 ^{1}H NMR spectrum of compound **106**

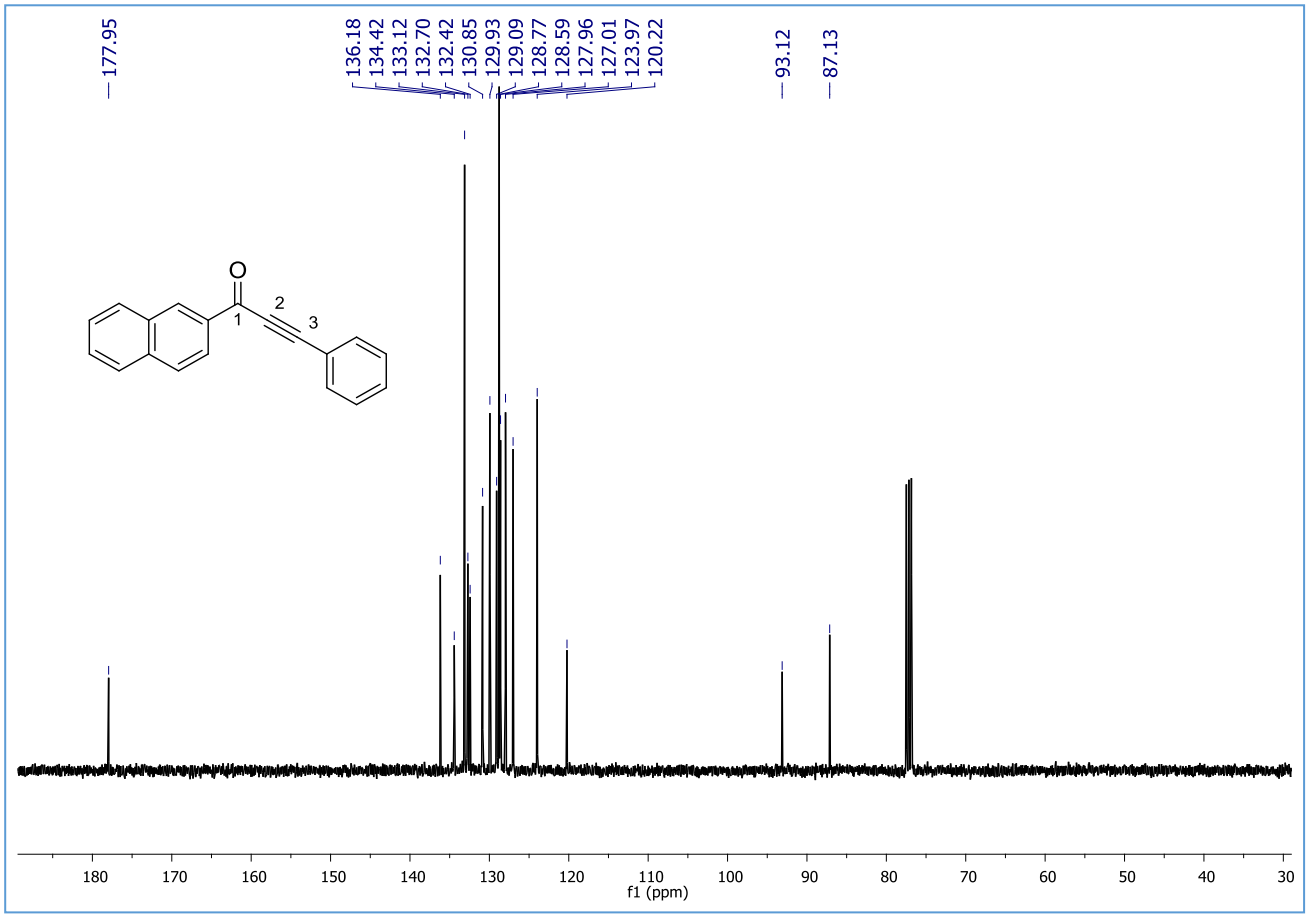

Figure A8 ^{13}C NMR spectrum of compound **106**

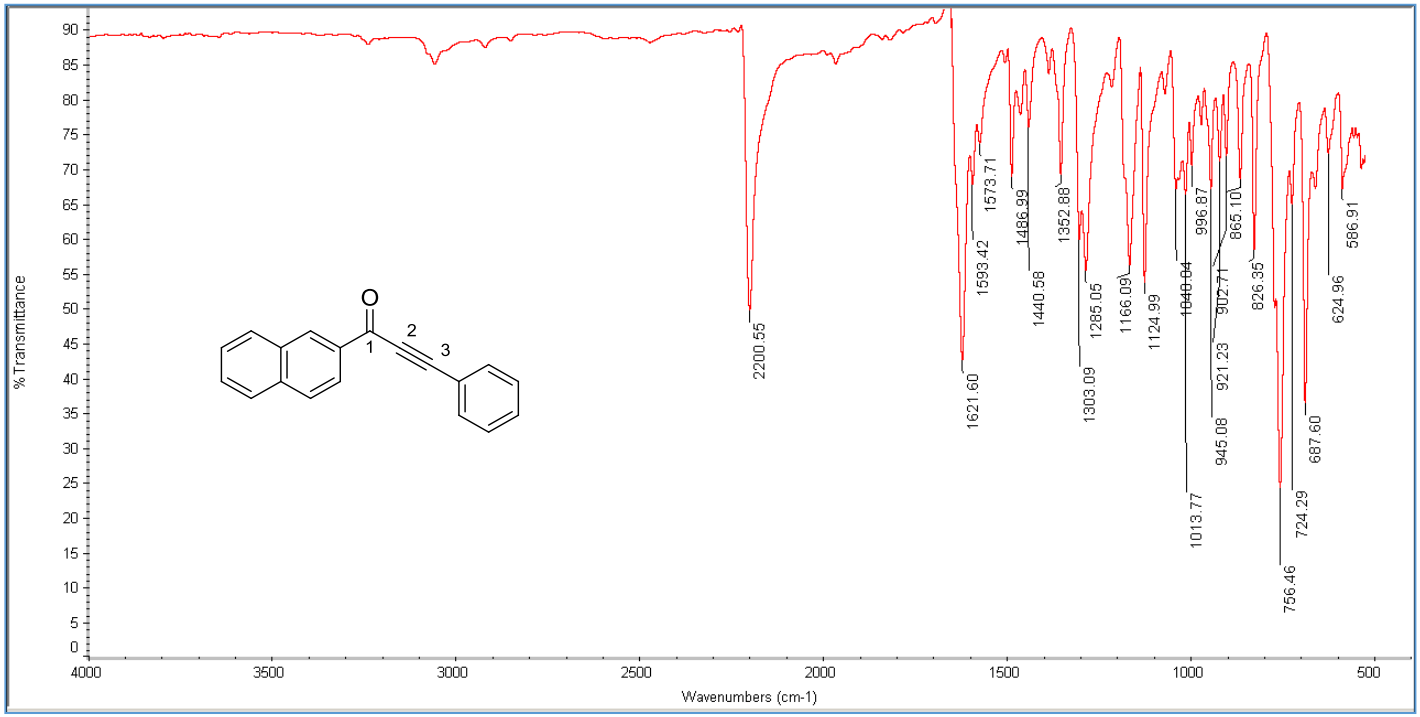

Figure A9 IR spectrum of compound **106**

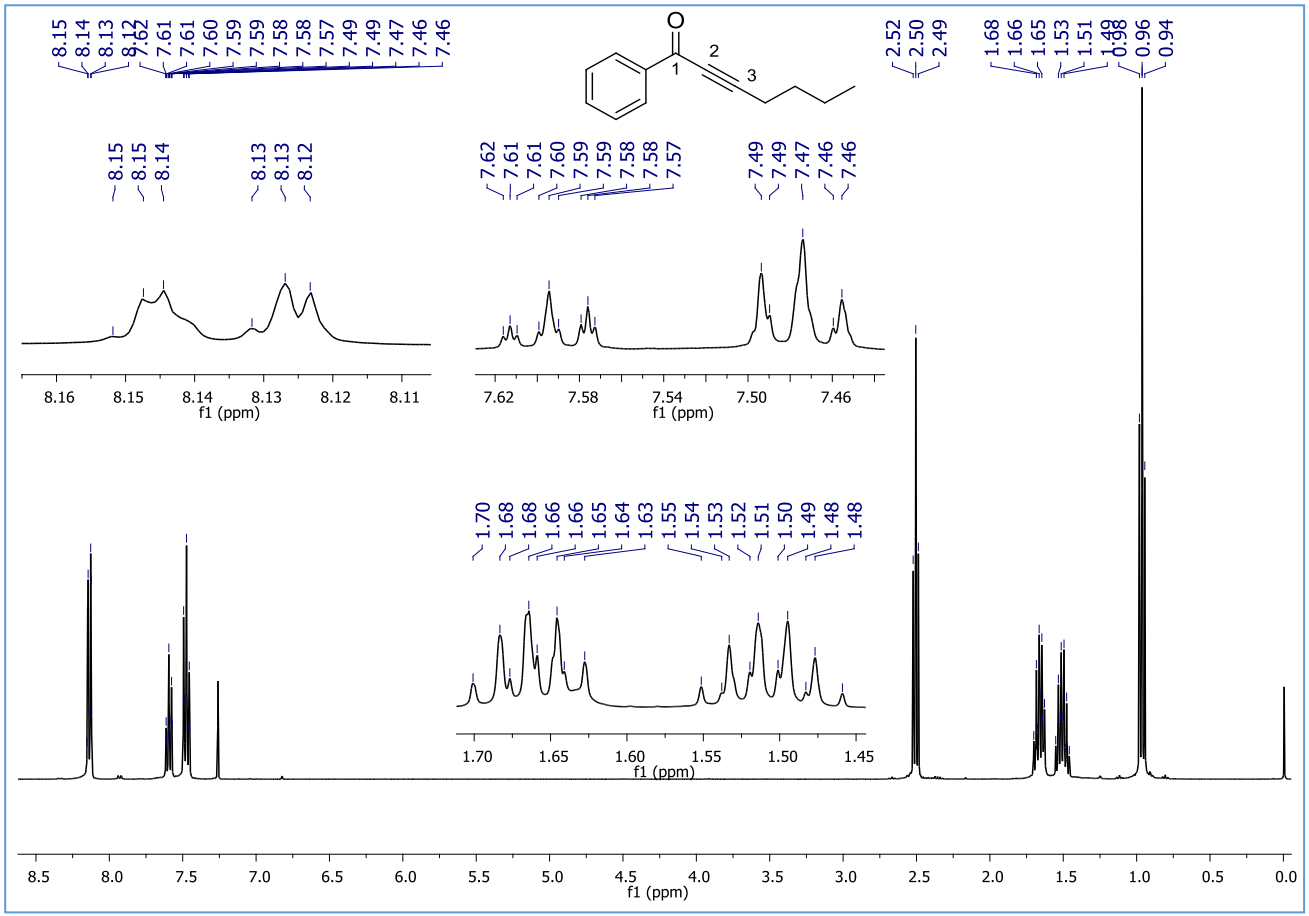

Figure A10 ^{1}H NMR spectrum of compound **107**

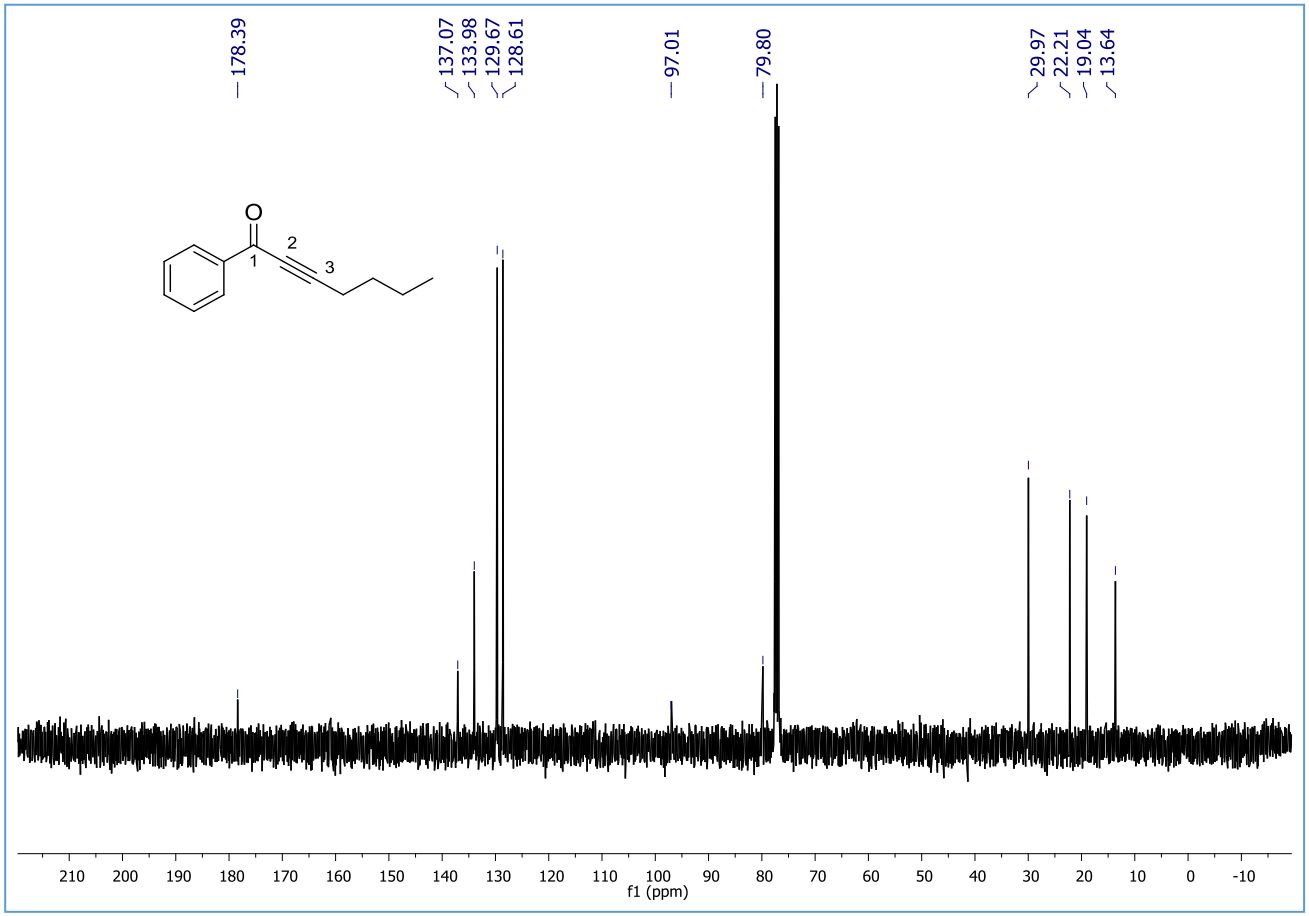

Figure A11 ^{13}C NMR spectrum of compound **107**

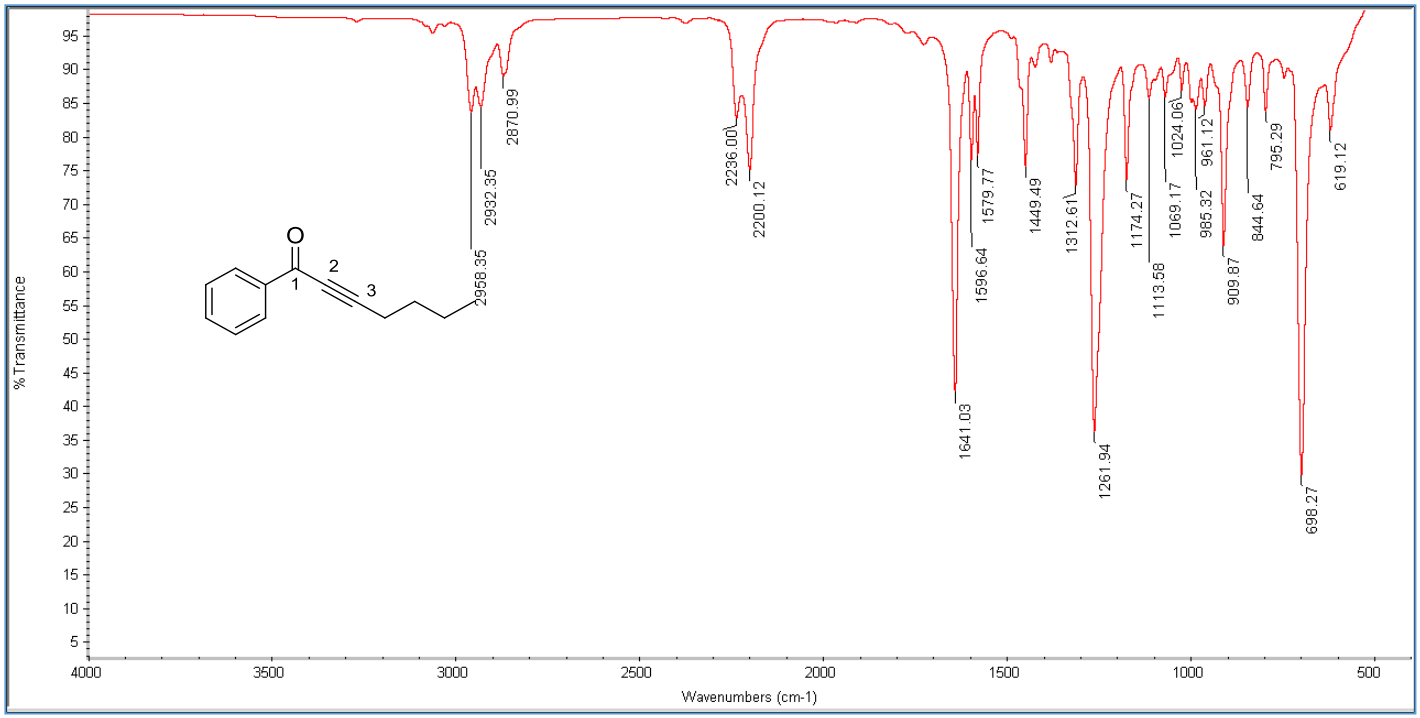

Figure A12 IR spectrum of compound **107**

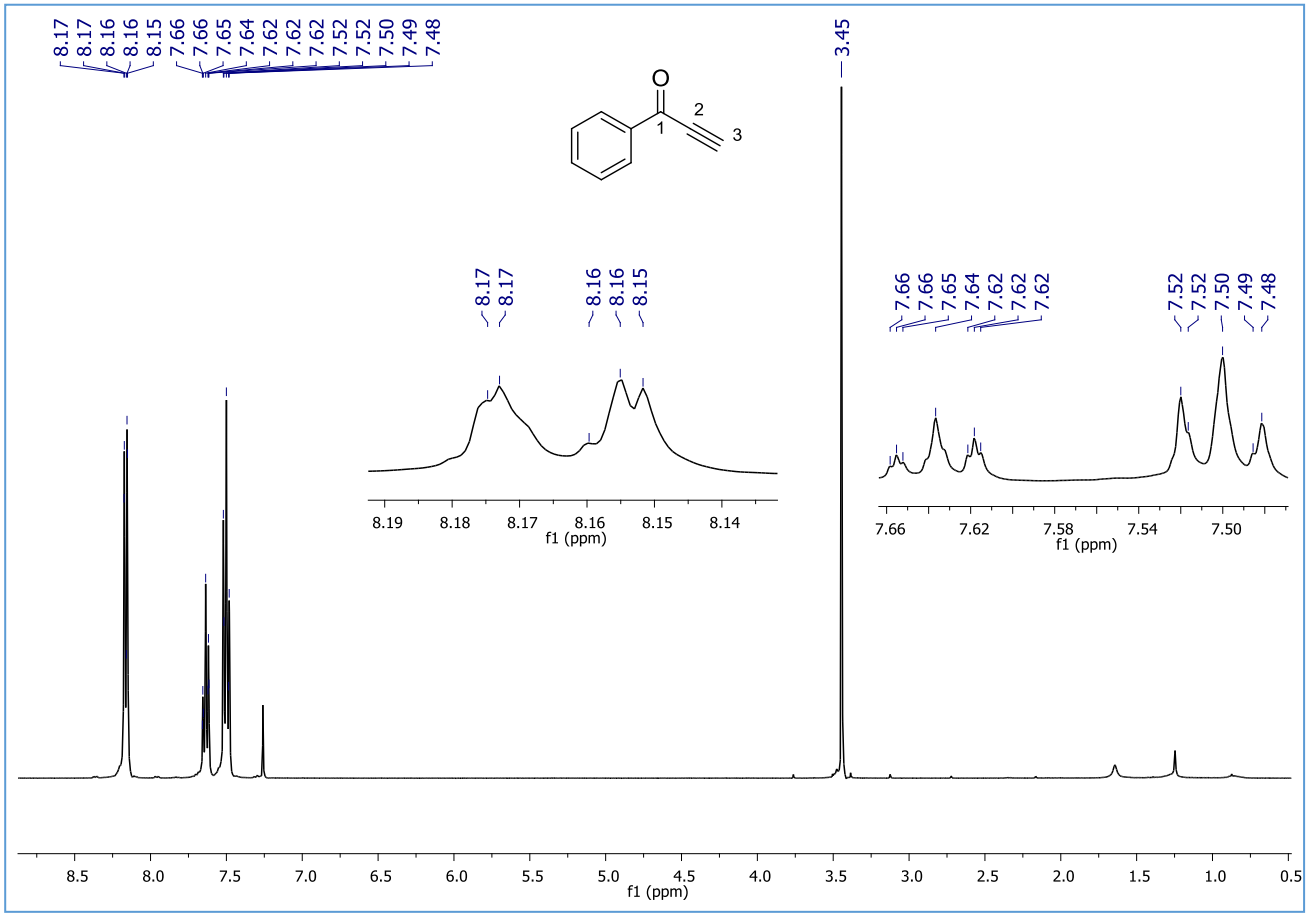

Figure A13 ^{1}H NMR spectrum of compound **108**

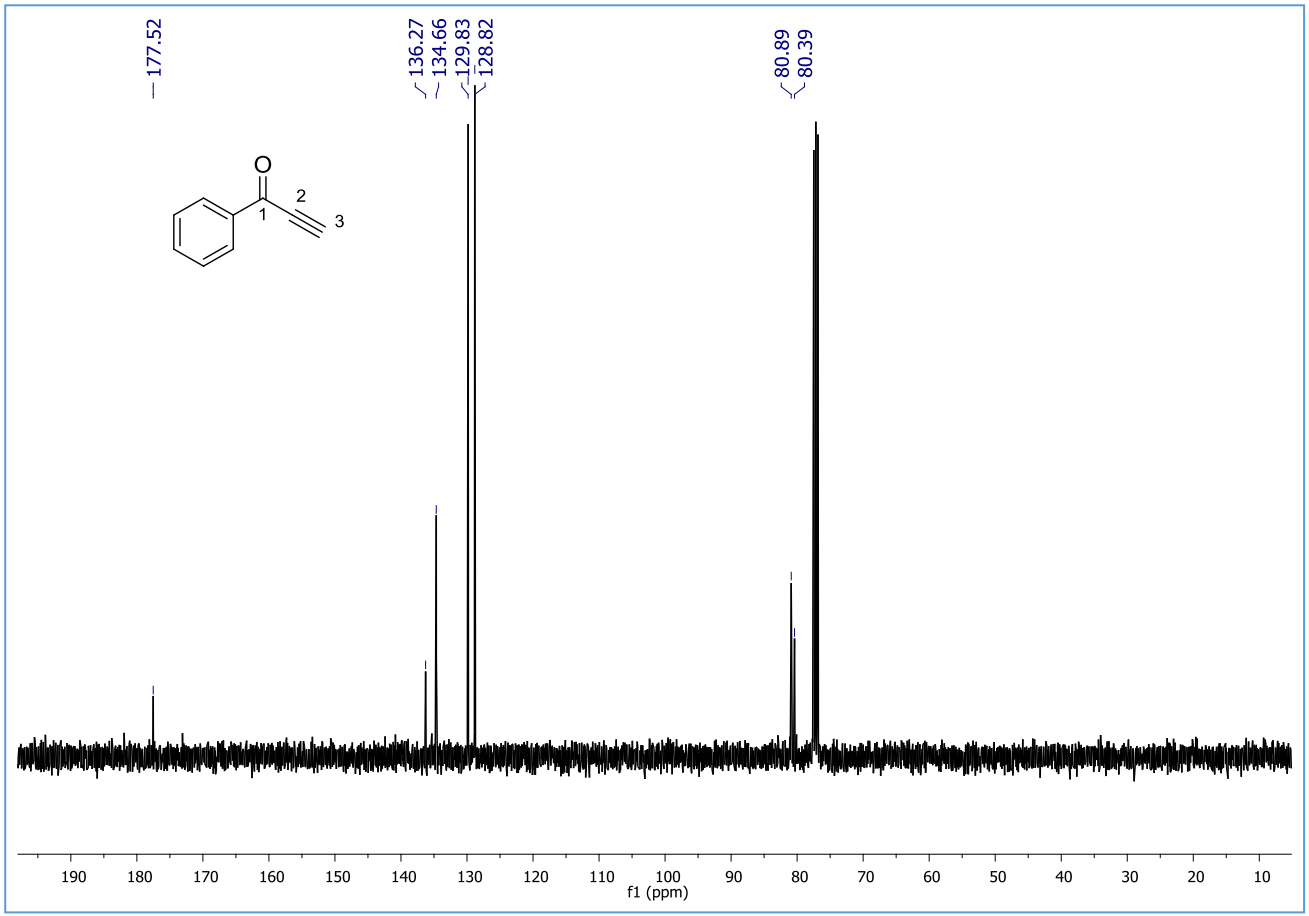

Figure A14 ^{13}C NMR spectrum of compound **108**

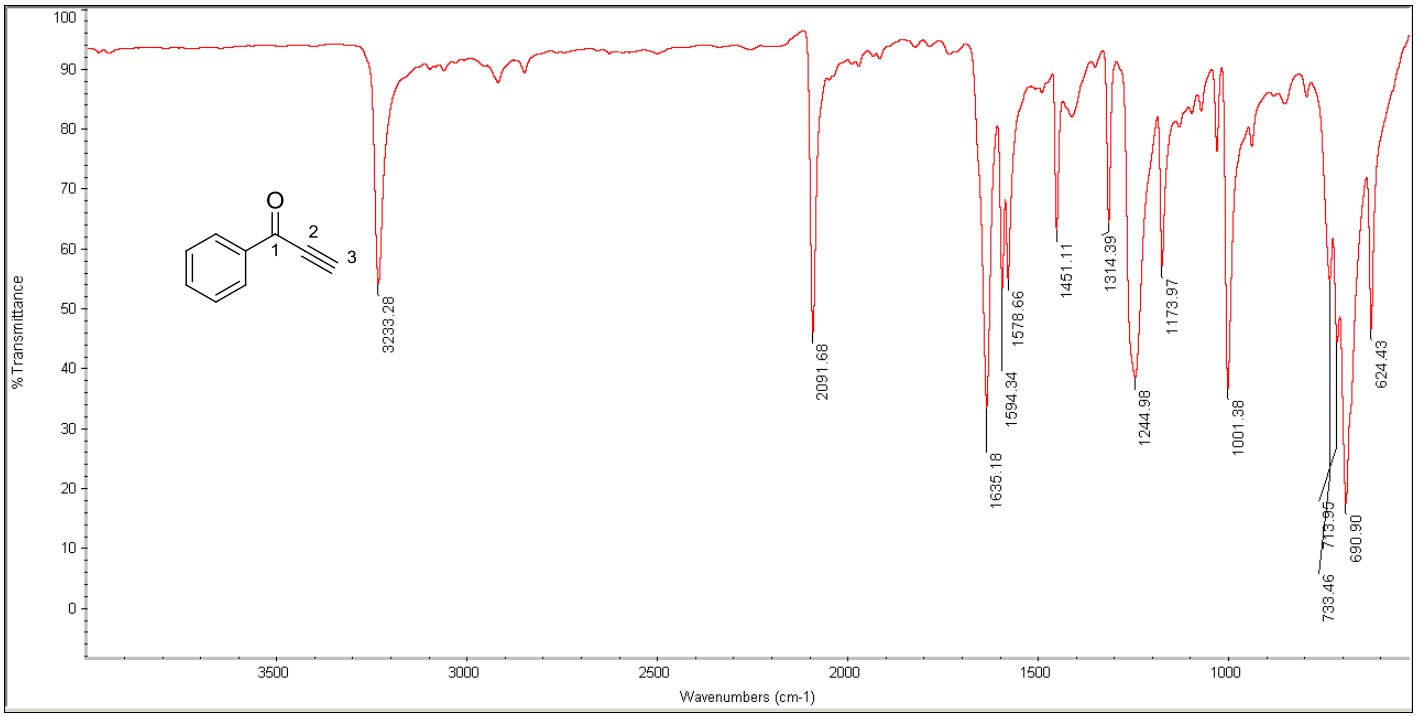

Figure A15 IR spectrum of compound **108**

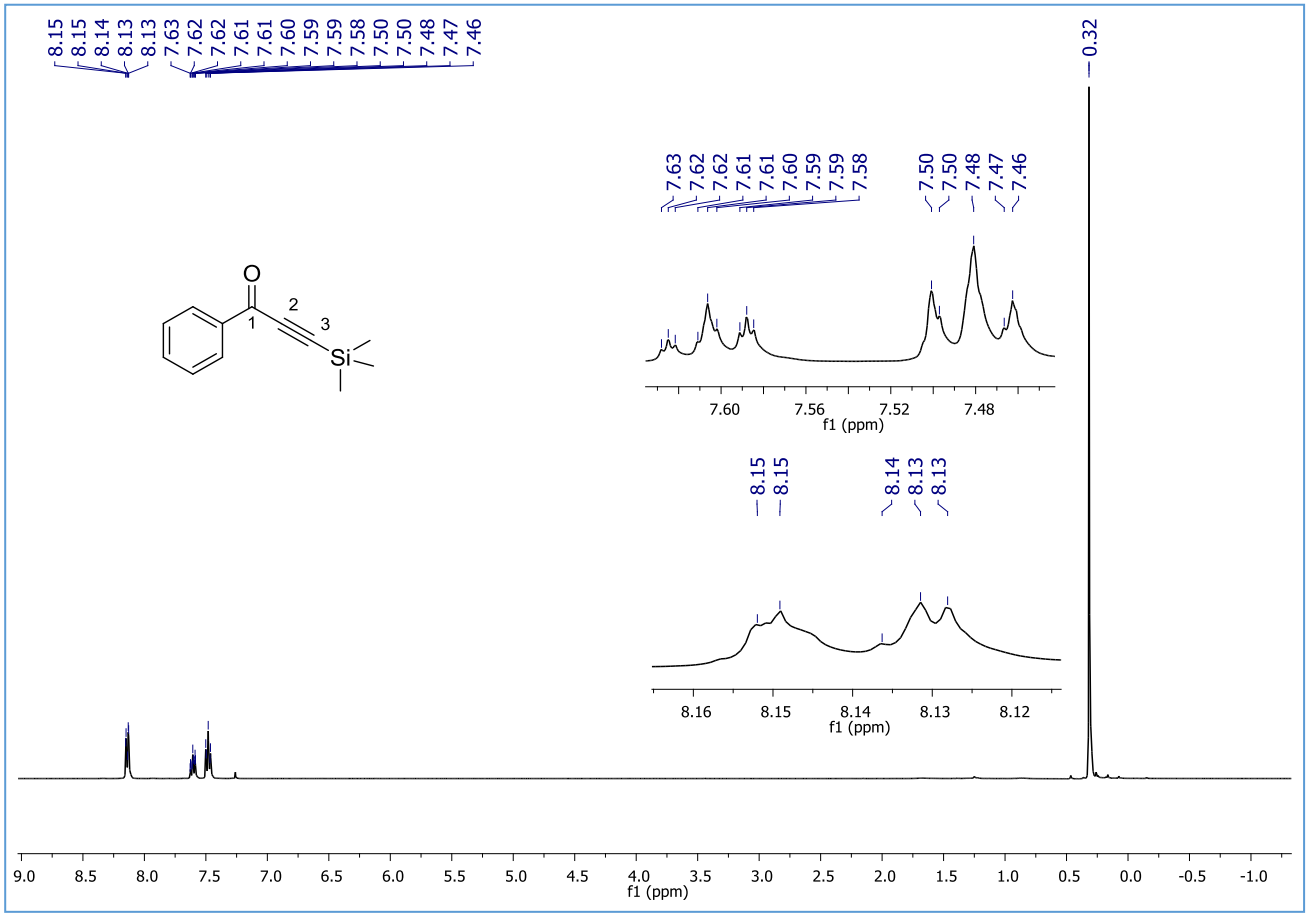

Figure A16 ^{1}H NMR spectrum of compound **109**

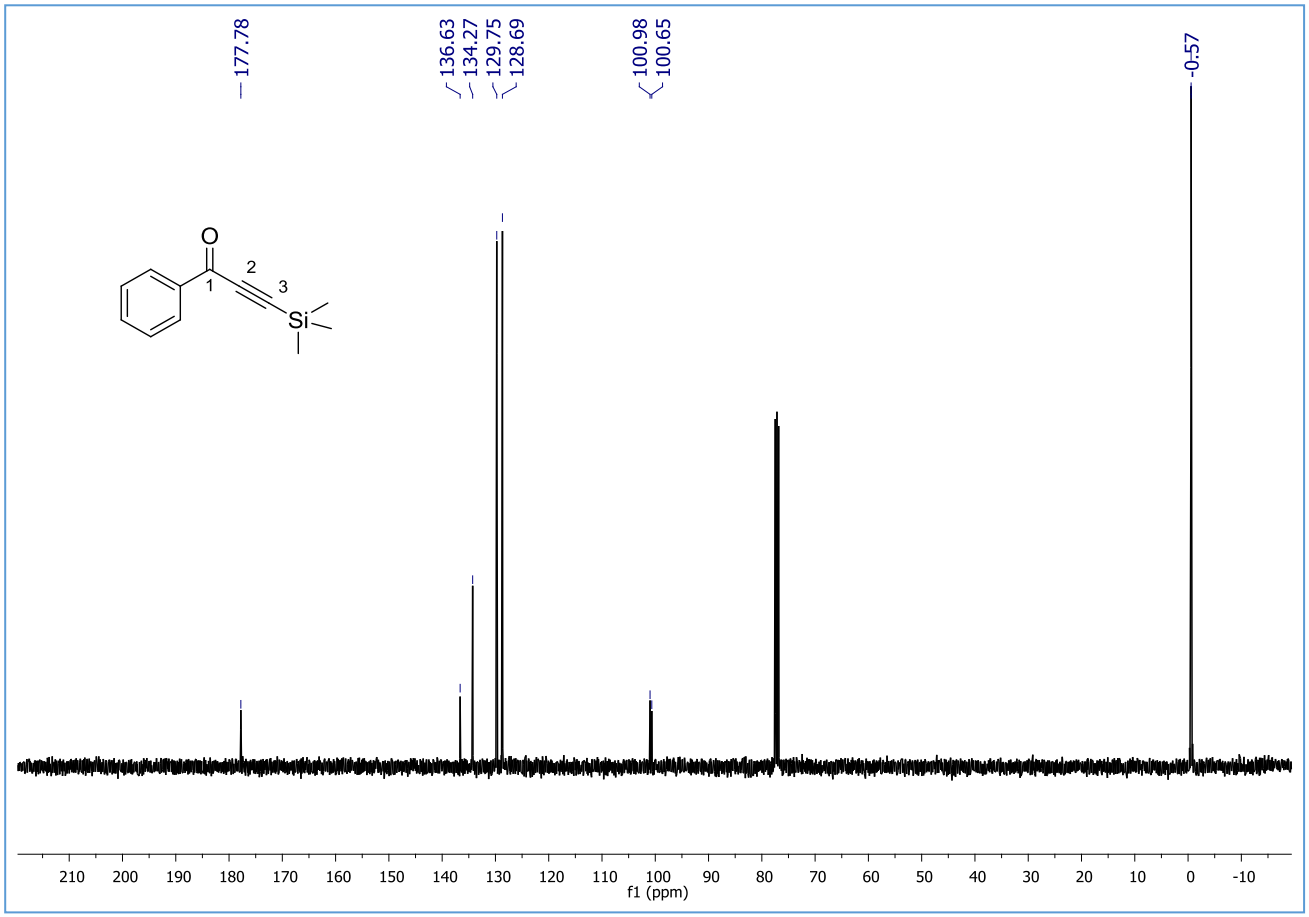

Figure A17 ^{13}C NMR spectrum of compound **109**

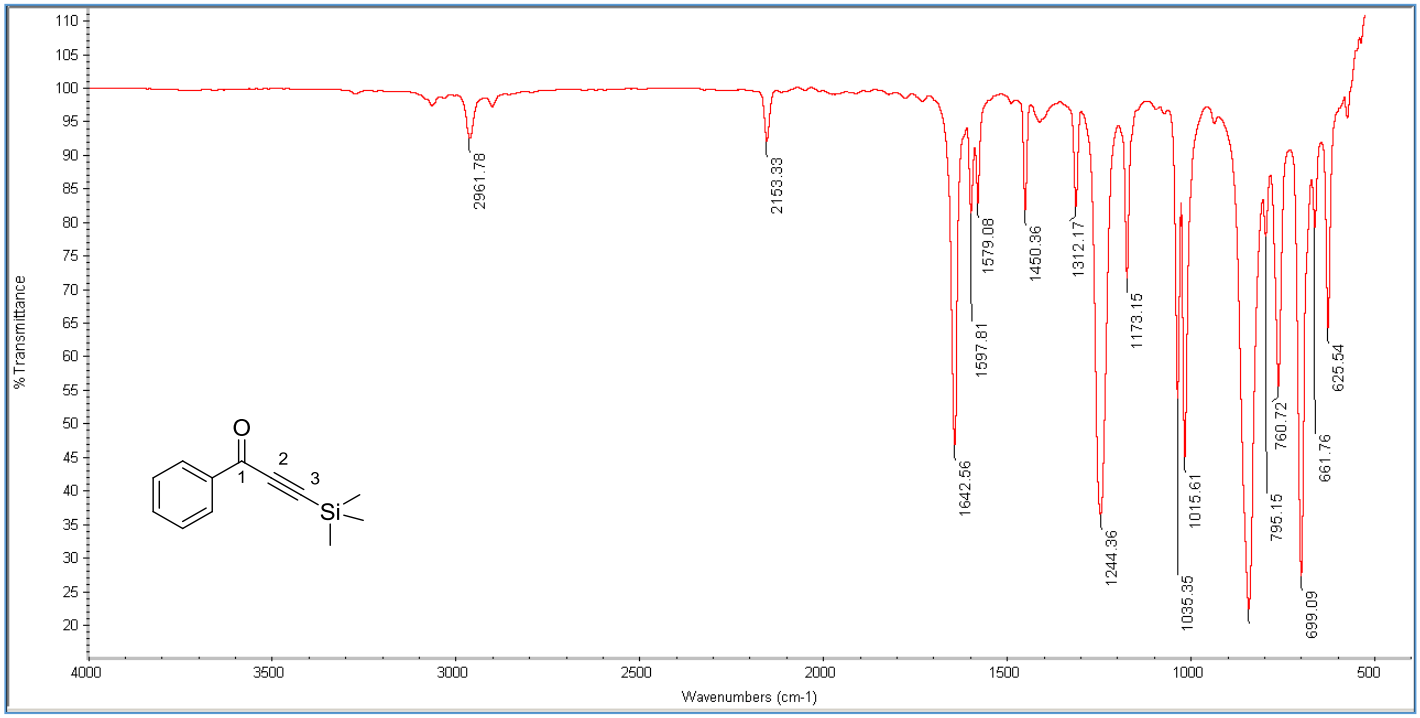

Figure A18 IR spectrum of compound **109**

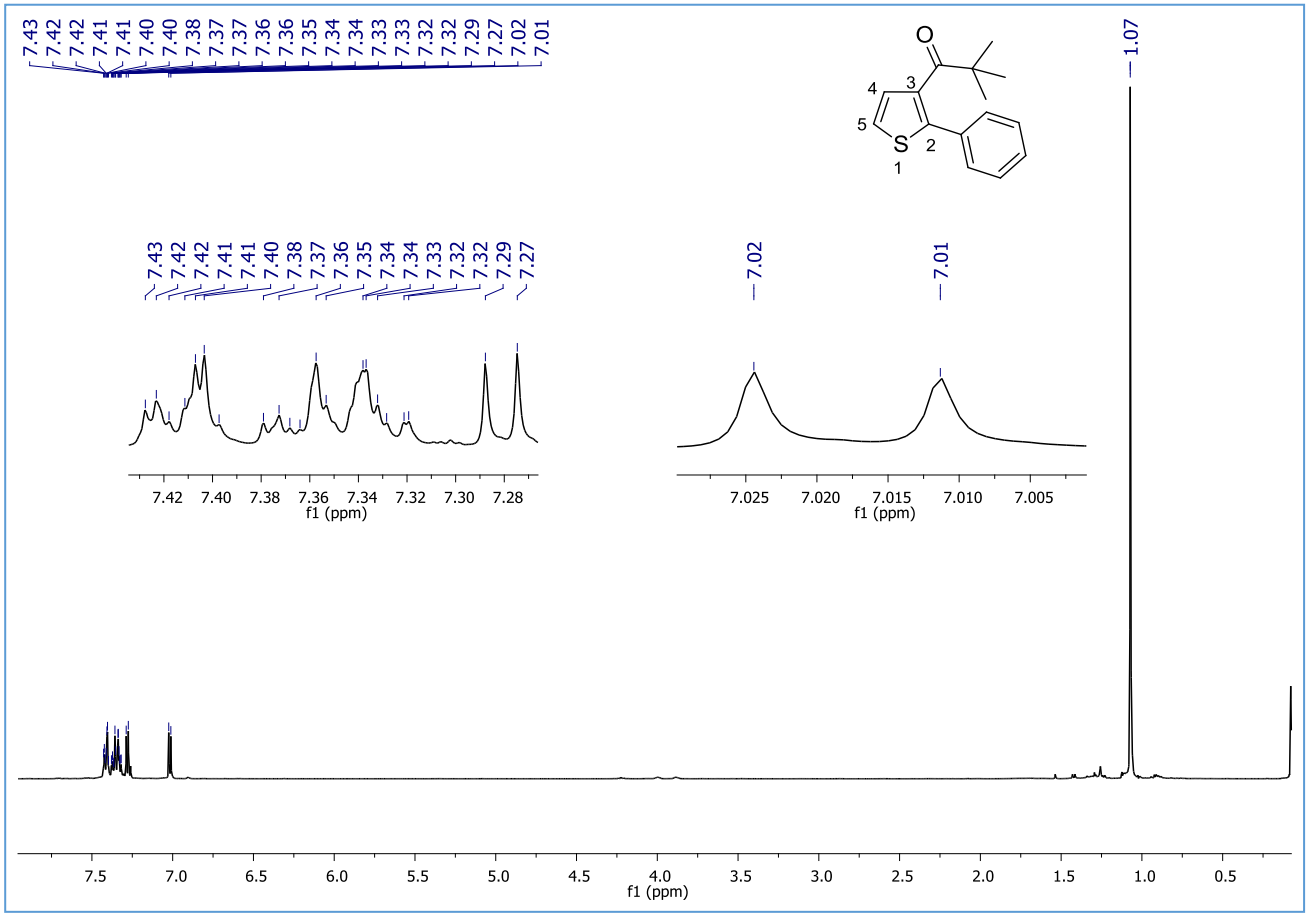

Figure A19 ^{1}H NMR spectrum of compound **110**

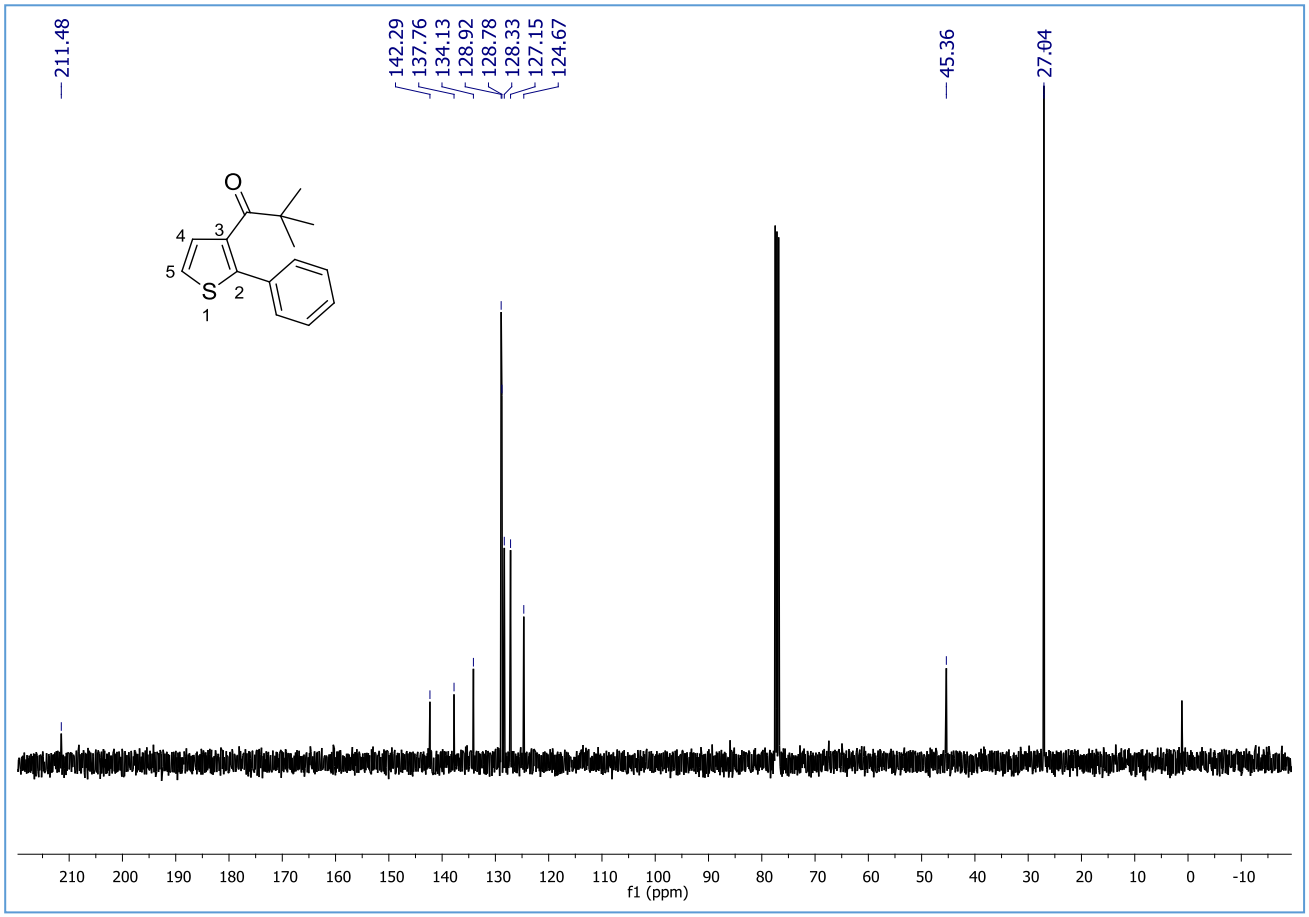

Figure A20 ^{13}C NMR spectrum of compound **110**

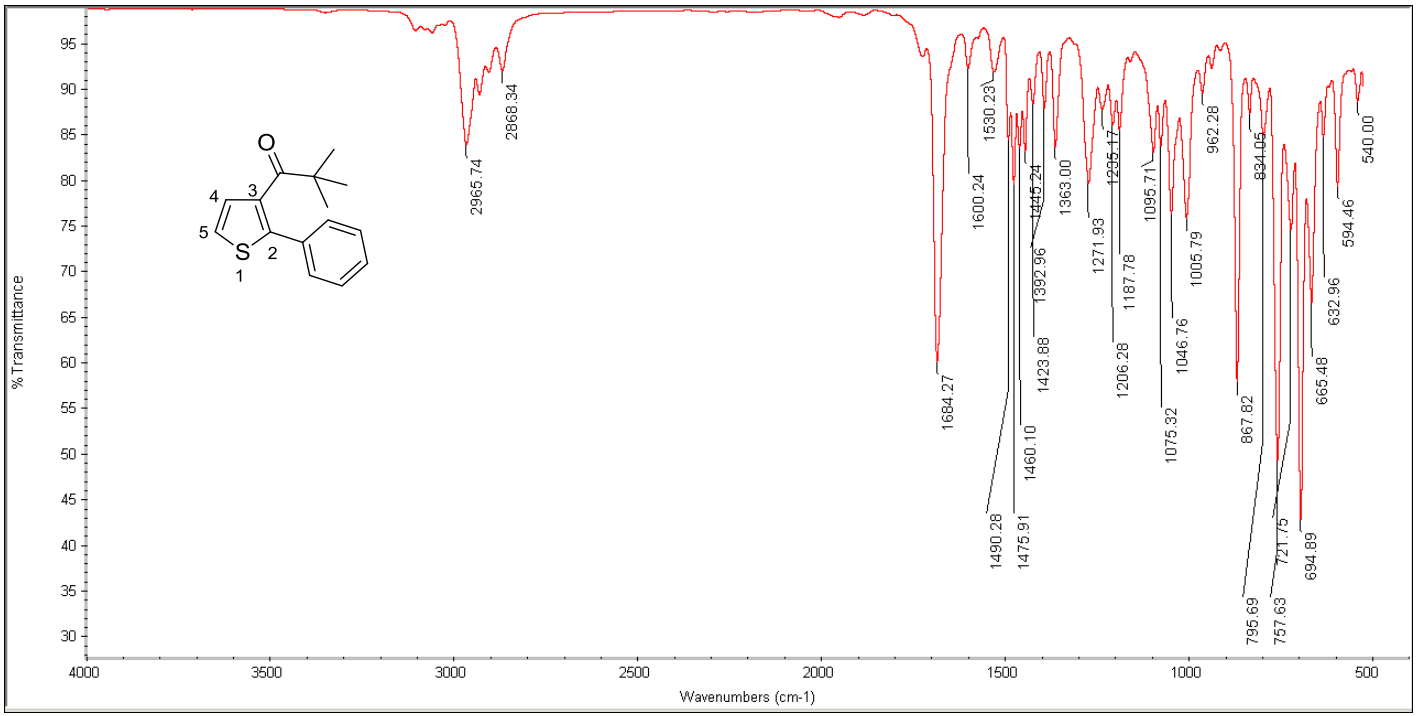

Figure A21 IR spectrum of compound **110**

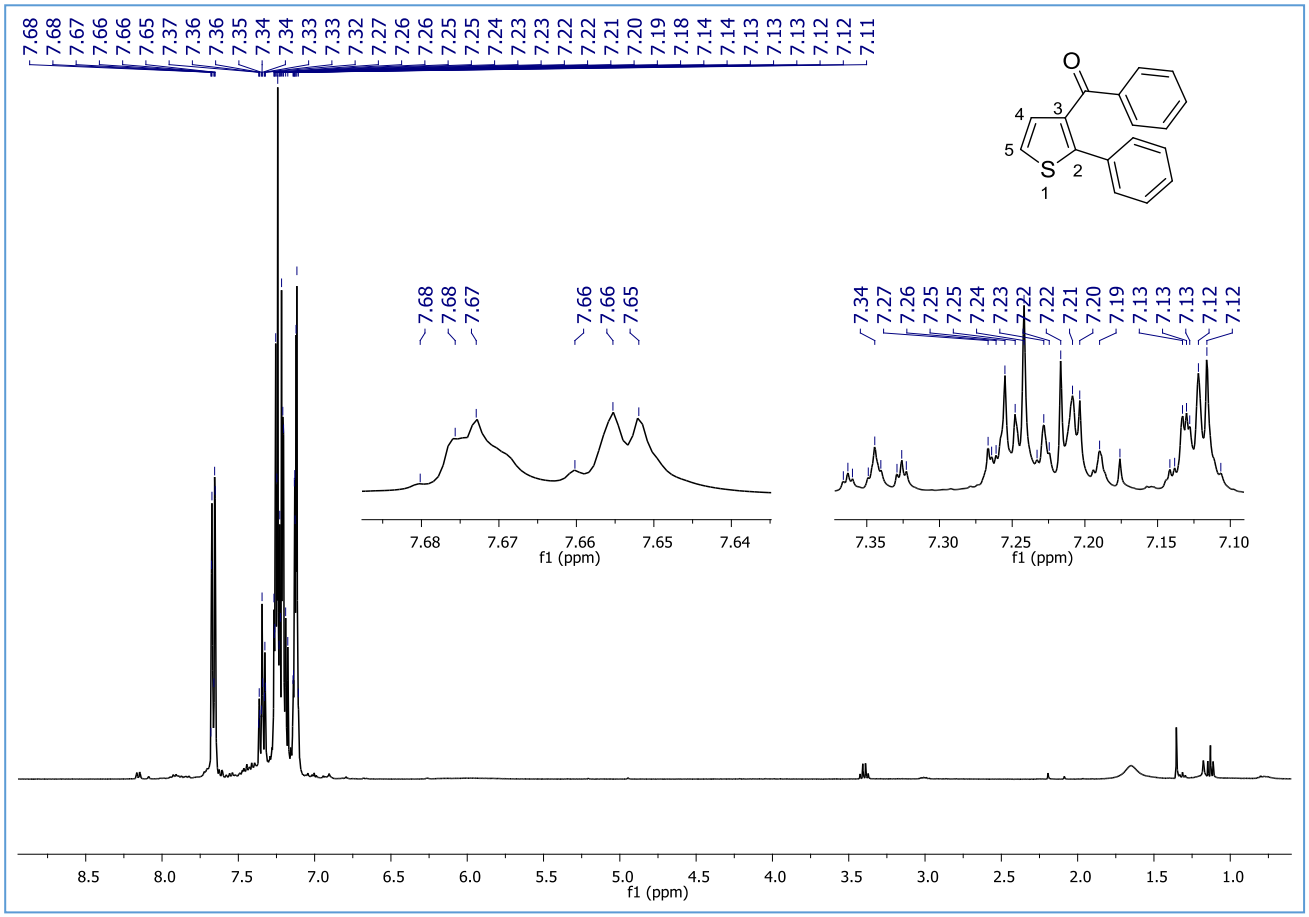

Figure A22 ^{1}H NMR spectrum of compound **111**

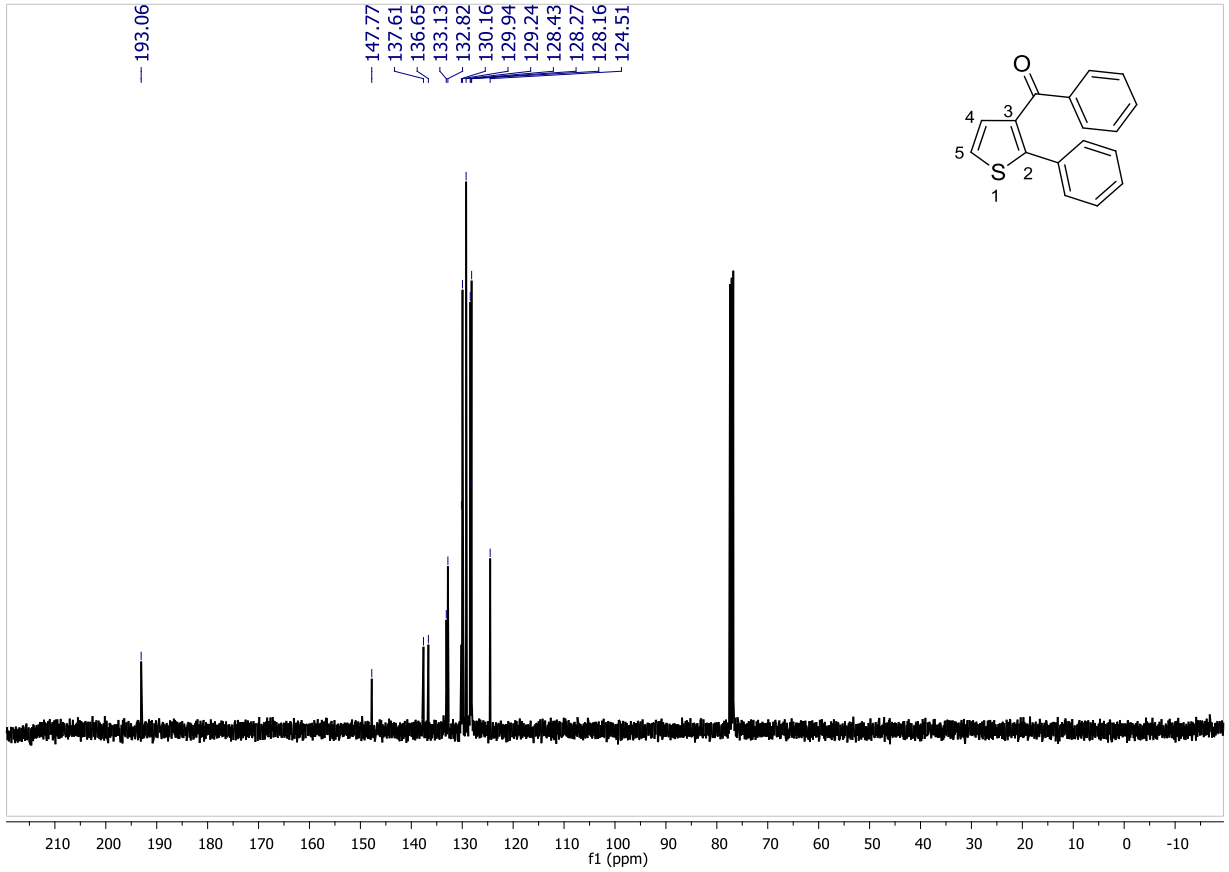

Figure A23 ^{13}C NMR spectrum of compound **111**

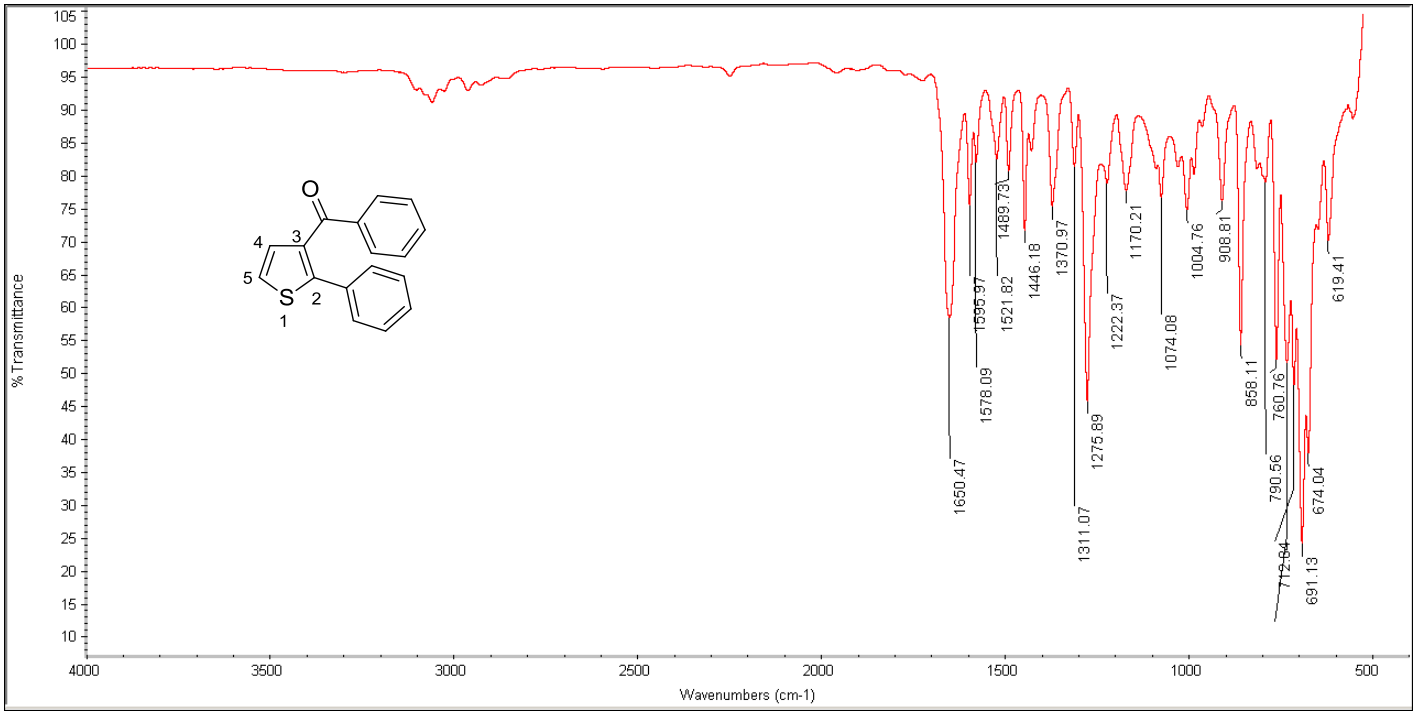

Figure A24 IR spectrum of compound **111**

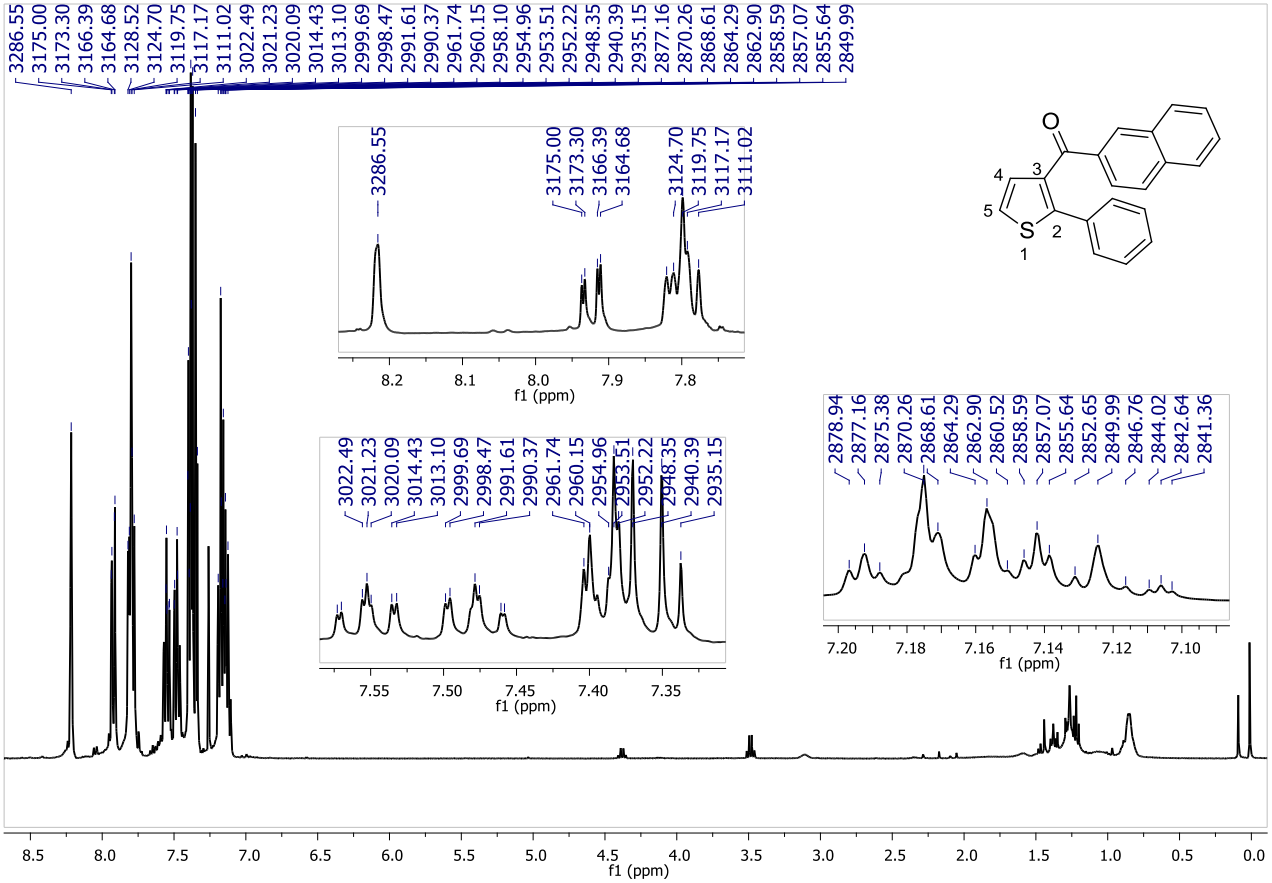

Figure A25 ^{1}H NMR spectrum of compound **112**

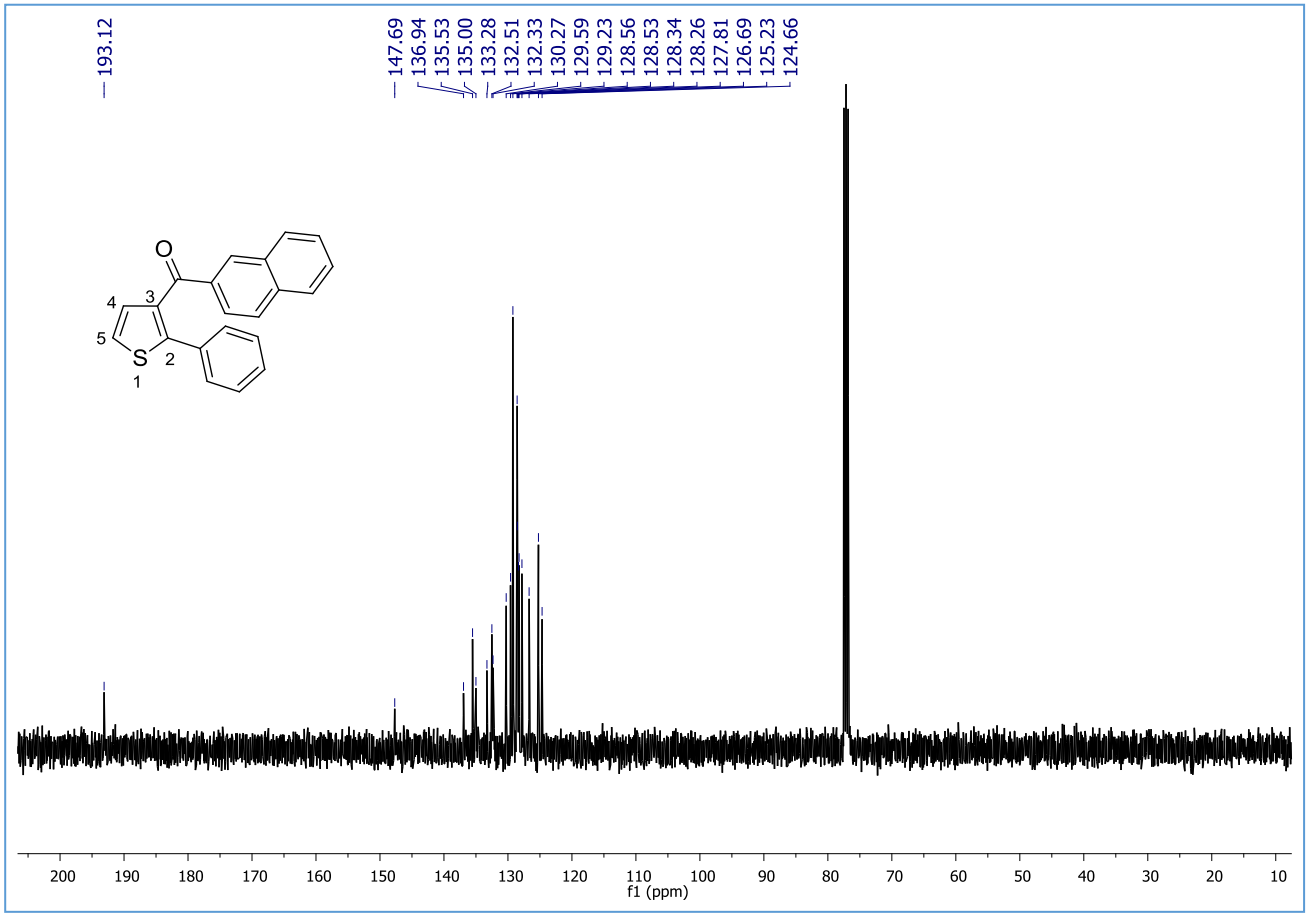

Figure A26 ^{13}C NMR spectrum of compound **112**

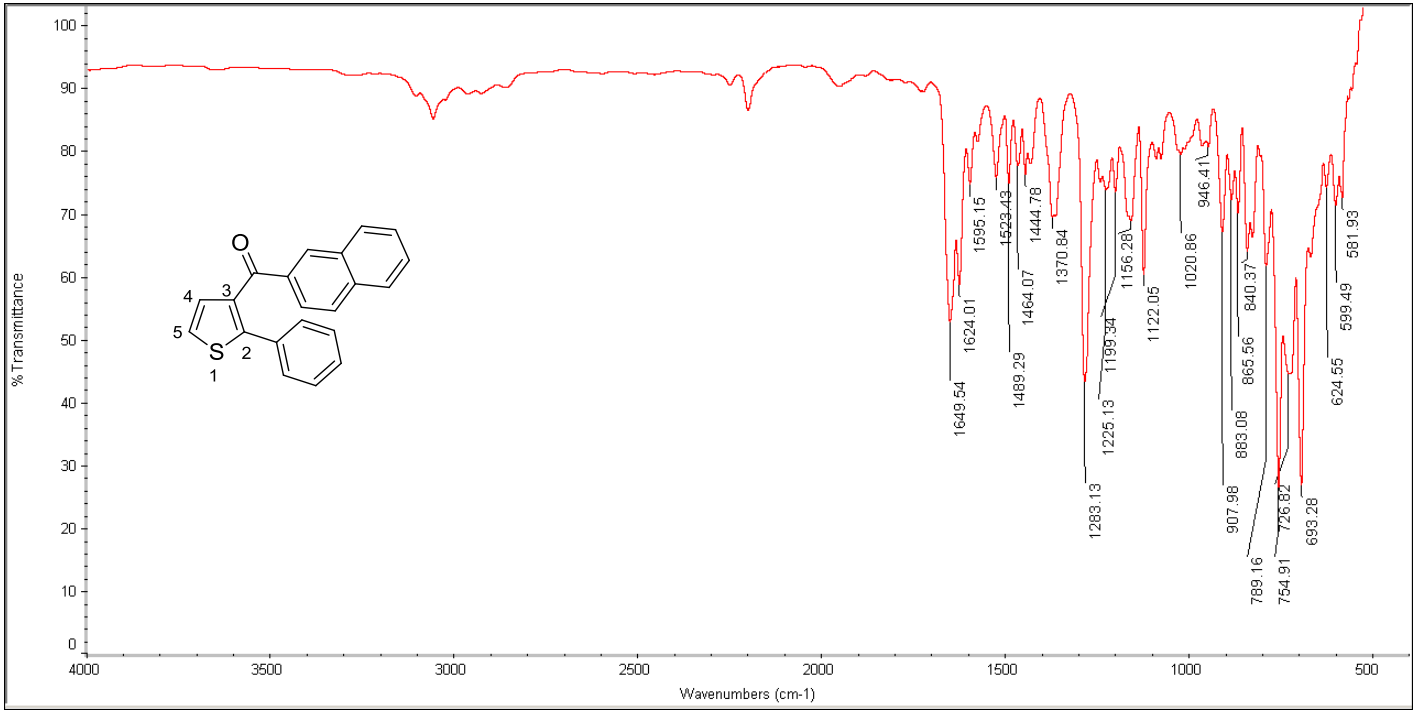

Figure A27 IR spectrum of compound **112**

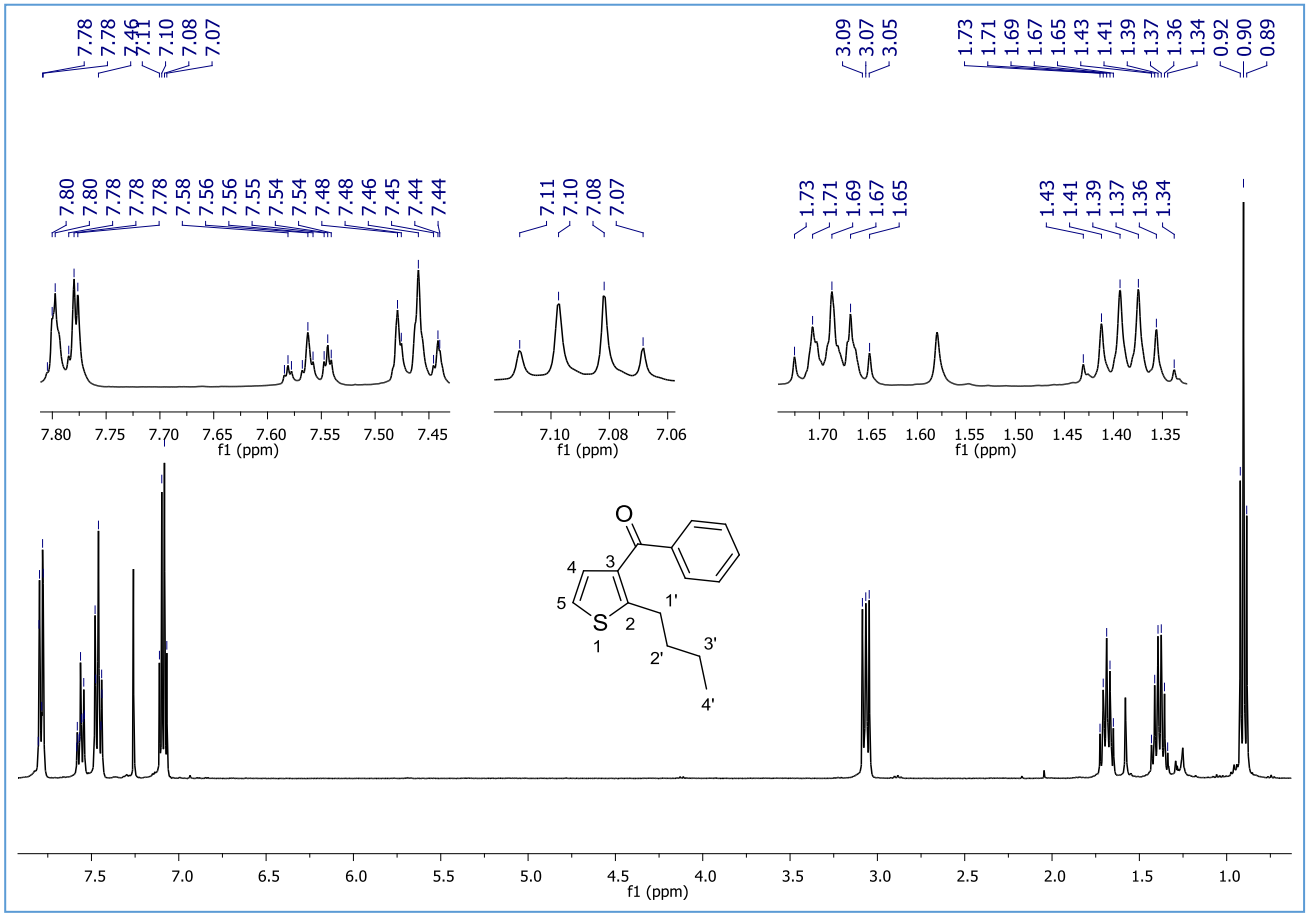

Figure A28 ^{1}H NMR spectrum of compound **113**

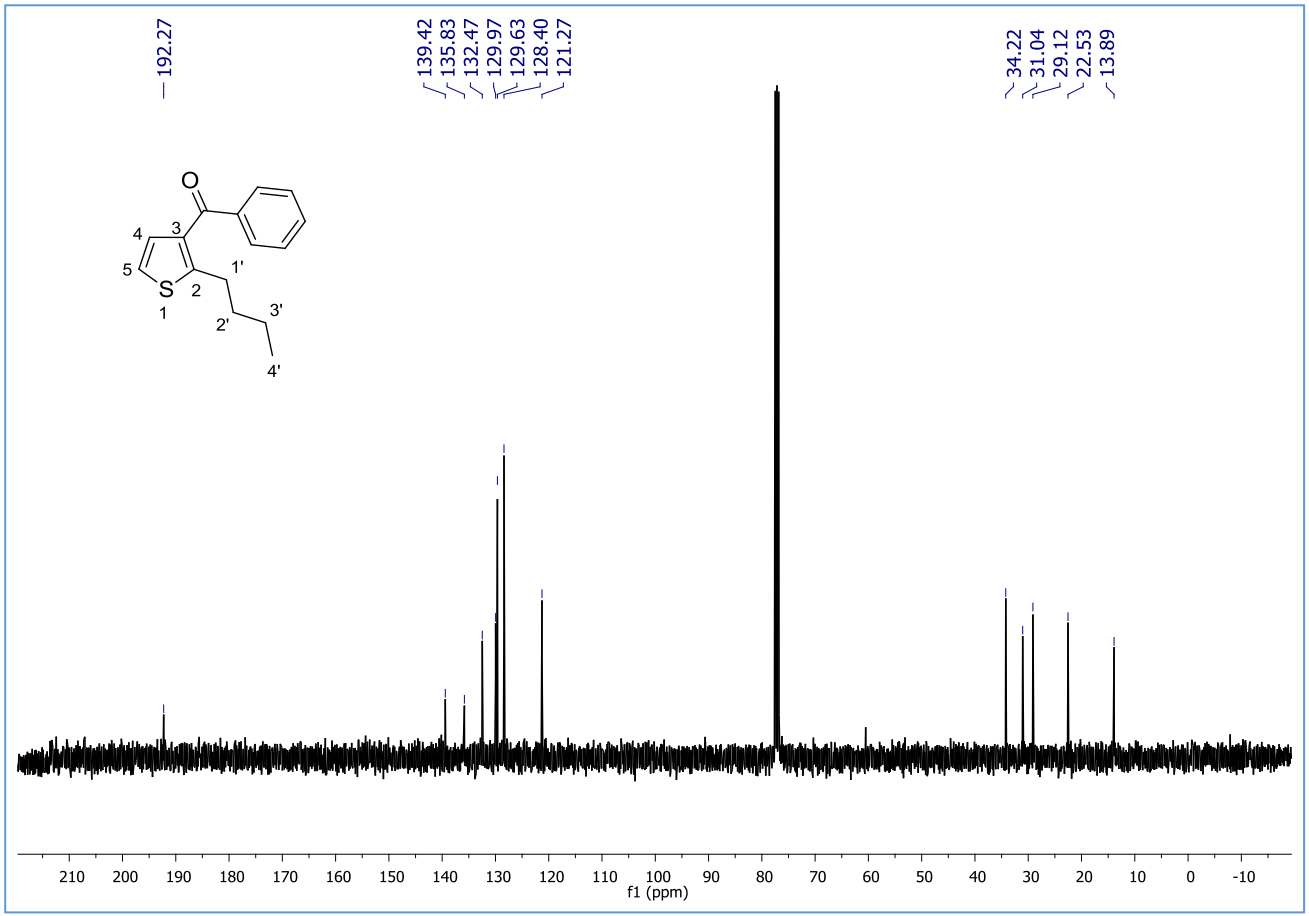

Figure A29 ^{13}C NMR spectrum of compound **113**

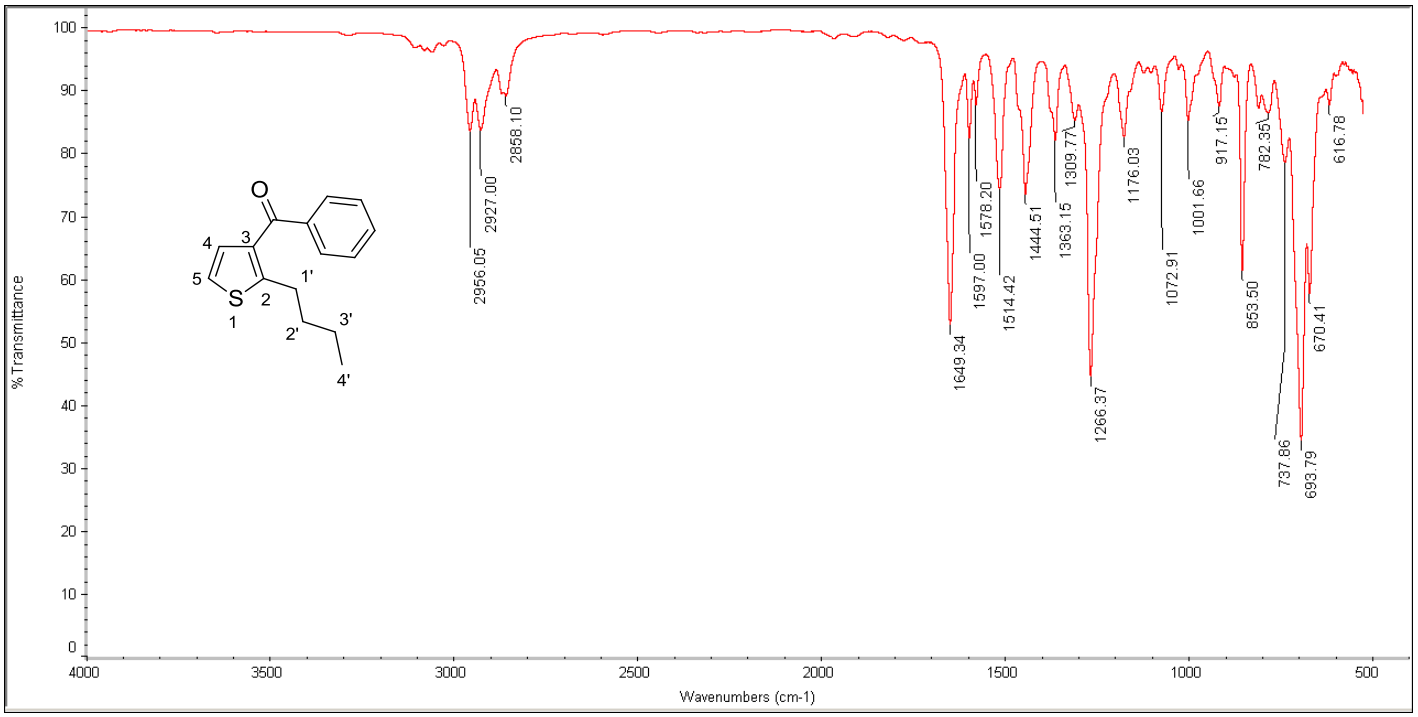

Figure A30 IR spectrum of compound **113**

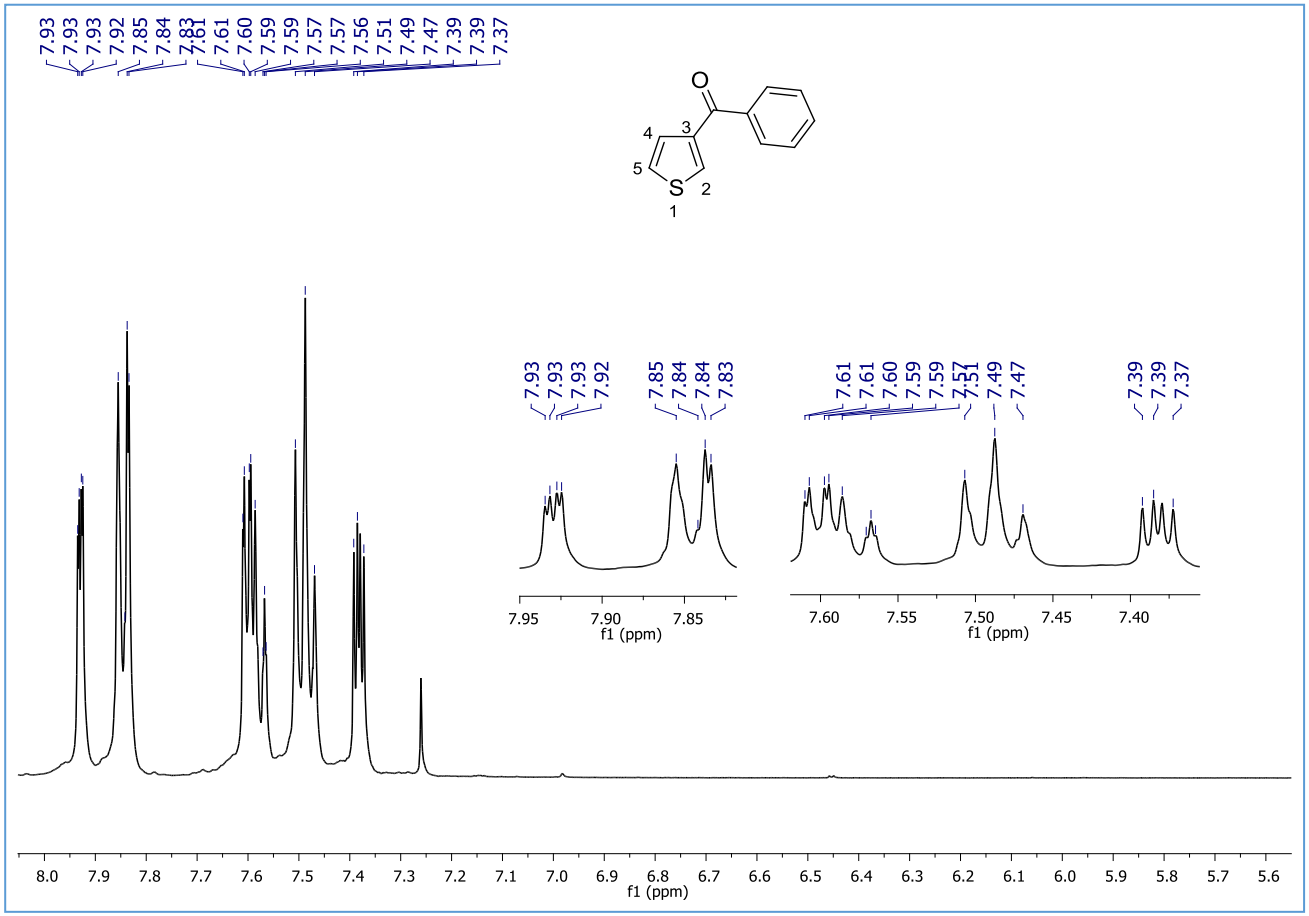

Figure A31 ^{1}H NMR spectrum of compound **114**

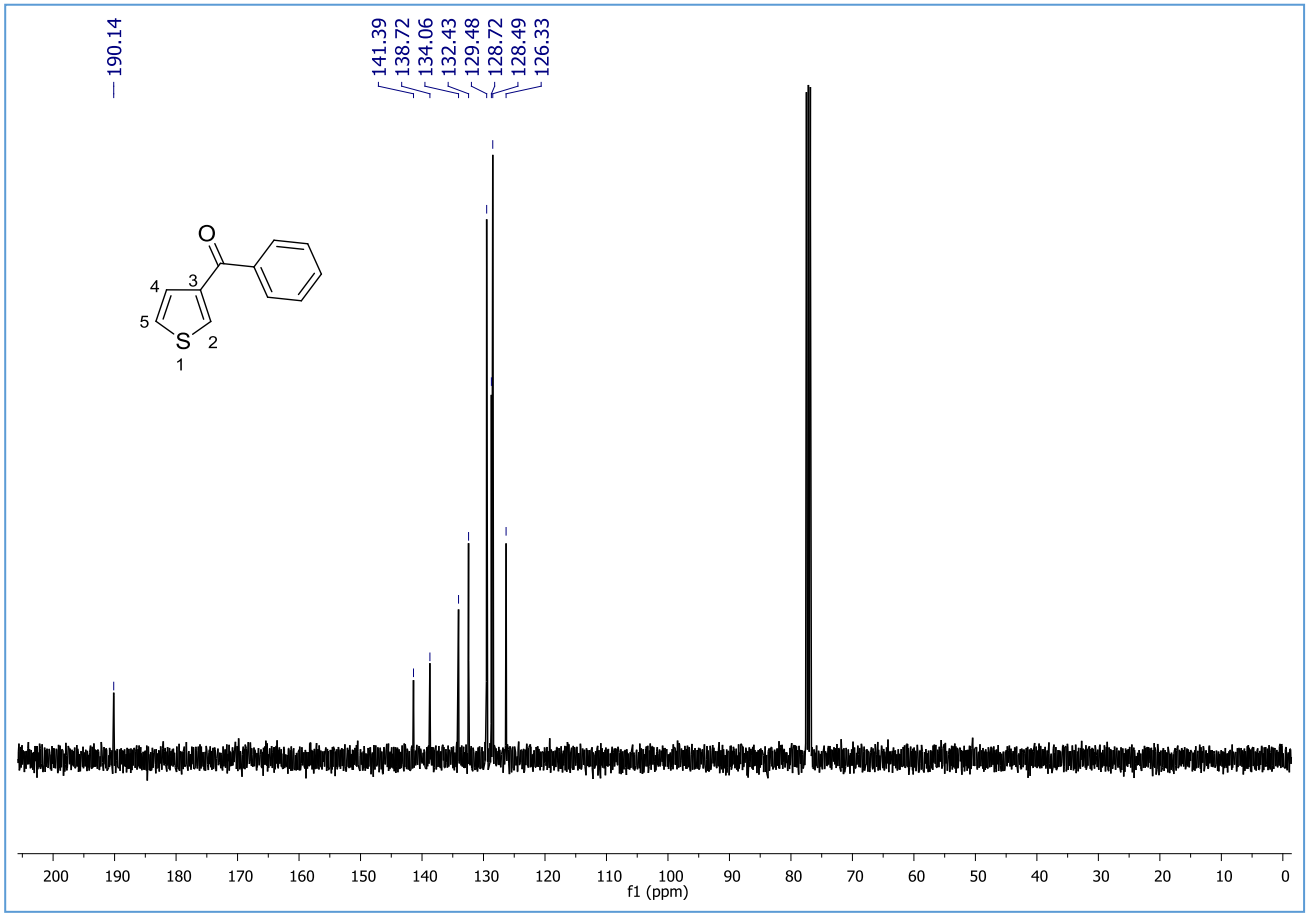

Figure A32 ^{13}C NMR spectrum of compound **114**

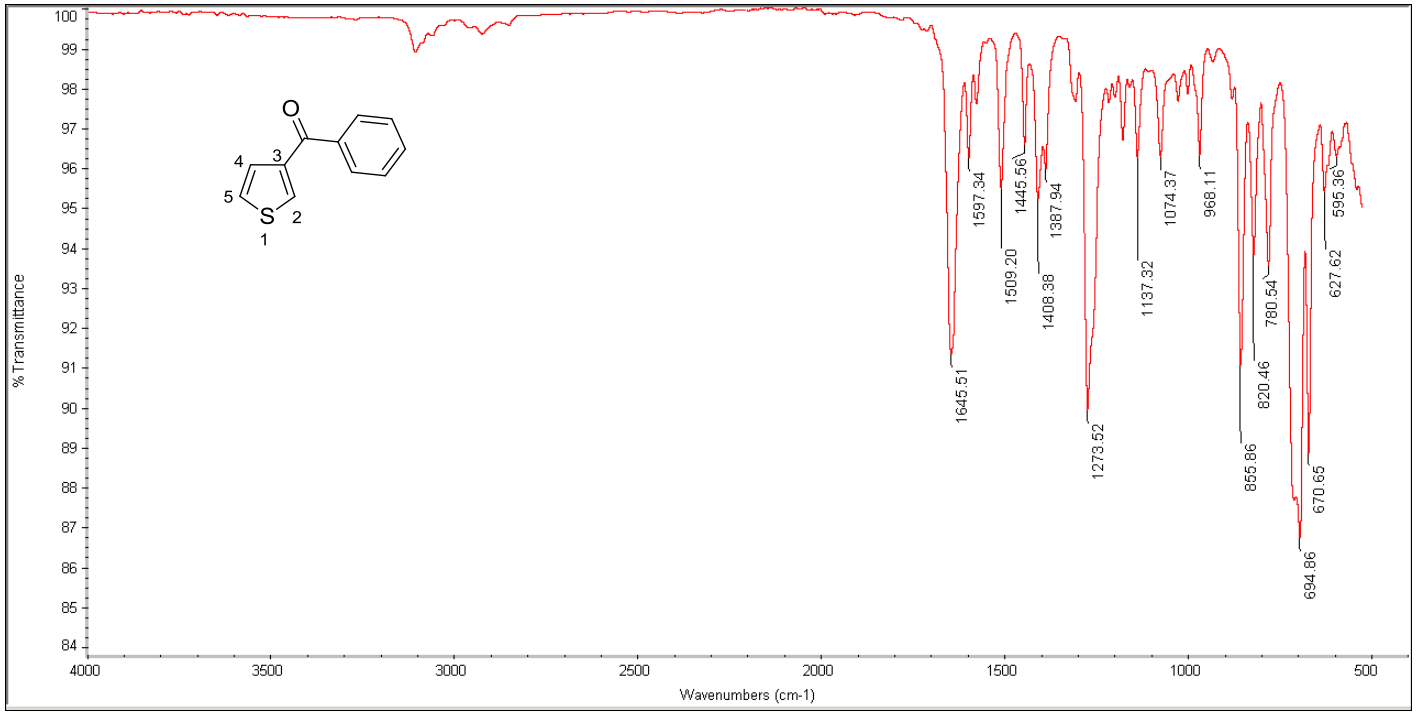

Figure A33 IR spectrum of compound **114**

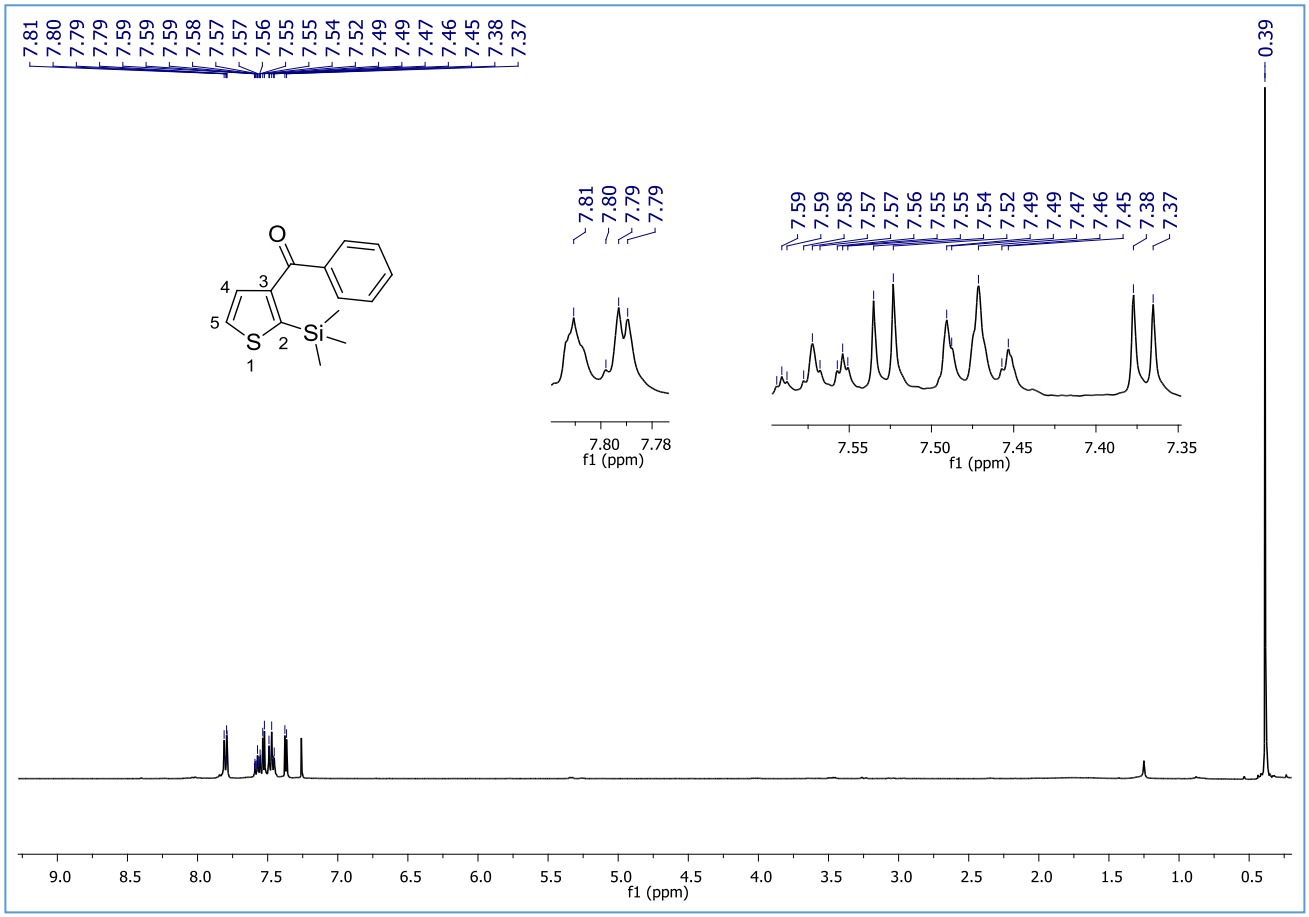

Figure A34 ^{1}H NMR spectrum of compound **115**

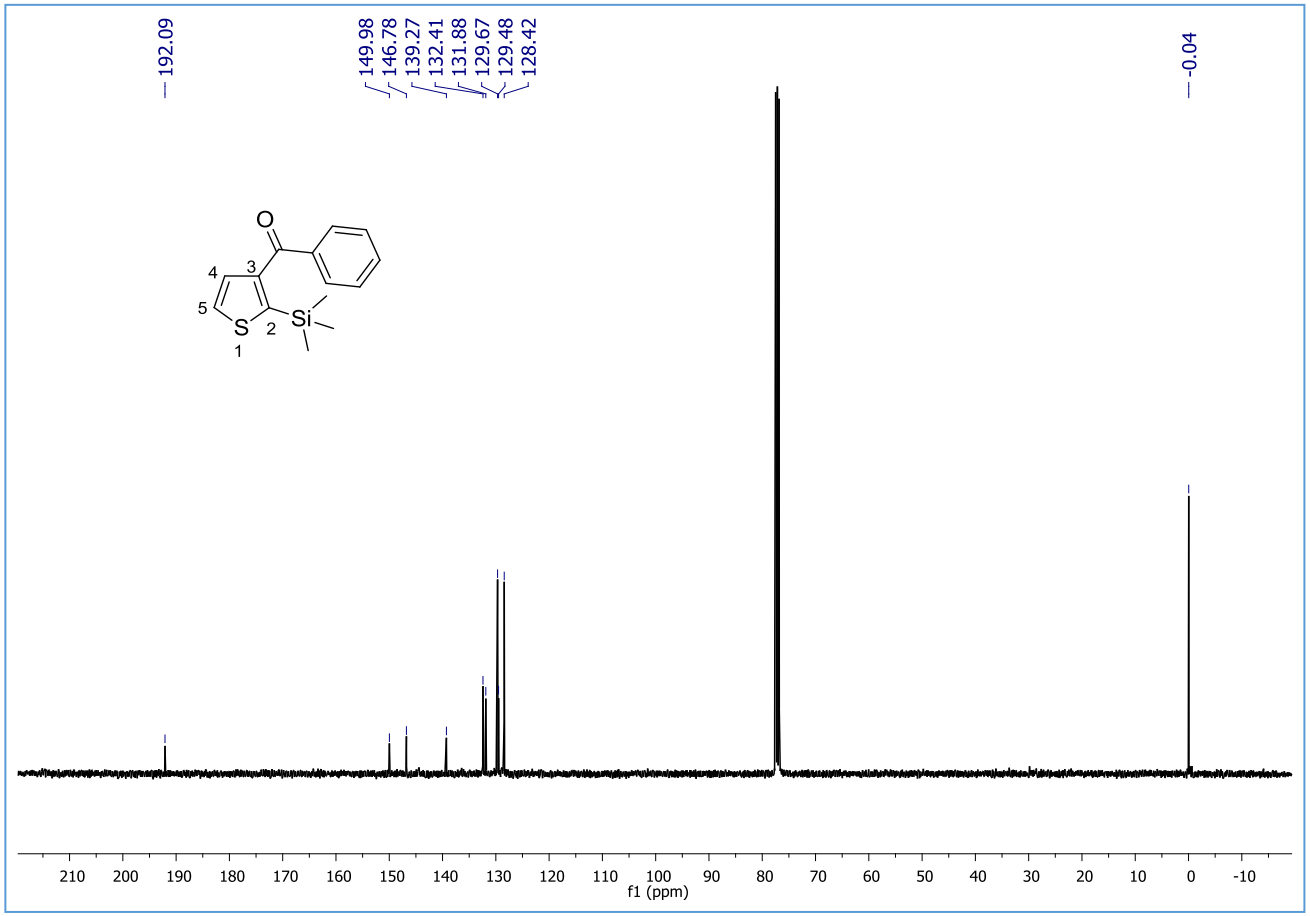

Figure A35 ^{13}C NMR spectrum of compound **115**

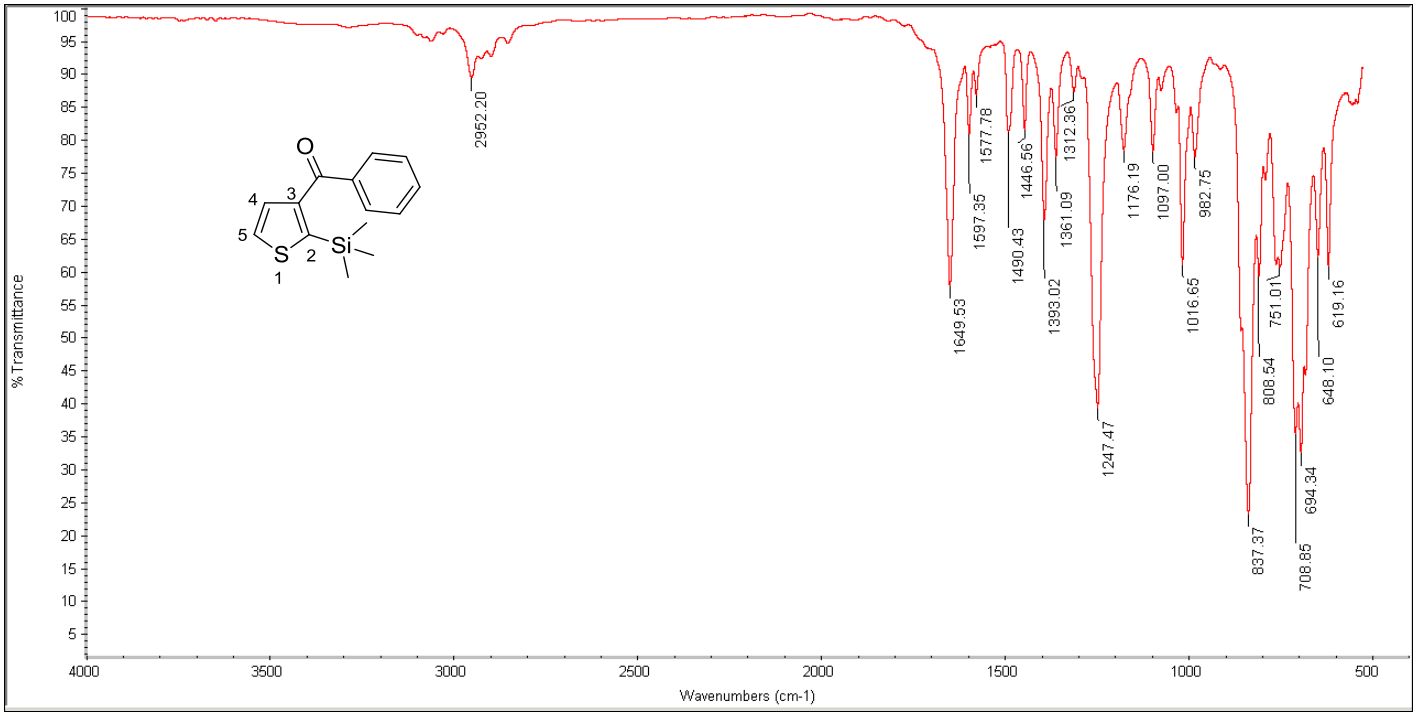

Figure A36 IR spectrum of compound **115**