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The Utilization of Microwave Irradiation in Organic Synthesis: Organotrifluoroborate and Alumina Chemistry

Arie A. Dadush
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a thesis written by Arie A. Dadush entitled "The Utilization of Microwave Irradiation in Organic Synthesis: Organotrifluoroborate and Alumina Chemistry." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

George Kabalka, Major Professor

We have read this thesis and recommend its acceptance:

Richard Pagni, Janice Musfeldt

Accepted for the Council:
Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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THE UTILIZATION OF MICROWAVE IRRADIATION IN ORGANIC SYNTHESIS: ORGANOTRIFLUOROBORATE AND ALUMINA CHEMISTRY

A Thesis
Presented for the
Master of Science
Degree

The University of Tennessee, Knoxville

Arie Amnon Dadush

May 2008

DEDICATION

This thesis is dedicated to my grandmother

Sara, Sahindi Moskovits

Who has loved and inspired me throughout my life, but is unfortunately unable to celebrate this day of academic achievement.

ACKNOWLEDGEMENTS

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ABSTRACT

The utilization of microwave irradiation in chemistry started in the 1950's. Due to operational difficulties, organic chemists only began using microwaves in the mid-1980's, when better instruments were invented. This work describe the utilization of microwaves in two areas of organic chemistry: microwave enhanced reactions using organotrifluoroborates and microwave irradiation reactions catalyzed by highly acidic alumina.

In part one, a basic understanding of microwave irradiation is presented followed by the exploration of three major reactions. The first comprises the coupling of allyl acetate and cinnamyl acetate with various substituted potassium arylvinyltrifluoroborates to produce a variety of 1,4-dienes. The second explores the effects of microwave irradiation on the synthesis of stilbenes which led to new and efficient methods to prepare a variety of substituted stilbenes. The third study explores an efficient synthetic method for the allylation of various substituted potassium alkenyltrifluoroborates with allyl halides.

In part two, three major topics are discussed. The first involves the activation of alumina via microwave irradiation. The second involves the stereo- and regioselectivity of microwave enhanced Diels-Alder reactions. The third chapter describes the Claisen and Fries rearrangement reactions under microwave conditions.

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LIST OF SYMBOLS AND ABBREVIATIONS

Symbol	Description
°C	Degree Celsius
γ	Gamma

Abbreviation	Description
3D	Three dimension
BX_3	Boron trihalides
BF_3K	Potassium trifluoroborate
n-BuLi	*n*- Butyllithium
cm	Centimeter
$CDCl_3$	Chloroform-*d*
CP	Cyclopentadiene
D-A	Diels-Alder
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMM	Dimethyl maleate
eq	Equivalent
g	Grams
GC	Gas Chromatography
GHz	Gigahertz
H_2O	Water
h	Hours
Hz	Hertz
HOMO	Highest occupied molecular orbital

IP	Isoprene
IR	Infrared spectrometer
J	Proton-proton coupling constant
KHF_2	Potassium hydrogen difluoride
L.A	Lewis acid
LUMO	Lowest occupied molecular orbital
m	Meter
MA	Methyl acrylate
MHz	Hertz
mL	Milliliter
min	Minute
mmol	Millimoles
NMR	Nuclear magnetic resonance
^{1}H nmr	Proton nuclear magnetic resonance
^{13}C nmr	Carbon-13 nuclear magnetic resonance
^{11}B nmr	Boron-11 nuclear magnetic resonance
MO	Molecular orbital theory
mol	Moles
M	Molarity (mols/L)
MS	Mass Spectroscopy
pK_a	The negative logarithm of the acid dissociation constant
$Pd(dppf)Cl_2$	1,1-Bis(diphenylphosphino)dichoropalladium(II)
$Pd(OAc)_2$	Palladium acetate
sec	Second
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
W	Watt

Part One

MICROWAVE ENHANCED REACTIONS USING ORGANOTRIFLUOROBORATES

CHAPTER 1

MICROWAVE THEORY

1.1.1 Introduction

The utilization of microwave irradiation in chemistry started in the 1950's.[1,2] Organic chemists began using microwaves in the mid-1980's. Difficulties related to rapid, uncontrolled heating of organic solvents resulted in complications such as violent explosions under closed vessel conditions.[3] In order to eliminate some of the problems encountered using solvents, a new approach involving solvent free and dry media reactions was adopted during the mid-1990's.[5] Even though solvent free reactions have gained in popularity, a few key problems remained. These include inefficient mixing, non-uniform heating, and temperature control. These problems were overcome when better, more accurate instruments were invented that allowed the user to control temperature, pressure, and stirring. The first "successful" paper reporting the use of microwaves in organic synthesis appeared in 1986 by the Gedye group who presented four types of reactions: hydrolysis of benzamide (fig 1.1.1), permanganate oxidation of toluene, esterification of benzoic acid, and S_N2 reaction between sodium 4-cyanophenoxide and benzyl chloride.[4] Microwaves, in general, enhance reaction rates, are more energy efficient, and can lead to higher product yields.

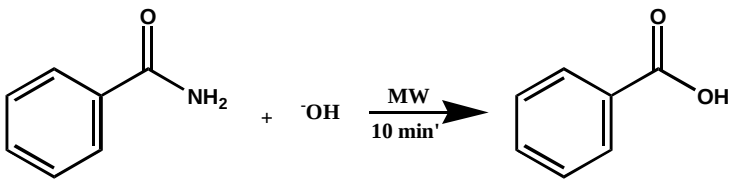
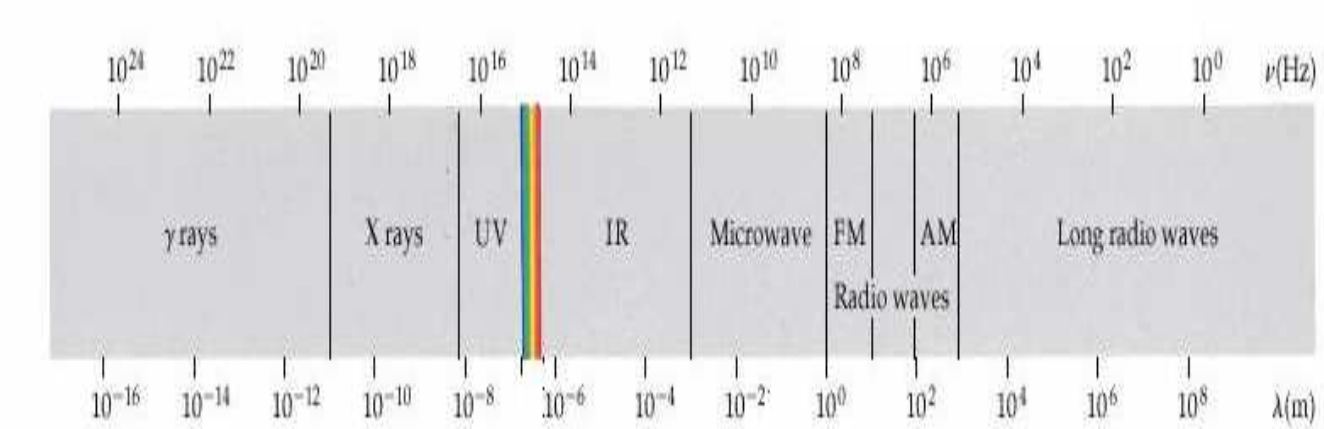


Fig 1.1.1 One of the first reactions using MW irradiation.

1.1.2 Microwave Theory

Microwaves are electromagnetic waves with a frequency of 0.3 to 300 GHz (corresponding to wavelengths of 1 m to 1mm). The microwave region in the electromagnetic spectrum lies between radiowaves and infrared (fig1.1.2a). Today, most microwave instruments (both domestic microwave ovens and laboratory instruments) operate at a frequency of 2.45 GHz (wavelength of 12.25 cm). There are two main reasons for using this wavelength: to avoid interference with cellular phones and other telecommunication devices and because this frequency is optimal for the alignment of the substance matrix with the applied field. Microwaves, which travel at the speed of light, consist of oscillating electric and magnetic fields known as photons (fig1.1.2b). Microwaves obey the laws of optic. Depending on the type of material, they can be transmitted, absorbed, or reflected. The energy generated by the microwave photon at the frequency of 2.45 GHz is relatively low (1.6×10^{-3} electron volts). This energy level is much lower than the energy level of a covalent or hydrogen bond (0.04 to 0.44 eV) which indicates that microwave energy at this frequency can not cleave these bonds. Therefore, microwaves can not induce chemical reactions by direct absorption of electromagnetic energy, as opposed to ultraviolet and visible radiation.[6] If this is the case, how does microwave irradiation affect the reaction? The answer lies in the efficient heating of the reaction by "microwave dielectric heating" or coupling effects.[7] Dielectric heating depends on the ability of the material (solvent or reagent) to absorb the electric component of microwave energy and convert it to heat.[8,9] This component can generate heat within the molecule by two main mechanisms: dipolar polarization and ionic conduction. The dipolar polarization mechanism can be defined as the interaction of the molecular matrix with the electric field component.[10] A polar molecule can generate heat using microwave irradiation due to the dipole moment. When molecules (dipoles or ions) are exposed to microwave irradiation, they will try to align themselves to the applied electric field vector. When the applied field oscillates, the dipole field will attempt to realign itself with the alternating electric field. As a result of this oscillation, energy will be lost in a form of heat through molecular friction and dielectric loss.[3] As mentioned above, in the frequency of 2.45 GHz, the field is between two extremes.



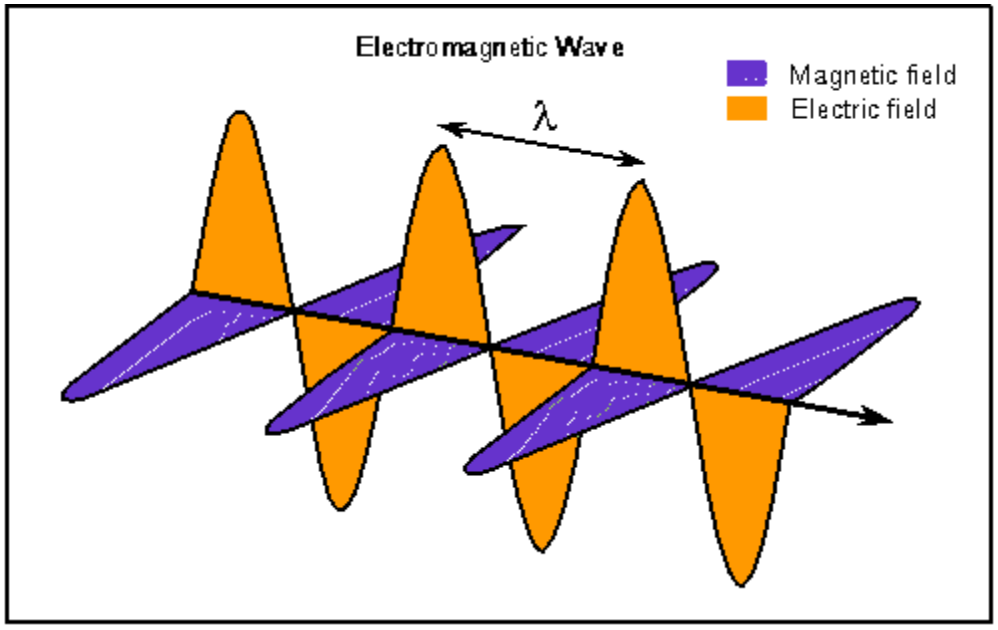


Fig 1.1.2a (on the top) The electromagnetic spectrum and 1.1.2b (bottom) The electromagnetic wave

The first extreme is high-frequency where the dipole does not have enough time to realign, and the second is low-frequency where the dipole realigns too fast with the applied field (in both instances, no heating takes place). Lying between these two extremes, irradiation at 2.45 GHz allows molecules to generate a phase difference between the orientation of the field and that of the dipole. This results in energy loss (heating) from the dipole by collisions and molecular friction. It is important to note that the ability of the matrix to align itself with the frequency of the applied field is directly related to the amount of heat generated by this process. The ability of a specific molecule or matrix to convert electromagnetic energy into heat (for efficient absorption and rapid heating) depends on the dielectric properties and can be determined by a term know as "loss tangent" which can be calculated.[11] The second mechanism involved in the "microwave dielectric heating" effect is the ionic conduction mechanism. This mechanism is far stronger than that of the dielectric heating mechanism, but only applies for reactions carried out in solvent systems. When particles such as ions dissolve in a medium and are exposed to microwave irradiation, they oscillate and collide with each other resulting in formation of heat.

1.1.3 Microwave Versus Thermal Heating.

Chemists traditionally use thermal/conductive energy heat sources to synthesize materials.[12] These methods are slow and inefficient when compared to microwave heating. One reason that traditional heating is ineffective is due to the thermal conductivity and convection currents of materials that must be penetrated in order to reach the reacting molecule. For example, the temperature of a reaction flask is generally higher than that of the reaction mixture. Another problem that can arise involves temperature gradients that can develop within the sample. A temperature gradient can cause local overheating which in turn leads to local decomposition. The utilization of microwave energy is quite different than thermal heating. In microwave irradiation, there

is direct coupling of microwave energy (with the molecule in the reaction mixture), the result is efficient internal heating and faster reaction rates.[13] Most microwave reaction vessels are transparent to microwave irradiation. There is no energy loss due to the vessel, and the temperature gradient is inverted compared to thermal heating.

1.1.4 Microwave Effects

Even though a large number of publications discuss microwave irradiation, the exact reasons for microwave enhancement of chemical processes still elude scientists.[14] There are speculations related to the existence of "microwave effects." These effects can be a result of specific wave-material interactions that lead to an increase in the pre-exponential factor in the Arrhenius law (the rate constant of a chemical reaction depends on the temperature and activation energy) or orientation effects of polar species in an electromagnetic field that result in a decrease in the activation energy.[15] In layman terms, enhancements in thermal/kinetic effects will result in high reaction temperatures that are reached when polar molecules are irradiated by microwaves. The dielectric heating mechanism mentioned in section 1.1.2 can also cause "microwave effects". This microwave effect can be defined as "acceleration of chemical transformation in a microwave field that can not be achieved or duplicated by conventional heating, but which is essentially a thermal effect."[3] This can result in the superheating of solvents at atmospheric pressure due to the rapid absorption of microwave irradiation by the solvent. For example, ethylene glycol, which has high "loss tangent" (high microwave absorbing solvent), can be rapidly heated to temperatures above its boiling point. Another factor is the non-thermal microwave effect. This effect can be described as an a rate acceleration that can not be rationalized by the two explanations noted previously. An example of this phenomenon follows. As mentioned in section 1.1.2, the frequency for a typical microwave is 2.45 GHz. The time period of microwave radiation is on the order of nanoseconds while molecular relaxation in liquid states during cooling by conduction of water, for example, is on the order of microseconds.[16] The energy input (microwave irradiation), and the output (molecular vibration and mass transport) result in a very fast

accumulation of energy. In other words, in a coupled system, the constant energy accumulation far exceeds the rate at which energy can be dissipated by conventional modes of cooling.

1.1.5 Medium Effects

The use of polar solvents (medium effect) is important in microwave reactions.[17,18] As noted in section 1.1.4, there are major interactions between microwaves and polar solvent molecules. This interaction results in energy formation and can induce the reaction, while the specific microwave effects on the reactants can be masked by the solvent absorption.[19] When using solvents with high "lost tangent" (such as ethylene glycol with "lost tangent" of 1.350) the conversion of microwave energy to heat is high. On the other hand, if a non-polar solvent is used (such as toluene with a "lost tangent" of 0.040), a specific absorption by the reactants will occur because the solvent is transparent to microwave irradiation. In cases where the reactants are polar, energy transfers can occur from the reactants to the solvents.[20,21] In some cases a solvent free reaction using microwave effect can also occur (in fact, under such conditions, a safer, cost effective, and environmentally friendly reaction can be achieved).[22] This will be discussed in section 2.1.1.

1.1.6 Microwave Devices

Most organic syntheses using microwave irradiation that were reported in the 1980's and the beginning of 1990's, were carried out using domestic microwave ovens. A domestic microwave oven uses pulsed irradiation (on-off cycles of the magnetron). In such devices, it is almost impossible to monitor and control temperature and pressure (safety issues). Today, most industrial microwave reactors are equipped with a built-in magnetic stirrer as well as temperature monitors (fiber optic probes or IR sensors) and pressure controls. In most cases, temperature and pressure can be manipulated by software that controls power input to the reactor. Today, there are two different approaches to microwave reactor design; multimode (Fig1.1.6a) and monomode reactors (Fig1.1.6b).

In a multimode microwave (much like household microwave ovens), the microwaves enter the cavity and are reflected by the walls. The microwaves can be distributed fairly uniformly throughout a large volume using a mode stirrer. In a monomode reactor, which has much smaller cavity, the electromagnetic irradiation is focused directly into the reaction vessel. Due to the geometry and the location of the cavity (located at a fixed distance from the radiation source), the microwaves are generated as standing waves. Each microwave instrument has its own benefits and disadvantages. The multimode microwave unit can accommodate any size of glassware (sometimes a few at a time) but, because the irradiation is spread "all over" the microwave, reaction efficiency decreases. In the monomode microwave, the irradiation is focused on one small vessel at a time.

Microwave reactions can be carried out is sealed vessels under pressure (closed vessel mode) or in unsealed vessels at atmospheric pressure (open vessel mode). An open vessel reactor often is sealed with a cap to maintain an inert atmosphere. Modern monomode reactors are design for straightforward monitoring of closed vessel reactions.

Fig 1.1.6a The monomode reactor MW

Fig 1.1.6b The multimode reactor MW.

1.1.7 Use of Microwaves in Organic Reactions

1.1.7.1 Suzuki-Miyaura Reaction

Suzuki-Miyaura cross coupling reactions are versatile and widely used for the selective construction of carbon-carbon bonds.[23,24] The reaction uses a palladium-catalyst, ligand, and a base to cross-couple organoboron reagents with organic halides. The availability of different catalysts and more stable organoborane reagents such as the potassium trifluoroborates have broadened the possible applications of this important reaction. The utilization of the Suzuki reaction in microwave synthesis has gained popularity in recent years due to its efficiency.[25-30] One of the attractions of using the Suzuki coupling in microwave syntheses is its simplicity and the ability to use water as solvent. The use of water has a huge advantage in environmentally friendly (Green) chemistry.

Commercialization and large scale production of such reactions are now possible (Fig. 1.1.7.1a).[31] Furthermore, the ease of preparation, stability, and low toxicity of the boron reagents increase the utility of these reactions. The reaction mechanism involves the oxidative addition of the palladium to the organic halide to form an organopalladium intermediate. The addition of the base enables the formation of the boronate complex which then transmetallates with the organopalladium species. Reductive elimination yields the product and regenerates the palladium catalyst (Fig. 1.1.7.1b).

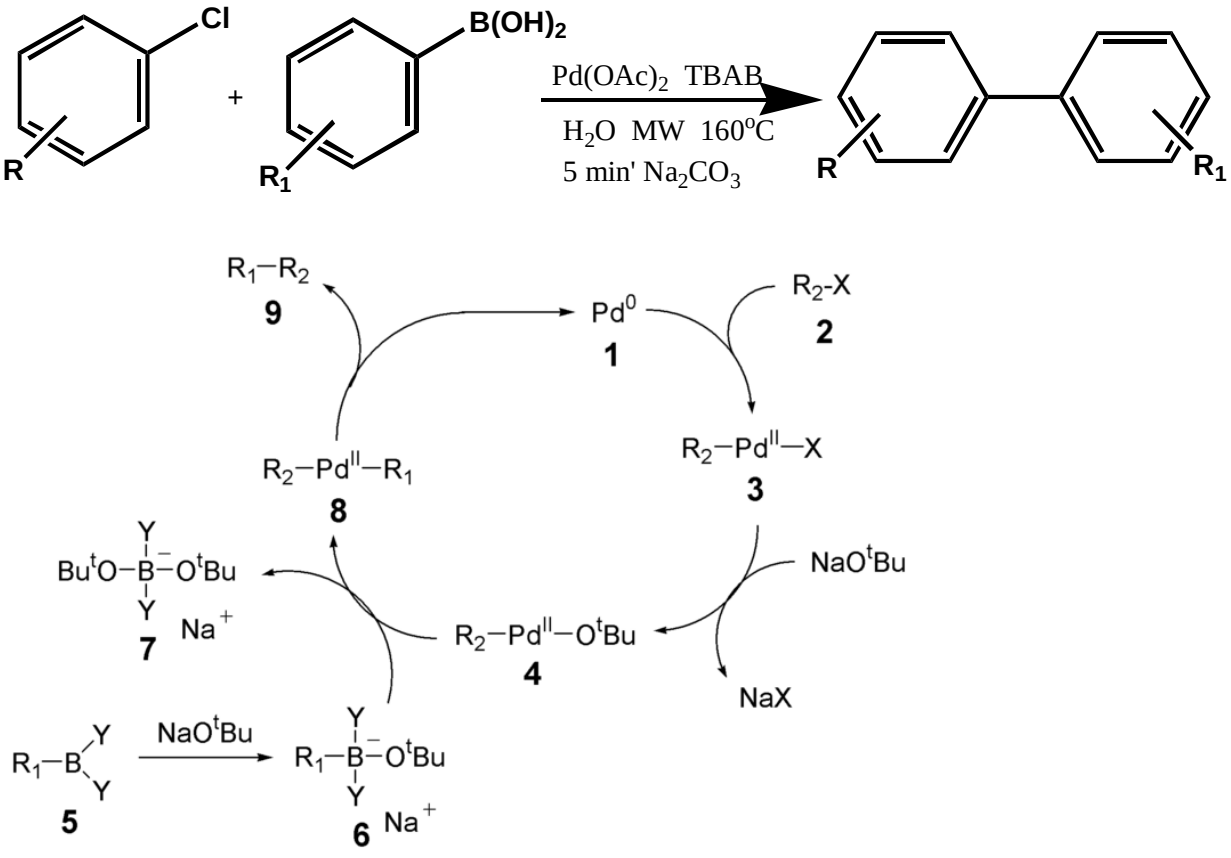


Fig 1.1.7.1a Suzuki couplings of allylboronic acids and 1.1.7.1b The palladium catalytic cycle.

1.1.7.2 Heck Reaction

The Mizoroki-Heck reaction is widely used for carbon-carbon bond formation.[32] It is a stereoselective, palladium-catalyzed vinylic substitution reaction between alkenes and unsaturated halides or triflates. The Heck reaction using microwave was first reported in 1996.[33] The reaction mechanism is much like the Suzuki coupling reaction (in the Suzuki reaction the aryl halide is coupled to an arylboronic acid). An example of Heck reaction is presented in fig 1.1.7.2 where an aryl bromide and acrylic acid form a cinnamic acid.

1.1.7.3 Stille Coupling Reaction

The Stille Coupling reaction involves carbon-carbon bond formation between organostannanes and organic halides or pseudohalides. A major advantage of the Stille coupling is the diversity of substituted organic molecules that can be obtained using relatively straightforward methods of preparation. At the same time, the low polarity (as well as poor solubility in water) and the toxicity of tin compounds are serious disadvantages. The reaction mechanism is much like that of the Suzuki coupling reaction (reduction/oxidation via a palladium-catalyzed cycle). One major difference between the Stille and Suzuki reactions is that, in the latter, base is required to activate the boronic acid for the transmetallation to occur (enhances the polarization of the ligand). However, in some cases where organotrifluoroborates are used, the presence of a base is not necessary.[34] Stille coupling reactions using microwave synthesis were first reported in 2002.[35]

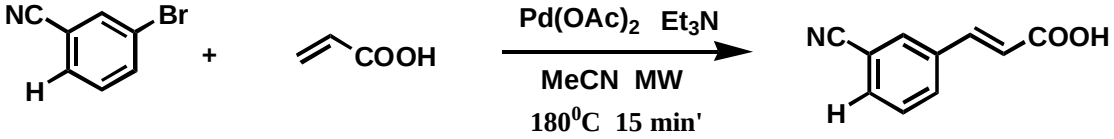


Fig 1.1.7.2 Formation of cinnamic acid using the Heck reaction

1.1.7.4 Sonogashira Coupling Reaction

The Sonogashira coupling reaction is a palladium/copper catalyzed reaction between terminal acetylenes and aryl or vinyl halides. [36] Sonogashira reactions using microwaves were first reported in 1996 by Erdmlyi and Gogoll.[37] The reaction mechanism is similar to the Suzuki coupling reaction (reduction/oxidation) with the addition of a copper cycle to form the organocopper intermediate that will ultimately transmetallate with the palladium intermediate.

1.1.8 Organotrifluoroborates in Microwave Enhanced Cross Coupling Reactions

Organometallic reagents and organotrifluoroborates, in particular, are of importance in organic and pharmaceutical synthesis.[38] Boron tolerates a wide range of functional groups and can easily transmetallate with transition-metal catalysts.[39] Furthermore, the availability and low toxicity of these compounds make them highly desirable.[40] Organoboranes (and boronic acids), in contrast to organotrifluoroborate, are not stable under atmospheric conditions due to the vacant p orbital of the boron atom. This vacant orbital permits acid-base reactions with oxygen and water, resulting in decomposition of the reagent.[41] In addition, vinylboronic acids can be lost via polymerization side reactions. Vinylboronic esters can also result in mixtures of Suzuki and Heck coupled products due to lack of selectivity.[42] This has led to the increasing use of organotrifluoroborate. Organotrifluoroborate salts, with the formula $[R_nBF_{4-n}]^-$ ($n \leq 3$), are exceptionally stable to air and moisture. They can be stored at room temperature without precaution. At the same time, their stability does not affect their high reactivity in a large variety of reactions. The first description of organotrifluoroborates was published in 1940 by Fowler and Krauss.[43] They prepared tetrabutylammonium triphenylfluoroborates by reaction of a triphenylborane-ammonia complex with 1 equivalent of tetraalkylammonium fluoride. Not until the late 1960's were more efficient methods of preparation were available.[44] Thierig and Umland reported that the hydroxyl groups of arylboronic acids could be replaced with potassium hydrogen difluoride to

form potassium aryl trifluoroborates (Fig.1.1.8). In time, different modifications led to better yields and pure products.[45] As noted in the previous sections, organotrifluoroborates are of growing interest for cross coupling reactions. Cross coupling reactions that are useful for the creation of carbon-carbon bonds, are highly desirable in the preparation of pharmaceuticals, herbicides, natural products, polymers and liquid crystalline materials.[46-49] The Suzuki cross coupling reaction is one of the most versatile and frequently used procedures for carbon-carbon bond formation.[50,51] For reasons discussed above, which include low toxicity, ease of accessibility, air stability, and environmental factors,[52] the Suzuki reaction is one of the most useful reactions for carbon-carbon bond formation. Furthermore, the need for this type of reaction has led to a continuous development of new and efficient methods. Microwave synthesis is a technique that can provide answers to some core issues such as: reaction time, "Green" chemistry, solvent, and catalyst-free reactions. Numerous papers have described how microwave irradiation reduces reaction time, in some cases from days to minutes.[53-55] When using ionic liquids as solvents in microwave reaction, the rate for heating can easily exceed 10 °C s^{-1} without significant pressure build-up.[56] As for "Green" chemistry, reducing reaction time results in less power/energy use. In addition, water can be used as a solvent, it is cheap, readily available, nontoxic, nonflammable, and has clear advantages for its use in organic synthesis. Leadbeater has reported Suzuki coupling reactions using microwave irradiation without the use of palladium catalyst,[57] and we have developed Suzuki coupling reactions in the absence of solvents.[58] Today, the use of controlled microwave conditions can be considered almost a routine synthetic procedure. The next three chapters will focus on the reaction of potassium vinyltrifluoroborates and alkynyltrifluoroborates.

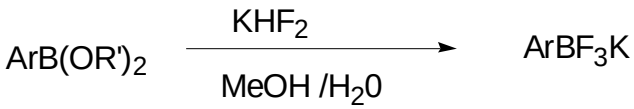


Fig 1.1.8 Preparation of aryl trifluoroborate.

CHAPTER 2

MICROWAVE ENHANCED PALLADIUM-CATALYZED CROSS COUPLING REACTIONS OF POTASSIUM VINYLTRIFLUOROBORATES AND ALLYL ACETATES: A NEW ROUTE TO 1,4-PENTADIENES

1.2.1 Introduction

As discussed in Chapter 1, reactions involving the coupling of potassium organotrifluoroborates with organic electrophiles are of great importance in organic chemistry as the result of their efficiency in creating carbon-carbon bonds.[59] Vinyltrifluoroborates are readily prepared, remarkably stable, and quite reactive. In 2005, we reported the rapid palladium catalyzed cross-coupling of allyl acetates with a variety of potassium vinyltrifluoroborates that provided 1,4-pentadienes under microwave irradiation (Fig1.2.1). The uniqueness of the study was that these reactions involved straightforward allylation reactions.[60] There are reports describing the palladium-catalyzed coupling of arylboronic acids with allyl halides[61,62] and allyl acetates[63,64] but efficient reactions involving the production of 1,4-dienes had not yet been explored. The 1,4-diene framework comprises an important structural assembly. This framework can be seen in many molecules of biological importance[65-67] as well as in molecules involved in organic synthesis.[68-76] In addition, the 1,4-dienes can be transformed into conjugated 1,3-dienes in the presence of sulfur dioxide via an ene reaction.[77,78]

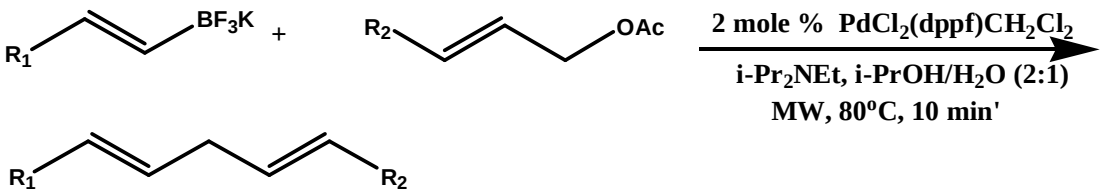


Fig 1.2.1 Synthesis of 1,4 –Dienes

1.2.2 Results and Discussion

In an effort to optimize reaction conditions, potassium *trans*-2-[4-(trifluoromethyl) phenyl]vinyltrifluoroborate was allowed to react with allyl acetate in the presence or absence of a palladium catalyst and a base. No carbon-carbon bond formation occurred in the absence of palladium or a base. Five different palladium catalysts were evaluated as potential catalysts. These include: $PdCl_2(dppf)•CH_2Cl_2$, $Pd_2dba_3•CHCl_3$/dppf, Pd_2dba_3/(*o*-tolyl)$_3$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2$. Four different bases were examined as potential bases. These include: diisopropylethylamine, cesium carbonate, potassium carbonate, and triethylamine. Of the conditions studied, the best results were obtained using 2 mol percent of $PdCl_2(dppf)•CH_2Cl_2$ in the presence of 3.0 equivalent of diisopropylethylamine (Hünig's base) in 2-propanol/water (2:1) at 80 °C under microwave irradiation for 10 minutes. After optimization of the reaction conditions, we explored the cross coupling of allyl acetates with various vinyltrifluoroborate electron withdrawing and electron donating groups (Table 1.2.2). Electron withdrawing groups on the aromatic ring had little effect on the yields while electron donating groups reduced the yields. In addition, we studied the reaction of cinnamyl acetate and geranyl acetate with various vinyltrifluoroborates. We observed that electron donating groups yielded the best results in the case of cinnamyl acetate and poorest results in the case of geranyl acetate. Electron withdrawing groups led to an improvement in the reaction yields. The reaction of aliphatic potassium vinyltrifluoroborates, such as potassium *trans*-1-nonenyltrifluoroborate, was also studied using cinnamyl acetate and geranyl acetate. The resulting products were obtained in good yields and the coupling reactions were stereoselective where the *E* isomers were the only observed products. As for regioselectivity, although traces of the isomeric products were observed in the products derived from cinnamyl acetate, regiochemistry was generally preserved. Slightly larger regiochemical losses were observed in the products generated from geranyl acetate; a minor isomer can be detected by the presence of an absorption peak near 112 ppm in the carbon-13 spectra due to the terminal methylene carbon.

Table 1.2.2. Pd-Catalyzed allylation of potassium vinyltrifluoroborates with allyl acetates.[a]

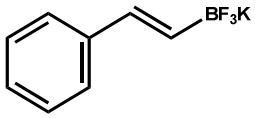
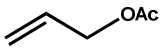
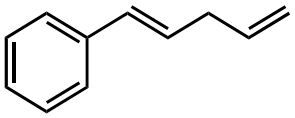
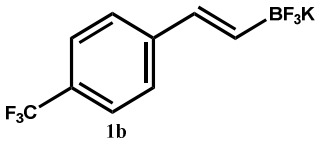
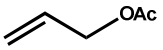
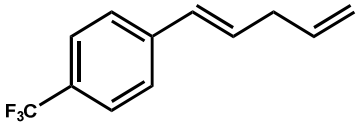
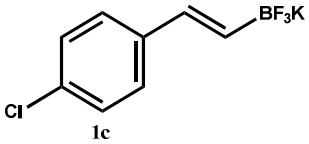
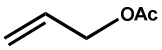
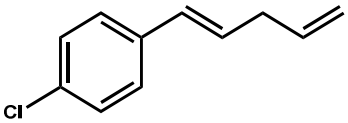
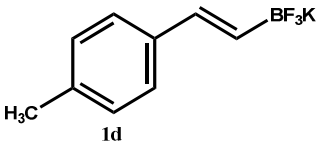
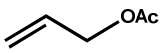
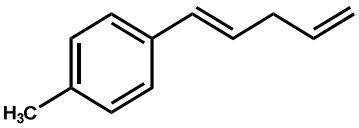
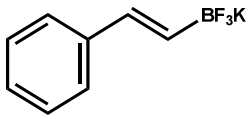
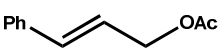
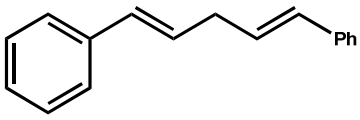
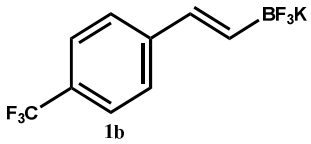
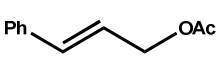
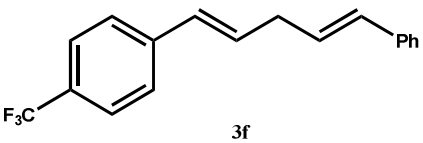
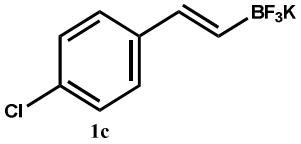
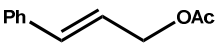
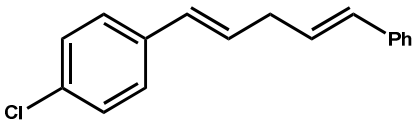
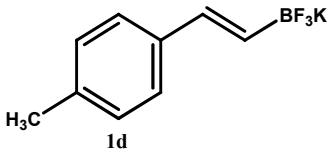
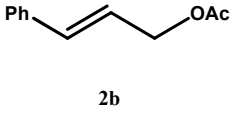
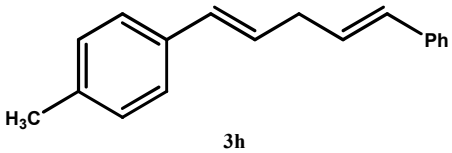
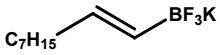
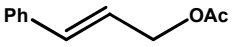
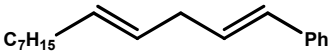
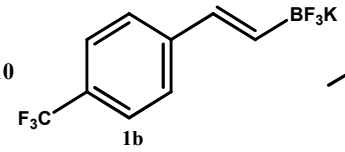
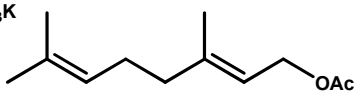
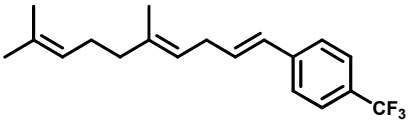
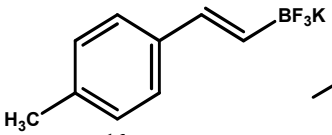
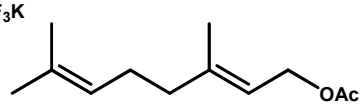
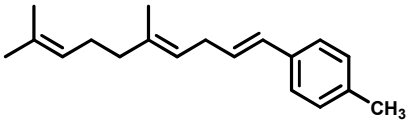
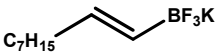
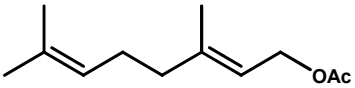
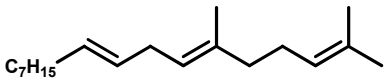
Entry	alkenyl trifluoroborates	allylating agent	product	yield (%) [b]
1	 1a	 2a	 3a	97
2	 1b	 2a	 3b	89
3	 1c	 2a	 3c	94
4	 1d	 2a	 3d	71
5	 1a	 2b	 3e	76
6	 1b	 2b	 3f	90
7	 1c	 2b	 3g	81

Table 1.2.2 (cont')

Entry	alkenyl trifluoroborates	allylating agent	product	yield (%) [b]
8	 1d	 2b	 3h	97
9	 1e	 2b	 3i	80
10	 1b	 2c	 3j	93
11	 1d	 2c	 3k	56
12	 1e	 2c	 3l	74

[a]Reaction conditions: **1** (0.5 mmol), allylating agent **2** (0.5 mmol), i-Pr_2NEt (1.5 mmol), $PdCl_2(dppf)$-CH_2Cl_2 (0.001 mmol), 2-propanol/water (2:1), 80°C, MW, 10min' [b] Isolated yields.

1.2.3 Conclusion

In conclusion, a new procedure was developed which provides a general and efficient method for coupling allyl acetate and cinnamyl acetate with various substituted potassium arylvinyltrifluoroborates to produce a variety of 1,4-dienes in good to excellent yields.[60]

1.2.4 Experimental Section

All glassware was dried in an oven at 110 °C and flushed with dry nitrogen. All reactions were performed under an argon/nitrogen atmosphere. Water and isopropanol were degassed by purging with argon/nitrogen. Flash chromatography was performed using silica gel (32–63 µm, 60 Å). All nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) were obtained using a Varian 300 MHz instrument. All products were dissolved in $CDCl_3$ and the chemical shifts were reported relative to TMS (0.1 % (v/v)). Potassium organotrifluoroborates were prepared utilizing literature methods.[59] The required organotrifluoroborates were readily accessible from the corresponding organoboronic acids (commercially available from Aldrich Chemical Co. and Frontier Scientific Co.) by the addition of potassium hydrogen difluoride. Microwave activation was performed using a CEM Discover System in the closed vessel mode. For the reactions of allyl acetate and cinnamyl acetate, the following settings were used: Power: 100 Watt, Ramp time: 05:00 minutes, Hold time: 10:00 minutes, Temperature: 80 ^{0}C. For geranyl acetate: The hold time was increased to 20:00 minutes.

1.2.4.1 General Procedure for Preparation of Potassium (1-Hexyn-1-yl) trifluoroborate.

The boronic acid (4 mmol) was dissolved in a 250-mL round-bottomed flask containing methanol (~10 mL). Potassium hydrogen difluoride (20 mmol, 1.6 g) was placed in a 50

mL beaker and dissolved in water (~40 mL). The potassium hydrogen difluoride/water mixture was then added dropwise to the boronic acid/methanol mixture and the mixture stirred for 3.5 hr. The resulting slurry was taken up in acetone and then the solvent evaporated under reduced pressure using a rotary evaporator. The residue was dissolved in acetone, filtered, and the solution dried over anhydrous sodium sulfate. The solvent was then evaporated under reduced pressure on a rotary evaporator, re-dissolved in a minimum amount of boiling acetone, and allowed to cool. Diethyl ether was added until no cloudiness was observed in the supernatant. The resulting solid was then filtered and washed with diethyl ether. Partial evaporation under atmospheric conditions and addition of diethyl ether led to the second crop of the product. The solid was dried under high vacuum to give the product (~ 70% yield).

1.2.4.2 Representative Procedure for Coupling of Potassium (1-Hexyn-1-yl)-trifluoroborate and Allyl Acetates Under Microwave Condition.

In a dry Pyrex tube containing magnetic stirring bar, potassium vinyltrifluoroborate (0.50 mmol) and $PdCl_2(dppf)\bullet CH_2Cl_2$ (0.02 mmol, 9.0 mg) were loaded and capped with an airtight rubber cap. The tube was flushed with argon to maintain a moisture free environment. The allylating agent (0.50 mmol) and Hünig's base (1.5 mmol, 265 μL) were then added using a Hamilton syringe. 2-Propanol/water (2:1, 5.0 mL) was then added followed by an argon purge. The resulting mixture was placed in a CEM microwave unit in the closed vessel mode and allowed to react at 80 °C for 10 minutes. The reaction mixture was then transferred to a separatory funnel and diluted with diethyl ether (20 mL). The solution was washed with water (3 X 20 mL) to remove byproducts. After extraction, the organic layer was separated and dried over anhydrous sodium sulfate. The ether solution was filtered, concentrated, and the product was subjected to silica gel chromatography using hexane/ethyl acetate (100/1) as eluent. The product was separated from the hexane/ethyl acetate using a rotary evaporator to obtain the pure product.

1.2.5 Analytical Data

3a Penta-1,4-dienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 5H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 6.3 Hz, 1H), 5.90 (m, 1H), 5.08 (m, 2H), 2.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 136.4, 130.8, 128.4, 128.1, 127.0, 126.0, 115.6, 36.9.

3b 1-Penta-1,4-dienyl-4-trifluoromethylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (m, 4H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, *J* = 6.3 Hz, 1H), 5.90 (m, 1H), 5.10 (m, 2H), 2.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 140.6, 135.8, 131.0, 129.6, 126.1, 125.5, 125.4, 125.3, 116.1, 36.9. ^{19}F NMR ($CDCl_3$, 282.3 MHz): δ -88.7.

3c 1-Chloro-4-penta-1,4-dienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (m, 4H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 6.3 Hz, 1H), 5.88 (m, 1H), 5.09 (m, 2H), 2.95 (m, 2H).

3d 1-Methyl-4-penta-1,4-dienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.07 (m, 4H), 6.36 (d, *J* = 16.2 Hz, 1H), 6.16 (m, 1H), 5.88 (m, 1H), 5.07 (m, 2H), 2.94 (m, 2H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 136.6, 134.8, 130.6, 129.1, 127.0, 125.9, 115.5, 36.9, 21.1

3e 1,1'-(1*E*,4*E*)-1,4-Pentadiene-1,5-diylbisbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.80 (m, 10H), 5.08 (d, *J* = 15.6 Hz, 2H), 4.80 (dt, *J* = 6.6 Hz, 2H), 1.64 (t, *J* = 6.3 Hz, 2H).

3f 1-[(1*E*,4*E*)-5-Phenyl-1,4-pentadienyl]-4-(trifluoromethyl) benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.20 (m, 9H), 6.48 (d, *J* = 15.6 Hz, 2H), 6.31 (m, 2H), 3.13 (t, *J* = 6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 141.0, 137.3, 131.4, 131.0, 129.7, 128.6, 128.5, 127.2, 126.0, 125.4, 116.0, 36.1. ^{19}F NMR ($CDCl_3$, 282.2 MHz): δ -88.6.

3g 1-Chloro-4-[(1*E*,4*E*)-5-phenyl-1,4-pentadienyl]benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (m, 9H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.26 (m, 2H), 3.12 (t, *J* = 6.6 Hz, 2H).

3h 1-Methyl-4-[(1*E*,4*E*)-5-phenyl-1,4-pentadienyl]benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (m, 9H), 6.42 (m, 2H), 6.23 (m, 2H), 2.93 (m, 2H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 137.5, 136.7, 134.7, 130.8, 129.1, 128.4, 127.0, 126.0, 125.9, 36.1, 21.1.

3i (1*E*,4*E*)-1,4-Dodecadienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 6.38 (d, J = 15.9 Hz, 1H), 6.21 (dt, *J* = 6.6 Hz, 1H), 5.49 (m, 2H), 2.89 (m, 2H), 2.01 (m, 2H), 1.27 (m, 10H), 0.87 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5MHz): δ 137.7, 132.0, 130.1, 129.3, 128.4, 127.7, 126.8, 125.9, 95.9, 32.6, 31.8, 29.4, 29.1, 22.6, 14.0.

3j 1-[(1*E*,4*E*)-5,9-Dimethyl-1,4,8-decatrienyl]-4-(trifluoromethyl)benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (m, 4H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.28 (m, 1H), 5.11 (m, 2H), 2.93 (t, *J* = 6.6 Hz, 2H), 2.12–1.22 (s, m, 13H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.2, 140.7, 137.2, 132.6, 132.4, 128.3, 126.2, 126.0, 125.4, 125.3, 124.5, 124.1, 121.5, 120.7, 112.4, 42.8, 41.1, 39.7, 31.9, 31.4, 31.4, 26.6, 25.7, 23.2, 17.6, 16.0. ^{19}F NMR ($CDCl_3$, 282.2 MHz): -88.6.

3k 1-[(1*E*,4*E*)-5,9-Dimethyl-1,4,8-decatrienyl]-4-methylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.06 (m, 4H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.12 (m, 1H), 5.13 (m, 2H), 2.88 (m, 2H), 2.30 (m, 2H), 2.08–2.16 (m, 11H). Calcd. for $C_{19}H_{26}$: C, 89.70; H, 10.30. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.8, 136.8, 135.0, 131.4, 129.3, 129.1, 128.4, 126.1, 125.8, 124.2, 111.9, 39.7, 31.4, 25.7, 23.2, 21.1, 17.6.

3l 2,6-Dimethyl- (6*E*,9*E*)- 2,6,9-Heptadecatriene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.37 (m, 2H), 5.14 (m, 2H), 2.68 (m, 2H), 2.16–0.85 (m, 28H). Calcd. for $C_{19}H_{34}$: 262.2661 Found: 262.2666.

CHAPTER 3

MICROWAVE ENHANCED CROSS-COUPLING REACTIONS INVOLVING ALKENYL- AND ALKYNYLTRIFLUOROBORATES

1.3.1 Introduction

The syntheses of stilbenes have been the subject of numerous investigations. Their function as antioxidants[79,80] in medicine and their application in macromolecular chemistry and nanoscience[81,82] make stilbenes very desirable. One of the more powerful tools to create a carbon-carbon bond is to create a bond between an organoboron compound and organic halide (or triflate) using a palladium catalyzed cross-coupling reaction.[83-86] As noted previously (1.1.8), problems arise when using alkenylboronic acids and esters in Suzuki-Miyaura coupling reactions. Polymerization of the vinylboronic acids can occur. In addition, vinylboronic esters are not always selective in cross-coupling reactions, yielding mixtures of Suzuki and Heck coupled products.[42,87] In order to solve some of the problems arising in organoboron coupling reactions, the use of potassium alkenyltrifluoroborates and alkynyltrifluoroborates was suggested.[88-92] In this chapter the effects of microwave irradiation are explored as an alternative to thermal heating in reactions using potassium organotrifluoroborates (Fig1.3.1).

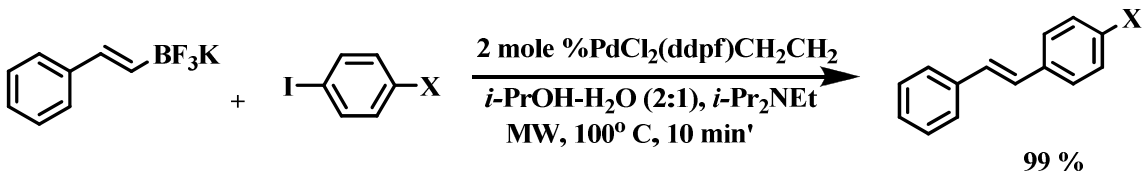


Fig 1.3.1 Synthesis of stilbenes.

1.3.2 Results and discussion

In an effort to optimize reaction conditions, potassium phenylvinyltrifluoroborate was allowed to react with iodobenzenes in the presence or absence of a palladium catalyst and a base. No carbon-carbon bond formation occurred in the absence of palladium or a base. Five different palladium catalysts were evaluated as potential catalysts. These include: $PdCl_2(dppf)•CH_2Cl_2$, $Pd_2dba_3•CHCl_3/dppf$, $Pd_2dba_3/(o\text{-tolyl})_3$, $Pd(OAc)_2/dppf$, and $Pd(OAc)_2$. Four different bases were examined as potential bases. These include: diisopropylethylamine, cesium carbonate, potassium carbonate, and triethylamine. Of the conditions studied, the best results were obtained using 2 mol percent of $PdCl_2(dppf)•CH_2Cl_2$ in the presence of 3.0 equivalent of diisopropylethylamine (Hünig's base) in 2-propanol/water (2:1) at 100 °C under microwave irradiation for 10 minutes. After the optimization of reaction conditions, we explored the cross coupling of potassium phenylvinyltrifluoroborate with various substituted iodobenzenes (Table 1.3.2a). Compounds containing electron withdrawing groups (Table 1.3.2a, entries 2-5) and electron donating groups (Table 1.3.2a, entries 6-8) all provided the cross-coupled styrene products in high yields. The product yields generally exceeded those obtained in the thermal reactions by ~10%.[80] In general, all reactions were very straightforward and stereoselective. Finally, after successfully utilizing microwaves to enhance Suzuki coupling of potassium *trans*-2-phenylvinyltrifluoroborate with aryl halides, the use of other substituted potassium arylvinyltrifluoroborates (Table 1.3.2b) was investigated. All reactants provided the cross-coupled stilbenes in excellent yields (Table 1.3.2b, entries 1-6). An aliphatic vinyltrifluoroborate also readily participated in the reaction (Table 1.3.2b, entry 7). Yields were generally somewhat lower for coupling reactions involving the alkynyltrifluoroborates; a situation also noted in thermal coupling reactions.[93] (Table 1.3.2b, entries 8–13).

Table 1.3.2a Pd-Catalyzed cross coupling reaction of potassium aryl vinyltrifluoroborates with aryl iodide.[a]

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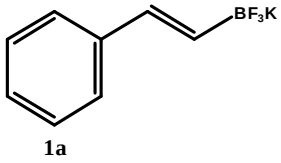
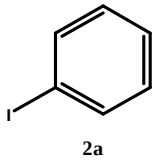
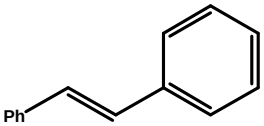
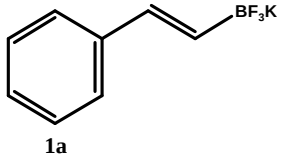
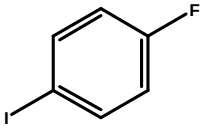
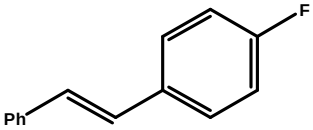
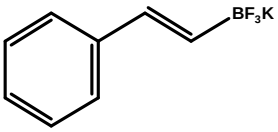
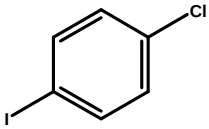
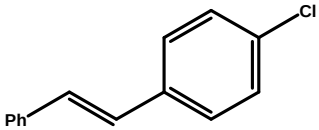
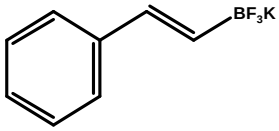
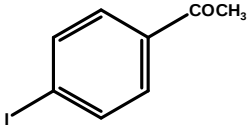
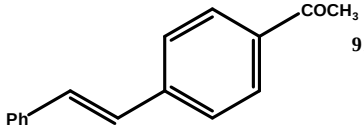
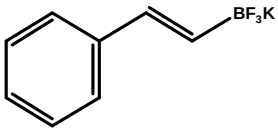
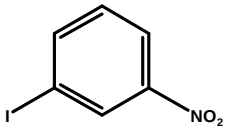
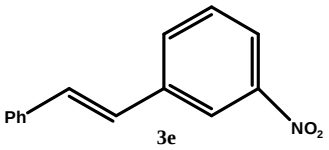
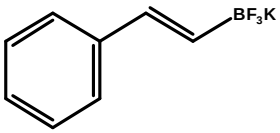
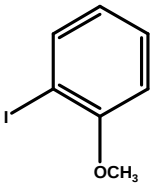
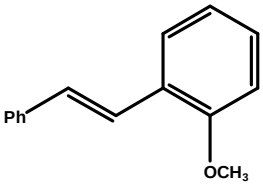
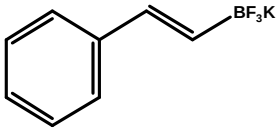
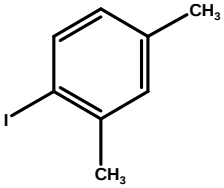
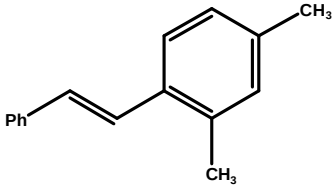
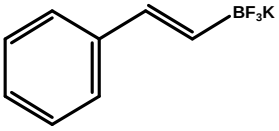
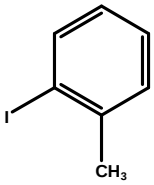
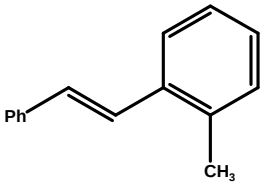
1	 1a	 2a	 3a	67
2	 1a	 2b	 3b	61
3	 1a	 2c	 3c	99
4	 1a	 2d	 3d	91
5	 1a	 2e	 3e	76

Table 1.3.2a (cont')

Entry	Aryl trifluoroborates	Aryl iodide	Product	yield (%) [b]
6	 **1a**	 **2f**	 **3f**	79
7	 **1a**	 **2g**	 **3g**	96
8	 **1a**	 **2h**	 **3h**	92

[a]Reaction conditions: **1** (0.5 mmol), allylating agent **2** (0.5 mmol), i-Pr_2NEt (1.5 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (0.001 mmol), 2-propanol/water (2:1), 80°C, MW, 10min' [b] Isolated yields.

Table 1.3.2b. Microwave enhanced cross-coupling reactions for the synthesis of syrenes and enynes.[a]

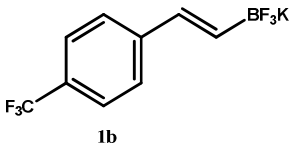
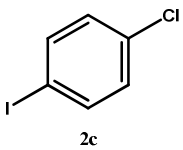
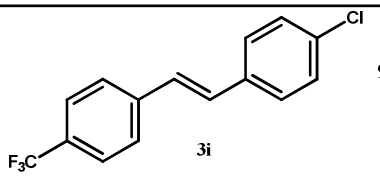
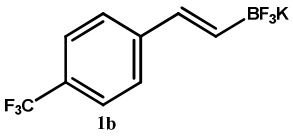
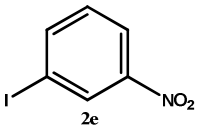
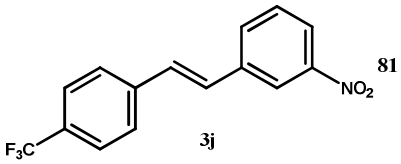
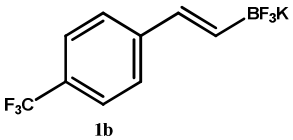
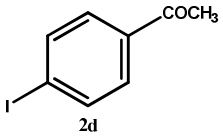
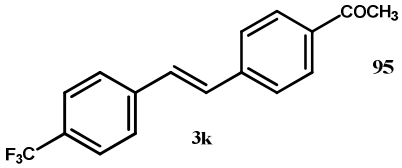
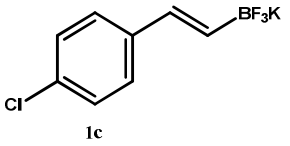
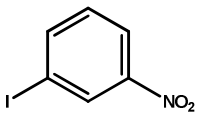
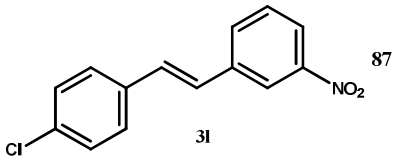
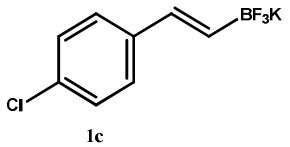
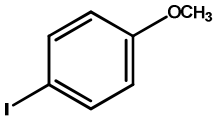
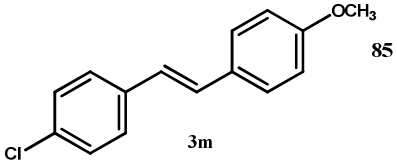
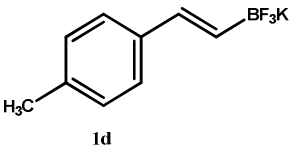
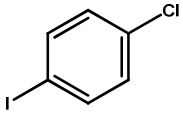
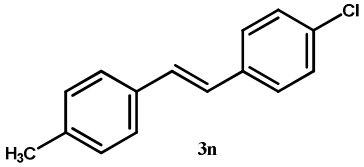
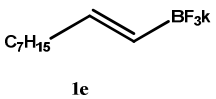
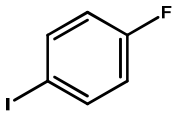
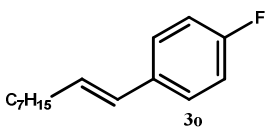
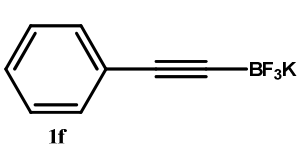
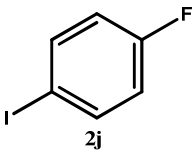
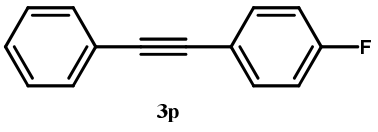
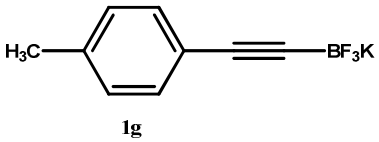
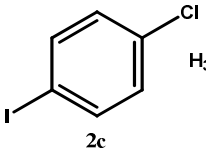
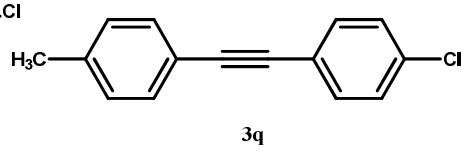
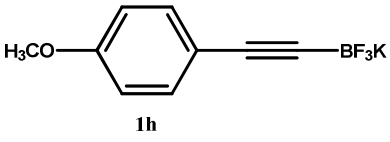
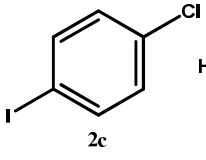
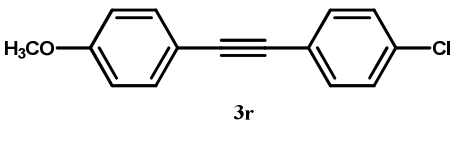
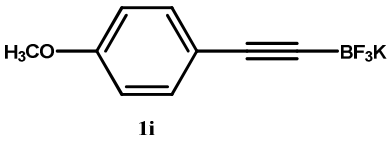
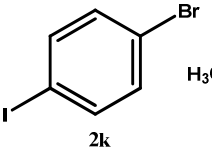
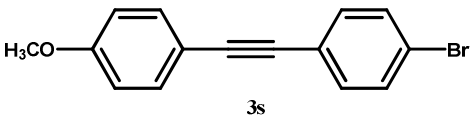
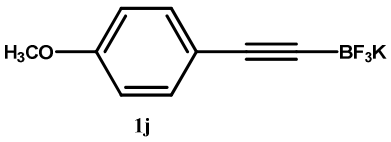
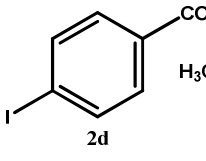
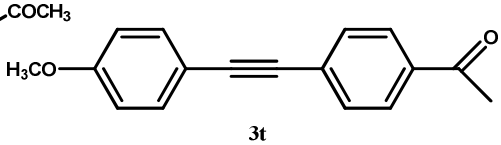
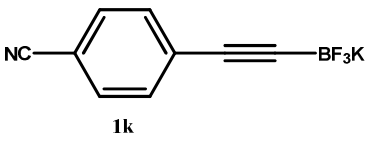
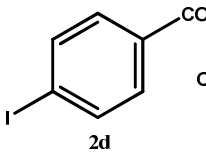
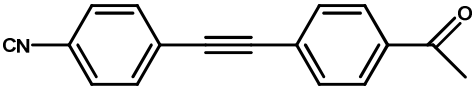
Entry	alkenyl trifluoroborates	allylating agent	product	yield (%)[b]
1	 1b	 2c	 3i	92
2	 1b	 2e	 3j	81
3	 1b	 2d	 3k	95
4	 1c	 2e	 3l	87
5	 1c	 2i	 3m	85
6	 1d	 2c	 3n	94
7	 1e	 2j	 3o	91

Table 1.3.2b (cont')

Entry	alkenyl trifluoroborates	allylating agent	product	yield (%) [b]
8	 1f	 2j	 3p	60
9	 1g	 2c	 3q	65
10	 1h	 2c	 3r	68
11	 1i	 2k	 3s	72
12	 1j	 2d	 3t	69
13	 1k	 2d	 3u	52

[a]Reaction conditions: **1** (0.5 mmol), allylating agent **2** (0.5 mmol), i-Pr_2NEt (1.5 mmol), $PdCl_2(dppf)$-CH_2Cl_2 (0.001 mmol), 2-propanol/water (2:1), 80°C, MW, 10min' [b] Isolated yields.

1.3.3 Conclusion

In conclusion, the effects of microwave irradiation on the synthesis of stilbenes were explored and led to new and efficient methods to prepare a variety of substituted stilbenes in good to excellent yields.[94]

1.3.4 Experimental Section

All glassware was dried in an oven at 110 °C and flushed with dry nitrogen. All reactions were performed under an argon/nitrogen atmosphere. Water and isopropanol were degassed by purging with argon/nitrogen. Flash chromatography was performed using silica gel (32–63 µm, 60 Å). All nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were obtained using a Varian 300 MHz instrument. All products were dissolved in $CDCl_3$ and the chemical shifts were obtained relative to TMS (0.1 % (v/v)). Potassium organotrifluoroborates were prepared utilizing literature methods.[59] The required organotrifluoroborates were readily accessible from the corresponding organoboronic acids (commercially available from Aldrich Chemical Co. and Frontier Scientific Co.) by addition of potassium hydrogen difluoride. Microwave activation was performed using a CEM Discover System in a closed vessel mode. For the reactions of organotrifluoroborates and aryl halides the following setting was used: Power: 100 Watt, Ramp time: 05:00 minutes, Hold time: 10:00 minutes, Temperature: 100 ^{0}C.

1.3.4.1 General Procedure for Preparation of Potassium (1-Hexyn-1-yl) trifluoroborate.

The boronic acid (4 mmol) was dissolved in a 250-mL round-bottomed flask containing methanol (~10 mL). Potassium hydrogen difluoride (20 mmol, 1.6 g) was placed in a 50 mL beaker and dissolved in water (~40 mL). The potassium hydrogen difluoride/water mixture was then added dropwise to the boronic acid/methanol mixture and the mixture stirred for 3.5 hr. The resulting slurry was taken up in acetone and then the solvent

evaporated under reduced pressure using a rotary evaporator. The residue was dissolved in acetone, filtered, and the solution dried over anhydrous sodium sulfate. The solvent was then evaporated under reduced pressure on a rotary evaporator, re-dissolved in a minimum amount of boiling acetone, and allowed to cool. Diethyl ether was added until no cloudiness was observed in the supernatant. The resulting solid was then filtered and washed with diethyl ether. Partial evaporation under atmospheric conditions and addition of diethyl ether led to the second crop of the product. The solid was dried under high vacuum to give the product (~ 70% yield).

1.3.4.2 Representative Procedure for Coupling of Organotrifluoroborate and Aryl Halide Under Microwave Condition.

In a dry Pyrex tube containing a magnetic stirring bar orgnotrifluoroborate (0.50 mmol) and $PdCl_2(dppf)\bullet CH_2Cl_2$ (0.02 mmol, 9.0 mg) were loaded and capped with an airtight rubber cap. The tube was flushed with argon to maintain a moisture free environment. The aryl halide (0.50 mmol) was then added along with diisopropyl ethyl amine (1.5 mmol, 265 μL) and 5 mL of isopropanol/water (2:1). Followed by argon purged, the resulting mixture was placed in a CEM microwave unit in a close vessel mode and allowed to react at 80 °C for 10 minutes. The reaction mixture was then transferred to a separatory funnel and diluted with diethyl ether (20 mL). The solution was washed with water (3 X 20 mL) to remove byproducts. After extraction, the organic layer was separated and dried over anhydrous sodium sulfate. The ether solution was filtered, concentrated, and the product was subjected to silica gel chromatography using hexane/ethyl acetate (100/1) as eluent. The product was separated from the hexane/ethyl acetate using a rotary evaporator to obtain the pure product.

1.3.5 Analytical Data

3a 1,2-Ethenediylbisbenzene

^{1}H NMR (300 MHz, CDCl3) δ: 7.51 (d, *J* = 8.4 Hz,4H), 7.35 (t, *J* = 7.2 Hz, 4H), 7.27 (t, *J*= 6.3 Hz, 2H), 7.11 (s, 2H); ^{13}C NMR (75MHz, CDCl3) δ: 137.3, 128.7 (2C), 127.6, 126.5.

3b 1-Fluoro-4-[2-phenylethenyl]benzene

^{1}H NMR: δ 7.55-7.47 (m, 4H), 7.40 (t, J = 7.6 Hz, 2H), 7.33-7.30 (m, 1H), 7.14-7.06 (m, 4H); ^{13}C NMR (75 MHz, CDCl3): δ 162.4 (d), 137.3, 133.6, 128.8, 128.6 (d, *J* = 2.3 Hz), 128.0 (d, *J* = 0.4 Hz), 127.7, 127.6, 126.5, 115.6 (d, *J* = 21.45 Hz)

3c 1-Chloro-4-[2-phenylethenyl]benzene

^{1}H NMR (300 MHz, CDCl3): δ 7.04 (s, 2H), 7.26-7.42 (m, 7H), 7.48 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl3): δ 126.52, 127.32, 127.63, 127.84, 128.70, 128.80, 129.28, 133.13, 135.81, 136.94.

3d 1-[4-[2-Phenylethenyl]phenyl]ethanone,

^{1}H NMR (300 MHz, CDCl3):δ 2.61 (s, 3H), 7.14 (d, 1H, *J*=16.4Hz), 7.22 (d, 1H, *J* =16.4Hz), 7.25-7.38 (m, 3H), 7.55 (d, 2H, *J* =7.9Hz), 7.59 (d, 2H, *J* =8.4Hz), 7.95 (d, 2H, *J* =8.4Hz); ^{13}C NMR (75MHz, CDCl3): δ 26.7, 126.6, 126.9, 127.6, 128.4, 128.9, 129.0, 131.6, 136.1, 136.8, 142.1, 197.6.

3e 1-nitro-3-[2-Phenylethenyl]benzene

^{1}H NMR (300 MHz, CDCl3):δ 7.05 (d, *J* = 16.5 Hz, 1H), 7.17 (d, *J* =16.5 Hz, 1H), 7.26-7.39 (m, 3H), 7.42-7.51 (m, 3H), 7.72(d, *J* = 8.4 Hz 1H), 8.02-8.05 (m, 1H), 8.28-8.29 (m, 1H); ^{13}C NMR (75 MHz, CDCl3):δ120.71, 121.83, 125.89, 126.71, 128.39, 128.71, 129.39, 131.56, 132.09, 136.11, 138.97, 148.54.

3f 1-Methoxy-2-[2-phenylethenyl]benzene

^{1}H NMR (CDCl3) δ 7.66 (dd, J = 7.7 Hz, J = 1.5 Hz), 7.55-7.62 (m, 3H), 7.26-7.43 (m, 5H), 7.19 (d, J = 16.8 Hz, 1H), 7.03 (t, J = 7.6 Hz), 6.95 (d, J = 8.2 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 157.0, 138.0, 129.1, 128.7, 128.6, 127.4, 126.6, 126.5, 126.4, 123.6, 120.8, 111.0, 55.6.

3g 2,4-Dimethyl-1-[2-phenylethenyl]benzene

1H NMR (400 MHz, CDCl3) d 7.49 (2H, d, J=7.5 Hz), 7.40 (2H, d, J=8.0 Hz), 7.34 (2H, t, J= 7.6 Hz), 7.23 (1H, t, J=7.2 Hz), 7.15 (2H, d, J=7.9 Hz), 7.09 (1H, d, J=16.4 Hz), 7.04 (1H, d, J=16.4 Hz), 2.38 (s, 3H), 2.35 (3H, s, CH3); 13C NMR (75 MHz, CDCl3): δ 137.6, 134.6, 129.5, 128.7, 127.8, 127.5, 126.49, 126.46, 123.4, 21.3.

3h 1-Methyl-2-[2-phenylethenyl]benzene

^{1}H NMR (400 MHz, CDCl3):δ 2.37 (s, 3H), 7.06-7.08 (m, 3H), 7.23-7.26 (m, 2H), 7.31-7.37 (m, 4H), 7.49-7.52 (m, 2H); ^{13}C NMR (75 MHz,CDCl3): δ21.45, 123.71, 126.48, 127.21, 127.54, 128.46, 128.47, 128.57, 128.67, 128.79, 137.26, 137.42, 138.22.

3i 1-[2-(4-Chlorophenyl)ethenyl]-4-(trifluoromethyl)benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56 (m, 4H, $-C_6H_4$), 7.43 (d, J = 8.7 Hz, 2H, $-C_6H_4$), 7.31 (d, J = 8.7 Hz, 2H, $-C_6H_4$), 7.05 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 140.3, 135.0, 133.8, 129.7, 128.9, 127.6, 125.6. ^{19}F NMR ($CDCl_3$, 282.3 MHz): δ −62.8.

3j 1-Nitro-3-[(1*E*)-2-[4-(trifluoromethyl)phenyl]ethenyl]benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.72 (d, J=12.0 Hz), 6.86 (d, J = 8.8 Hz), 6.88 (d, J = 12.0 Hz), 7.02 (dd, J=5.4,8.6 Hz), 7.05-7.11 (m), 7.23-7.27 (m), 7.38-7.44 (m), 7.49-7.54 (m) 7.60 (t, J=7.6 Hz), 7.75 (dd, J=1.2,8.0 Hz), 7.97 (dd, J=1.2, 8.0 Hz), 8.06-8.11 (m). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 115.4, 115.6, 116.2, 123.6 (d,J=8.8 Hz), 125, 126,

128.2,, 128.3, 128.4, 128.9, 130.9, 131, 132.4, 132.9, 133.3, 133.6, 148.4, 161, 161.9, 163.5, 164.4.

3k 1-[4-[2-[4-(Trifluoromethyl)phenyl]ethenyl]phenyl]ethanone

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97 (m, 2H), 7.61 (m, 6H), 7.21 (s, 2H), 2.61 (s, 3H).

3l 1-[2-(4-Chlorophenyl)ethenyl]-3-nitrobenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.72 (d, J=12.0 Hz), 6.86 (d, J = 8.8 Hz), 6.88 (d, J = 12.0 Hz), 7.02 (dd, J=5.4,8.6 Hz), 7.05-7.11 (m), 7.23-7.27 (m), 7.38-7.44 (m), 7.49-7.54 (m) 7.60 (t, J=7.6 Hz), 7.75 (dd, J=1.2,8.0 Hz), 7.97 (dd, J=1.2, 8.0 Hz), 8.06-8.11 (m). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 115.4, 115.6, 116.2, 123.6 (d,J=8.8 Hz), 125, 126, 128.2, 128.3, 128.4, 128.9, 130.9, 131, 132.4, 132.9, 133.3, 133.6, 148.4, 161, 161.9, 163.5, 164.4.

3m 1-Chloro-4-[2-(4-methoxyphenyl)ethenyl]benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.45 (m, 6H), 6.88-7.05 (m, 4H), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 55.3, 114.1, 125.3, 127.4, 127.7, 128.7, 128.8, 129.8, 132.7, 136.2, 159.4.

3n 1-Chloro-4-[2-(4-methylphenyl)ethenyl]benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 3H), 7.11 (s, 2H), 7.13-7.58 (m, 8H) ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 163.4, 134.0, 130.9, 128.4,

3o 1-Fluoro-4-(non-1-enyl)benzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (m, 2H), 6.96 (m, 2H), 6.32 (d, J = 15.9 Hz, 1H), 6.13 (dt, J = 15.9, 6.9 Hz, 1H), 2.18 (q, J = 7.2 Hz, 2H), 1.47–1.25 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 163.4, 134.0, 130.9, 128.4, 127.2, 115.3, 32.9, 31.8, 29.7, 29.3, 22.6, 14.1.

3p 1-Fluoro-4-(2-phenylethynyl)benzene

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.55-7.45 (m, 4H), 7.35-7.32 (m, 3H), 7.03 (dd, J = 8.9 and 8.7 Hz, 2H).

3q 1-Chloro-4-[(4-methylphenyl)ethynyl]benzene

^{1}H NMR (CDCl3, 200 MHz) δ 7.39-7.32 (m, 4H), 7.26-7.17 (m, 2H), 7.08 (d, *J* = 7.83, 2H Hz), 2.29 (s, 3H); ^{13}C NMR (CDCl3, 75.5 MHz) δ 138.6, 134.0, 132.7, 131.5, 129.1, 128.6, 122.1, 119.9, 90.5, 87.6, 21.4.

3r 1-Chloro-4-[(4-methoxyphenyl)ethynyl]benzene

^{1}H NMR (500.13 MHz, CDCl3) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.53 (td, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.36 (td, *J* = 7.7 Hz, 1.5 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl3) δ 160.3, 133.5, 132.5, 132.3, 131.7, 127.7, 127.5, 117.6, 114.8, 114.0, 113.9, 96.2, 84.6, 55.2.

3s 1-Bromo-4-[2-(4-methoxyphenyl)ethynyl]benzene

^{1}H NMR (500.13 MHz, CDCl3) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.53 (td, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.36 (td, *J* = 7.7 Hz, 1.5 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl3) δ 160.3, 133.5, 132.5, 132.3, 131.7, 127.7, 127.5, 117.6, 114.8, 114.0, 113.9, 96.2, 84.6, 55.2.

3t 1-[4-[2-(4-Methoxyphenyl)ethynyl]phenyl]ethanone

^{1}H NMR (300 MHz, CDCl3):2.59 (s, 3H), 3.82 (s, 3H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.47-7.58 (m, 4H), 7.91 (d, *J* =8.4 Hz, 2H); ^{13}C NMR (75MHz, CDCl3): δ26.5, 55.2, 87.5, 92.9, 114.0, 114.6, 128.2, 128.5, 131.4, 133.2, 135.8, 159.9, 197.3

3u 4-[2-(4-Acetylphenyl)ethynyl]benzonitrile

^{1}H NMR (300 MHz, CDCl3):2.59 (s, 3H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* =8.4 Hz, 2H), 7.83 (d, *J* =8.4 Hz, 2H); ^{13}C NMR (75MHz, CDCl3): δ 22.5, 87.5, 92.9, 114.0, 114.6, 116.2, 128.2, 128.5, 131.4, 133.2, 135.8, 159.9, 197.3

CHAPTER 4

MICROWAVE ENHANCED CROSS-COUPLING REACTIONS OF ALLYL CHLORIDES WITH VINYLTRIFLUOROBORATES

1.4.1 Introduction

In the previous chapters, the reaction of potassium alkenyltrifluoroborates with allyl acetate and aryl halides was explored. The presence of the benzene ring (in the aryl halides) and the reactivity of the carbonyl in the acetates enabled good to excellent yields. The question that remained concerned the reactivity of alkene halides. As noted previously (1.2.1), the 1,4-diene framework is an important structural assembly. This framework can be seen in many molecules of biological importance[59-61] as well as in molecules involved in organic synthesis.[62-70] The use of allyl halides as opposed to allyl acetates would allow a wide variety of compounds to be utilized. In this chapter, the allylation of potassium alkenyltrifluoroborates with allyl halides (Fig. 1.4.1) via a palladium catalyzed, cross coupling reaction is explored. It was found that the allylation reaction occurs rapidly under microwave irradiation and produces 1,4-pentadienes in high yields.

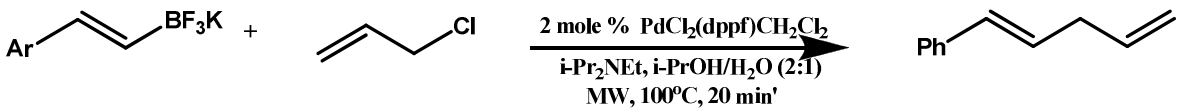


Fig 1.4.1 The allylation of potassium aryltrifluoroborates with allyl chloride

1.4.2 Results and discussion

In an effort to optimize reaction conditions, potassium phenylvinyltrifluoroborate, was allowed to react with three different halides: allyl iodide, allyl bromide and allyl chloride (Table 1.4.2a). The procedure for all three reactions was identical. The reactants were placed in the presence or absence of a palladium catalyst and a base. No carbon-carbon bond formation occurred in the absence of palladium or a base. Five different palladium catalysts were evaluated as potential catalysts: $PdCl_2(dppf)\bullet CH_2Cl_2$, $Pd_2dba_3\bullet CHCl_3$/dppf, Pd_2dba_3/(*o*-tolyl)$_3$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2$.. Four different bases were examined as potential bases. These include: diisopropylethylamine, cesium carbonate, potassium carbonate, and triethylamine. Of the conditions studied, the best results were obtained using 2 mol percent of $PdCl_2(dppf)\bullet CH_2Cl_2$ in the presence of 3.0 equivalent of diisopropylethylamine (Hünig's base) in 2-propanol/water (2:1) at 100 °C under microwave irradiation for 10 minutes. Allyl chloride gave the best results out of the three examined. The reaction time was increased from 10 to 20 minutes to obtain a better yield. After the optimization of reaction conditions, we explored the cross coupling of allyl chloride with various substituted potassium phenylvinyltrifluoroborate (Table 1.4.2b). Compounds containing electron withdrawing groups (Table 1.4.2b, entries 1, 2) and electron donating groups (Table 1.4.2b, entry 3) all provided the cross-coupled styrene products in good yields, while electron donating groups enhanced the yields. Finally, after successfully utilizing microwaves to enhance Suzuki coupling of potassium phenylvinyltrifluoroborate with allyl chloride, we investigated the use of other substituted allyl chlorides with various potassium phenylvinyltrifluoroborates (Table 1.4.2c). All provided the cross-coupled product in good yields.

Table 1.4.2a. Microwave enhanced cross-coupling reactions of potassium phenylvinyltrifluoroborate with allyl halides.[a]

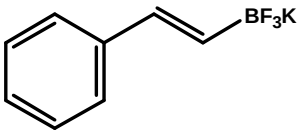
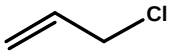
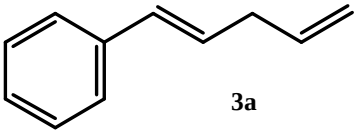
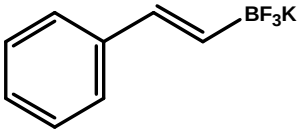
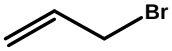
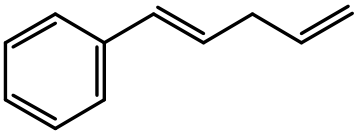
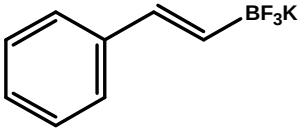
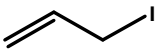
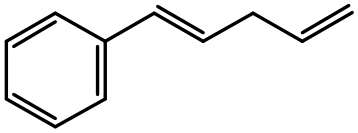
Entry	phenylvinyltrifluoroborate	allylating agent	product	yield (%)[b]
1			 **3a**	**81**
2				**65**
3				**55**

Table 1.4.2b. Microwave enhanced cross-coupling reactions of potassium arylvinyltrifluoroborate with various allyl chlorides.[a]

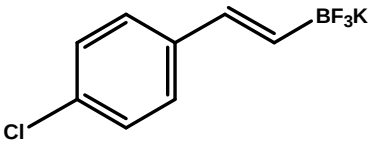
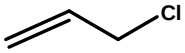
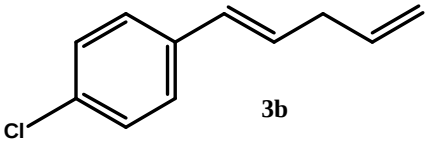
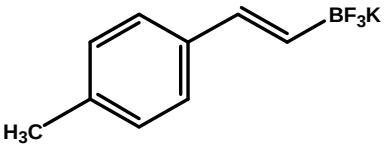
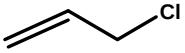
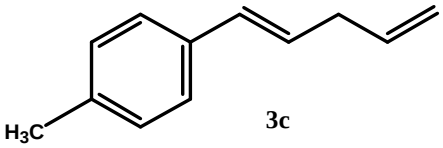
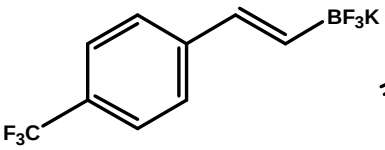
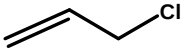
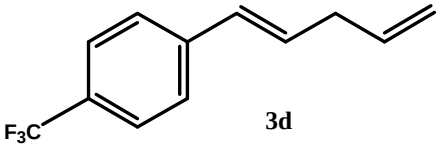
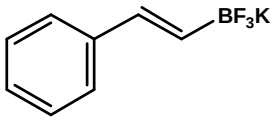
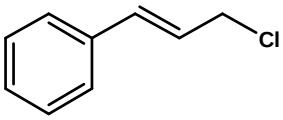
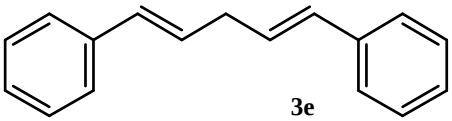
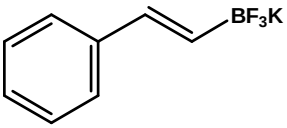
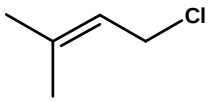
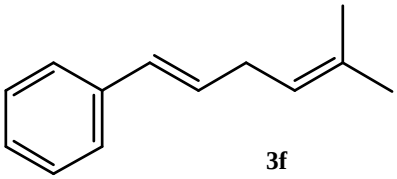
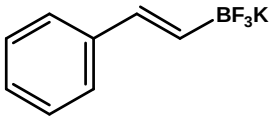
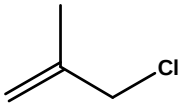
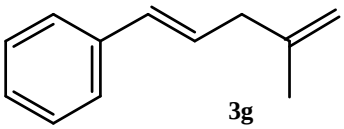
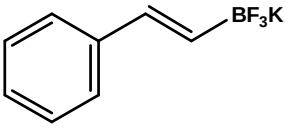
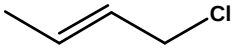
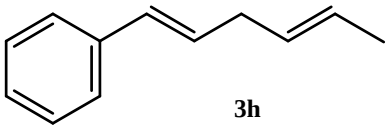
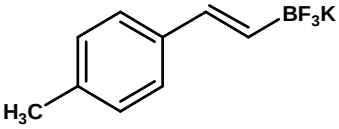
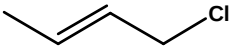
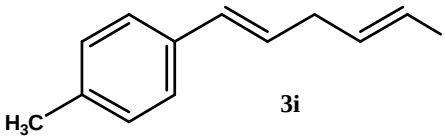
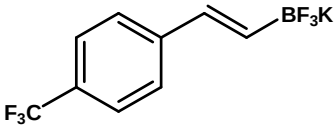
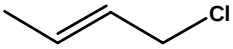
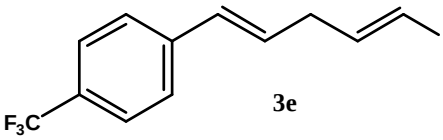
Entry	arylvinyltrifluoroborate	allylating agent	product	yield (%)[b]
1			 **3b**	**71**
2			 **3c**	**79**
3			 **3d**	**89**

Table 1.4.2b (cont')

Entry	arylvinyltrifluoroborate	allylating agent	product	yield (%)[b]
4			 **3e**	**46**
5			 **3f**	**54**
6			 **3g**	**64**
7			 **3h**	**51**
8			 **3i**	**81**
9			 **3e**	**75**

[a]Reaction conditions: **1** (0.5 mmol), allylating agent **2** (0.5 mmol), i-Pr_2NEt (1.5 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (0.001 mmol), 2-propanol/water (2:1), 80°C, MW, 10min' [b] Isolated yields.

1.4.3 Conclusion

In conclusion, a general and efficient synthetic method for the allylation of various substituted potassium alkenyltrifluoroborates with allyl halides was discovered. The reaction proceeds to form a variety of 1,4-dienes in good to excellent yields.[95]

1.4.4 Experimental Section

All glassware was dried in an oven at 110 °C and flushed with dry nitrogen. All reactions were performed under an argon/nitrogen atmosphere. Water and isopropanol were degassed by purging with argon/nitrogen. Flash chromatography was performed using silica gel (32–63 µm, 60 Å). All nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were obtained using a Varian 300 MHz instrument. All products were dissolved in $CDCl_3$ and the chemical shifts were obtained relative to TMS (0.1 % (v/v)). Potassium organotrifluoroborates were prepared utilizing literature methods.[59] The required organotrifluoroborates were readily accessible from the corresponding organoboronic acids (commercially available from Aldrich Chemical Co. and Frontier Scientific Co.) by addition of potassium hydrogen difluoride. Microwave activation was performed using a CEM Discover System in a closed vessel mode. For the reactions of organotrifluoroborates and aryl halides the following setting was used: Power: 100 Watt, Ramp time: 05:00 minutes, Hold time: 20:00 minutes, Temperature: 100 ^{0}C.

1.4.4.1 General Procedure for Preparation of Potassium (1-Hexyn-1-yl) trifluoroborate.

The boronic acid (4 mmol) was dissolved in a 250-mL round-bottomed flask containing methanol (~10 mL). Potassium hydrogen difluoride (20 mmol, 1.6 g) was placed in a 50 mL beaker and dissolved in water (~40 mL). The potassium hydrogen difluoride/water mixture was then added dropwise to the boronic acid/methanol mixture and the mixture stirred for 3.5 hr. The resulting slurry was taken up in acetone and then the solvent

evaporated under reduced pressure using a rotary evaporator. The residue was dissolved in acetone, filtered, and the solution dried over anhydrous sodium sulfate. The solvent was then evaporated under reduced pressure on a rotary evaporator, re-dissolved in a minimum amount of boiling acetone, and allowed to cool. Diethyl ether was added until no cloudiness was observed in the supernatant. The resulting solid was then filtered and washed with diethyl ether. Partial evaporation under atmospheric conditions and addition of diethyl ether led to the second crop of the product. The solid was dried under high vacuum to give the product (~ 70% yield).

1.4.4.2 Representative Procedure for Coupling of Potassium (1-Hexyn-1-yl)trifluoroborate, and Allyl Chloride Under Microwave Condition.

In a dry Pyrex tube filled with a magnetic stirring bar potassium vinyltrifluoroborate (0.50 mmol) and $PdCl_2(dppf)•CH_2Cl_2$ (0.02 mmol, 9.0 mg) were loaded and capped with an airtight rubber cap. The tube was flushed with argon to maintain a moisture free environment. The allylating agent (0.50 mmol) and Hünig's base (1.5 mmol, 265 μL) were then added using a Hamilton syringe. 2-Propanol/water (2:1, 5.0 mL) was then added followed by an argon purge. The resulting mixture was placed in a CEM microwave unit in the closed vessel mode and allowed to react at 100 °C for 20 minutes. The reaction mixture was then transferred to a separatory funnel and diluted with ethyl ether (20 mL). The solution was washed with water (3 X 20 mL) to remove byproducts. After extraction, the organic layer was separated and dried over anhydrous sodium sulfate. The ether solution was filtered, concentrated, and the product was subjected to silica gel chromatography using hexane/ethyl acetate (100/1) as eluent. The product was separated from the hexane/ethyl acetate using a rotary evaporator to obtain the pure product.

1.4.5 Analytical Data

3a Penta-1,4-dienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (m, 5H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 6.3 Hz, 1H), 5.90 (m, 1H), 5.08 (m, 2H), 2.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 136.4, 130.8, 128.4, 128.1, 127.0, 126.0, 115.6, 36.9.

3b 1-Chloro-4-penta-1,4-dienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (m, 4H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 6.3 Hz, 1H), 5.88 (m, 1H), 5.09 (m, 2H), 2.95 (m, 2H).

3c 1-Methyl-4-penta-1,4-dienylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.07 (m, 4H), 6.36 (d, *J* = 16.2 Hz, 1H), 6.16 (m, 1H), 5.88 (m, 1H), 5.07 (m, 2H), 2.94 (m, 2H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 136.6, 134.8, 130.6, 129.1, 127.0, 125.9, 115.5, 36.9, 21.1

3d 1-Penta-1,4-dienyl-4-trifluoromethylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (m, 4H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, *J* = 6.3 Hz, 1H), 5.90 (m, 1H), 5.10 (m, 2H), 2.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 140.6, 135.8, 131.0, 129.6, 126.1, 125.5, 125.4, 125.3, 116.1, 36.9. ^{19}F NMR ($CDCl_3$, 282.3 MHz): δ -88.7.

3e 1,1'-(1*E*,4*E*)-1,4-pentadiene-1,5-diylbisbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.80 (m, 10H), 5.08 (d, *J* = 15.6 Hz, 2H), 4.80 (dt, *J* = 6.6 Hz, 2H), 1.64 (t, *J* = 6.3 Hz, 2H).

3f (5-Methyl-hexa-1,4-dienyl)benzene

^{1}H NMR (CDC13, 250 MHz): δ 6.20 (d, 1H, 3J,,=15.gHz), 6.10 (dt, 1H, 3Ja,=15.ghz, 3J..=6.4Hz), 5.22 (t, IH, 3J,.=7.5Hz), 2.83 (dd, 2H, 3J,,=7.5Hz, 3J..=6.4Hz), 1.67 (s, 3H), 1.59 (s, 3H).

3g (4-Methyl-penta-1,4-dienyl)benzene

1H-NMR (CDC13, 250 MHz): δ 1.74-1.78 (3H, m, allylic CH3); 2.97 (2H, d, J= 7.6 Hz, allylic CH2); 4.77-4.82 (2H, m, C=CH2); 5.74 (lH, dt, J= 11.5 and 7.6 Hz, CH=CHPh); 6.54 (lH, d, J= 11.5 Hz, CH=CHPh); 7.20-7.40 (5H, m, Ph).

3h (Hexa-1,4-dienyl)benzene

^{1}H NMR (CDC13, 300 MHz): δ 7.35-7.16 (m, 5 H, ArH), 6.39 (d, 1 H, ***J*** = 16Hz, PhCH), 6.20 (dt, 1 H, *J* = 16 Hz, *J* = 6 Hz, =CHCH2), 5.58 (dq, 1 H, *J* = 12 Hz, *J* = 7 Hz, =CH), 5.48 (dtd, 1 H, *J* = 12 Hz, *J* = 7 Hz, *J* = 1 Hz, =CH), 2.96 (t, 2 H, *J* = 6 Hz, CH2), 1.66 (d, 3 H, *J* = 6 Hz, CH3); ^{13}C NMR (CDC13, 75 MHz): δ 137.67, 129.91, 128.65, 128.35, 127.50, 126.78, 125.91, 125.09 (Ar C and C=C), 30.30, 12.68 (CH2 and CH3).

3i 1-Hexa-1,4-dienyl-4-methylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.07 (m, 4H), 6.36 (d, *J* = 16.2 Hz, 1H), 6.16 (m, 1H), 5.88 (m, 1H), 5.07 (m, 2H), 2.90 (m, 2H), 2.20 (s, 3H), 1.70 (m, 3H) ^{13}C NMR ($CDCl_3$, 75.5 MHz): 136.6, 134.8, 129.1, 127.0, 125.9, 122, 122, 36.9, 21.1, 17

3j 1-Hexa-1,4-dienyl-4-trifluoromethylbenzene

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (m, 4H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, *J* = 6.3 Hz, 1H), 5.90 (m, 1H), 5.10 (m, 2H), 2.98 (m, 2H), 1.70 (m, 3H) ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 140.6, 135.8, 131.0, 129.6, 126.1, 125.5, 125.4, 125.3, 125, 116.1, 36.9. ^{19}F NMR ($CDCl_3$, 282.3 MHz): δ -88.7.

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Part Two

REACTIONS CATALYZED BY HIGHLY ACIDIC ALUMINA VIA MICROWAVE IRRADIATION

CHAPTER 1

ALUMINA AND MICROWAVE

2.1.1 Alumina

2.1.1.1 Introduction

Inorganic solid-phase reagents comprise a wide range of supports and materials.[1] In part two, metal oxides in general and alumina in particular, are examined in microwave assisted reactions. Running a reaction without the aid of a catalyst usually requires an elevated temperature and a long reaction time.[14] The addition of a catalyst (such as activated alumina) can reduce temperature and reaction time in addition to increasing stereoselectivity, regioselectivity, and reaction rates.[2] Solids such as silica, alumina, and clay can induce reactions on their surfaces in addition to being used as an acid or a base.[3,4] Alumina is a metal oxide containing aluminum and oxygen ions. Both anhydrous and hydrated alumina are available. The surface characteristics can be varied in a number of ways and this can affect the course of many organic reactions.[5] There are several forms of alumina which include: α, γ, δ, η, θ, κ, and χ. Alumina matrices are commercially available and can be prepared from naturally occurring aluminum ore (Bauxite) via the Bayer process.[1] The α type is the only one that is not classified as a transition alumina, and can not act as a catalyst due to its three dimensional structure.[6] α-Alumina contains a low surface area, low porosity, high density, high mechanical strength, and has thermal stability. The classification of the remaining transition alumina types (γ, δ, η, θ, κ, and χ) is dependent on the dehydration process used to form them. These types can be achieved by longer dehydration and calcinations of the hydrated, natural occurring aluminum oxide (Fig 2.1.1a).

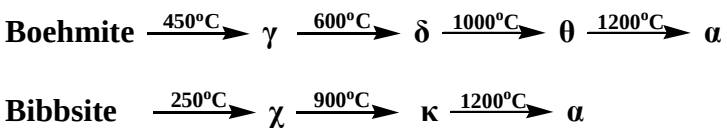


Fig 2.1.1 Procedures for the formation of transition alumina

2.1.1.2 Advantages and Disadvantages of Inorganic Solid[3]

There are advantages and disadvantages to using a solid catalyst in an organic reaction. The pros for using inorganic solids include:

- Green chemistry, inorganic solids are normally environmentally friendly and can be recycled;
- Safety, they are non volatile and odorless;
- Commercial availability, they can be used off the shelf and some has long shelf life;
- Simple isolation procedure and purification (as far as solvent choice);
- Inorganic solids can offer superior reaction selectivity and control;

The cons include:

- Scale up, some reagents require a slow loading of reactants which results in very long reaction times;
- Special apparatus, many procedures require extreme conditions for preparation such as high temperatures and oxidative free environments;
- Properties can vary significantly, differ commercial manufacturing procedures can result in reagents with different structures and compositions;
- Inorganic solids are often non-homogeneous and it can be difficult to quantify surface properties;

2.1.1.3 Gamma Alumina

The chemical reactivity of this transition alumina enables it to play a role as a catalyst in organic chemistry. Among the transition aluminas, gamma alumina (γ-Al_2O_3) has been studied and used more often than any other form due to its high surface area and enhanced catalytic activity. Gamma alumina can be produced in an acidic, neutral, or basic form and has a maximum surface area of 200 m^2/g. The numbers of catalytic sites that will be exposed depends on the activation period (heating time). The structure and surface of this alumina was extensively studied as early as 1960's.[7] However, it was a decade later that Knozinger and Ratnasamy used a Spinel Defect Model to identify the

gamma alumina framework.[8] In their study, they show that the unit cells are comprised of 21 and 1/3 aluminum atoms per 32 oxygen atoms (thus the formula Al_2O_3). This "1/3 alumina" leaves vacant cation position in the lattice while the oxygen anions arrange in four distinct layers.[9] These layers can be represented by A to D; were A is the top layer (surface) and B-D follow. Each layer contains a different geometric orientation for the aluminum cations (Fig 2.1.1.3a). For example, in the top layer there are 24 cations in which 8 are in octahedral and 16 are in tetrahedral geometry (Table. 2.1.1.3). The top layer is oriented in such a way that if one used a topographic view to describe the surface, it would seem like mountain terrain rather then a flat one. In some cases, the lower layers are exposed due to formation of "craters" in the top layer. As for the oxygen/anion layers, they contain two different types: hydrated and anhydrous. In the hydrated form, the first two layers contain five types of hydroxyl groups. These hydroxyl groups identify many of the reactive sites of the alumina and have distinctive infrared and NMR spectra (Fig 2.1.1.3b).[10,11] New bottles of gamma alumina are naturally hydrated with about 3 mmols of surface hydroxyl groups per 1 gram of alumina (according to the manufacturer). This amount can be measured by titrating the alumina with methyllithium and measuring the volume of the methane gas released. Commercially, to remove the hydroxyl groups from the surface (a.k.a activation) alumina has to be heated under a vacuum. As a result, water is released and

Table 2.1.1.3 Layer of gamma alumina.

Layer	Geometry	
	Octahedral	Terahedral
A	8	16
B	24	-
C	12	12
D	24	-

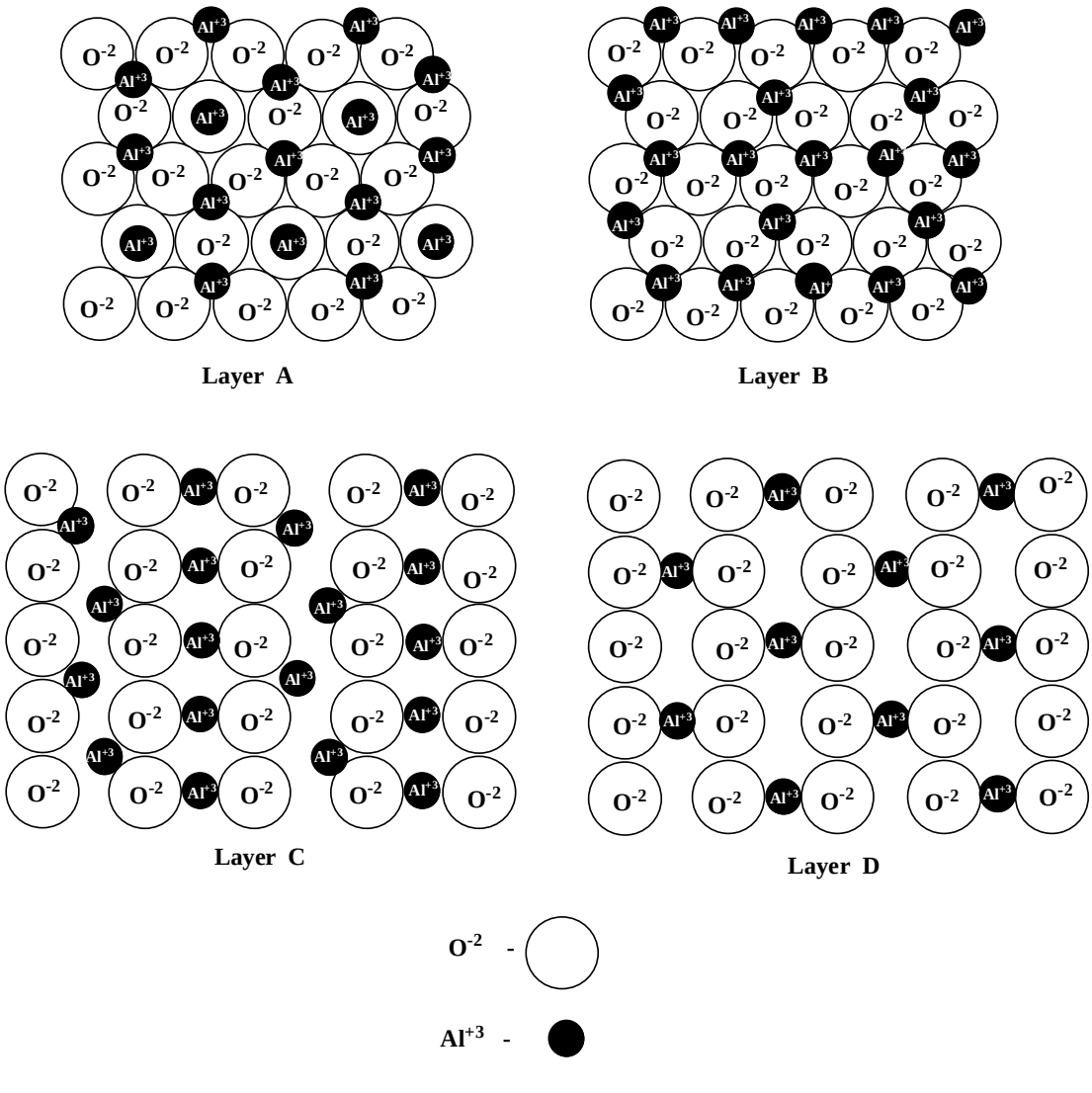


Fig 2.1.1.3 a The Knozinger and Ratnasamy layers of gamma alumina

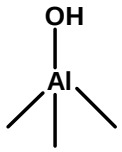
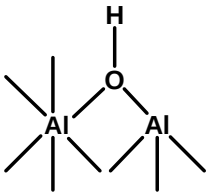
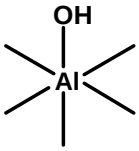
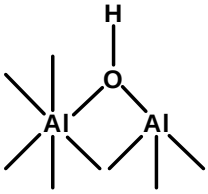
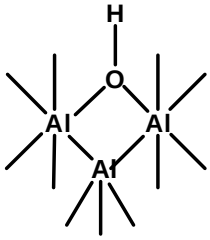
Type	A Layer	Hydroxyl Stretching (in cm^{-1})
Ia		3760 - 3780
IIa		3730 - 3735
	B Layer	
Ib		3785 - 3800
IIb		3740 - 3745
III		3700 - 3740

Fig 2.1.1.3b Types of hydroxyl groups on the A and B layers of gamma alumina

aluminum cation and oxygen anion sites are exposed. The higher the temperature and the longer the activation, the more hydroxyl groups can be removed. Hence, greater activity of alumina can be achieved. The activation process can take between hours and days (depending on the activation level one wishes to achieve) where the reverse process can be achieved in minutes simply by exposing the alumina to atmospheric condition (Fig 2.1.1.3c).

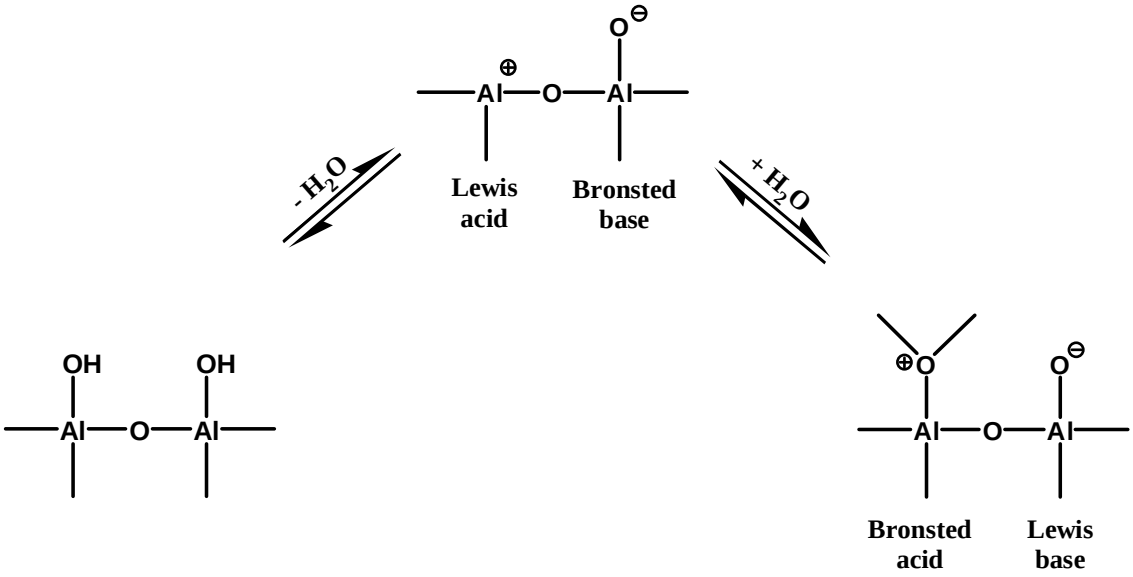


Fig 2.1.1.3c Activation and dehydration of gamma alumina

2.1.1.4 Gamma Alumina and Organic Reactions

As mentioned in the previous section, alumina, in general, and gamma alumina (Brockmann Grade I), in particular, have been extensively studied. Posner, Kropp as well as Kabalka and Pagni have extensively studied organic reaction on activated and unactivated alumina.[12-16] Fig 2.1.1.4a contains a summary of some of these reactions. The reactivity of the alumina depends on the acid and basic sites located on the surface as well as length of hydration and method of preparation. It is important to note that surface acidity or basicity can also be modified by the addition of promoters such as acids or bases. One major advantage of using alumina in organic synthesis is that in most cases, no solvent is needed. This can allow (Green chemistry) removal and purification of the product with a minimum solvent. As mentioned previously, the stereoselectivity of a reaction can be control by using alumina. Kabalka and Gooch have demonstrated that vinylboronic acid bound to the surface of alumina yields *E* and *Z* vinyl iodides when treated with iodine. They demonstrated that the *E*/*Z* isomer ratio could be modified by using different hydrated surfaces and activation (Fig 2.1.1.4b).[17] Previously, alumina was activated using "thermal heating" under a vacuum which resulted in the removal of hydroxyl groups from the surface. The removal of these hydroxyl groups was not the only thing that occurred. As a result of the activation, a few acidic and basic sites were exposed in the form of aluminum cations and oxygen anions (Fig 2.1.1.4c). These active sites mimic the catalytic effect of enzymes in such a way that they cause selectivity on the surface and moderated reactions can be observed. The most effective catalytic effects result from activation of alumina at 400 ^{o}C for 4 hours (Fig 2.1.1.4d). One of the reasons for this "magical number" is the fact that, at this temperature, there are equal amount of exposed acid and basic sites. Only 1 mmol of hydroxyl groups remains on the surface per 1 gram of alumina (this can be calculated by weight loss). The acidity of the alumina using this activation process decrease the pK_a to a range of -3.0 and -8.2 from the original value of 7.0 for the unactivated natural alumina. To modify the acidity of the activated alumina even further, the use of chemisorption or physisorption can be utilized.[18]

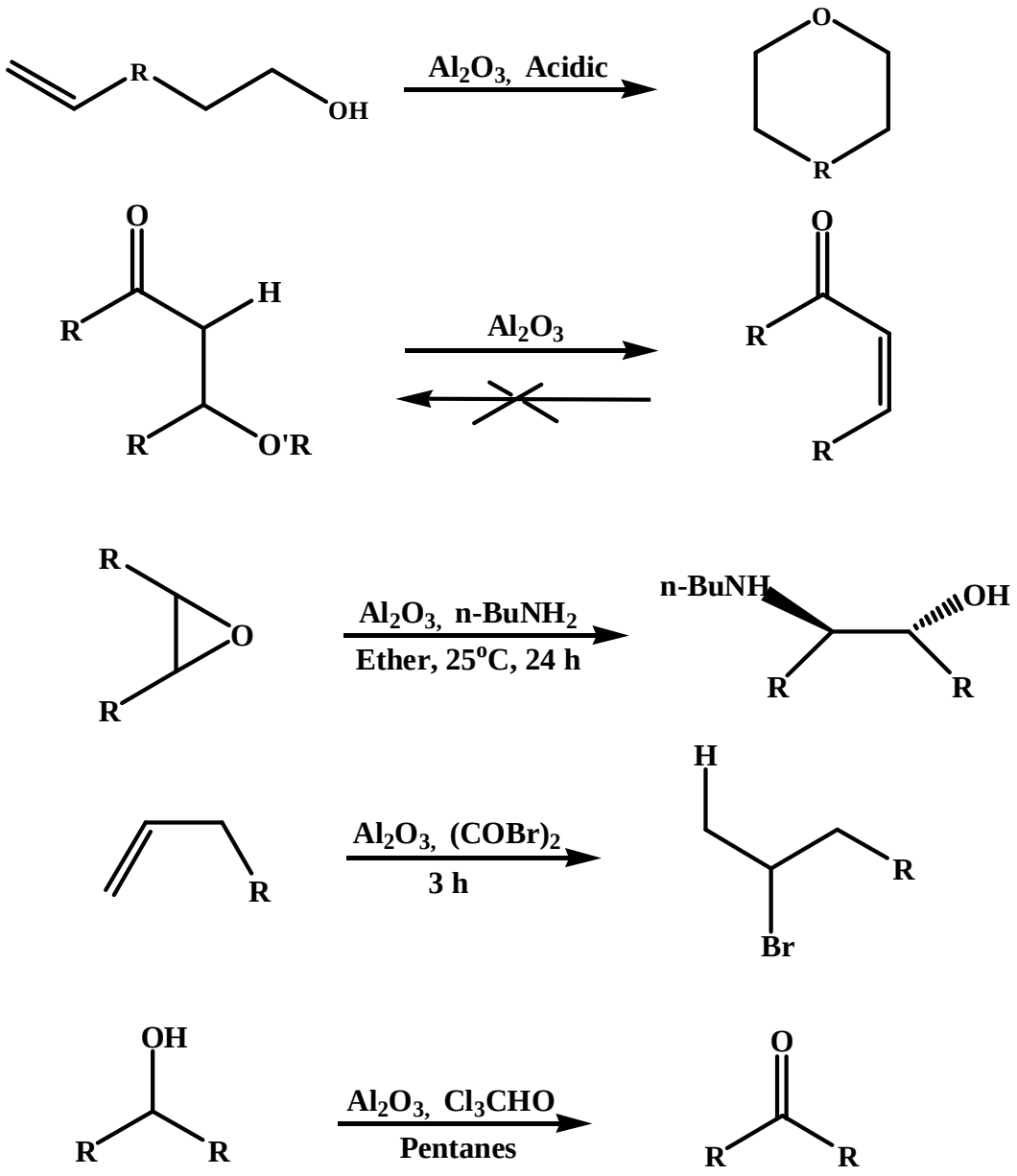


Fig 2.1.1.4a Selected reactions catalyzed by gamma alumina

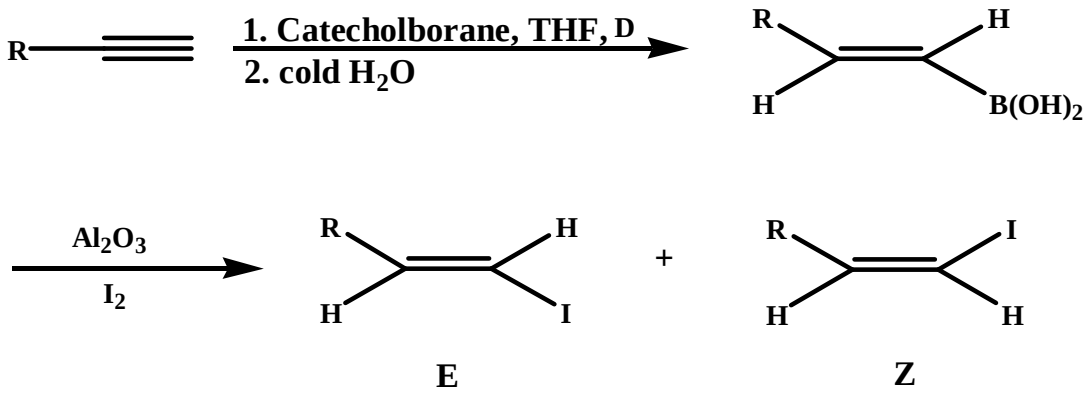


Fig 2.1.1.4b Modification of *E*/*Z* isomers using gamma alumina

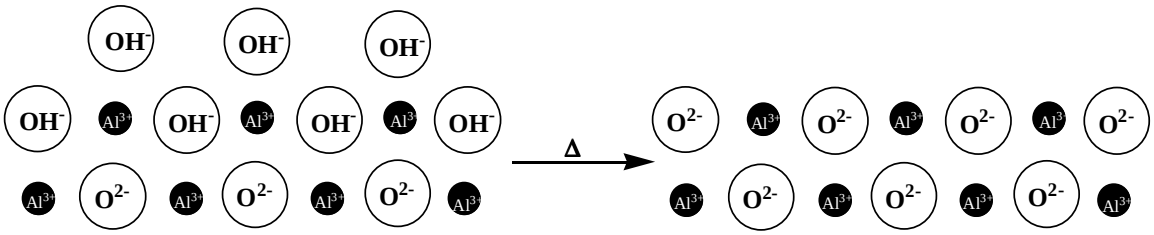


Fig 2.1.1.4c Activation of gamma alumina by dehydration

Fig 2.1.1.4d Optimum temperature and time for the activation of gamma alumina using "thermal condition"

2.1.2 Microwave and Solid Phase

2.1.2.1 Introduction

In the past, before the era of "microwave-assisted organic synthesis" (where temperature and pressure could be easily monitored and controlled), a solvent free synthesis was the only method available if one wished to use microwave irradiation in organic synthesis. The reason was that there was no pressure build-up, and domestic microwave ovens could be safely used. A solvent free reaction, or a dry media reaction, is a reaction that does not use solvents and the reactants (and catalysts - if needed) are either pre-adsorbed or mixed into the dry media. Dry media can be of two types. The first involves microwave transparent materials such as silica, alumina, or clay. The second involves a strongly absorbing inorganic support such as graphite. There are advantages to using dry media which include: cost effectiveness (dry media can be recycled), and environmentally friendliness. Generally, in a lab scale reaction, the use of a dry media technique is straightforward. However, when scaling up a reaction there are few problems that should be noted. These problems include: inefficient mixing, non-uniform heating, and difficulties involved in temperature monitoring. To overcome these problems, specific engineering techniques must be developed.

2.1.2.2 Solvent Free Techniques and Inorganic Solids

As previously discussed, a solid organic material does not absorb microwave energy, therefore, no heating will occur. In order to overcome these "problems" there are three approaches that can be taken. The first approach involves the use of glassware that can absorb the microwave irradiation and generate heat for the reaction. The second involves the addition of a small amount of polar solvent, such as water; the polar solvent allows dielectric heating to take place and subsequently generate heat. [A good example is the reaction of benzoin with urea to produce 4,5-diphenyl-4-imidazolin-2-one.[19] Placing

these two reactants, neat, in the microwave will have no effect. Only with the addition of a few drops of water (or appropriate glassware), will the reaction go to completion (Fig 2.1.2.2).[20]]

The third approach involves the use of weakly absorbing inorganic materials. These materials can be divided into two groups. The first are inorganic materials such as silica, clay and alumina which can act as support materials and can eliminate the use of solvent. These inorganic materials can immobilize reactants on porous solid supports. The second group of inorganic support materials are those that can act as catalysts. Alumina, belongs to both groups. It has hydroxyl groups on the surface that can act as an acid, in addition to being used as an activation site. Alumina can absorb and convert the energy from the microwaves and transfer this energy to the reactants. There are many organic compounds that do not couple well with microwaves and require high temperature. In such cases, inorganic materials that can couple well with microwaves and, at the same time, provide mechanical and environmental support to the reactants are highly desirable.

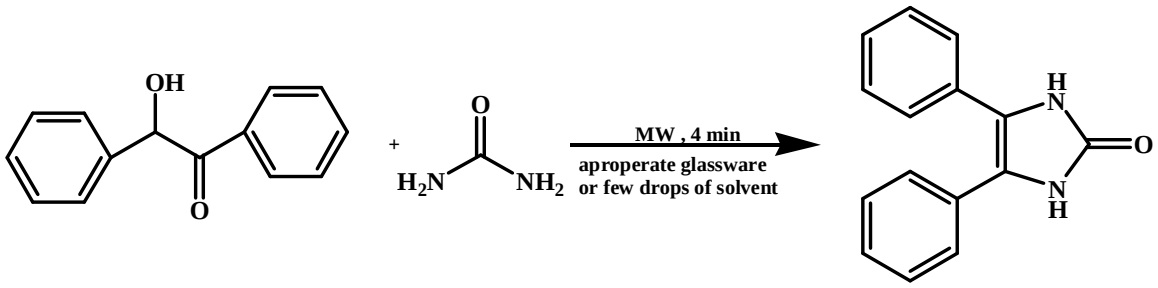


Fig 2.1.2.2 Synthesis of imidazolin-2-one

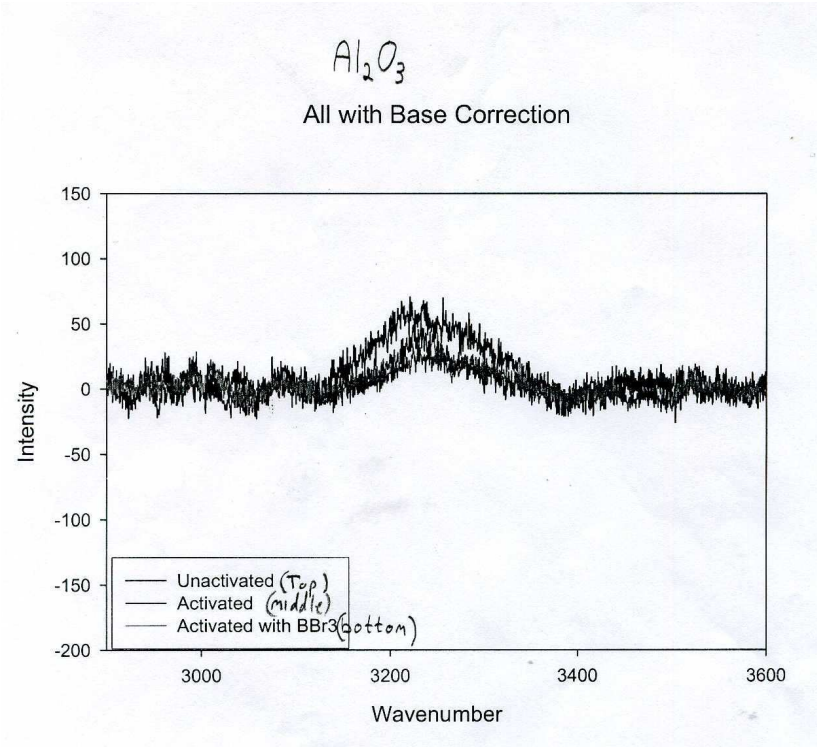
2.1.2.3 Open vs. Closed Vessel Conditions

Today, microwave irradiation can be carried out in two different ways: open vessel and closed vessel. Each method has it own advantages and disadvantages. The closed vessel method refers to the fact that the reaction takes place in pressurized environment. In the open vessel mode, the reaction mixture is open to the environment. When using a solvent, the closed vessel mode permits rapid dielectric heating which allows the temperature to far exceed the boiling point of the solvent. One thing that should be mentioned, without going into great detail, is that solvents will change their dielectric constant (see section 1.1.2.1) under such conditions. The use of a solvent in an open vessel mode permits reflux. When using a "solvent free" synthesis, the open vessel mode allows the escape of volatile products (by the use of a vacuum pump or an oil trap outlet, for example). When choosing a solvent for an open vessel mode, one should consider dielectric constant, boiling point, and solubility. Today most reactions are carried out under closed vessel conditions due to significant rate enhancements.

2.1.2.4 Microwave Effects on alumina

It is now known that something significant occurs on the surface of alumina under microwave irradiation. The presence of hydroxyl groups on the surface of the alumina can induce the coupling of the alumina with the microwaves. The hydroxyl groups are polar and can generate dielectric heat. Raman and NMR spectroscopies provide evidence for these phenomena. Raman spectroscopy of unactivated alumina reveals broad hydroxyl group absorption with maximum intensity at approximately 3230 cm^{-1}. When the same alumina has been activated at 130 °C by microwave irradiation, the area under the peak due to the hydroxyl groups stretch decreases by approximately 20% (Fig 2.1.2.4a). Solid state proton NMR analysis of unactivated alumina reveals a sharp singlet due to the surface layer hydroxyl groups. When the same alumina has been activated at 130 °C by microwave irradiation, the presence of at least five broad singlets in the proton NMR spectrum (Fig 2.1.2.4b) are observed. The current results can be compared with

those of Knözinger and Ratnasamy. In their review, they noted that several hydroxyl group stretches had been detected by vibrational spectroscopy when alumina was activated thermally at various temperatures. These results clearly show that adjacent hydroxyl groups react via proton transfer to form water, which is then driven from the surface. This ultimately creates surface hydroxyl groups that are in different environments and, as a result, yield different peaks in the proton NMR spectrum. Furthermore, this dehydration reaction exposes aluminum ions to the surface, which then catalyze various reactions. In the next chapters, the efficiency of microwave activated alumina on various reactions such as Diels-Alder, Claisen, and Fries rearrangements is described.



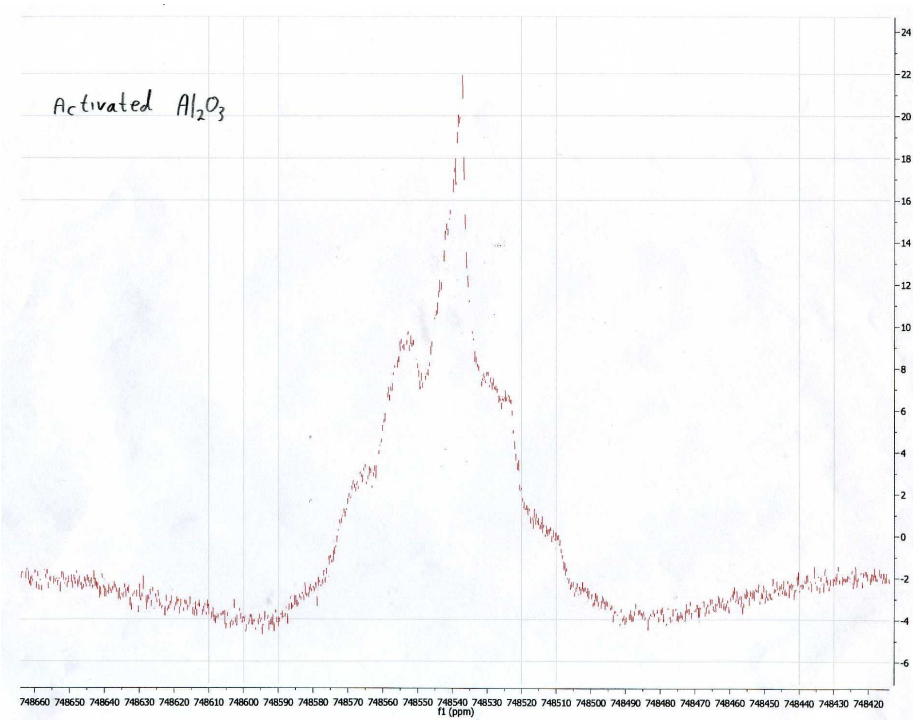


Fig 2.1.2.4a (top) Raman spectroscopy of activated alumina and 2.1.2.4b (bottom) Solid state proton NMR of activated alumina.

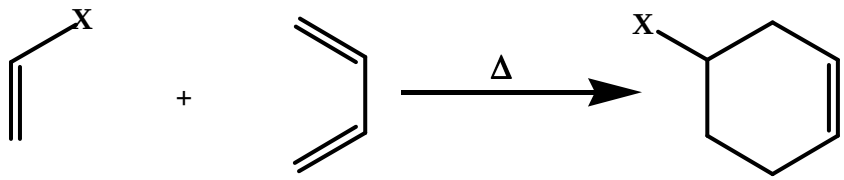
CHAPTER 2

DIELS-ALDER REACTION

2.2.1 Diels-Alder

2.2.1.1 Introduction

The Diels-Alder reaction is one of the most important reactions in organic chemistry. The Diels-Alder reaction involves a 2+4 cycloaddition between a conjugated diene (4 π-electrons) and an electron deficient dienophile (2 π-electrons). The reaction creates a six-member ring, which enables up to four stereogenic centers (Fig2.2.1.1a). The end product of this one step reaction, and the driving force behind the reaction, is the formation of two new σ-bonds (at the expense of the two π-bonds), which are energetically more stable. In most cases, the reaction is facilitated by the dienophile containing electron withdrawing groups. In general, carrying out a Diels-Alder reaction without the aid of a catalyst requires elevated temperatures and long reaction times.[14] The use of Lewis acids,[2] in addition to the use of microwave irradiation,[21] can increase stereoselectivity, regioselectivity, and reaction rate. The stereoselectivity of the reaction, where *endo* is usually prefered over *exo*, is due to a plane-to-plane orientation,[22] HOMO-LUMO interaction,[23] and the transition state.[24]



Dienophile Diene

Fig 2.2.1.1 General Diels-Alder reaction.

2.2.1.2 Diels-Alder in organic synthesis

Cycloaddition reactions in general, and Diels–Alder reaction in particular, are among the most efficient ways to synthesize six-member rings.[25] Over the years, numerous groups used a variety of solvents, catalysts, reaction conditions, etc. to enhance rates, yields, stereo and regioselectivity.[26] The use of homogeneous Lewis acid, can lead to problems. The synthesis usually requires preparation of large amounts of catalyst, leading to problems involving hazardous waste disposal, and harm to the environment.[27] The use of a heterogeneous medium (solids) such as alumina can eliminate some of these problems. In this section (and the next one), a brief review of some of the methods that have been used will be discussed. A typical Diels–Alder cycloaddition reaction that has been studied throughout the years is that of cyclopentadiene (CP) with methyl acrylate (MA) (Fig 2.2.1.2a). The reaction results in a mixed product of *endo/exo* adduct. For reasons previously mentioned, the *endo* adduct is preferred. Although the *endo* adduct is preferred over the *exo* one, this ratio can be manipulated by various methods. When an uncatalyzed reaction between CP and MA is carried, the ratio observed is 7.3:1 (*endo/exo* respectively). With the addition of unactivated alumina, the ratio changes to 5.5:1. When using activated alumina (thermal condition 400 ^{o}C) the ratio increases to 50:1 (mainly due to the expanded acid sites). This ratio can be increased to 99:1 by using $AlCl_3$ in benzene.[33] More details about stereoselectivity in the reaction of CP and MA can be found in Michael McGinnis's dissertation (pages 14-17).[9]

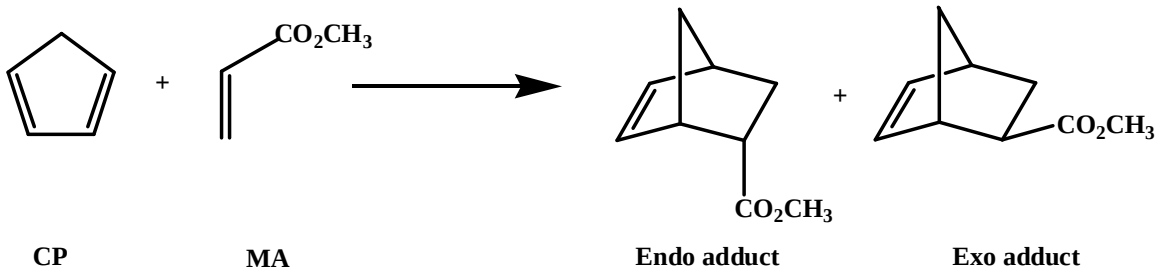


Fig 2.2.1.2a Diels-Alder reaction of CP and MA.

In addition to the reaction of CP with MA, the reactions between isoprene (IP) and MA, and of dimethyl maleate (DMM) and CP have been studied (Fig 2.2.1.2b). These reactions were studied using activated alumina/boron trihalide mixtures (next section) in the presence and absence of a solvent (toluene). The reaction of IP and MA was carried out at room temperature for an hour and, depending on the boron trihalides and solvents used, the yields ranged from 1% (for Al_2O_3/BF_3) to 80% (for Al_2O_3/BCl_3 in toluene). The *para/meta* ratio ranged from 6:1 *para/meta* (for Al_2O_3/BF_3) to 49:1 (for Al_2O_3/BBr_3). As for the reaction of DMM and CP, it was carried out at room temperature for an hour, as before, depending on the boron trihalides and solvents used, the yields range from 5% (for Al_2O_3/BBr_3) to 97% (for Al_2O_3/BBr_3 in toluene). The *trans/endo/exo* ratio obtained was 4:10:1 (for Al_2O_3/BBr_3) and 50:1:0 (for Al_2O_3/BBr_3 in toluene) (respectively).

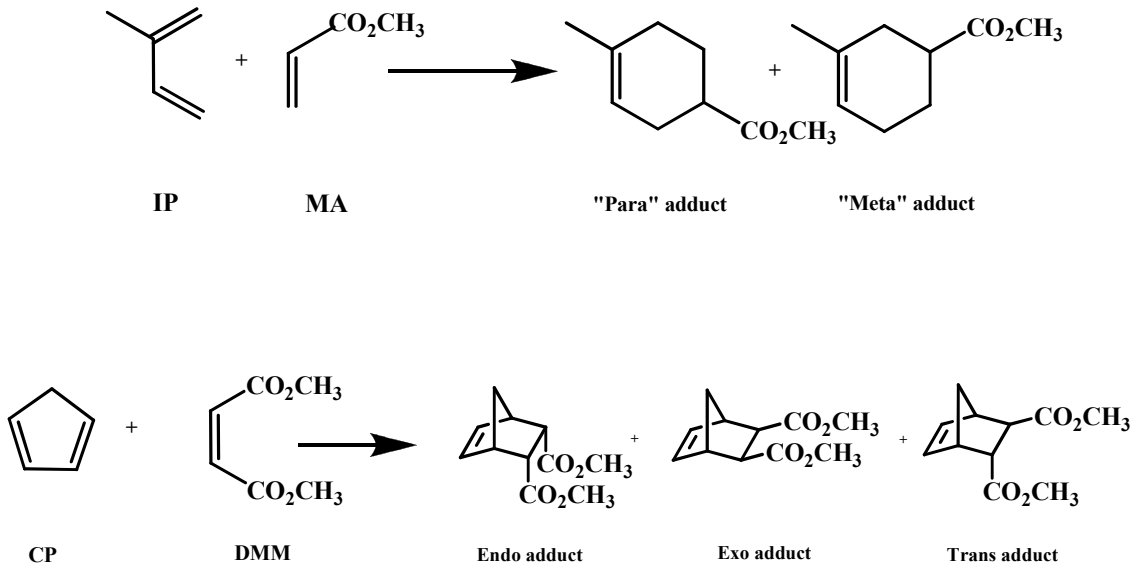


Fig 2.2.1.2b Diels-Alder reaction between IP and MA (above) and between CP and DMM (bottom).

2.2.1.3 Diels-Alder reaction and Lewis acids with the addition of boron trihalides

The Diels-Alder reaction can be influenced by the addition of various Lewis acids. The Lewis acid can contribute to enhanced stereoselectivity as well as improved yields. When a Lewis acid such as activated alumina is added to the reactants, a complex between the acid and the dienophile forms (Fig 2.2.1.3a). This interaction allows the electron withdrawing substituent on the dienophile to make the double bond more electron deficient. The result of this electron deficient double bond is a faster and a more selective reaction (Fig 2.2.1.3b). In addition to alumina being a Lewis acid, the addition of stronger acids such as boron trihalides can enhance the reactivity even further.[34] In the complex of Al_2O_3/BX_n, the enhancement is due to the boron's empty 2p orbital which allows the boron trihalide to chemically bond to the surface of the alumina. The boron halide can bond to the hydroxyl groups (in the unactivated form) or to the oxide anions (in the activated alumina). The Lewis acidity decreases in the following order: $BI_3 > BBr_3 > BCl_3 > BF_3$. When boron trihalide reacts with alumina, it creates a unique surface, depending on the halide use (Fig 2.2.1.3c). In addition, each boron trihalide results in a different acidity that can be measured using indicators/dyes. The use of a boron trihalide can have a major drawbacks. For example, reactions using BBr_3 will result in the release of HBr to the environment. In addition, boron trihalides often polymerize the reactants and lead to a lower yields. The preparation of activated Al_2O_3/BX_n is very tedious: This procedure involves a vacuum system, an open flame to dry the alumina, the addition of a solvent such as hexane, and long reaction times (the slurry reaction mixture has to be stirred for 3 hours). Nevertheless, the use of boron trihalide can lead to significant results. For example, in the reaction between IP and MA, the large regioselectivity obtained by using activated alumina can be attributed to steric interactions between the surface of the alumina and IP. These interactions force the methyl group away from the surface, which results in a preferred formation of the "*para*" product (Fig 2.2.1.3d).

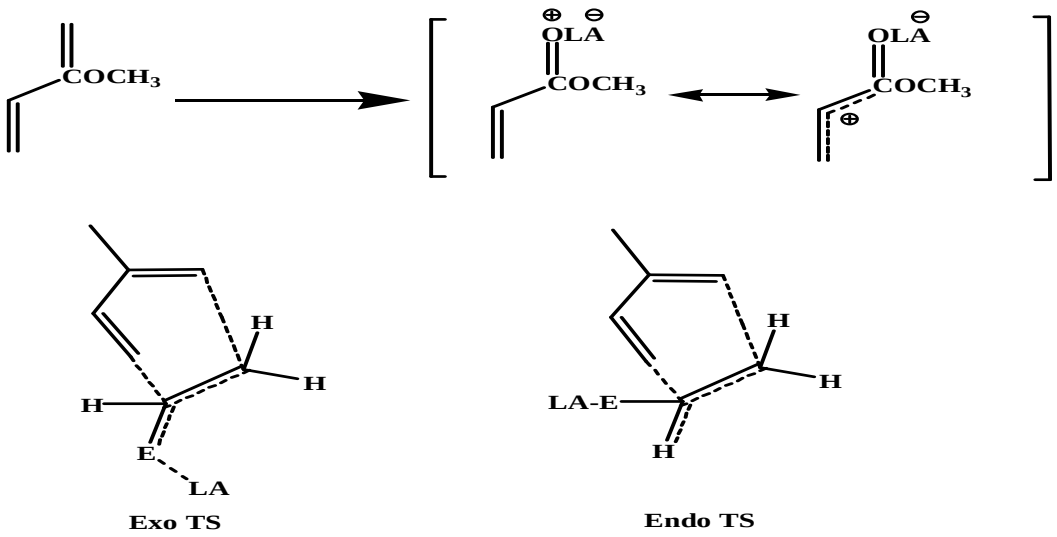


Fig 2.2.1.3a,b The Lewis Acid effect on Diels-Alder reaction.

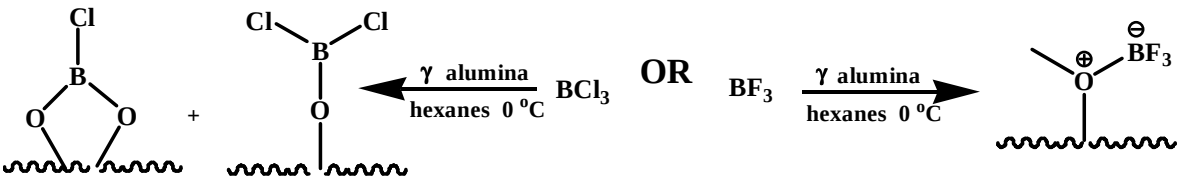


Fig 2.2.1.3c Reaction of BCl_3 (left) and BF_3 (right) with alumina.

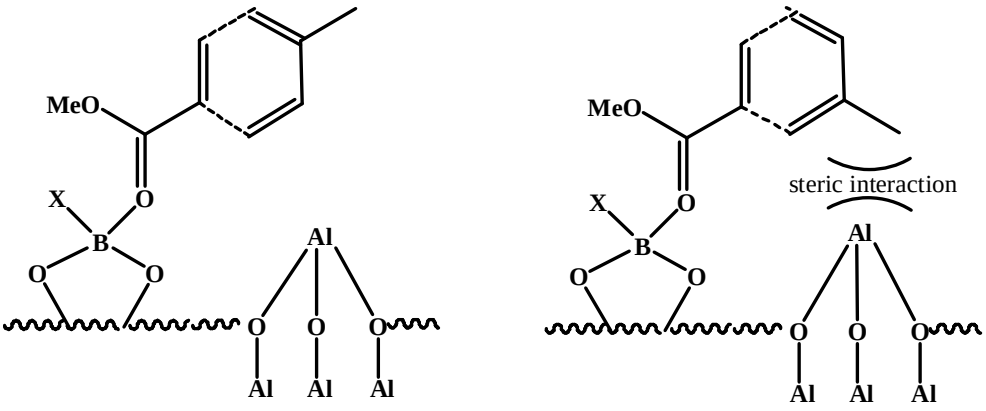


Fig 2.2.1.3d Transition state of IP and MA on bromanated alumina.

2.2.1.4 Diels-Alder reaction and microwave heating

Microwave irradiation of Diels–Alder reactions has become increasingly popular in recent years.[28] There are reasons for the use of microwave irradiation in Diels–Alder reactions: microwave irradiation can accelerate the reaction and can lead to reaction efficiency. In addition, one can use high temperatures without pressure build up when using a closed vessel mode. In the last few years, the use of microwaves for Diels-Alder has involved two approaches: homogeneous and heterogeneous. In 1986, Giguere reported the use of domestic microwave ovens in various Diels-Alder reactions, both neat and using p-xylene as a solvent (Fig 2.2.1.4a).[29] With the development of better microwave instrumentation, solvents such as ionic liquids, dimethylformamide, methanol, acetone, glycol, dimethyl sulfoxide, and even water have been used for Diels-Alder reactions.[30] At the same time, the use of solid supports such as clay were studied to enhance the Diels-Alder reaction.[31] Each approach has its advantages and disadvantages. Ionic liquids, for example, couple very well with microwaves through ionic conduction and hence can be quickly heated at a rate of 10 °C per second without significant pressure build-up.[32] For example the Diels-Alder reaction between 2,3-dimethylbutadiene and methyl acrylate requires 18-24 hours at 95 ^{o}C using "traditional" heating methods (oil bath). Using microwave irradiation (Fig2.2.1.4b), this reaction goes to completion within 5 minutes (with the addition of small amount of ionic solvents).

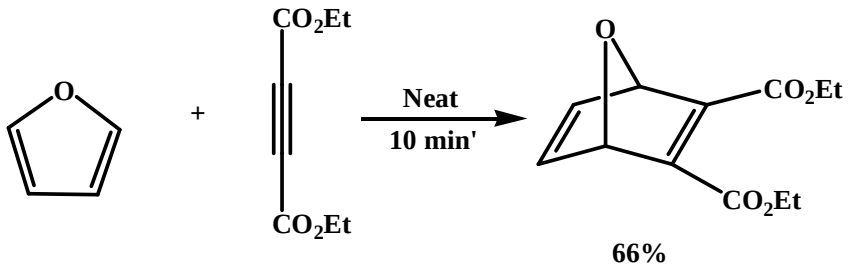


Fig 2.2.1.4a One of the first reported Diels-Alder reaction using MW.

The use of water as a solvent in microwave reactions can have a drastic affect on Diels-Alder reactions. Yu reported the use of a recyclable Lewis Acid catalyst, an organotungsten, using water as a solvent (Fig 2.2.1.4c).[35] Yields of 90% were obtained at 50 ^{o}C in less than one minute. For comparison, studies of typical Diels-Alder reaction using water as a solvent (under thermal conditions) were reported to be in the hours range.[35,36]

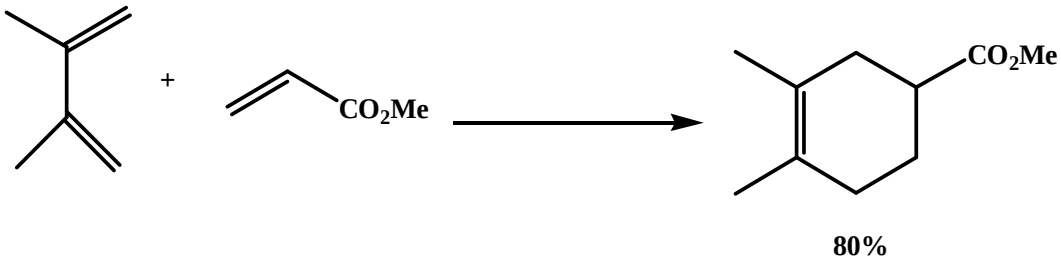


Fig 2.2.1.4b The first known use of D-A reaction in MW.

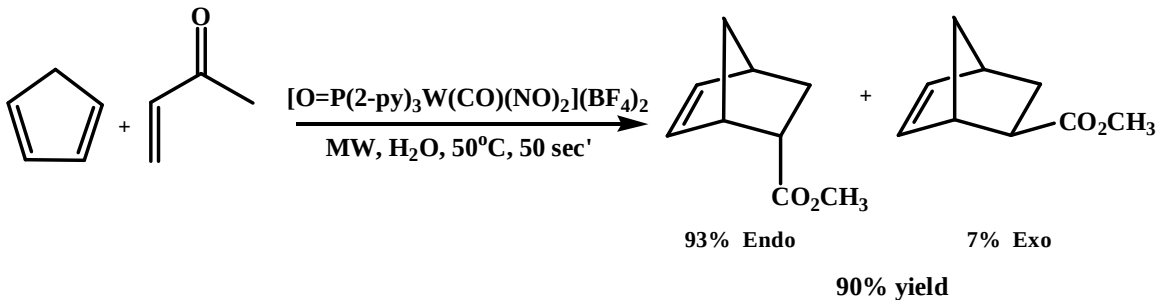


Fig 2.2.1.4c Organotungsten Lewis Acid catalyst D-A reaction.

2.2.2 Results and discussion

This study constitutes the first use of activated alumina for Diels-Alder reactions using microwave irradiation. One of the main goals for applying microwave irradiation to alumina and the Diels-Alder reaction was to compare the results obtained in previously in our lab. The first phase of the project was to determine the best method to activate the alumina. An open bottle of gamma alumina (the exact date this bottle was initially opened could not be determined- although a conservative guess would be about 10 years) was used. The first reaction employed 2 gram of Al_2O_3 in a septum capped test tube (along with a stirrer) flushed with argon via a needle inserted through the septum and an exit needle attach to an oil trap. The alumina was irradiated for ten minutes at 120 ^{0}C. This method was inefficient: the desired temperature was not reached and accumulation of vapor water was observed at the top of the test tube. After a few additional trials, conditions were optimized. Best results were obtained when one gram of alumina was irradiated at 300 Watt for twenty minutes at a temperature of 130 ^{o}C (Table 2.2.2a). The vent to the oil trap was replaced by a needle attached to a vacuum pump. This adjustment solved the condensation problem. The next phase involved the determination of the percentage of water lost during activation. This was done by measuring the weight of the sample before and after the activation. The average weight loss was about 0.051g per 1g (approximately 5.1%) of alumina activated for bottle # 1. When a different bottle of alumina was used (bottle # 2), it was observed that less weight was lost. The average weight loss for this bottle was about 0.017g per 1g (approximately 1.7 %) of alumina activated. A new bottle was purchased (bottle # 3). The average weight loss for samples from the new bottle was about 0.004g per 1g (approximately 0.4%) of alumina activated. According to the manufacture, the moisture content at the time of packing was 1.8%. From these data, it is reasonable to conclude that the older the bottle the more moisture it contained and thereby will lose more weight during activation.

Table 2.2.2a Selected result for activation of alumina (bottle #1, per 1 gram).

Trail #	Power	Temperature ^{o}C	Time Ramp/Hold	Weight loss
1	200W	90	20/10	0.043g’
2	200W	100	20/10	0.045g’
3	200W	90	20/5	0.017g
4	200W	90	20/15	0.055g
5	300W	150	10/10	0.058g
6	200W	90	5/15	0.047g
7	300W	130	5/20	0.056g
8	300W	130	5/30	0.056g
9	300W	130	5/40	0.057g

Table 2.2.2b Selected results for reaction time of C.P and M.A.

Trail #	Power	Temperature ^{o}C	Time Ramp/Hold	Endo/Exo Ratio	Yield (%)
1	100	60	20/15	81/19	48
2	100	60	10/7	79/81	49
3	100	60	5/15	87/13	55
4	100	70	20/15	88/12	54
5	100	50	10/10	80/20	45
6	100	60	15/15	91/9	60

The next phase of this study was focused on the *endo/exo* ratio and the yields obtained by reacting CP and MA on the surface of the alumina. As before (keeping the activation of the alumina at 300 W, 130 ^{o}C, 20 minutes), the optimum method to obtain the best ratios and yields were determined.

1. CP and MA were added to unactivated alumina and the mixture stirred for 15 minutes. A 30% yield and a 70/30 *endo/exo* ratio were obtained.
2. CP and MA were added to activated alumina and the mixture stirred the reactants for 15 minutes (no microwaves). A 40% yield and an 89/11 *endo/exo* ratio were obtained.
3. CP and MA were added to unactivated alumina and placed in the microwave (100 W, 15 minutes, 60 ^{o}C). A 50% yield and an 89/11 *endo/exo* ratio were obtained.
4. CP and MA were placed in a test tube (no alumina) and irradiated in the microwave (100 W, 15 minutes, 60 ^{o}C). A 60% yield and a 68/32 *endo/exo* ratio were obtained.

From these results, the following can be concluded:

1. A high yield of product under microwave irradiation can be obtained without the aid of alumina.
2. Higher stereoselectivity is obtained using activated alumina.

In addition to the above results, reactions were repeated using a new bottle of gamma alumina handled inside an air-free/ moisture-free (glove box) environment. A duplicate set of experiments was carried out under atmospheric conditions. The purpose of this experiment was to determine the behavior of the same alumina under varying conditions. Over the course of two weeks, reactions of CP with MA were carried out on activated and unactivated alumina (Table 2.2.2c). From these results, the following was concluded:

1. Microwave irradiation can restore the alumina to its initial state in terms of the endo*/exo* ratio obtained in Diels-Alder reactions.
2. Microwave irradiation can increase the yield obtained.

Table 2.2.2c Control experiment using moisture free and atmospheric conditions.

Time	Condition	Weight loss	Endo/Exo Ratio	Yield
0 Day	Unactivated	-	91/9	31%
0 Day	Activated	5%	91/9	44%
1 Day	Activated	5%	90/10	48%
3 Day	Activated	7%	89/11	44%
1 Week	Activated	7%	88/12	45%
2 Weeks	Unactivated	-	81/19	15%
2 Weeks	Activated	10%	83/17	47%
2 Weeks	Unactivated From Glove Box	-	90/10	30%
2 Weeks	Activated From Glove Box	4%	93/7	46%

In an effort to increase stereoselectivity, the reaction of CP with MA was carried out with the aide of a Lewis acid boron tribromide (BBr_3). BBr_3 was added dropwise at 0 ^oC to activated alumina (300 W, 130 ^oC, 20 minutes) followed by the addition of CP and MA and the mixture stirred for 5 minutes. The adducts formed in 40% yield and a 99/1 *endo/exo* ratio was obtained using bottle # 1 whereas a 45% yield and a 99/1 ratio was obtained with bottle # 3. The reaction of isoprene with methyl acrylate was carried out on BBr_3/alumina (where the alumina was activated at 300 W, 130 ^oC, 20 minutes) and then stirred for five minutes at 0 °C. The product was the *para* adduct exclusively, although it formed in very low yield (5%). Previous results using BBr_3/alumina

(unactivated) for the reaction of isoprene with methyl acrylate resulted in a 76% yield in 3 hours, with a *para* to *meta* selectivity of 49 to 1.[9] Raman spectroscopy carried on the boronated alumina (treated with boron tribromide) revealed that approximately 70% of the surface hydroxyl groups had been removed. Solid state proton NMR spectroscopy of the boronated alumina revealed the presence of at least seven types of hydrogen on the surface. Solid state ^{11}B demonstrated that there were boron atoms in four different environments on the surface. This might be due to the surface bound boron bonding to various numbers of bromine and oxygen atoms. In addition, the large number of peaks in the proton NMR spectrum of the boronated solid can contribute to the unreacted hydroxyl groups in different environments.

2.2.3 Conclusion

Microwave irradiation of alumina for short periods of time provides an effective, rapid, and convenient way to activate alumina. One explanation is that, while heating the solid thermally (from the outside in), adjacent hydroxyl groups on the surface of the solid form water which is then driven from the surface. In such cases, "normal" aluminum cations are initially exposed to the surface. These "normal" aluminum cations in the second layer of the solid are still surrounded by several hydroxyl groups from the first layer of the solid. Microwave activation, on the other hand, may superheat small regions of the surface, resulting in the liberation of several water molecules in close proximity to one another. This would expose aluminum cations to the surface in different environments than the previously noted "normal" aluminum cations. Aluminum cations in different environments should catalyze the Diels-Alder and other reactions in different ways.

2.2.4 Experimental Section

2.2.4.1 General Procedure

All glassware was oven dried at 110 ^{o}C and flushed with argon before use. In most cases, disposable syringes and needles were used. Gas chromatographic mass spectrometay was carried out using a HP GC-MS (6890 GC/ 5973 MSD, Column HP-5msi). All yields reported were calculated from peak areas generated by GC/MS where decane was used as internal standard. Solid state ^{1}H, ^{11}B, and ^{13}C NMR spectra were carried using a 400MHz solid state instrument. The standard for solid state NMR was measured using a rotor filled with sodium tetraphenylborate and D_2O. Raman spectroscopy was carried out using a Dilor XY Instrument (S.A., Inc., Edison, NJ). Liquid reagents that were moisture/oxygen sensitive (such as BBr_3) were transferred under positive argon pressure. Solids reagents that were sensitive to moisture/oxygen were transferred in a glove box and were used under an argon or nitrogen environment.

2.2.4.2 Representative Procedure for the reaction of CP and MA

A 10-mL test tube containing a magnetic stirrer bar and a cap was flushed with argon and weighed. One gram of alumina was added under argon and the test tube was capped, weighed and placed in a microwave chamber. A commercial vacuum pump was introduced to the test tube using a needle placed through the septum cap. Microwaves were then used to activate the reaction in the open vessel mode at 300 W for 5 minutes ramp time (20 ^{o}C /minute), 20 minutes hold time and 130 ^{o}C. When activation was complete, the test tube was weighed again and the percentage weight loss was calculated. Cyclopentadiene (0.12 mL, 1.5 mmol) was added dropwise to the test tube followed by the addition of methyl acrylate (0.13 mL, 1.5 mmol). Cyclopentadiene was prepared by cracking (distill) dicyclopentadiene at 38 ^{o}C (Acros Organics). The reaction mixture was placed in the microwave chamber and activated in the open vessel mode at 100 W for 15 minutes ramp time (3 ^{o}C /minute), 15 minutes hold time and 60 ^{o}C. When activation was

complete, the alumina mixture was washed using diethyl ether (10-mL) and the ether solution analyzed by GCMS. The reactions of isoprene and methyl acrelate were run and analyzed in the same fashion.

2.2.4.3 Procedure for the reaction of CP and MA on BBr_3/Al_2O_3

A 10-mL test tube containing a magnetic stirrer bar and a cap was flushed with argon and weighed. One gram of alumina was added under argon and the test tube was capped, weighed and placed in a microwave chamber. A commercial vacuum pump was introduced to the test tube using a needle placed through the septum cap. Microwaves were then used to activate the reaction in the open vessel mode at 300 W for 5 minutes ramp time (20 ^{o}C /minute), 20 minutes hold time and 130 ^{o}C. When activation was complete, the test tube was weighed again and the percentage weight loss was calculated. The test tube was placed in ice bath and flushed with argon via a needle inserted through the septum and an exit needle attach to an oil trap. Boron tribromide (0.15 mL, 1.5 mmol) was added dropwise and the mixture stirred for 5 minutes. Cyclopentadiene (0.12 mL, 1.5 mmol) was added dropwise into the test tube follow by the addition of methyl acrylate (0.13 mL, 1.5 mmol). Cyclopentadiene was prepared by cracking dicyclopentadiene dimmer at 38 ^{o}C. The reaction mixture was allowed to stir for 15 minutes. The Al_2O_3/BBr_3 and reaction mixture were then washed using diethyl ether (10 mL) and the ether solution analyzed by GCMS.

2.2.5 Analytical Data

1a 1-Hexa-1,4-dienyl-4-trifluoromethylbenzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dd, 1H, *J* = 5.6, 3.2 Hz), 5.92 (dd, 1H, *J* = 5.6, 3.2 Hz), 3.62 (s, 3H), 3.20(s, 1H), 2.94 (dt, 1H, *J* = 9.2, 4.0 Hz), 2.90 (s, 1H), 1.90 (ddd, 1H,

J = 11.6, 9.2, 3.6 Hz), 1.36-1.43 (m, 2H), 1.27 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 29.33, 42.56, 43.23, 45.68, 49.61, 51.29, 132.41, 137.65, 175.09.

1b 4-Methyl-cyclohex-3-enecarboxylic acid methyl ester and 3-methyl-cyclohex-3-enecarboxylic acid methyl ester

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (m, 1H), 3.69 (s, 3H), 3.67 (s, 3H) , 2.48 (m, 1H), 2.31 (m, 2H), 1.96-2.00 (m, 4H), 1.73 (s, 3H), 1.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): 23.33, 26.12, 33.21, 36.67, 42.22, 51.15, 125.32, 142.71, 175.41.

CHAPTER 3

CLAISEN AND FRIES REARRANGEMENTS

2.3.1 Claisen Rearrangement

2.3.1.1 Introduction

Claisen rearrangements can be divided into two major categories: aliphatic and aromatic. In the aliphatic cases, allyl vinyl ethers undergo [3,3]-sigmatropic rearrangement (σ bond migration in a π system) to give γ,δ-unsaturated carbonyl compounds. In the aromatic cases, allyl aryl ethers undergo sigmatropic rearrangement to form an intermediate which rapidly tautomerizes to an *ortho*-substituted phenol (Fig 2.3.1.1a). In some cases, the intermediates undergo Cope rearrangement to give the corresponding *para* substituted phenol.[37] This electrocyclic reaction is an intramolecular processes that can proceed under thermal or catalytic conditions. Claisen rearrangements, in general, require high reaction temperatures (~200 ^{o}C) and can result in several byproducts. In nature, Claisen rearrangements can be catalyzed by enzymes such as chorismate mutase.[38] The mechanism (Fig 2.3.1.1b) by which this reaction proceeds resembles that for the Diels-Alder reaction.

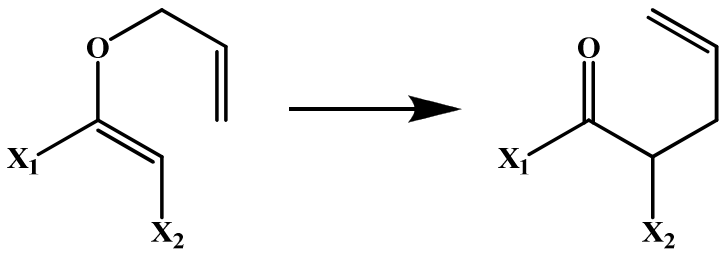


Fig 2.3.1.1a Claisen rearrangement of aliphatic compound.

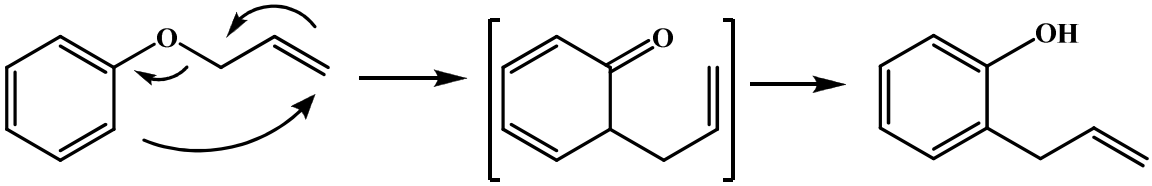


Fig 2.3.1.1a The mechanism for aromatic Claisen rearrangement.

2.3.1.2 Literature review of Claisen rearrangement

Numerous papers have been published about Claisen rearrangements. In fact, there is a magazine dedicated to publications involving Claisen rearrangements. Claisen rearrangement reactions are abundant in nature. For example, the first step of the metabolic transformation of chorismic acid into phenylalanine or tyrosine involves a Claisen rearrangement. The *ortho*-allylated poly-functionalized phenol derivatives are of great importance in biology, and just recently the study of the retrosynthesis of the toxin Ecklonialactone B was published.[39] The use of the Claisen rearrangement under microwave irradiation has not yet been fully explored. As with Diels Alder chemistry, using microwave irradiation to perform Claisen rearrangements can be carried out neat or with the aid of a solvent. Wada and Yanagida reported the double Claisen rearrangement of bis(4-allyloxyphenyl)sulfone to produce the bis(3-allyl-4-hydroxyphenyl)sulfone without the aid of a solvent (Fig. 2.3.1.2a).[40] Bis(3-allyl-4-hydroxyphenyl)sulfone is used in industry for heat/pressure sensitive recording. Another example of a neat synthesis using a Claisen rearrangement involves acetophenone. Acetophenone is of use in medicine and the cosmetic industry. In traditional methods, the conversion of 2-allyloxy-acetophenone to 3-allyl-2-hydroxyacetophenone can take up to 44 hours at 200 ^{o}C to reach completion. Using microwave irradiation with air cooling (see section 1.1.3) allows for completion of this reaction in 1 hour at 210 ^{o}C (Fig. 2.3.1.2b).[41]

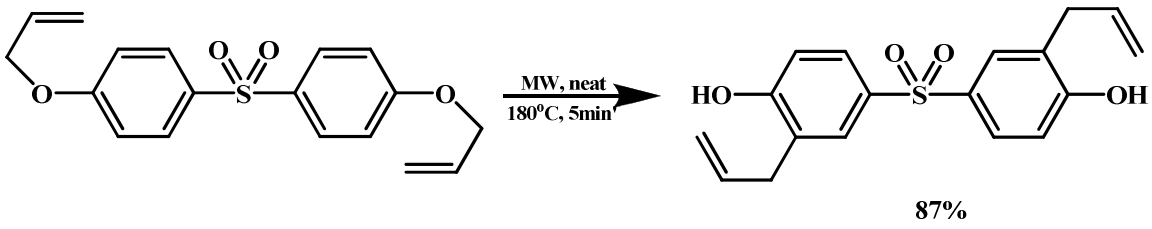


Fig 2.3.1.2a The synthesis of bis(3-allyl-4-hydroxyphenyl)sulfone.

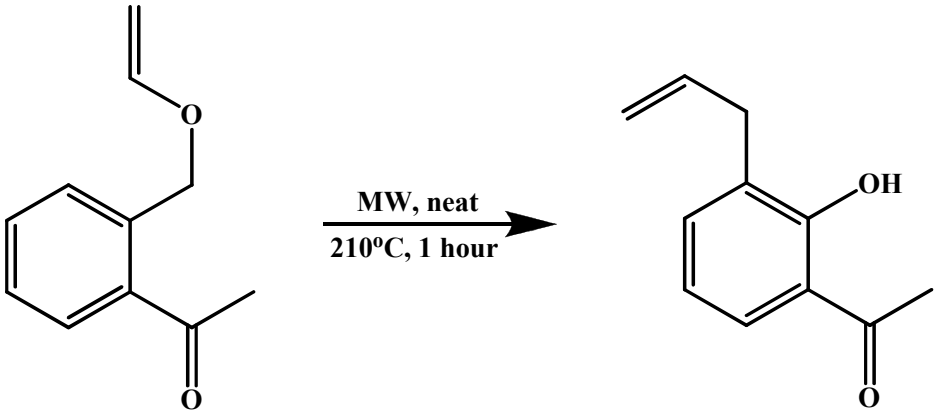


Fig 2.3.1.2b The synthesis of 3'-allyl-2'-hydroxy-acetophenone.

Evidence for the microwave effect (see section 1.1.4) in Claisen rearrangements can be seen in the work of Ley and coworkers.[42] They studied the role of allyl ether in the multi-step synthesis of carpanone (a natural product, hexacyclic molecule with five contiguous stereogenic centers, with no element of symmetry or optical activity). Employing microwave irradiation of the allyl ether was most effective when using 3 pulses of 15 minutes each at 220 °C (Fig 2.3.1.2c). When one burst of irradiation for 45 minutes or 8 short bursts for 2 minutes each were used, the yields decreased approximately by 15%.

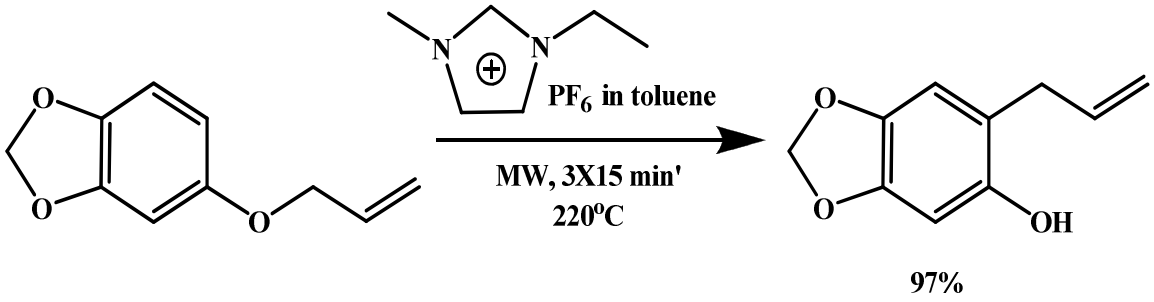


Fig 2.3.1.2c Step # 5 in the synthesis of carpanone.

2.3.2 Fries rearrangement

2.3.2.1 Introduction

Fries rearrangement involves the conversion of aryl esters to the corresponding acyl phenol. The reaction is usually catalyzed by Bronsted or Lewis acids such as $AlCl_3$ or BF_3. The pathway of the reaction is such that the acid forms a complex with both starting material and product. When a solvent is used as reaction media, the complex can result in the formation of an acylium ion (Fig 2.3.2.1). Hydrolysis of the reaction will result in the release of the acid from the product. Both *ortho* and *para* substitutions are possible. The selectivity of the reaction depends on the aryl group used as well as the temperature at which the reaction is carried out. One of the main drawbacks of using Fries rearrangement is the need for strong acids. Many acids used for this reaction are corrosive or toxic in nature. Furthermore, when hydrolysis is used to release the desire product, a violent reaction typically occurs.

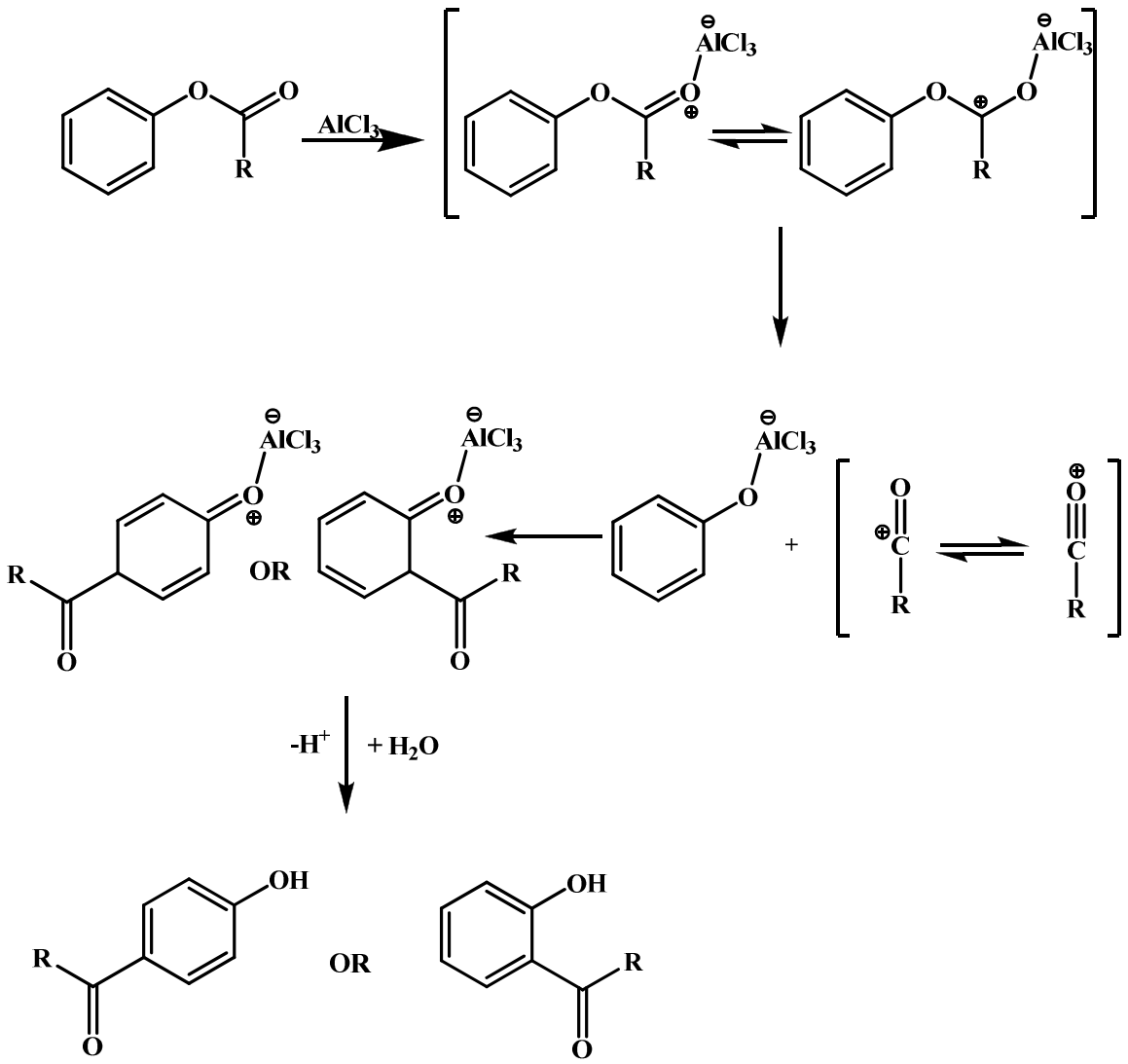


Fig 2.3.2.1 Reaction mechanism for Fries rearrangement.

2.3.2.2 Literature review for Fries rearrangement

Some of the main uses of Fries Rearrangement are in the pharmaceuticals industry.[43] For example, the *para* isomer from the rearrangement of phenylacetate is a key intermediate in the manufacture of paracetamol (*p*-acetaminophenol), while the *ortho* isomer can be converted to salicylic acid.[44] In the polymer industry, 2,4-dihydroxybenzophenone can undergo Fries rearrangement to form diphenol monomers that subsequently produce polymers.[45] To recover products, a hydrolysis step (which is followed by the destruction of the catalyst) is required. This can result in large amounts of inorganic, corrosive, and polluting by-products. In an effort to eliminate these problems, various catalysts and solvents have been explored. Paul examined the use of zinc powder in DMF in the rearrangement of acetylated phenols.[43] He utilized both microwave irradiation as well as oil-bath heating and produced moderate to good yields in an average of 5 hours. In addition to microwave irradiation and thermal heating, the use of photochemical excitation has been used for Fries rearrangements. Gritsan reported the rearrangement of 1-naphthyl acetate via phototransformation.[46] They studied the kinetics of the phototransformation of 1-naphthyl acetate. Their reaction resulted in three products typical for the photo-Fries rearrangement: 2-acetyl-1-naphthol, 4-acetyl-1-naphthol, and 1-naphthol.

2.3.3 Results and discussion

The study constitutes the first report of Claisen and Fries rearrangements using alumina and microwave irradiation. The initial study was carried out using allyl phenyl ether in an attempt to obtain 2-(2-propenyl)phenol. The main product obtained from this reaction was 2,3-dihydro-2-methylbenzofuran (Fig. 2.3.3a). Modification of the reaction conditions, resulted in various ratios between these two products and the starting material (Table 2.3.3a Entries 1-11). Calculation show that 2,3-dihydro-2-methylbenzofuran is eight times more likely to form over the 2-(2-propenyl)phenol.[47] This is due to alumina's

acidic environment and to the fact that $k_2/k_1 = 8$. In other words, the second rate constant, k_2, (from 2-(2-propenyl)phenol to that 2,3-dihydro-2-methylbenzofuran) is 8 time larger than the first rate constant, k_1, (from allyl phenyl ether to 2-(2-propenyl)phenol). After the conditions were optimized, a study of various substituted allyl phenyl ethers was conducted (Fig 2.3.3b). When substituted allyl aryl ethers were used, a ring closure was observed. But, when substitute allyl phenyl ethers were used, no ring closure was observed. In the synthesis of *m*-methoxyphenol, extraction using diethyl ether resulted in much lower yields in comparison to the use of methanol for extraction. A reasonable explanation might be the demethylation of the product by the diethyl ether. As for the Fries rearrangement, the only product that was obtained was phenol (Table 2.3.3a Entries 12-14). From these results it would appear that the acylium ion formed in the process of the rearrangement has a greater affinity for the alumina and does not undergo rearrangement.

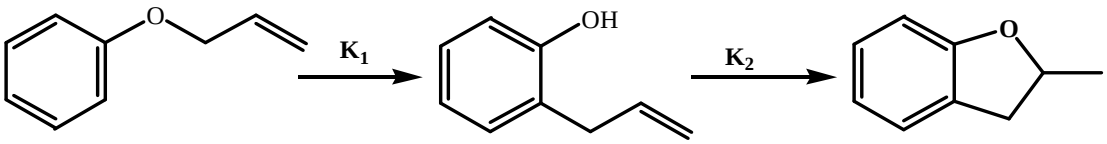


Fig 2.3.3a. The formation of 2,3-dihydro-2-methylbenzofuran.

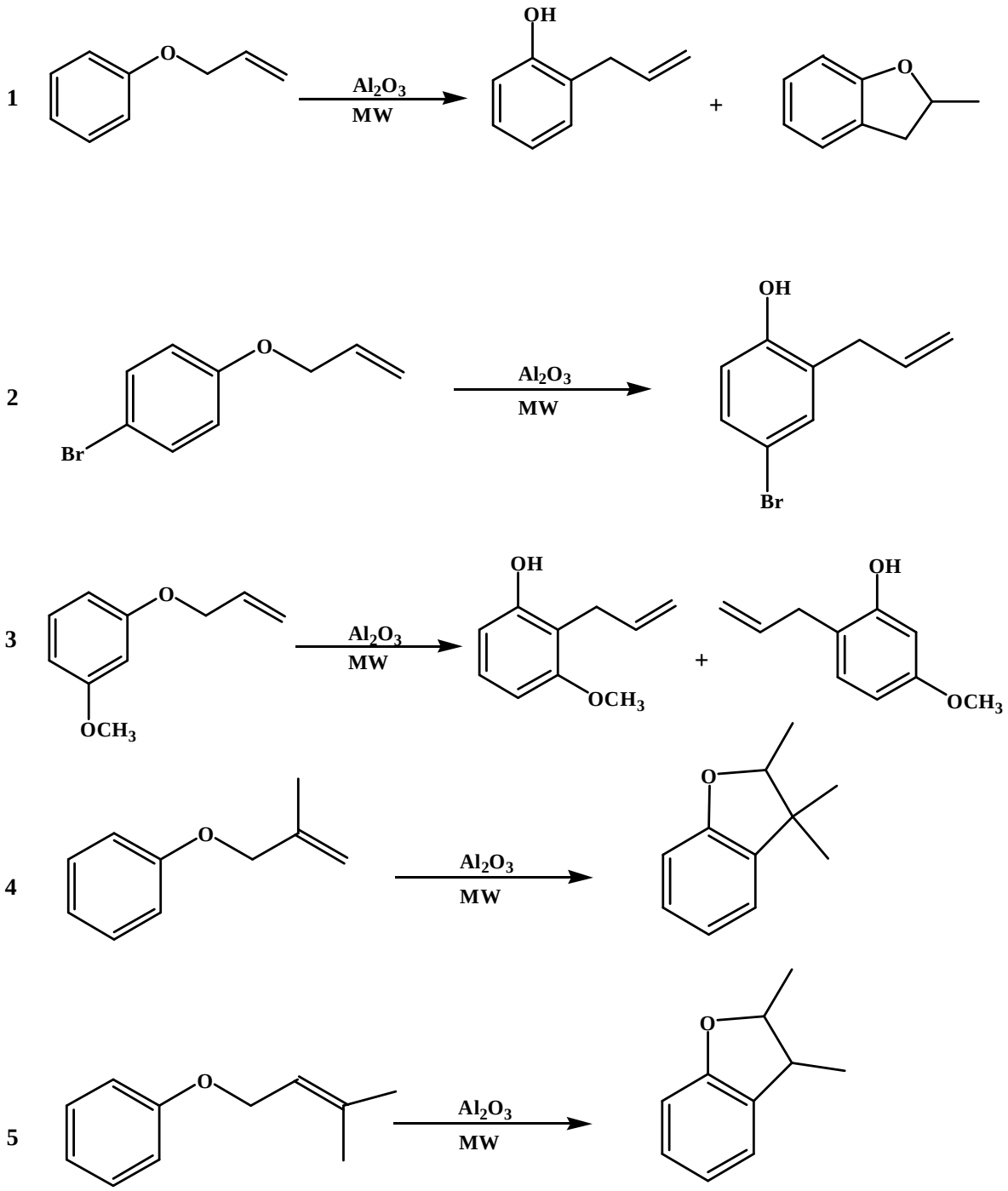


Fig 2.3.3b. The reaction of substituted allyl phenyl ether.

Table 2.3.3 Various reaction condition for the Claisen rearrangement of allyl phenyl ether.

Trail #	Condition	Results	Comments
1, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, stir for 5 min Wash with ether, run GC	Two peaks 1. (2-propenyloxy)benzene 2. 2,3-dihydro-2-methylbenzofuran (small ~ 1%)	No vacuum
2, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, M.W 100 W, 60 ^{0}C, ramp 15 min hold 15min	Two peaks 1+2 (small ~ 1%)	Closed Vessel, Power didn't exceed 10 W
3, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, M.W 100 W, 60 ^{0}C, ramp 15 min hold 15 min	Two peaks 1+2 (small ~ 1%)	Open Vessel
4, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 150 ^{0}C, ramp 10 min hold 10 min	Three major peaks. 1+2+3 ratio~ 3:2:1 respectively 3. 2-(2-propenyl)phenol	Mixture turned pink
5, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 100 ^{0}C, ramp 10 min hold 10 min	Two peaks (1+2) (small ~ 1%)	Condensation at the end of reaction
6, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 200 ^{0}C, ramp 10 min hold 10 min	Three major peaks. 1+2+4 4. Benzene,1,2,4,5 tetramethyl Ratio 1:9:0.2	Actual temp 183 ^{0}C Mixture turned pink
7, Claisen	Activate Alumina 130 ^{0}C, 20 min Add reagents, M.W 300 W, 150 ^{0}C, ramp 10 min hold 5 min	Three major peaks. 1+2+3 53%, 39%, 8% respectively	

Table 2.3.3 (cont')

Trail #	Condition	Results	Comments
8, Claisen	Activate Alumina 130 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 150 ^{0}C, ramp 10 min hold 20 min	Four major peaks. 1+2+3+4 14%, 82%, 1%, 3% respectively	Condensation at the end of reaction
9, Claisen	Activate Alumina 200 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 200 ^{0}C, ramp 10 min hold 10 min	Three major peaks. 1+2+4 12%, 84%, 4% respectively	Mixture turned slightly pink
10, Claisen	Mix alumina and reagents together and place in M.W 300 W, 200 ^{0}C, ramp 10 min hold 20 min	Three major peaks. 1+2+4 9%, 87%, 4% respectively	Condensation at top of test tube at the end of reaction. Top of alumina turn pink rest turn white
11, Claisen	Activate Alumina 200 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 100 ^{0}C, ramp 10 min hold 20 min	Two peaks 1+2 + standard (Decane)	Both 1+2 yield 88% Peak 1: 97% Peak 2: 3%
12, Fries	Activate Alumina 200 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 150 ^{0}C, ramp 5 min hold 20 min	Two peaks 1+2 1. Phenol 2. Acetic acid, phenyl ester Ratio 2, 3 respectively	
13, Fries	Activate Alumina 200 ^{0}C, 20 min, 300 W Add reagents, stir for 5 min Wash with ether, run GC	Two peaks 1+2 Ratio 1, 99 respectively	
14, Fries	Activate Alumina 200 ^{0}C, 20 min, 300 W Add reagents, M.W 300 W, 100^{0}C, ramp 5 min hold 10 min	Two peaks 1+2 Ratio 12, 88 respectively	

2.3.4 Conclusion

From the data presented, the rearrangement reaction appears to yield "non-traditional" results. Although the yields were moderate, using microwaves and alumina achieves the desired products in a fraction of the time and in an environmentally friendly fashion.

2.3.5 Experimental Section

2.3.5.1 General procedures

Unless otherwise noted, all reagents were purchased from commercial suppliers and were been used without further purification. All reactions were conducted under argon in a 10mL glass tube sealed with a plastic cap. Microwave heating was performed in a CEM Discover at 2.45 GHz in the open vessel mode. The irradiation power, as well as temperature, was monitored during the course of the reaction. After irradiation the reaction tube was allowed to cool to 50 ^{0}C with the help of high air pressure. All reagents were stirred during the reaction time. All spectra were obtained using Hewlett-Packard GC-MS (6890 GC/ 5973 MSD, Column HP-5msi). Decane (0.5 mmol, 99 + %) was used as the standard to determine the yields using the GC-MS. Sodium tetraphenylborate and DOH were used as references for boron and proton NMR, respectively. For the activation of alumina**,** 1 gram of alumina, Neutral, Brockman Activity I, moisture content 2.2% (Fisher Chemicals) was introduced into the tube, capped, and flushed with argon. Microwave irradiation was carried out using 300 W for 20 minutes at 130 ^{0}C with a ramp time of 5 minutes. The reaction was carried out under argon flow (to prevent the condensation on the top part of the test tube, which was not under irradiation) and an outlet to a commercial vacuum pump (to aid the removed of the water). The average weight lost after the irradiation was monitored.

2.3.5.2 Representative procedure for 2-allyl-4-bromophenol

In a round-bottomed flask, one equivalent of sodium iodide (20 mmol, 3 g) was dissolved in acetone (15 mL) along with one equivalent of allyl chloride (20 mmol, 1.6 mL). The precipitated NaCl was removed using vacuum filtration and the remaining liquid was placed in a rotorary evaporator. GCMS was carried out to confirm the formation of the allyl iodide. In a round-bottomed flask, one equivalent of 4-bromophenol (1.5 mmol, 2.6 g) was dissolved in THF (1 mL). The flask was capped and flushed with argon and one equivalent of butyllithium (1.5 mmol, 1.4 mL) was added dropwise followed by the addition of allyl iodide (2 mmol, 1.7 mL). The reaction mixture was placed in an oil bath at 70 ^{o}C for 48 hours. The separation of the desired product from the reaction mixture was carried out in two steps. The first was an extraction using aqueous NaOH (10 mL, 0.5 M), H_2O (10 mL), and diethyl ether. The organic layer (top layer) was collected. Al_2O_3 (60 g) was activated using MW (300 W, 130 ^{o}C, 40 minutes) and then packed into a column. The organic layer collected previously was passed through the column using hexanes/ethyl acetate (95/5 respectively). Solvent was removed using water steam and GCMS was carried out to confirm the formation of the 1-(allyloxy)-4-bromobenzene. A 10-mL test tube was flushed with argon and weighed along with a magnetic stirrer bar and a cap. One gram of alumina was added and the test tube was capped and weighed. The test tube was flushed with argon and placed in a microwave chamber. A commercial vacuum pump was attached via needle inserted through the cap. Microwave activation was carried out in an open vessel mode at 300 W for 5 minutes ramp time, 20 minutes hold time and 130 ^{o}C. After activation, the test tube was weighed again and the percentage weight loss was calculated. 1-(Allyloxy)-4-bromobenzene (0.08 mL, 0.5 mmol) was added dropwise to the test tube. The reaction mixture was placed in the microwave chamber and microwaved in an open vessel mode at 300 W with a 5 minutes ramp time, 20 minutes hold time and 150 ^{o}C. When activation was complete, the reaction mixture was washed using diethyl ether (10 mL) and the ether solution injected on to a GCMS for analysis. For *m*-methoxyphenol, methanol was used to extract the product (replacing the diethyl ether).

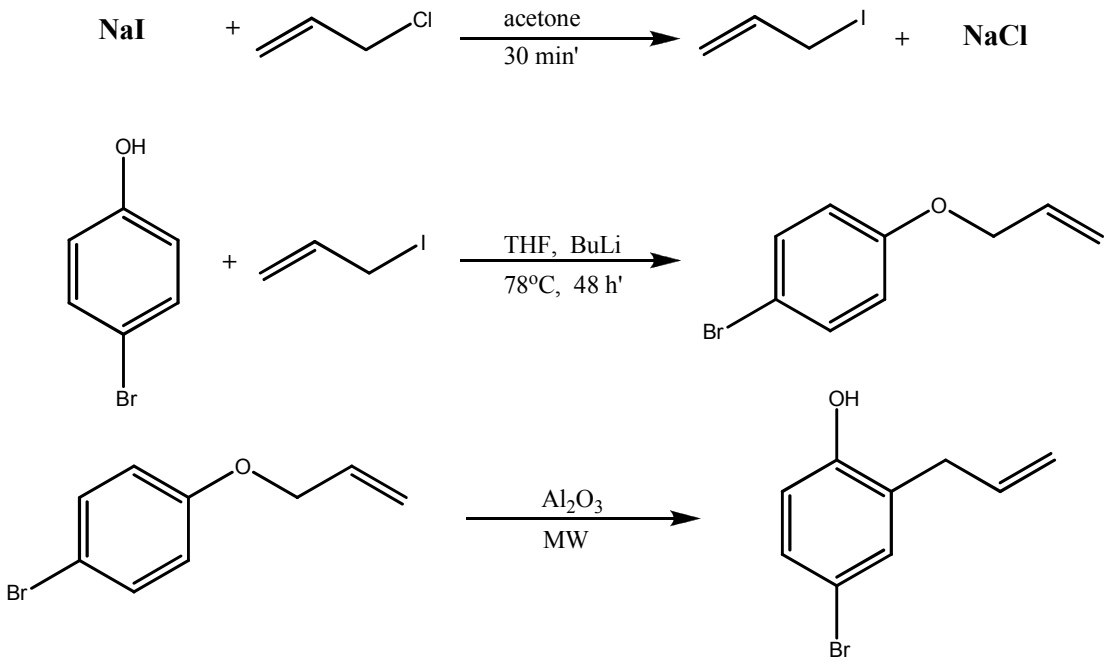


Fig 2.3.5.2 The synthesis of 2-allyl-4-bromophenol.

2.3.6 Analytical Data

1c 2,3-Dihydro-2-methylbenzofuran

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (3H, d, J = 6.1, CH3), 2.80 (IH, dd, J = 15.2, 7.6, PhCHH), 3.30 (1H, dd, J = 15.2, 8.8, PhCHH), 4.76-4.93 (1H, m, CHCH3), 6.68-6.89 (2H, m, ArH), 7.03-7.20 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.7 (CH3), 37.1 (PhCH2), 79.4 (OCH), 109.3, 120.1,124.9, 127.0, 127.9, 159.5 (ArC)

2c 2-Allyl-4-bromo-phenol

^{1}H NMR (300 MHz, CDCl3) δ 3.36 (dt, *J* = 6.4, 1.5 Hz, 2H), 4.99 (s, 1H), 5.14-5.20 (m, 2H), 5.93-6.02 (m, 1H), 6.67-6.71 (m, 1H), 7.20-7.26 (m, 2H). ^{13}C NMR (125 MHz, CDCl3) δ 34.7, 112.9, 117.2, 117.5, 127.7, 130.6, 133.0, 135.5, 153.2.

3c 2-Allyl-5-methoxy-phenol

^{1}H NMR (300 MHz, CDCl3) δ 3.46 (m, 2H), 3.80 (s, 3H), 5.07 (m, 1H), 5.10 (m, 2H), 5.98 (m, 1H), 6.48 (m, 1H), 6.49 (m, 1H), 7.07 (m, 1H); ^{13}C NMR (75 MHz) δ 27.32, 55.79, 103.32, 108.79, 113.61, 115.34, 127.51, 136.30, 155.14, 158.22.

4c 2,3,3-Trimethyl-2,3-dihydro-benzofuran

^{1}H NMR (CDCl3, 300 MHz): δ 7.17–7.11 (m, 2 H), 6.91–6.84 (m, 1H), 6.82–6.76 (m, 1 H), 4.37 (dq, J=8.4, 6.3 Hz, 1H), 3.14–3.05 (m, 1 H), 1.53 (d, J=6.3 Hz, 3H), 1.36 (d, J = 6.9 Hz, 6H); ^{13}C NMR (CDCl3, 75 MHz): δ 159.0, 132.4, 127.9, 123.6, 120.2, 109.3, 87.2, 43.8, 20.0, 17.9.

5c 2,3-Dimethyl-2,3-dihydro-benzofuran

^{1}H NMR (CDCl3, 300 MHz): δ 7.15–7.09 (m, 2 H), 6.89–6.84 (m, 1H), 6.79–6.75 (m, 1 H), 4.35 (dq, J=8.4, 6.3 Hz, 1H), 3.11–3.02 (m, 1 H), 1.49 (d, J=6.3 Hz, 3H), 1.32 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl3, 75 MHz): δ 161.0, 134.2, 129.7, 124.8, 122.4, 111.3, 88.3, 44.9, 23.0, 17.4.

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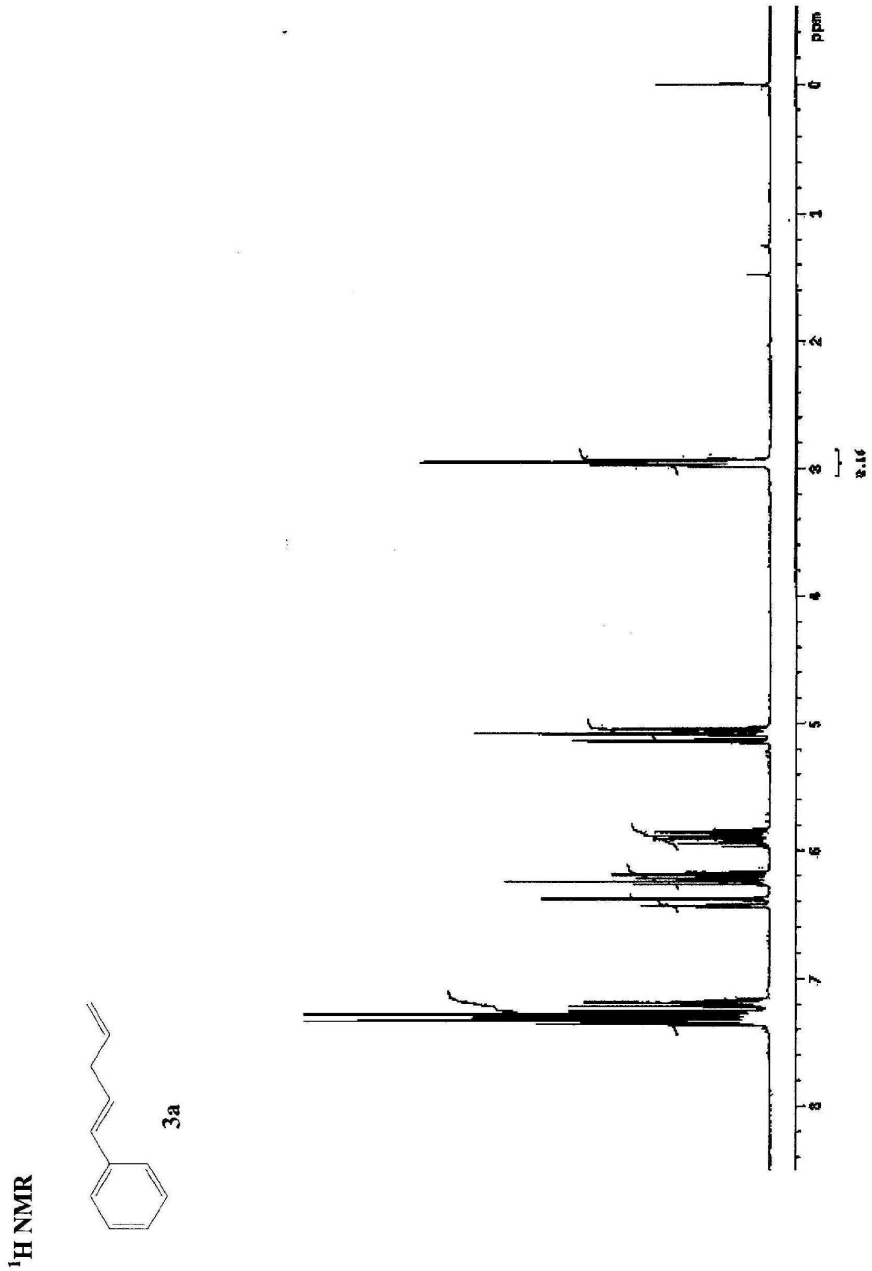
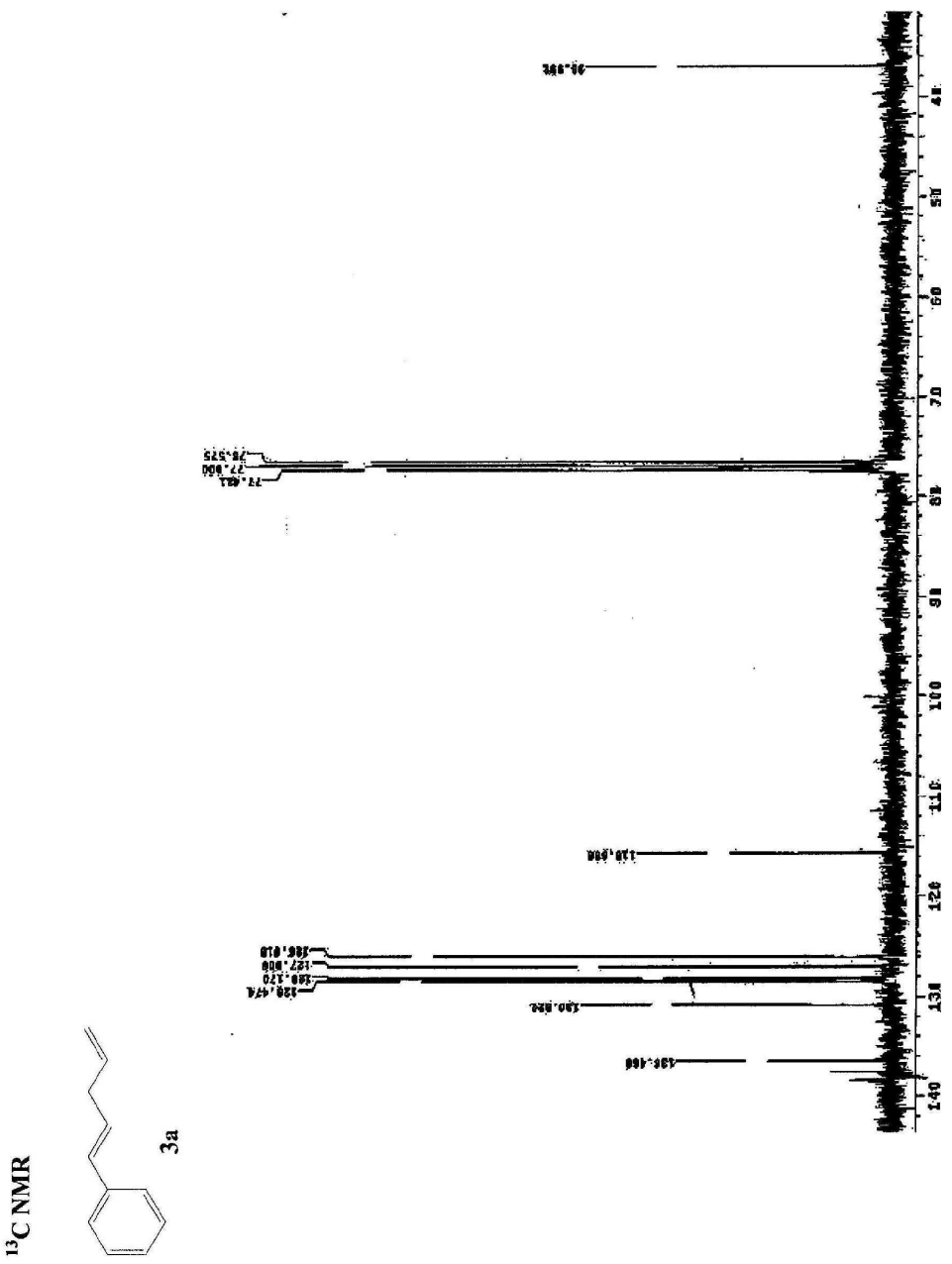
APPENDIX

NMR and GC Spectra of Representative, Intermediate and Target Compounds





^{1}H NMR

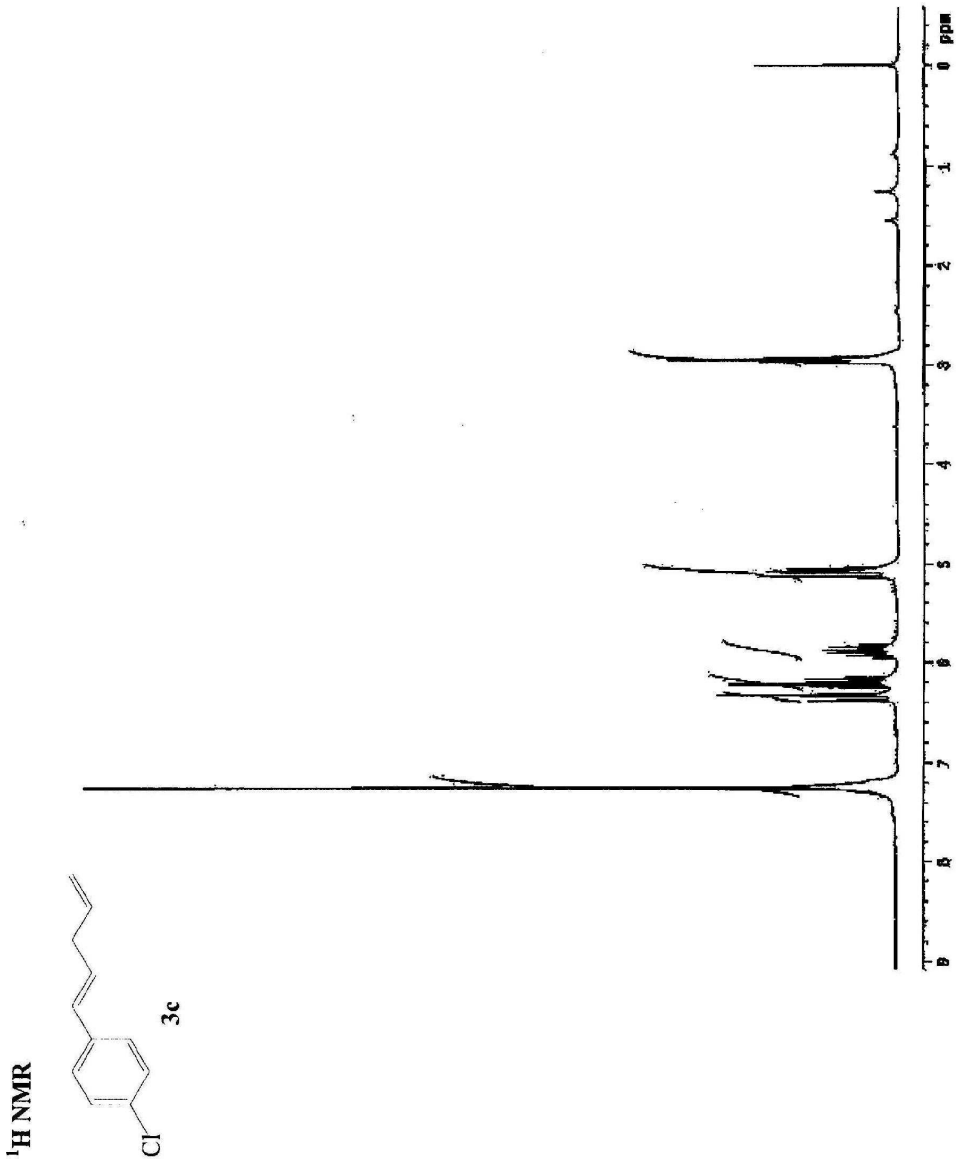
3b

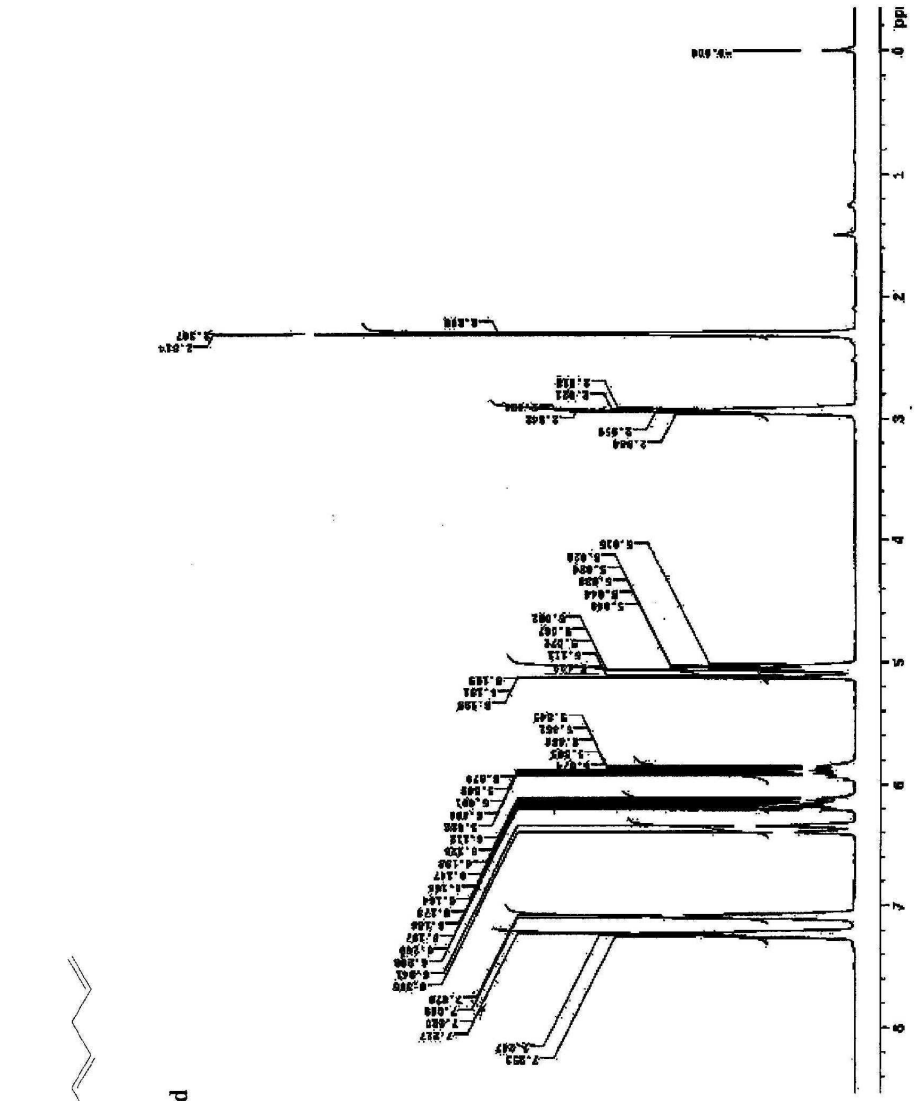
^{13}C NMR

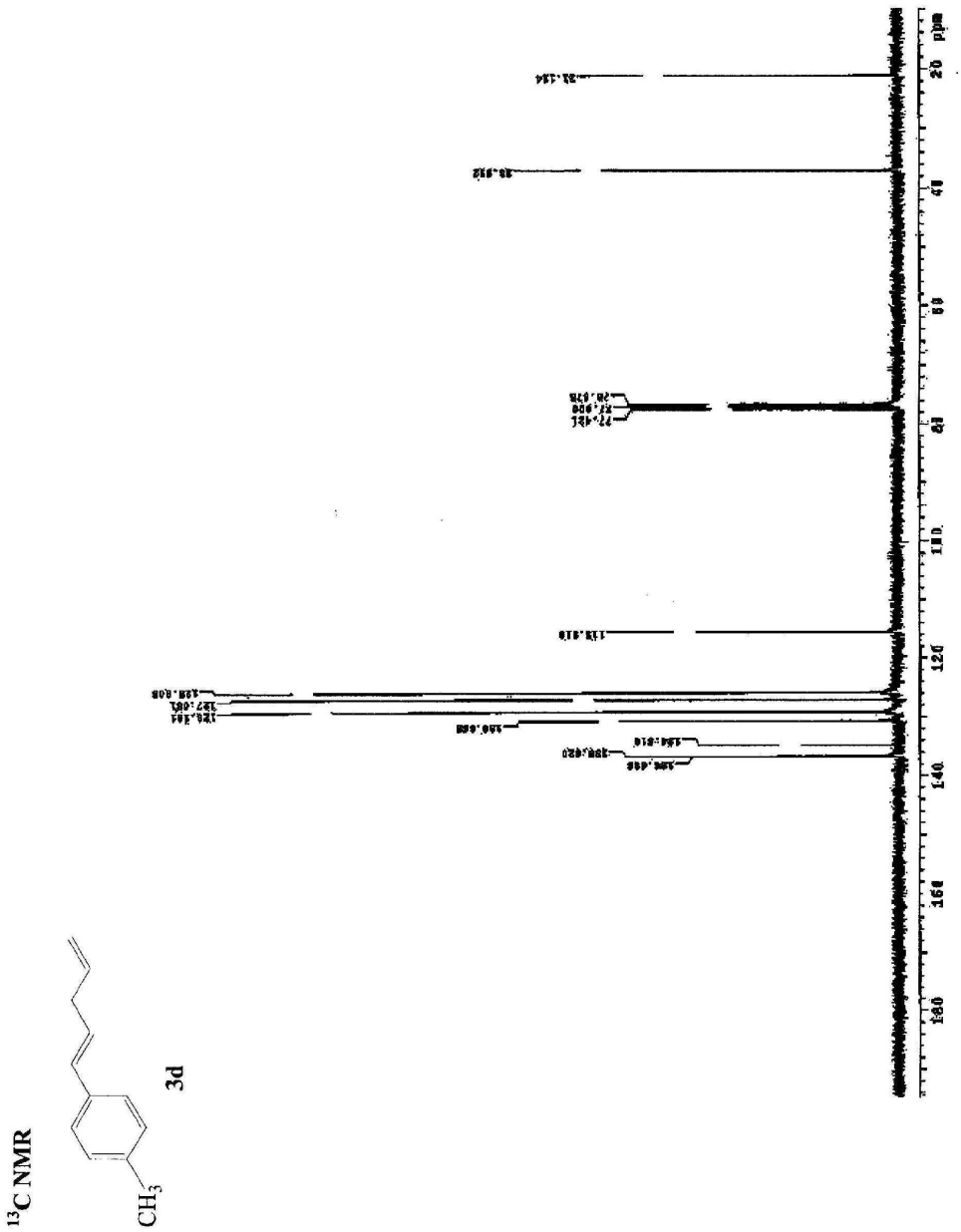
3b

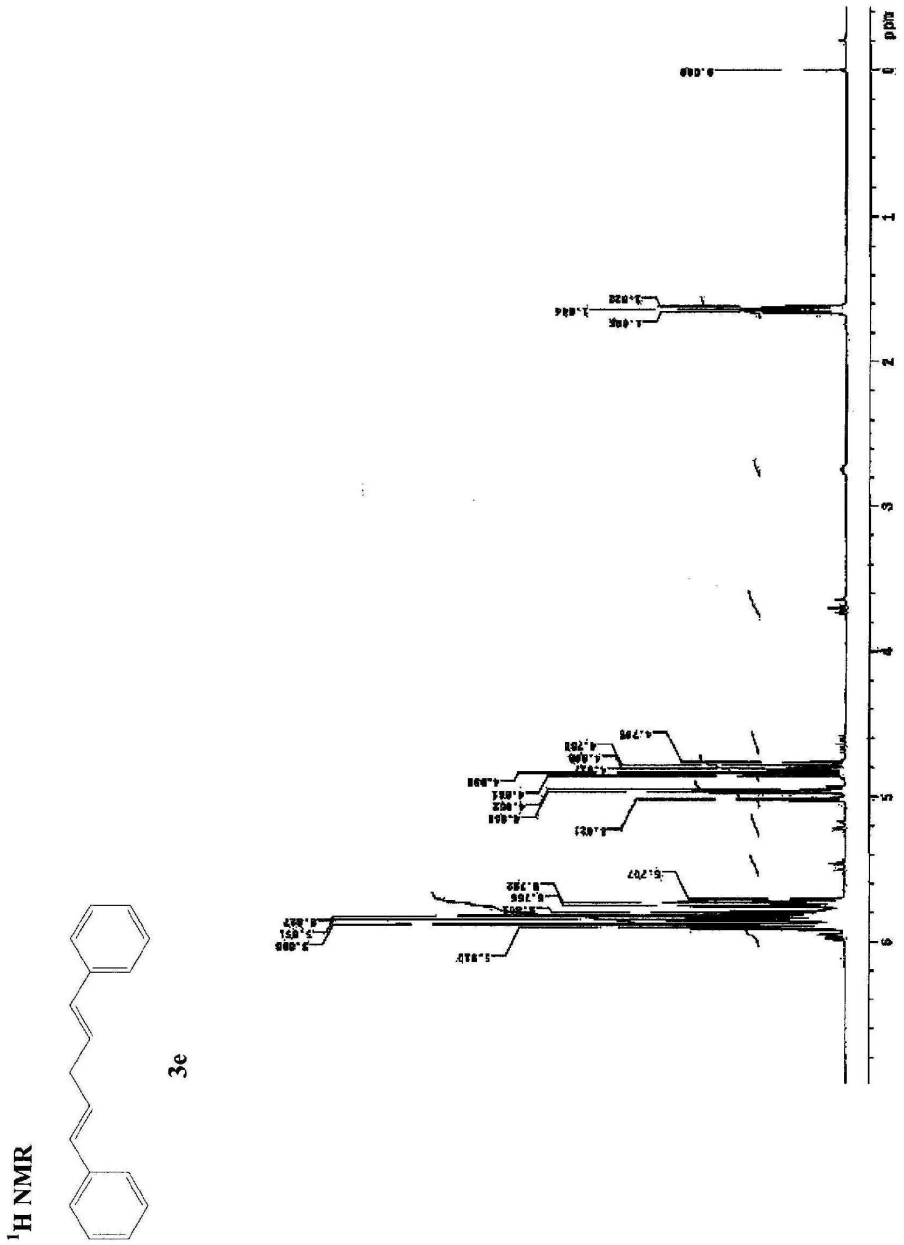
^{19}F NMR

3c

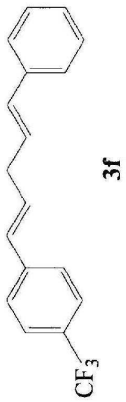








^{1}H NMR



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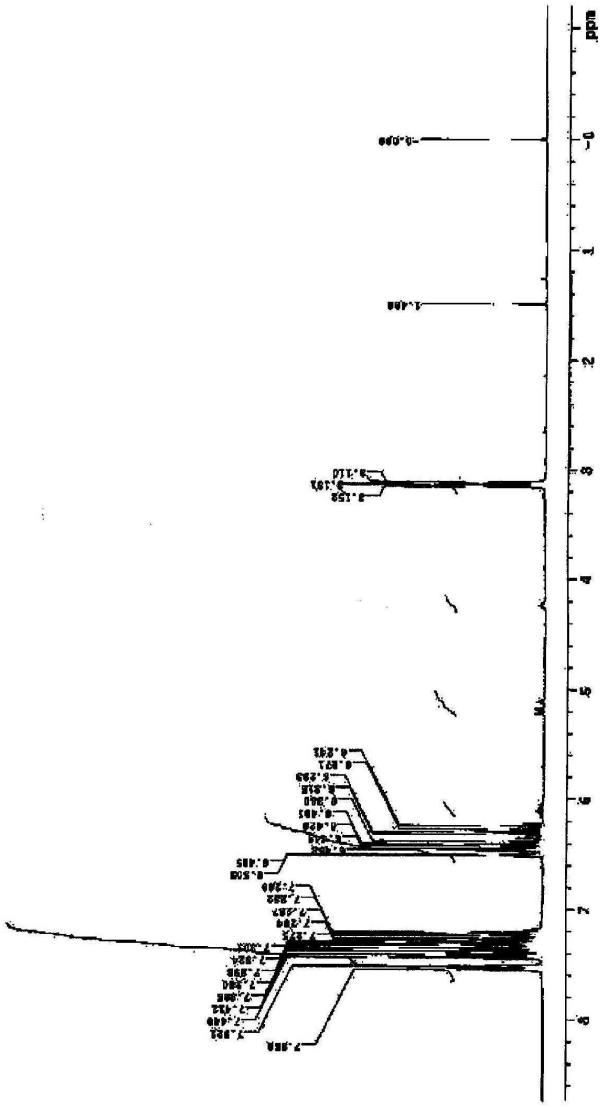
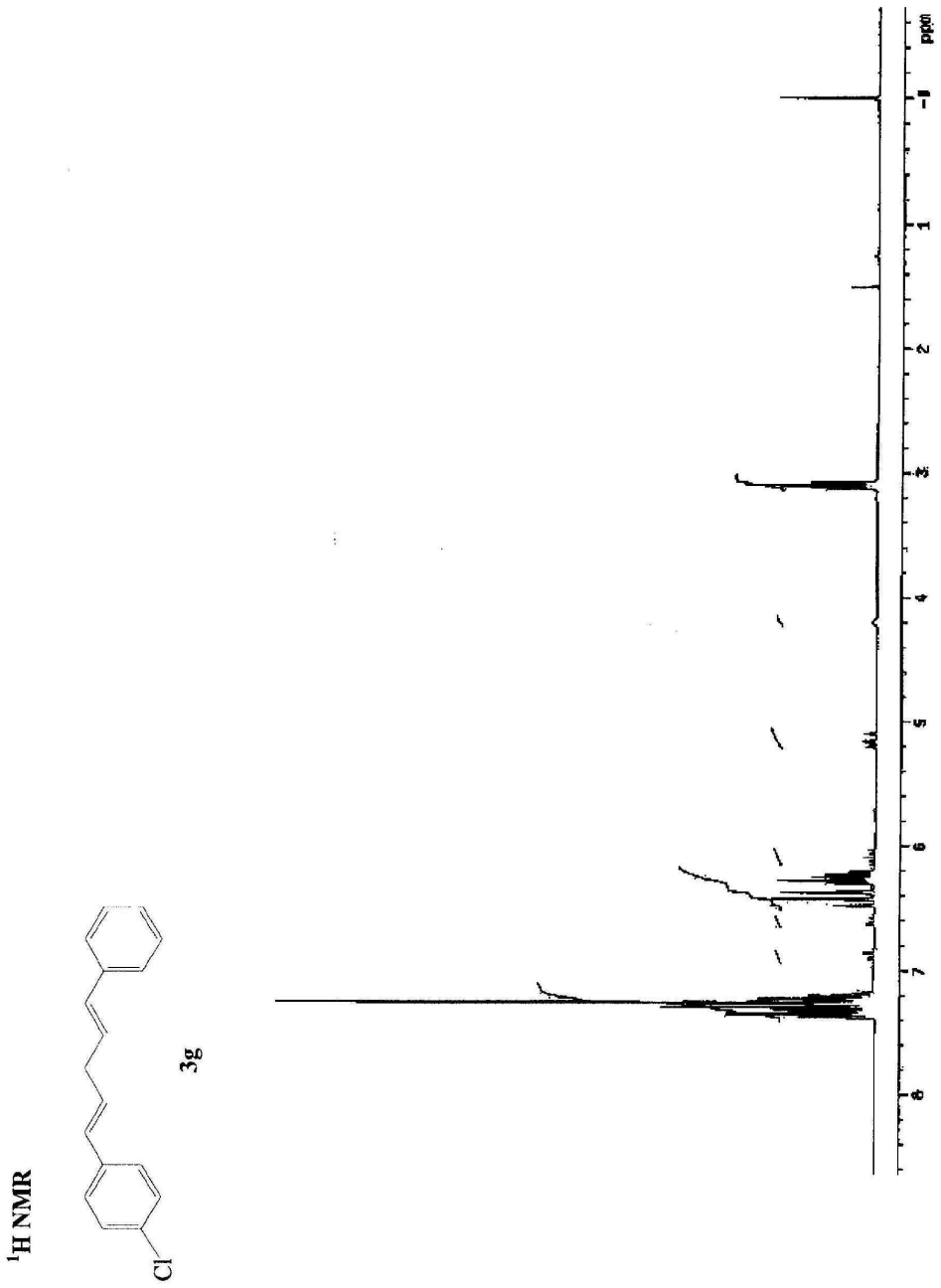


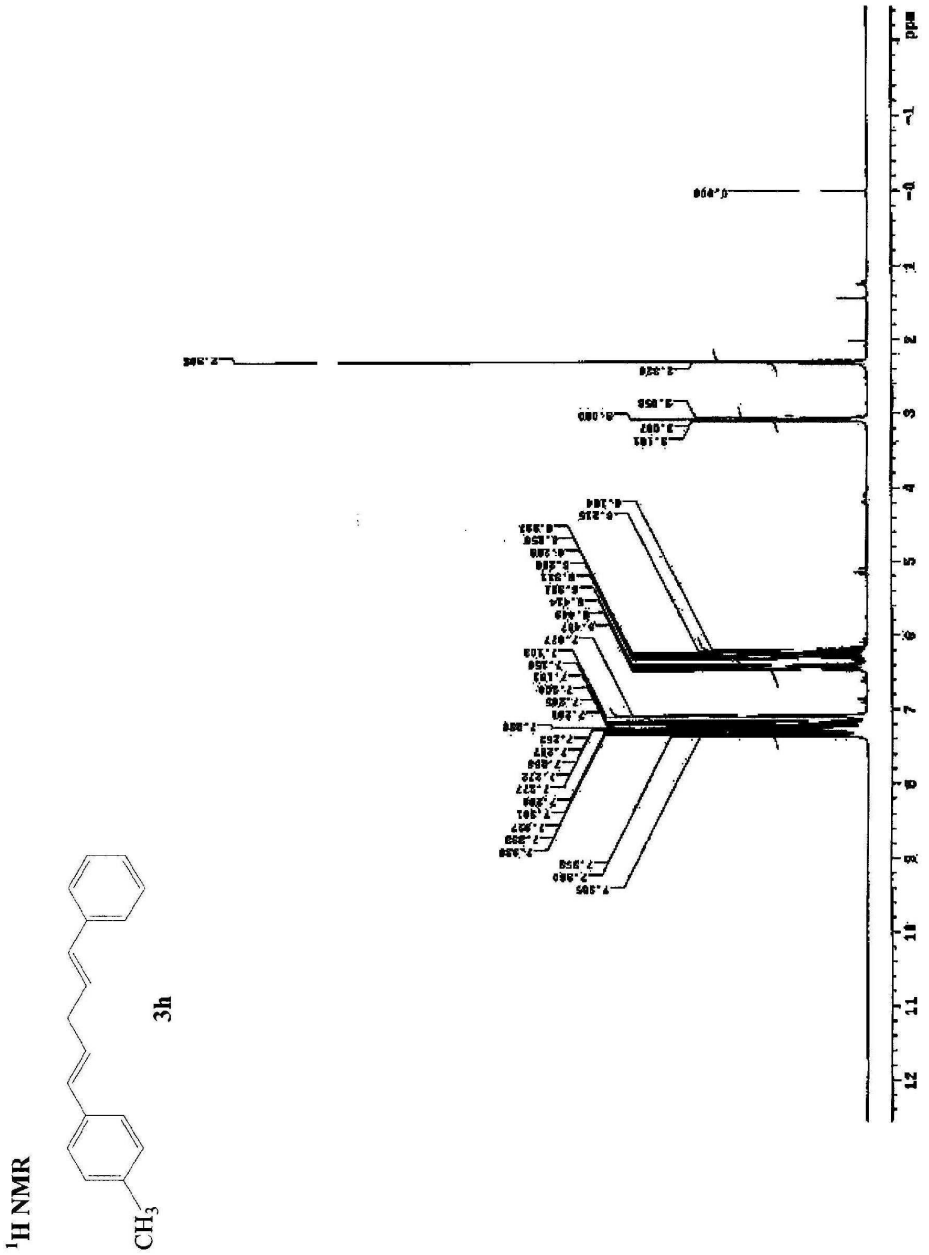
^{13}C NMR

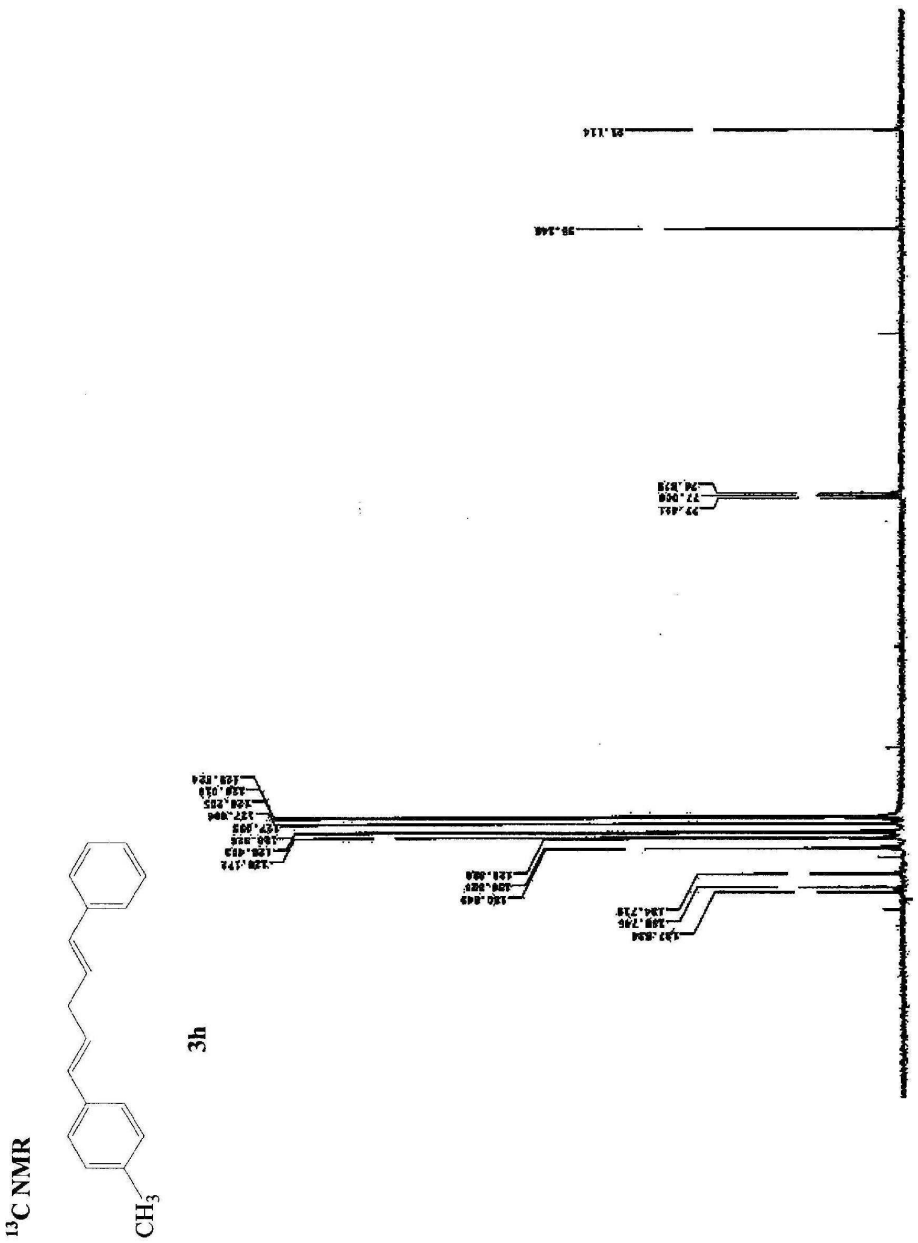
3f

^{19}F NMR

3f





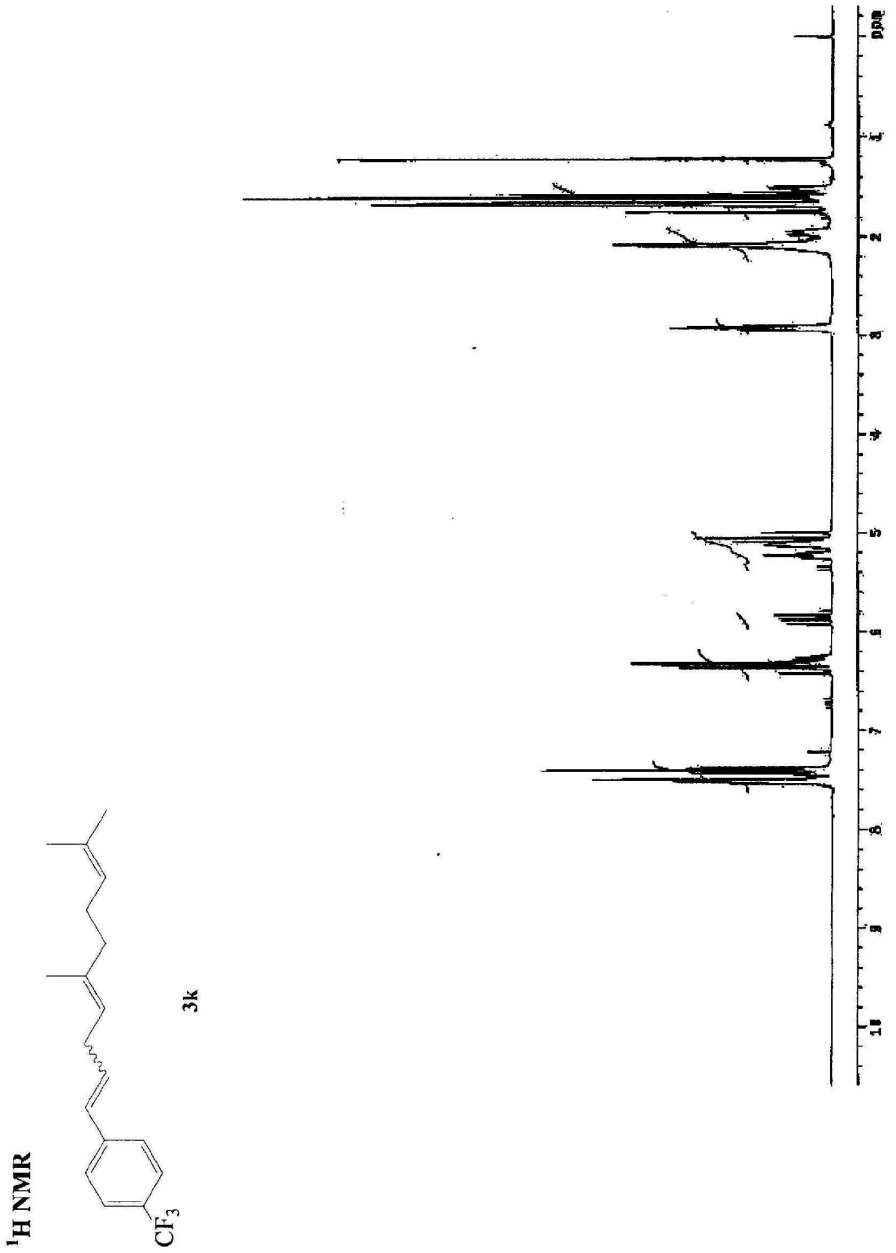


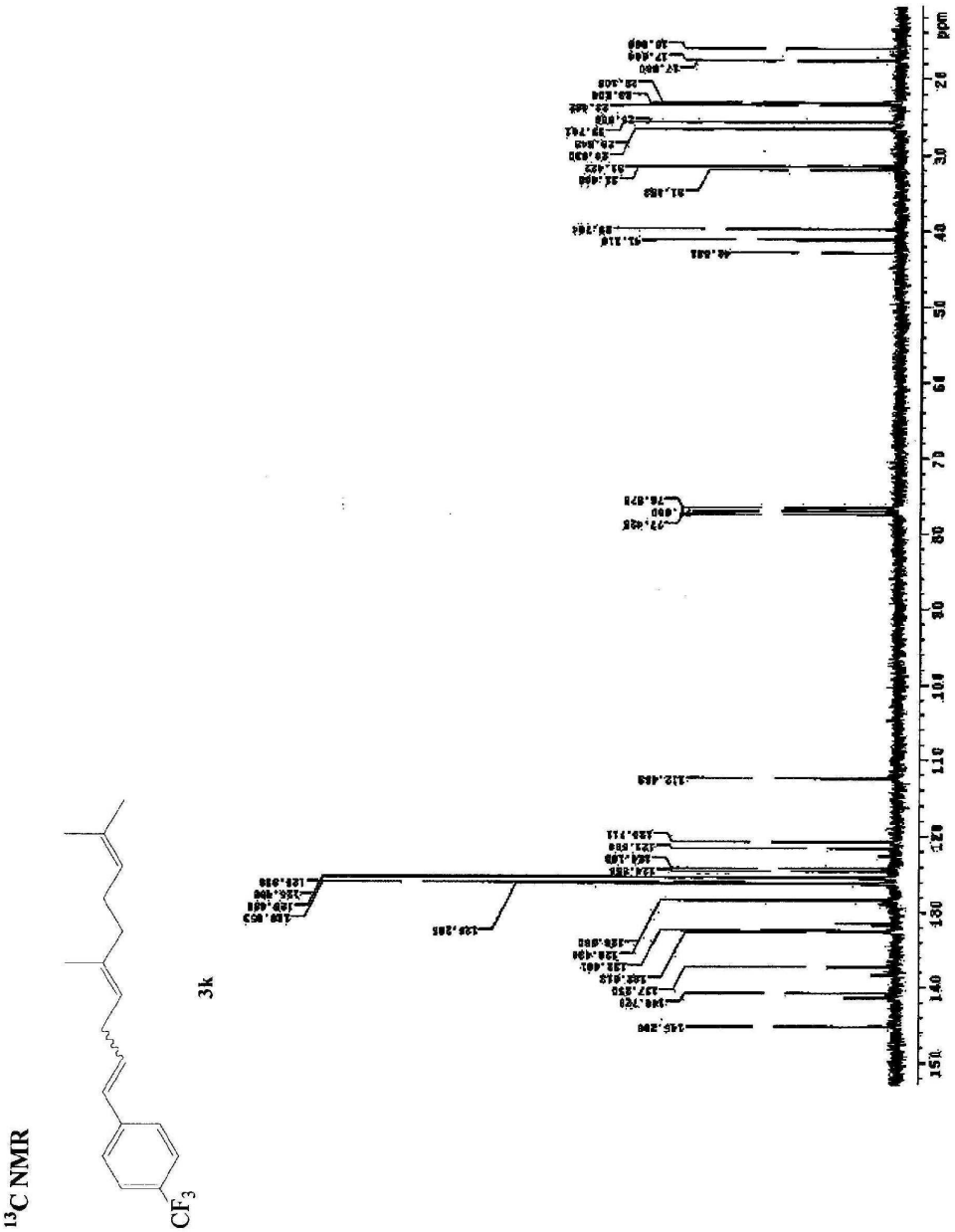
^{1}H NMR

3i

^{13}C NMR

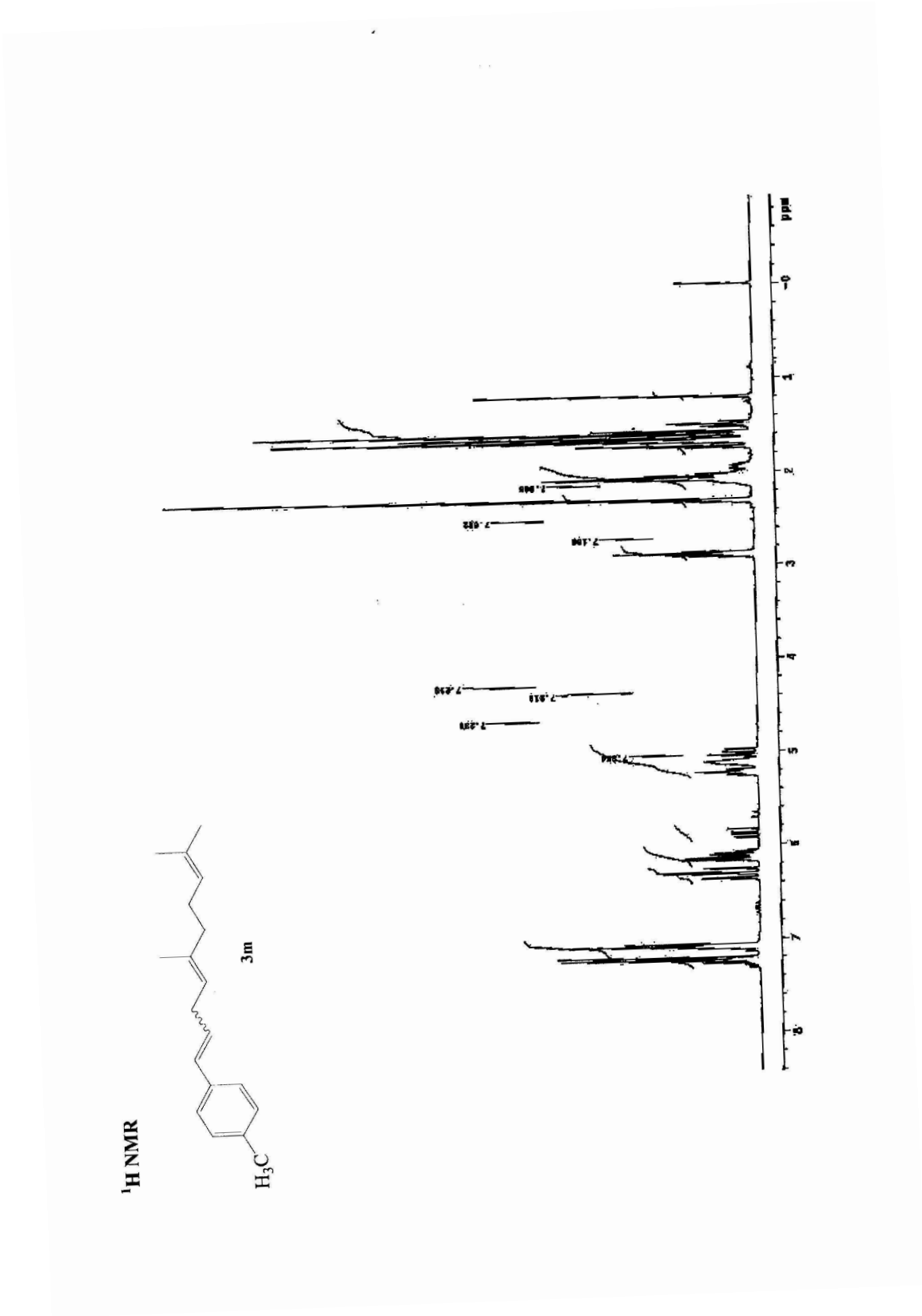
3i

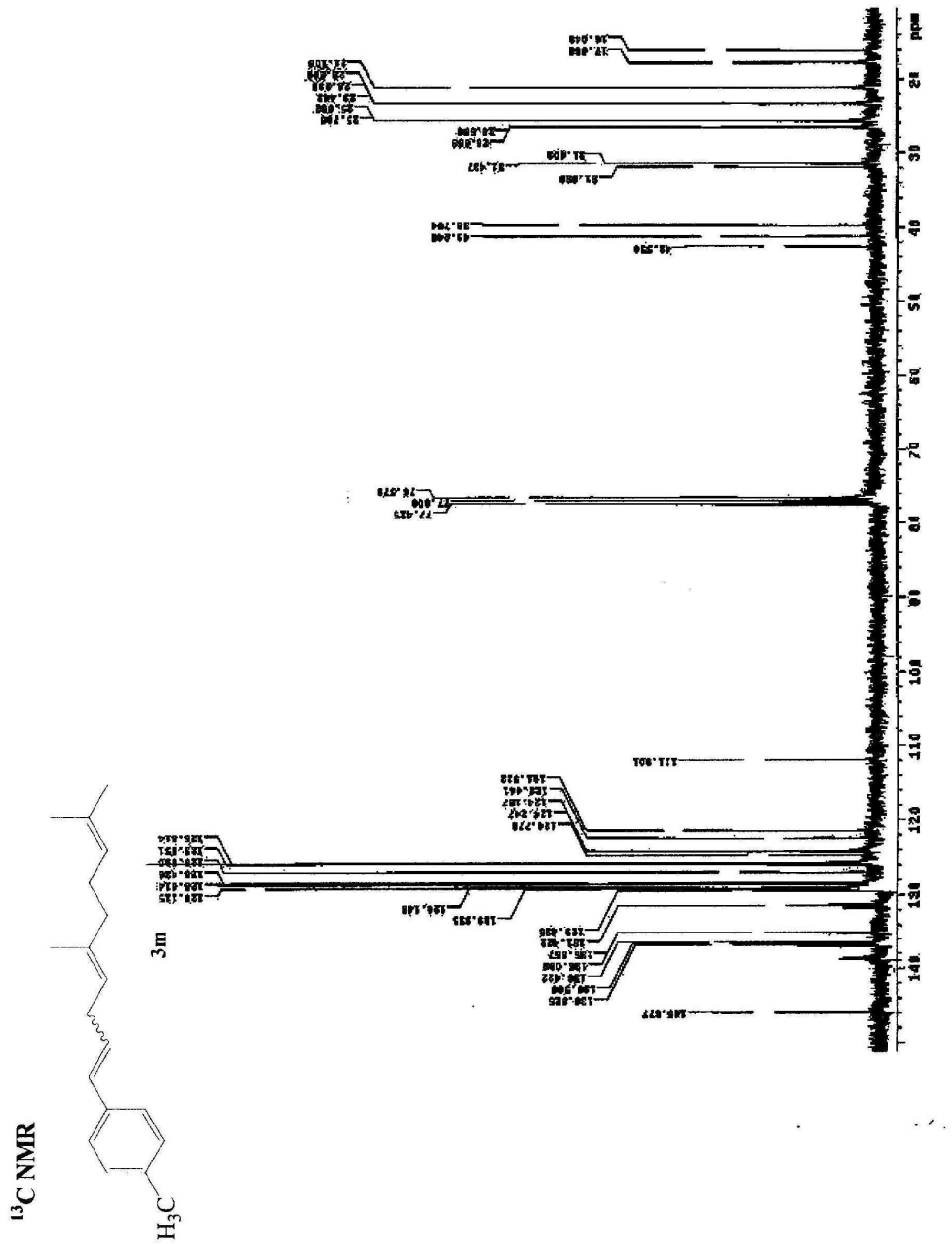


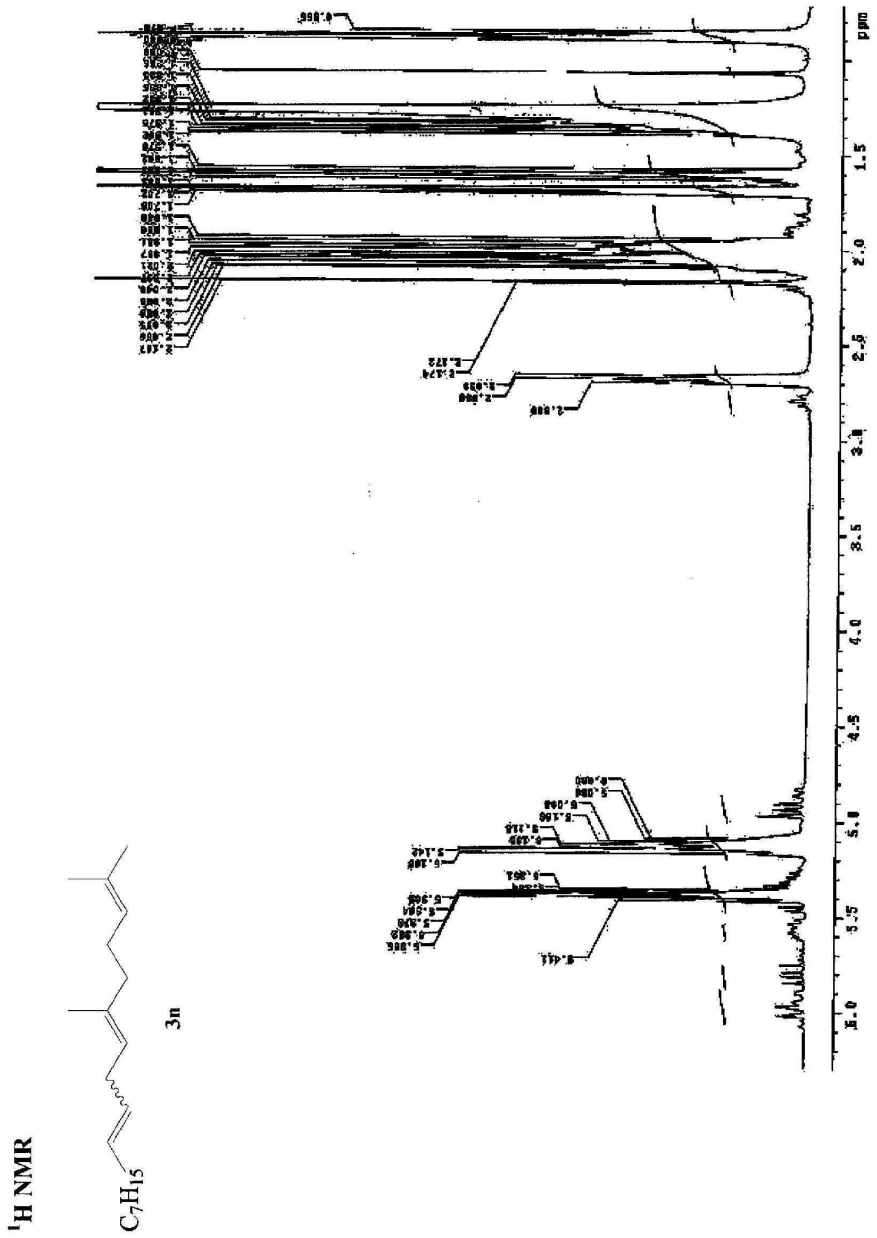


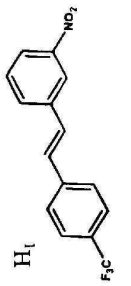
^{19}F NMR

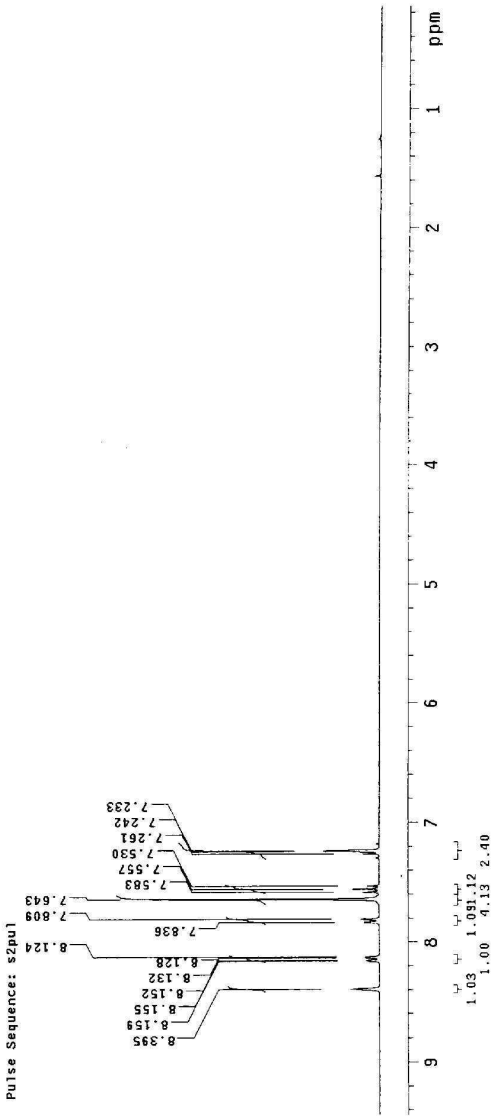
3k

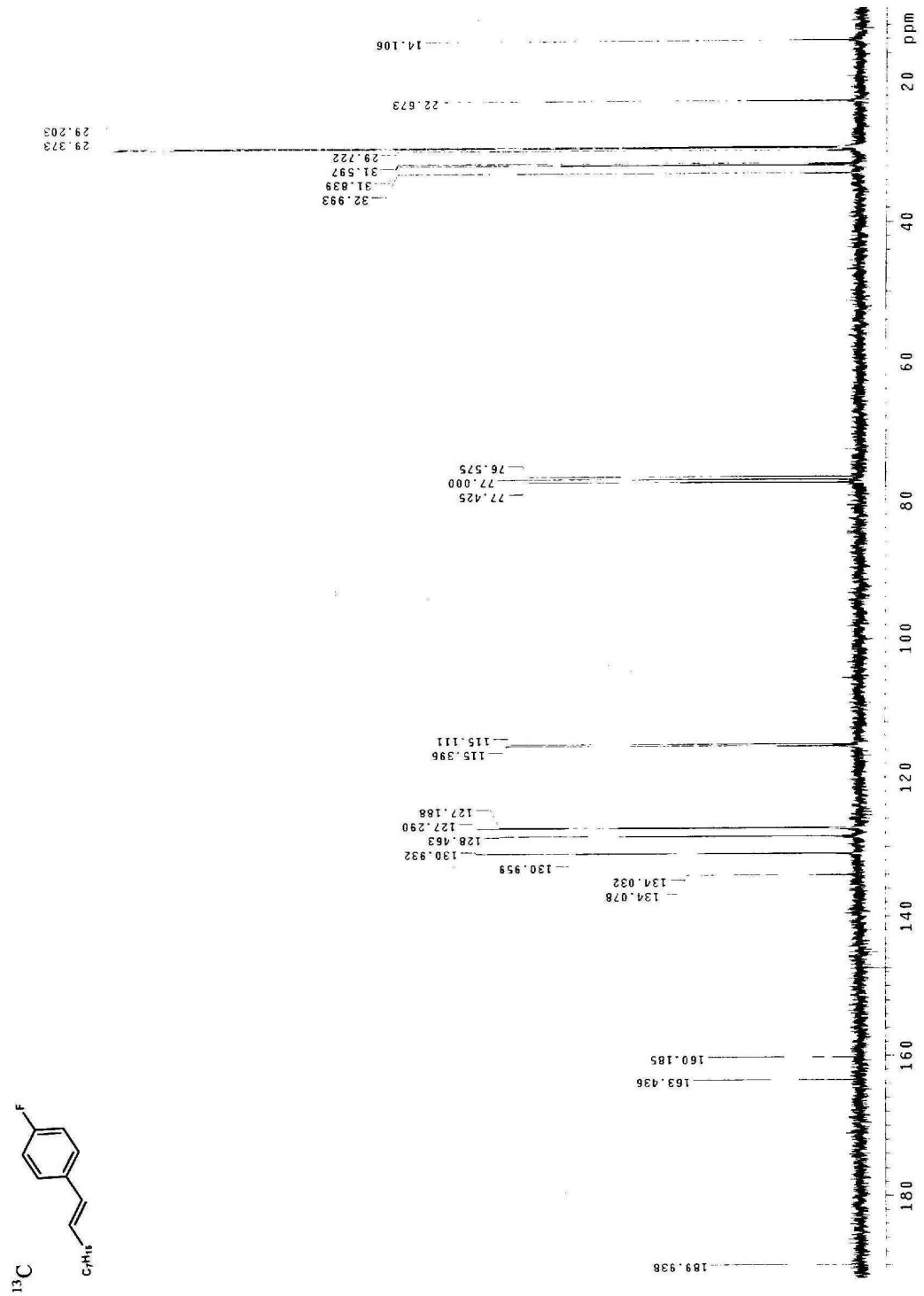


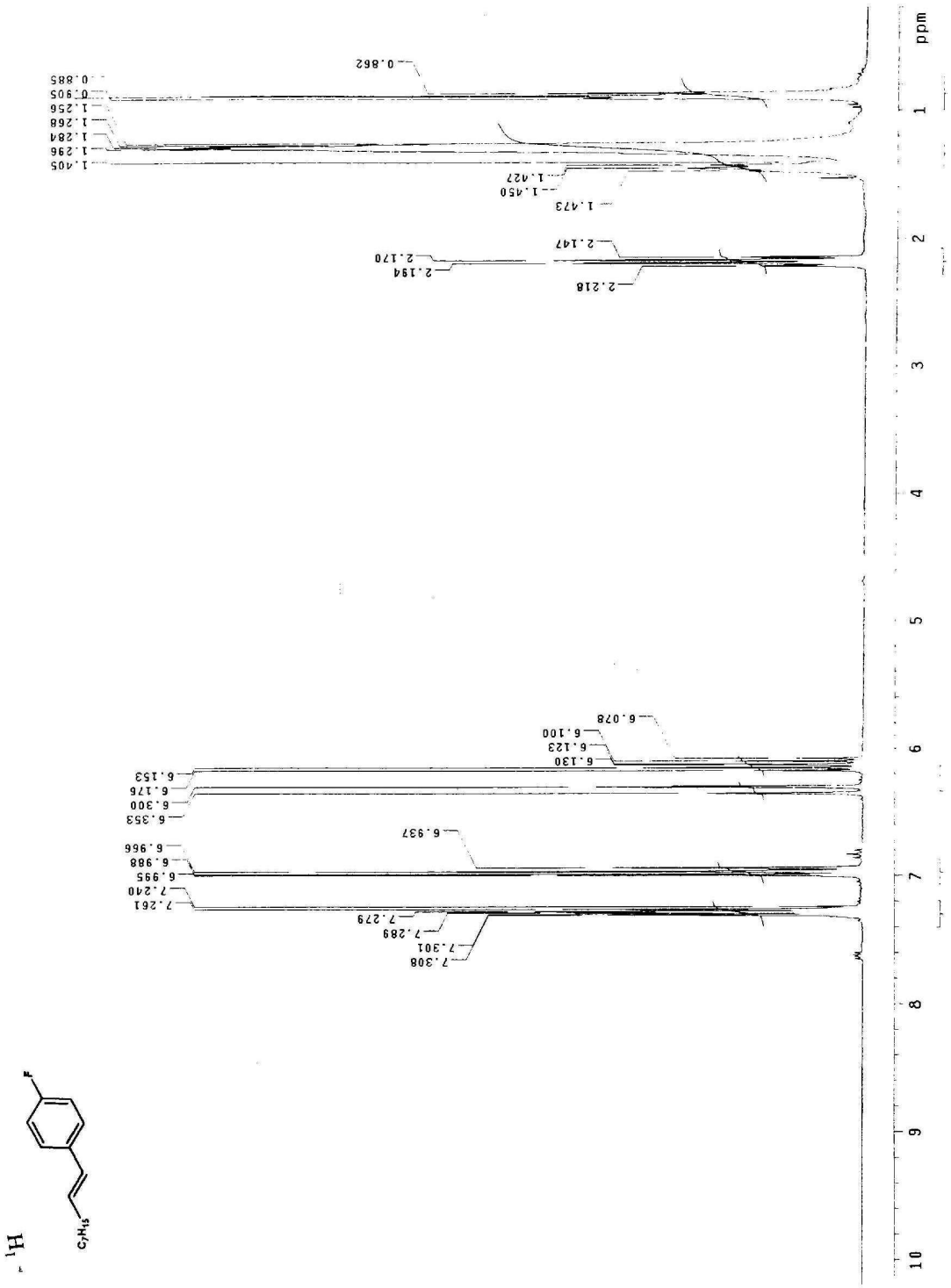


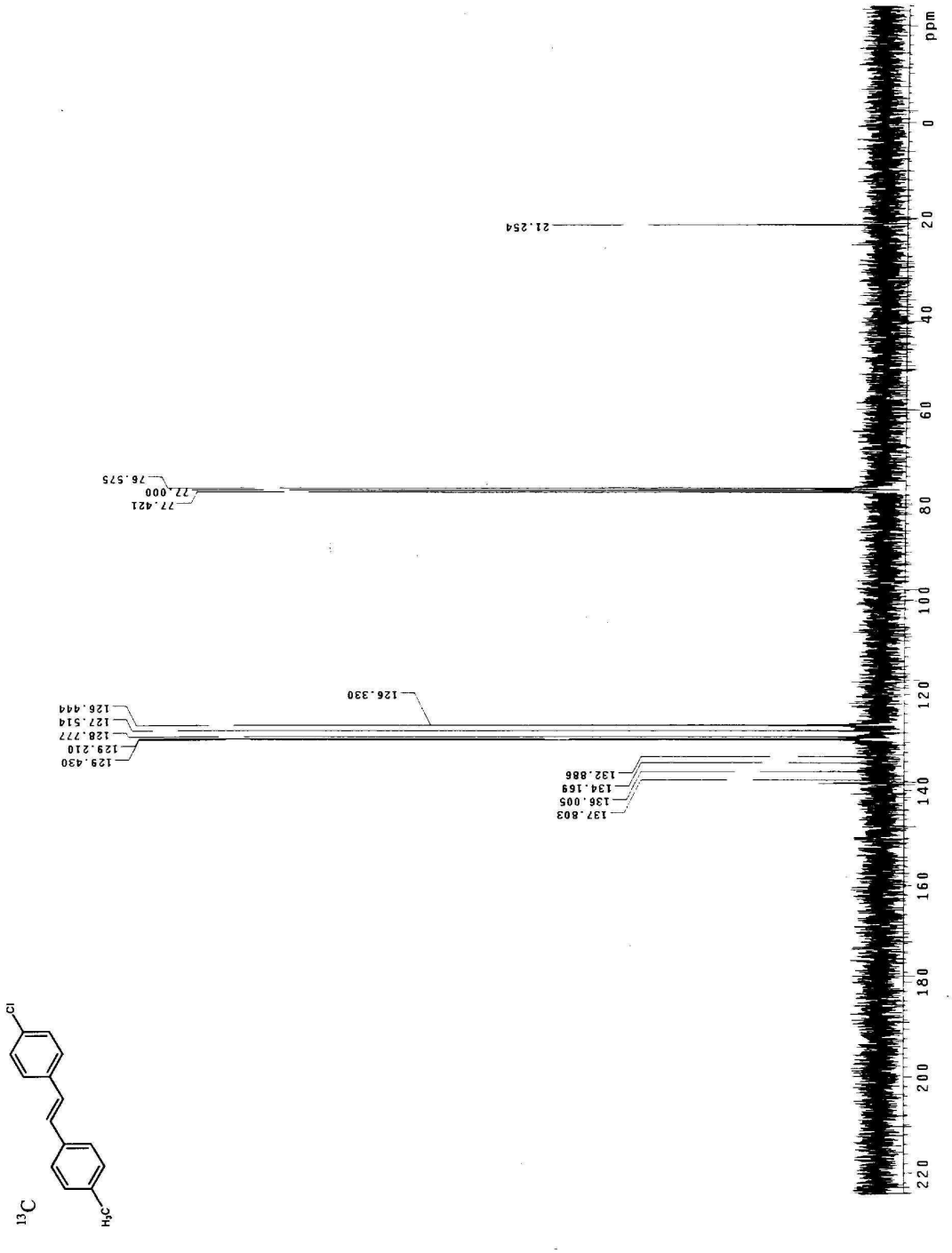


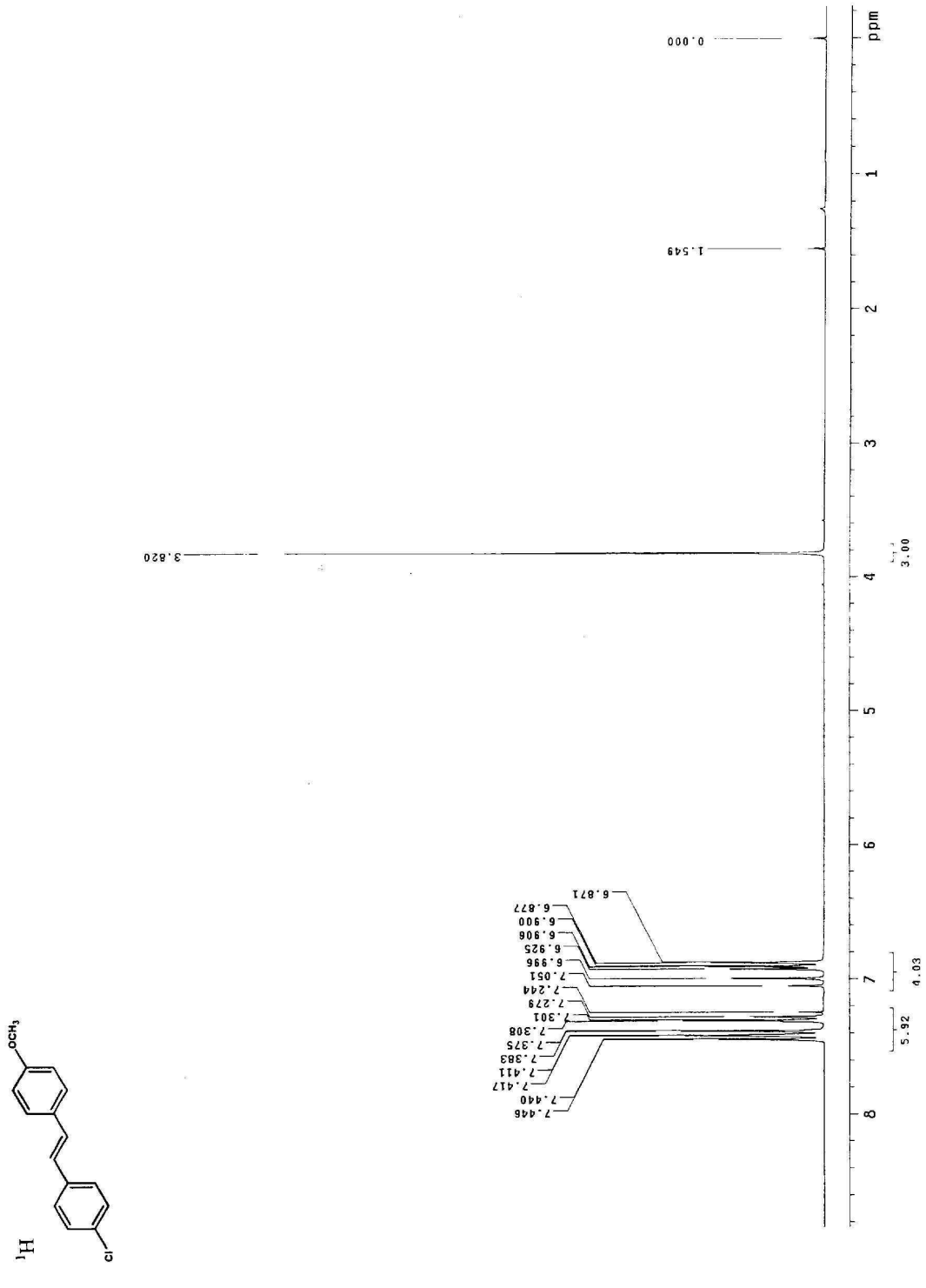


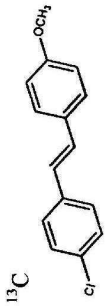


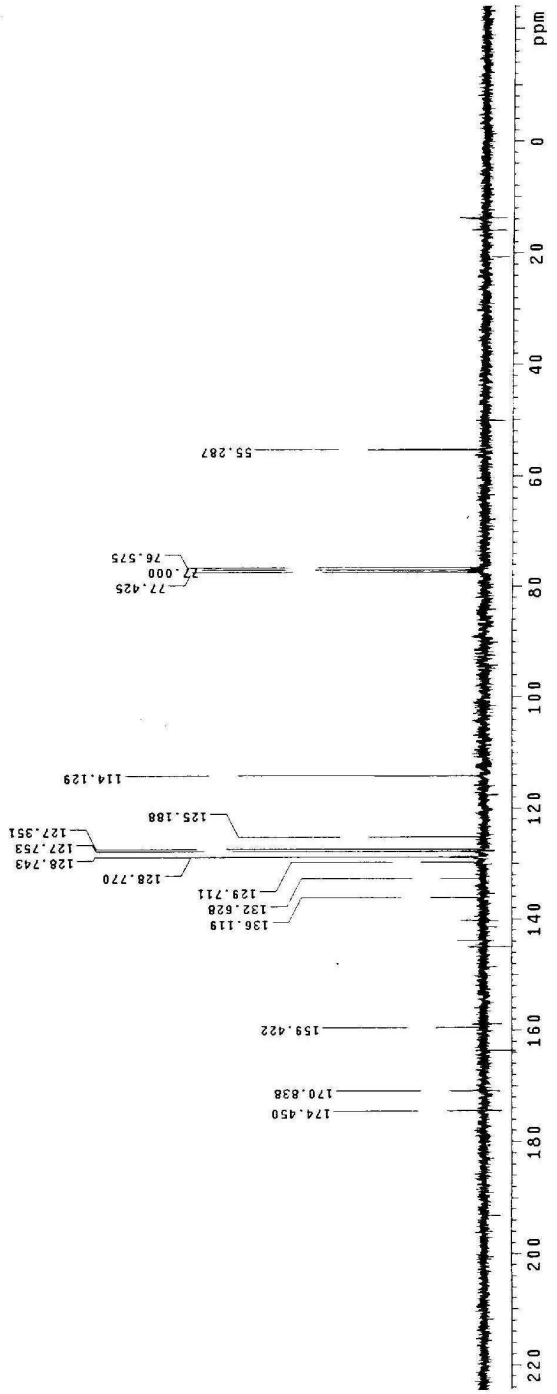


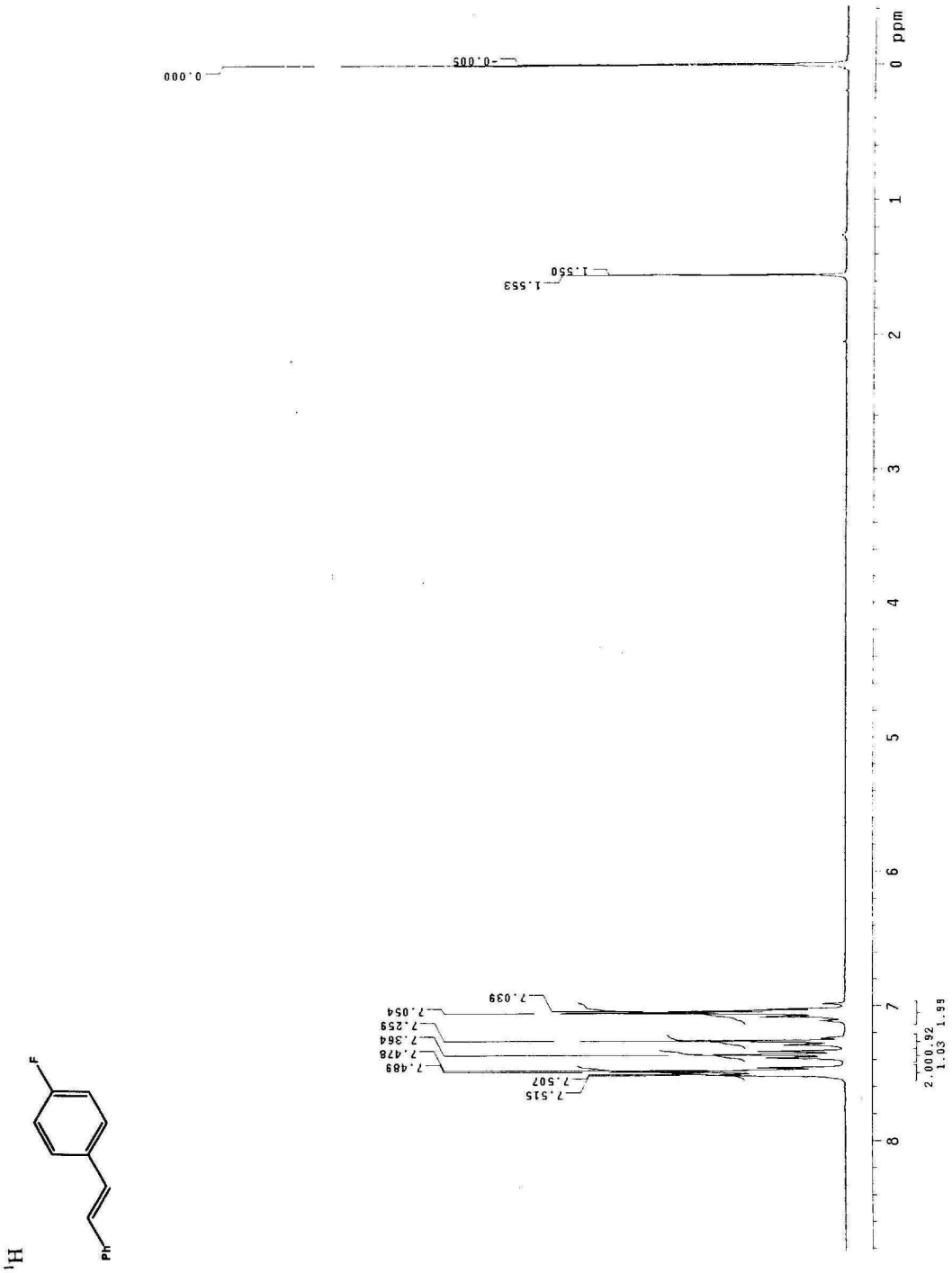


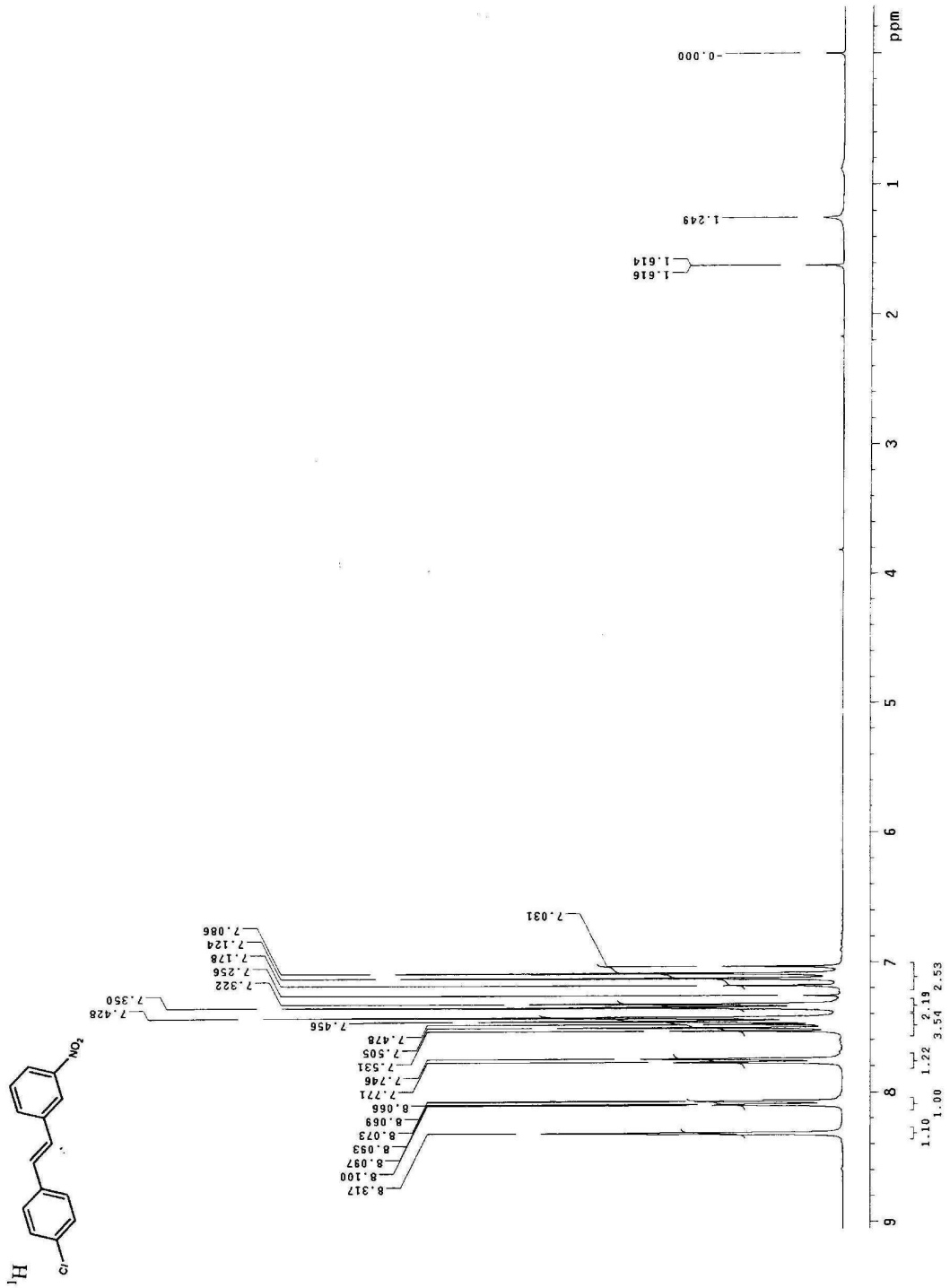


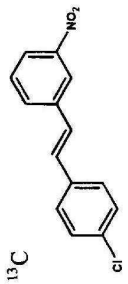


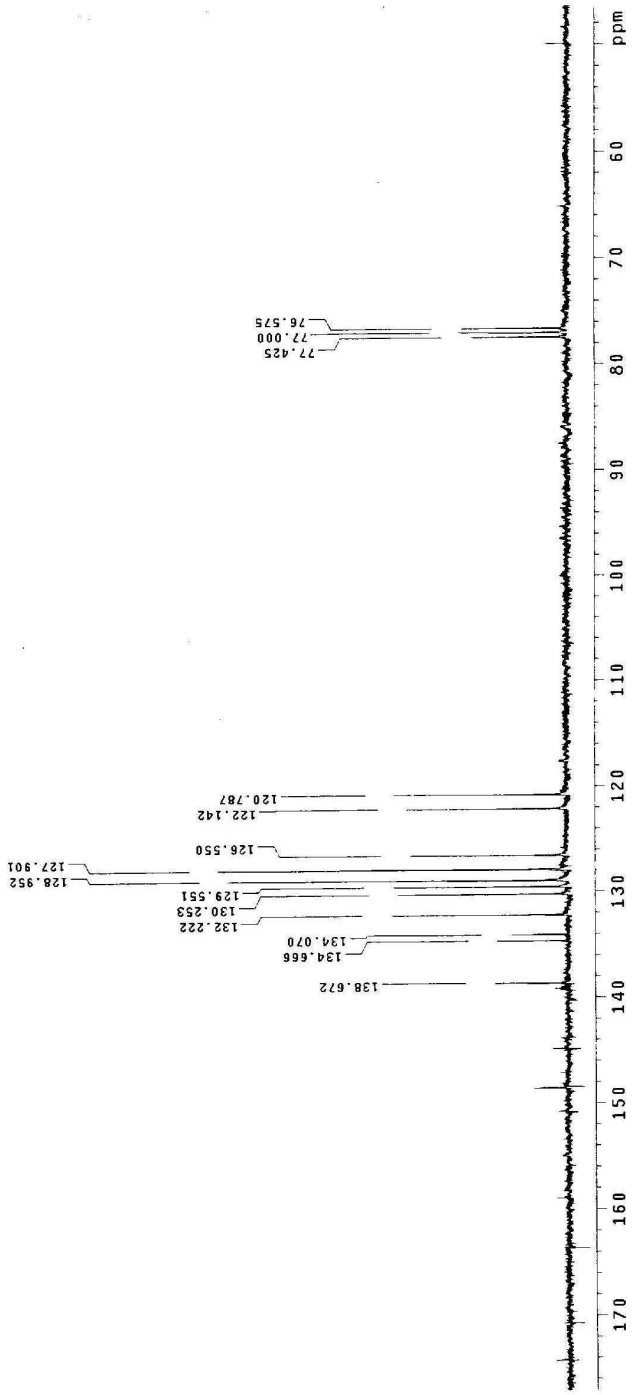


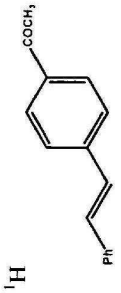












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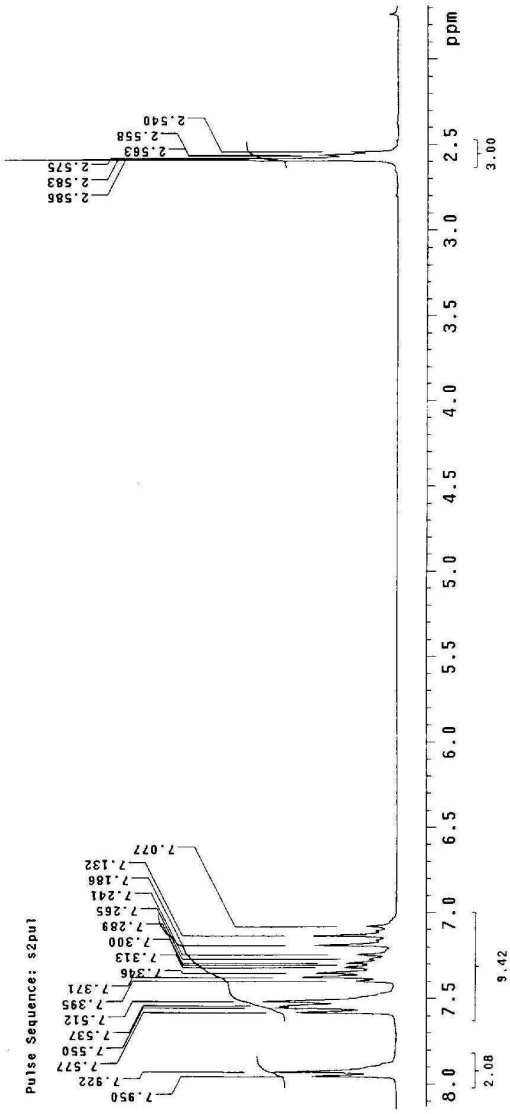

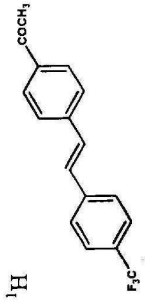

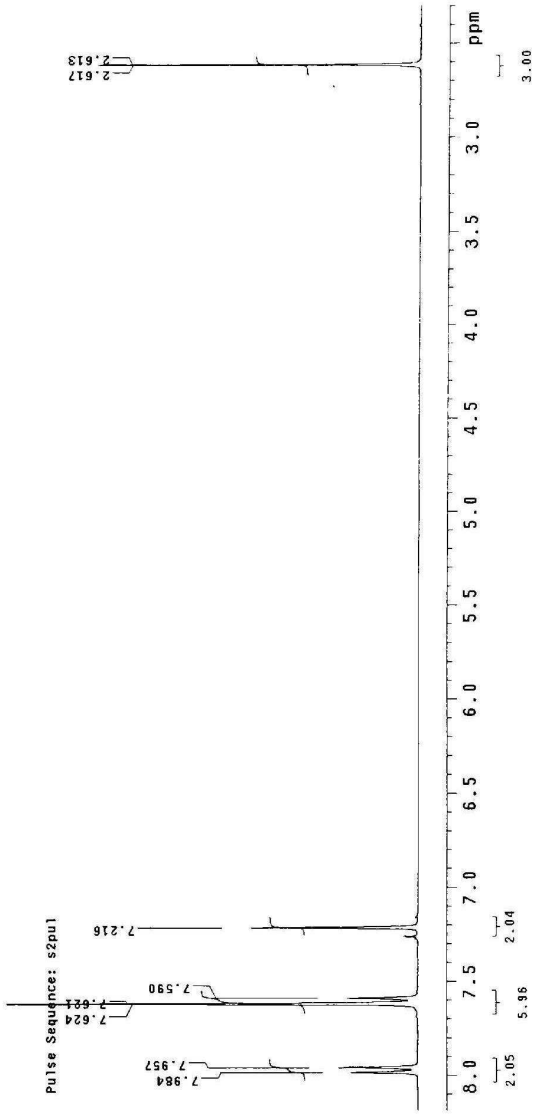

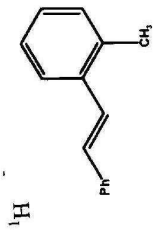

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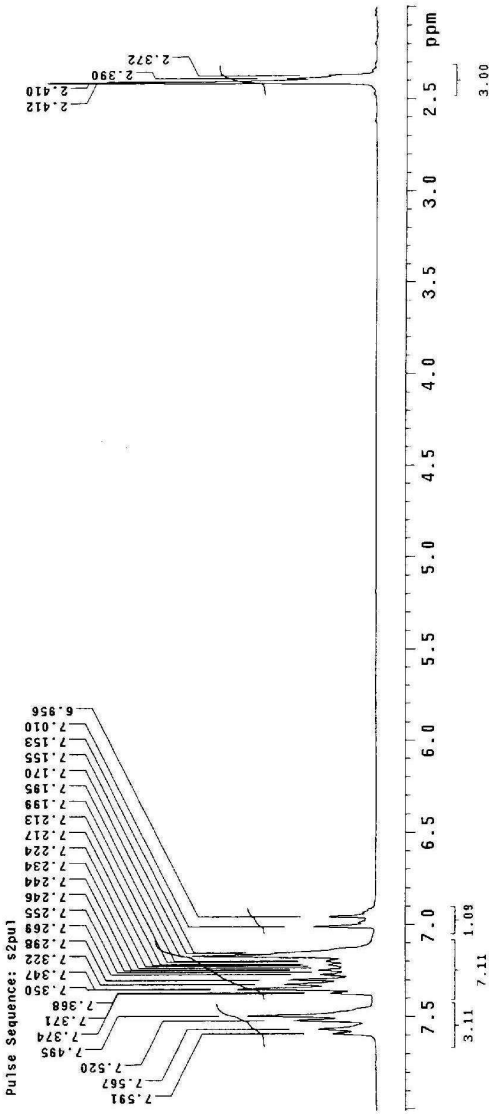

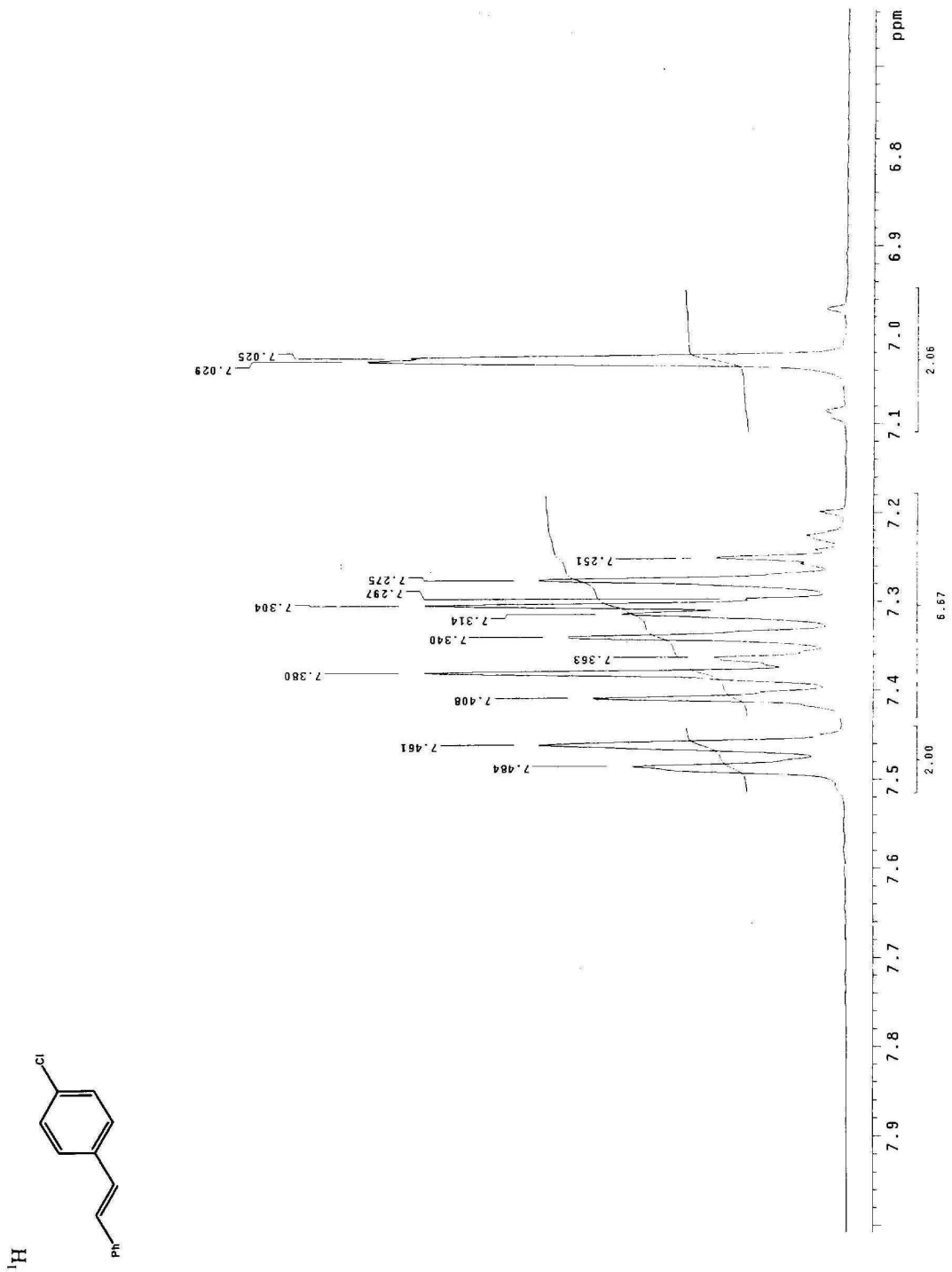

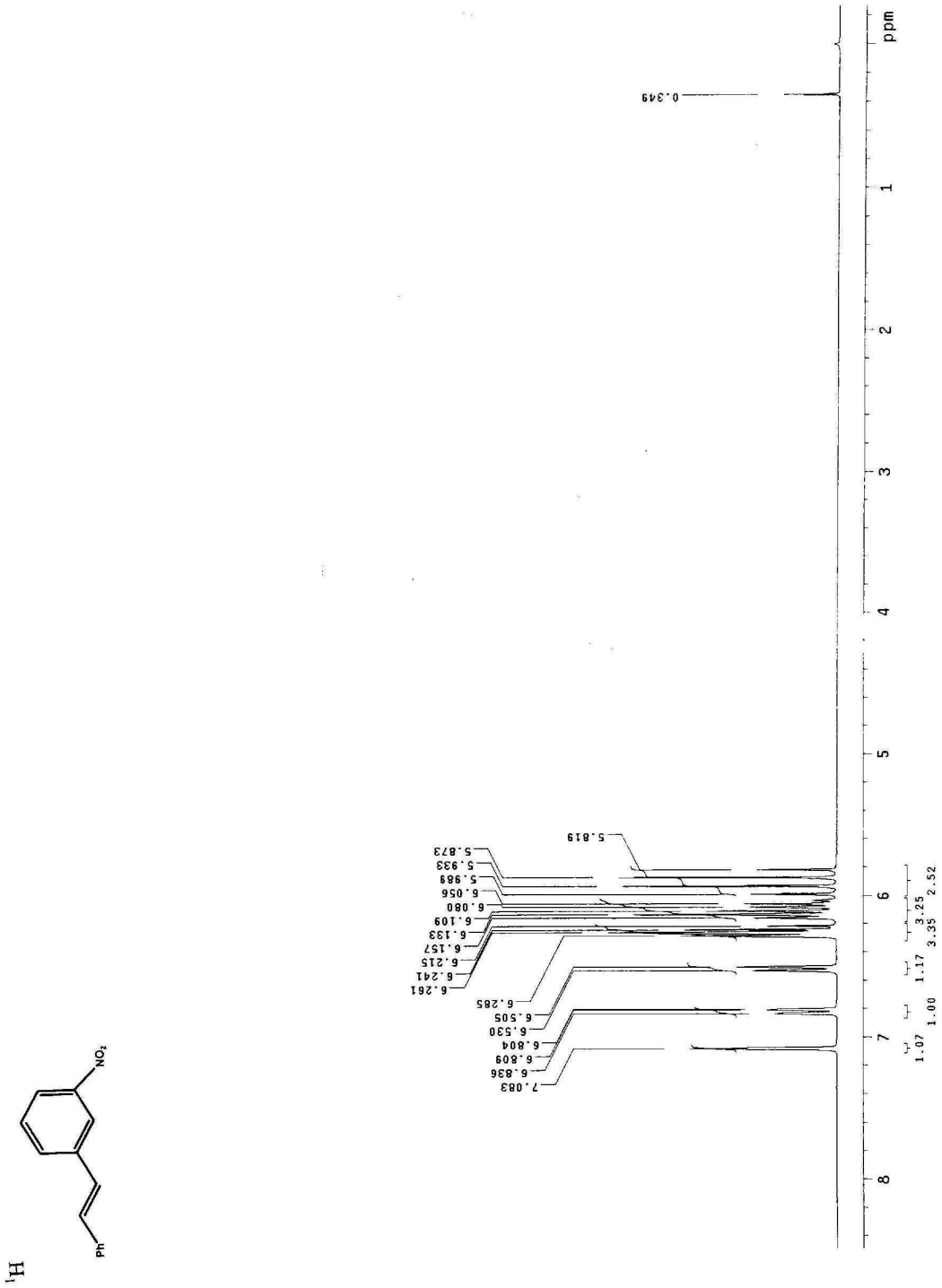

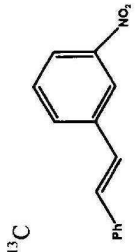

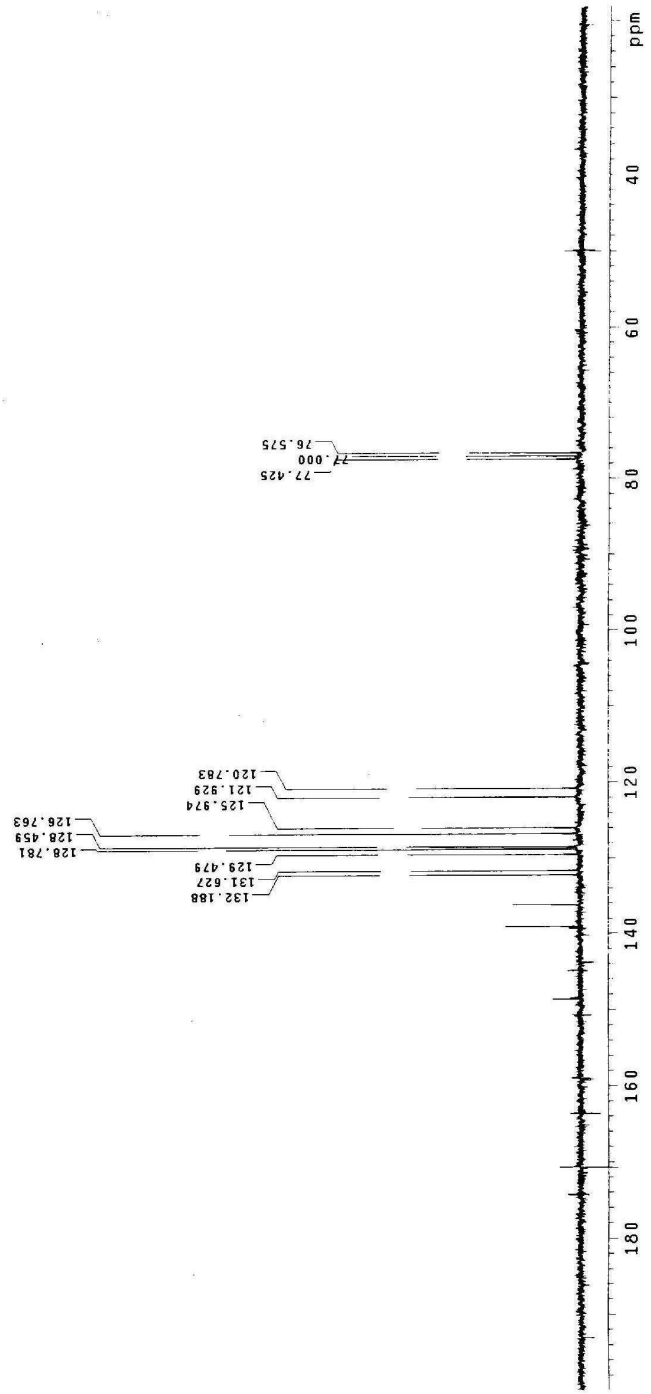

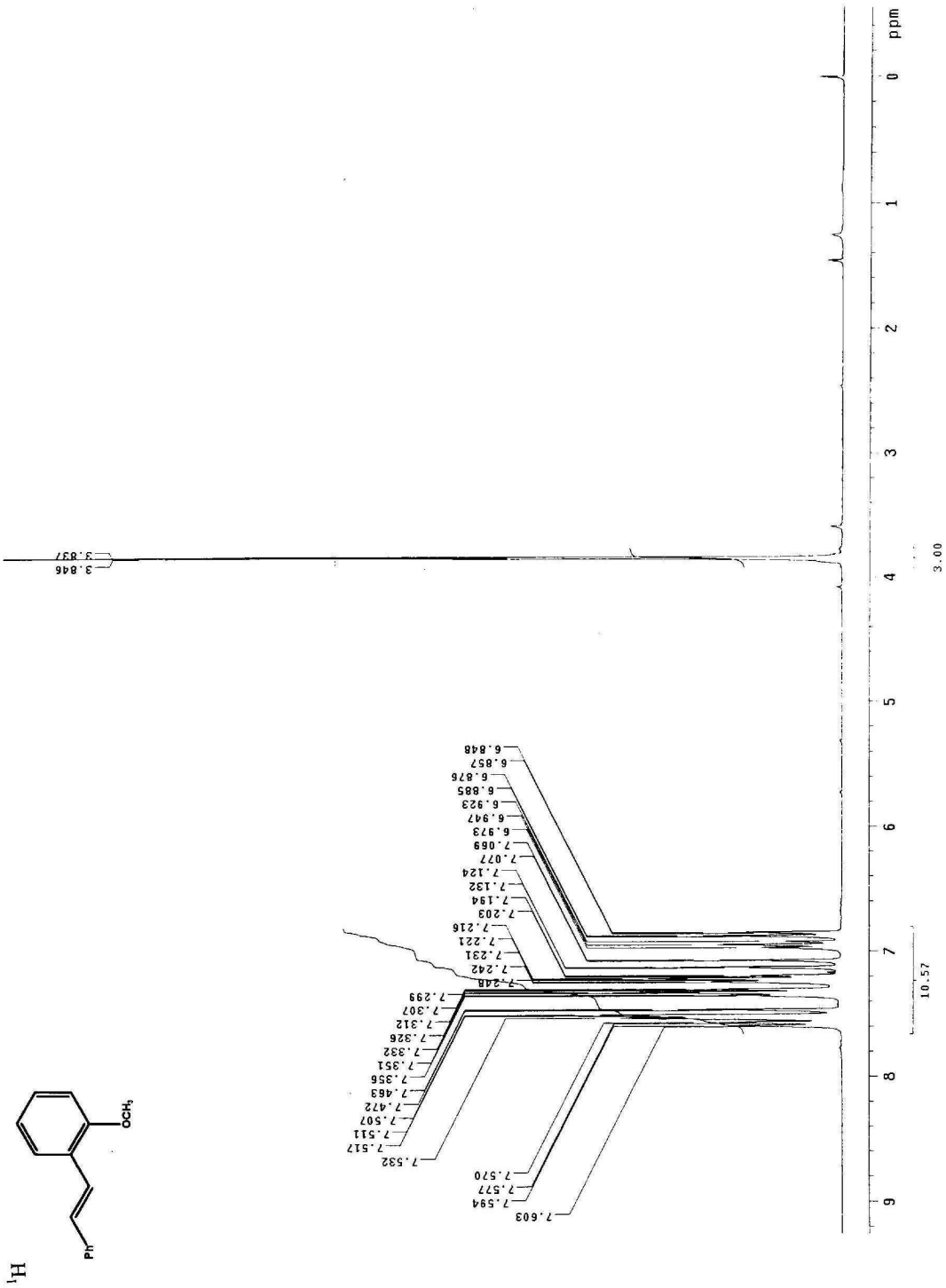

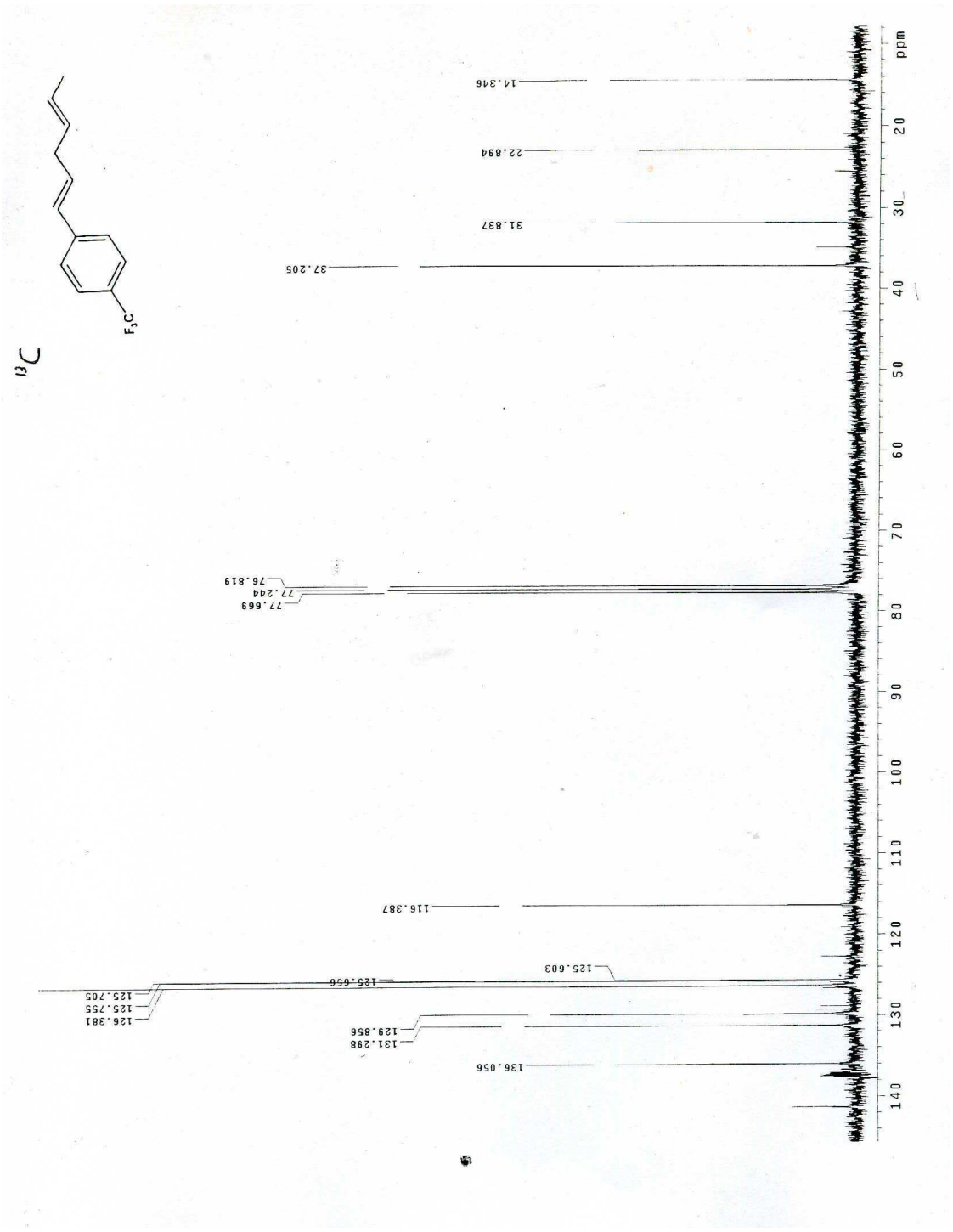

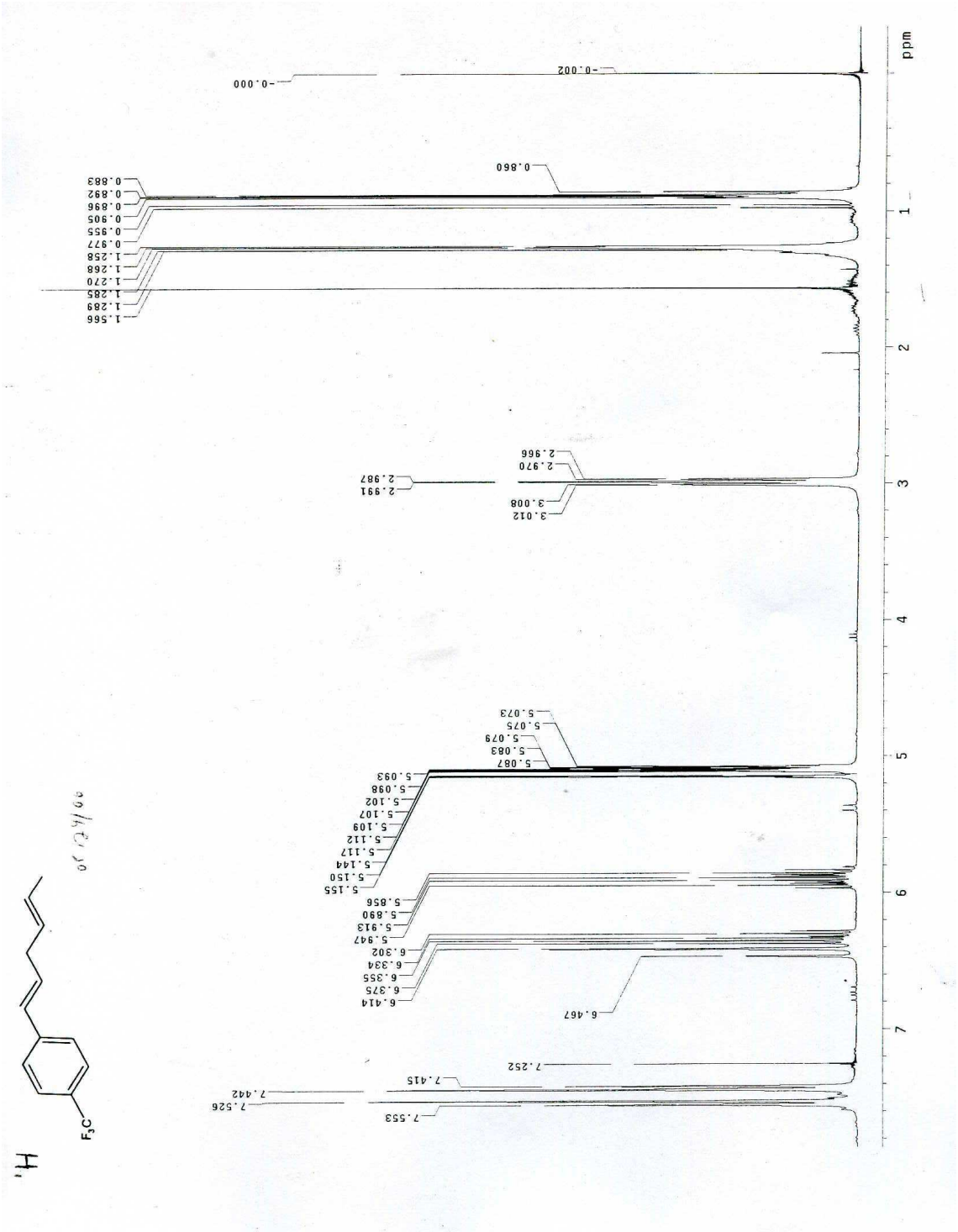

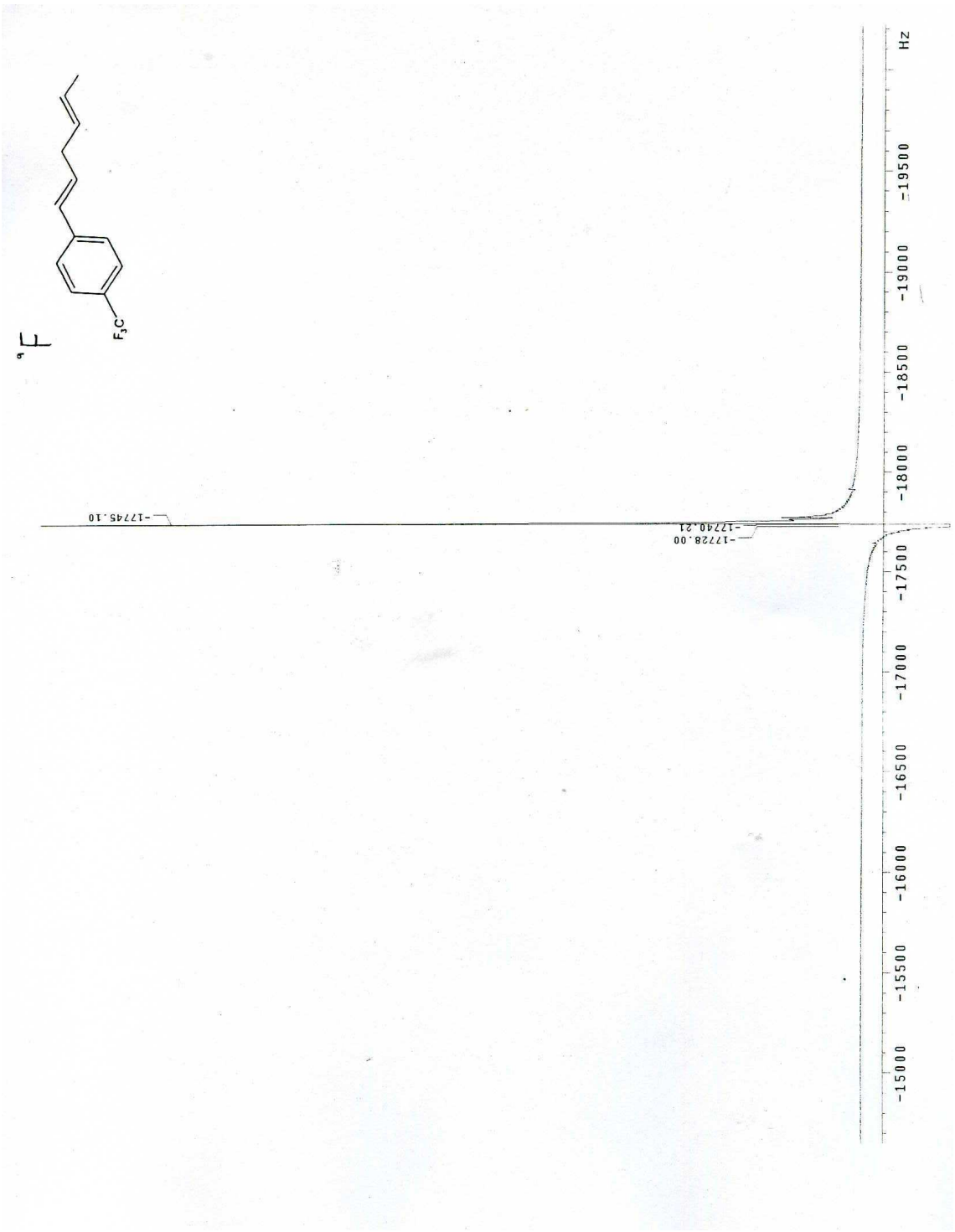

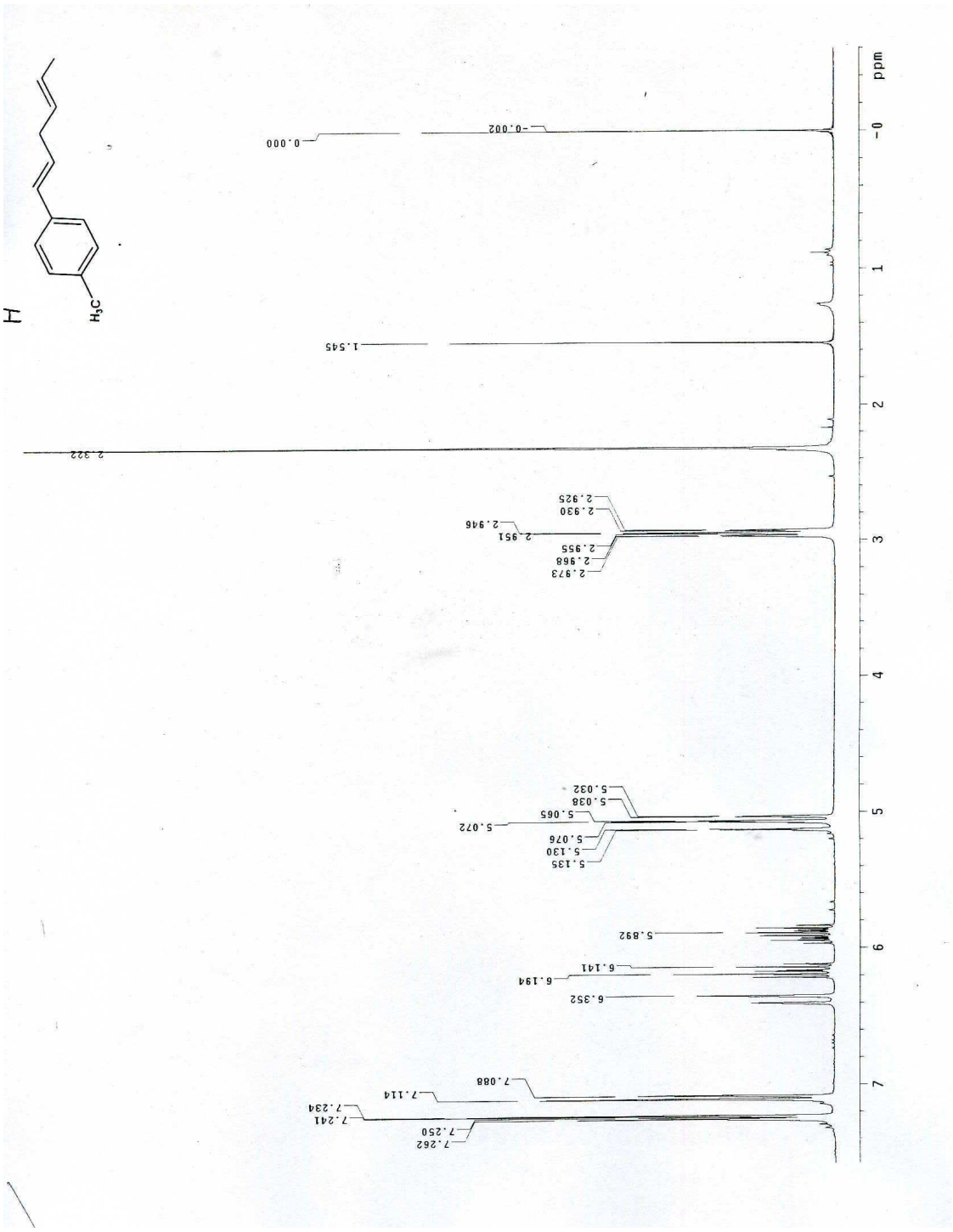

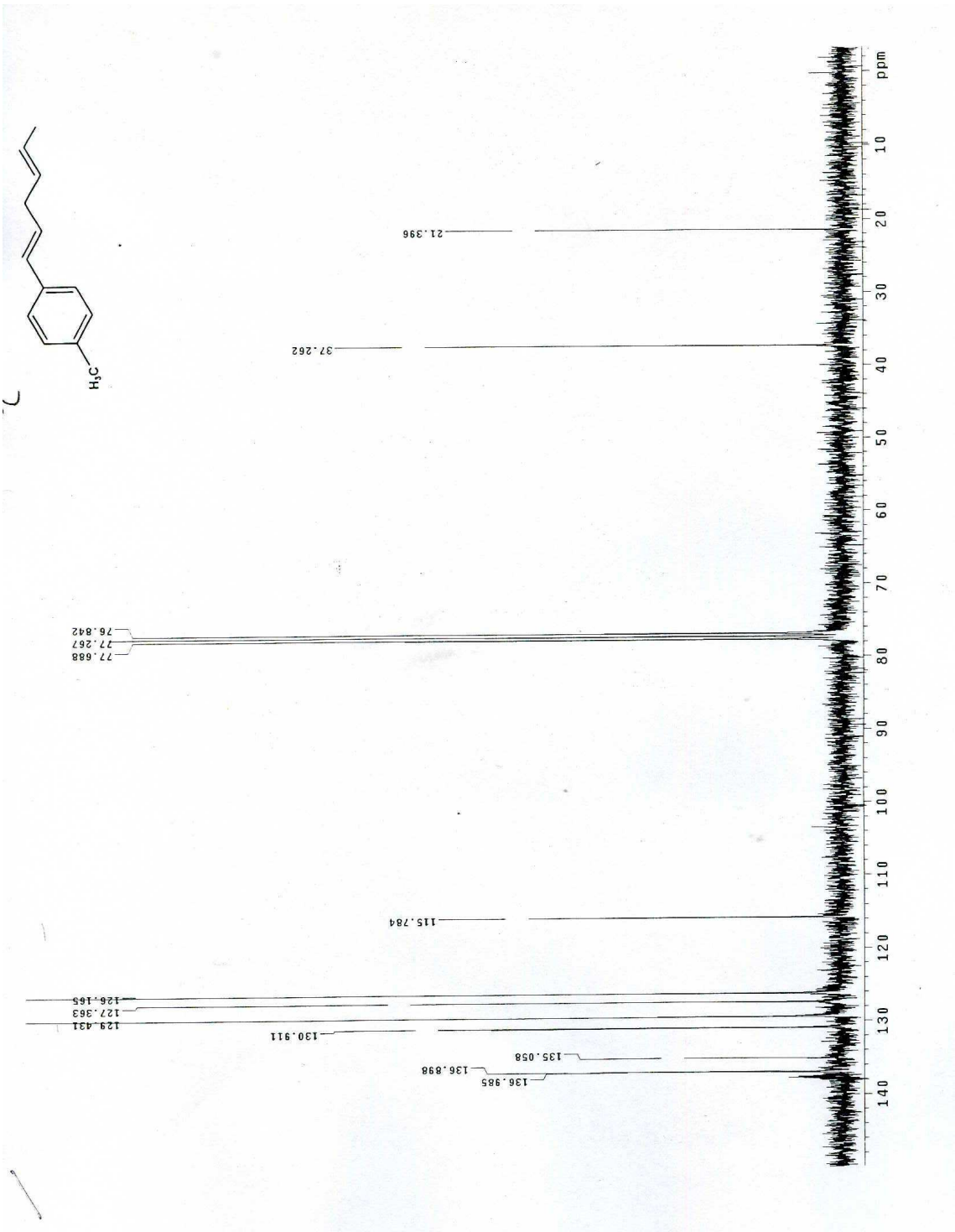

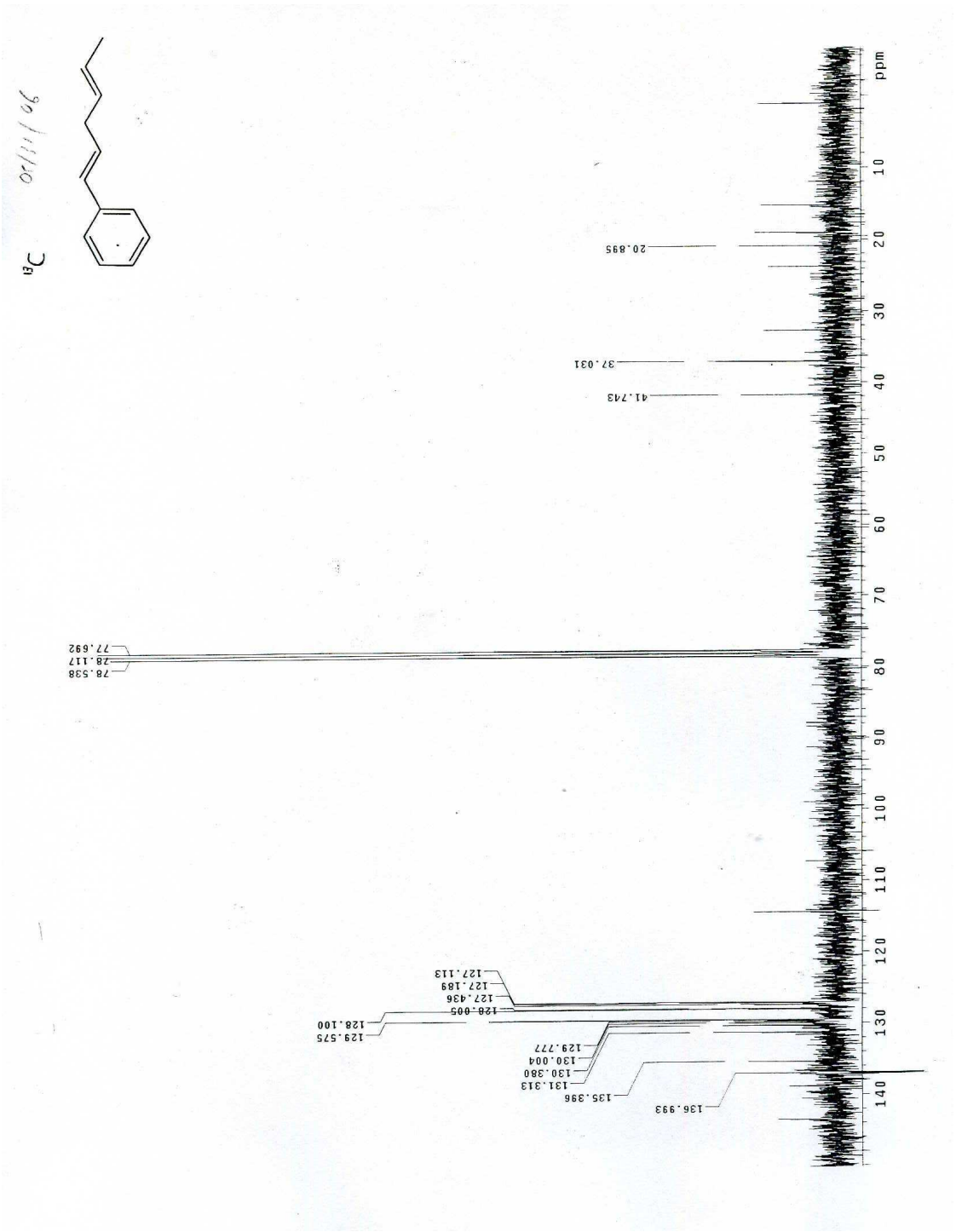

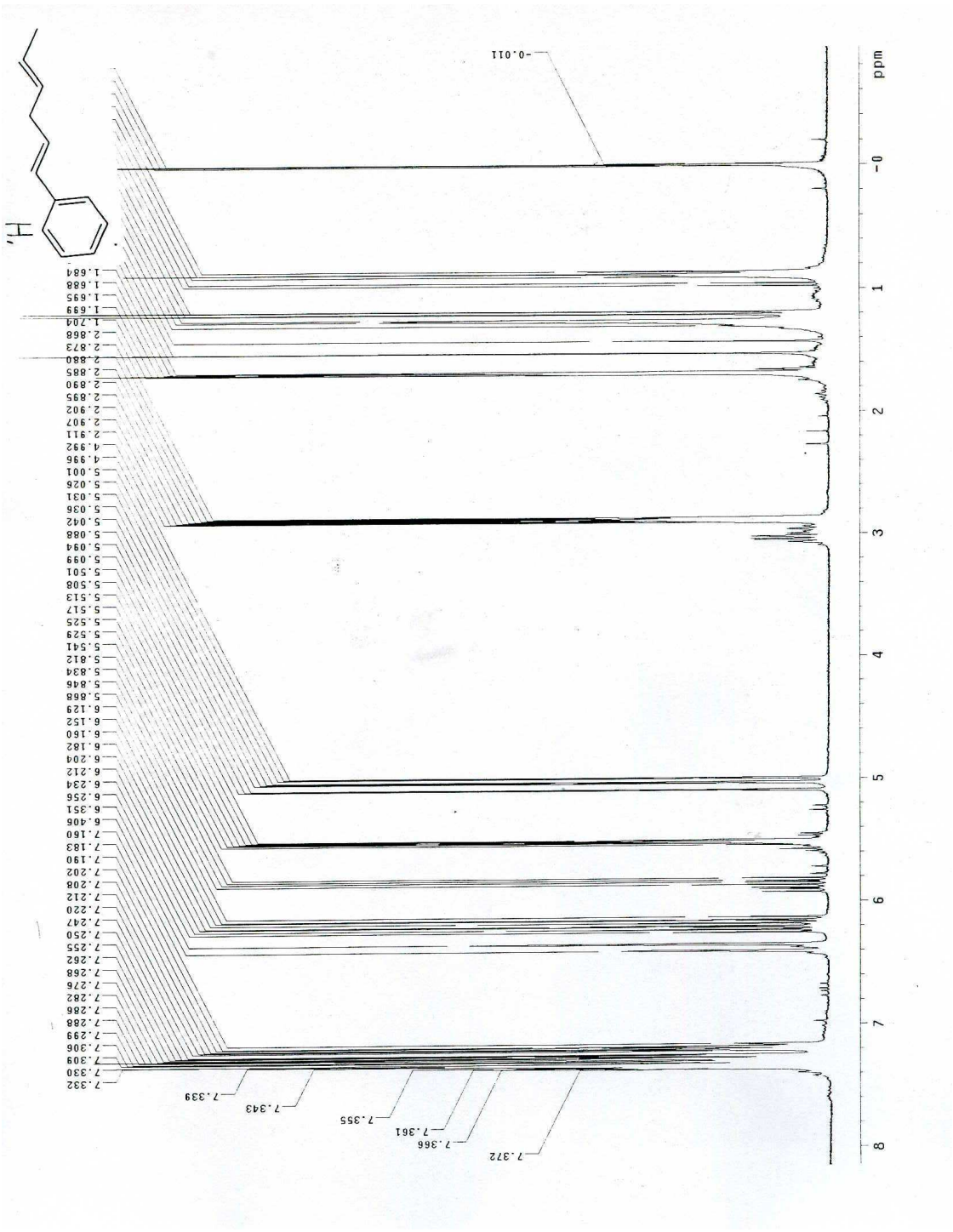

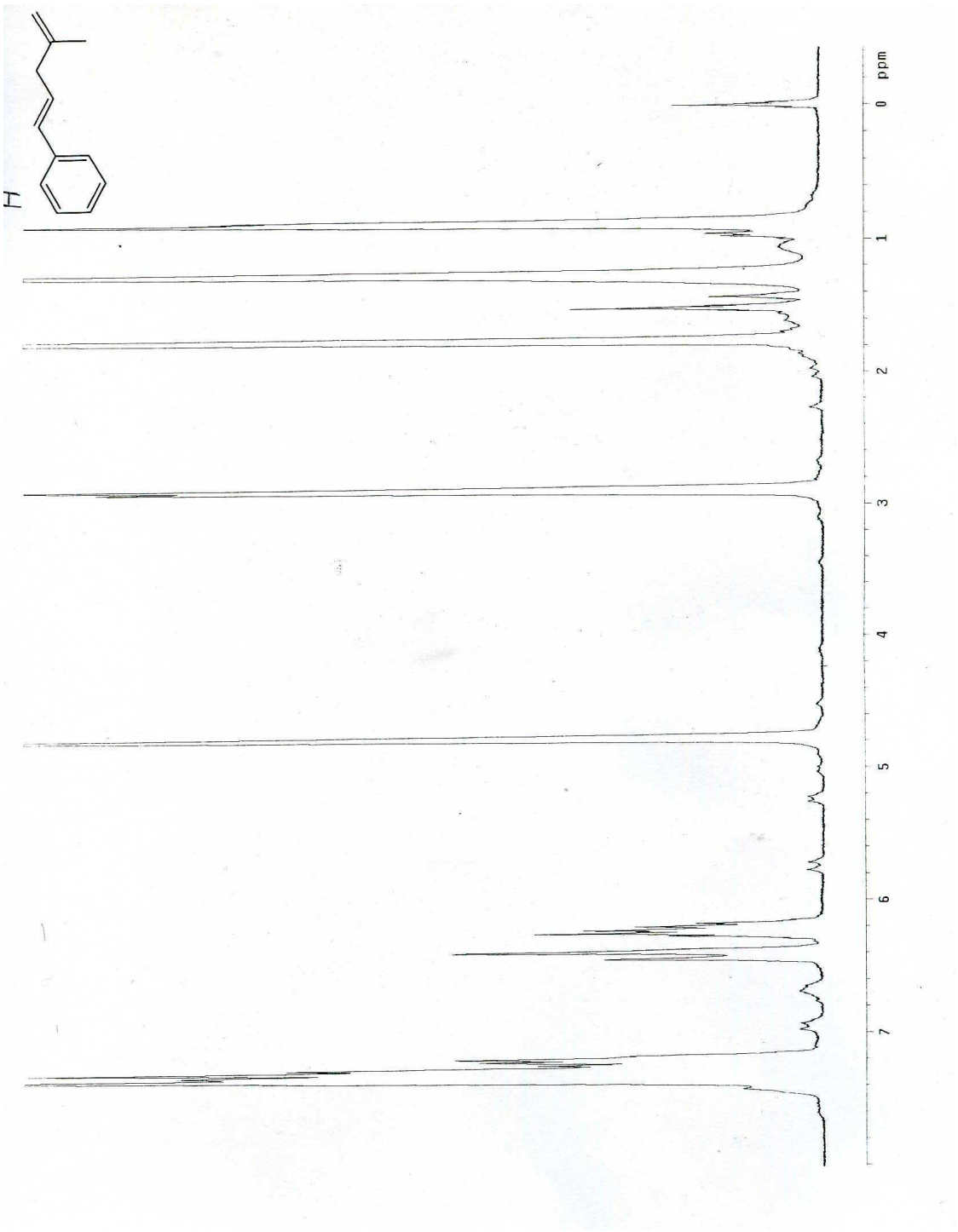

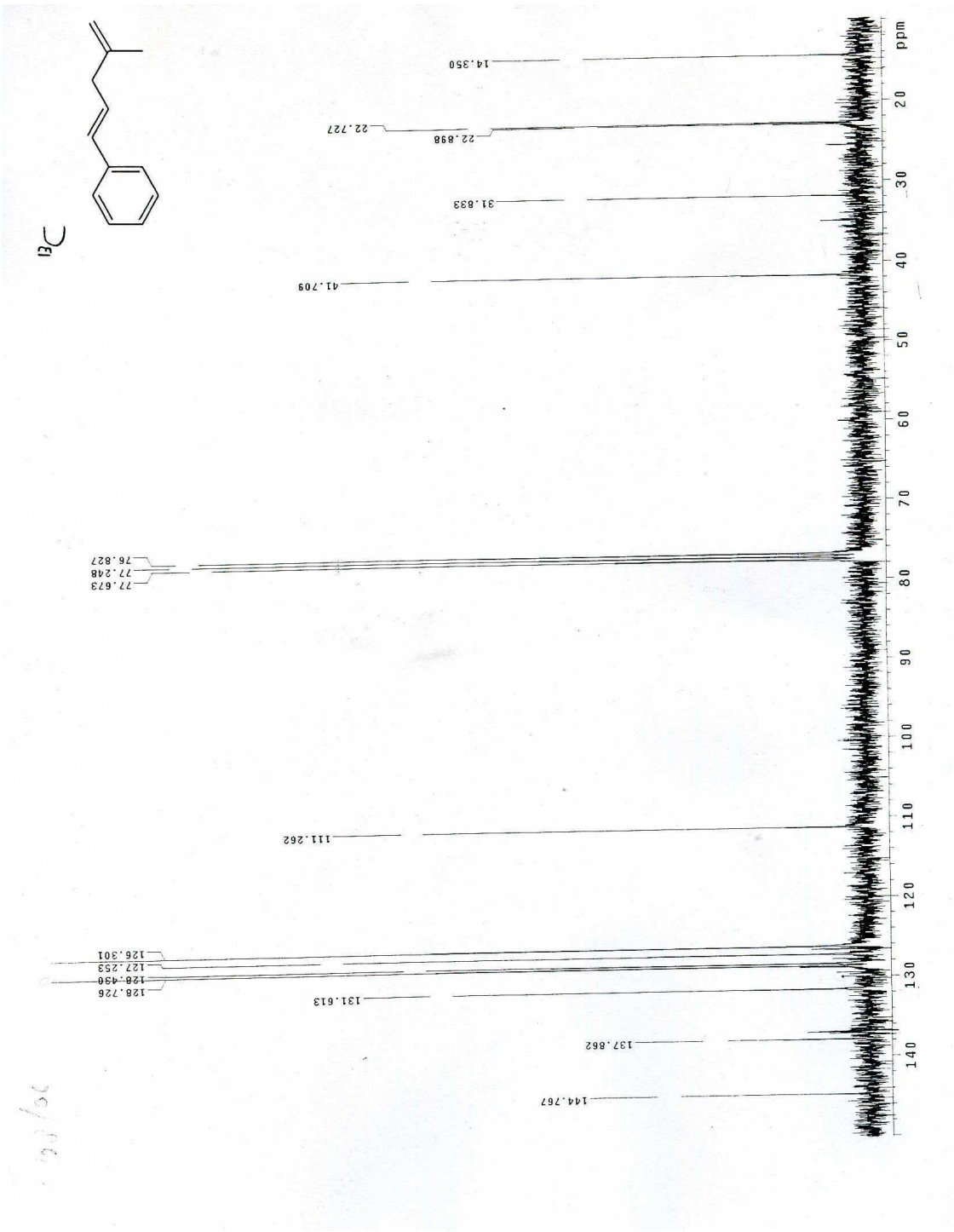

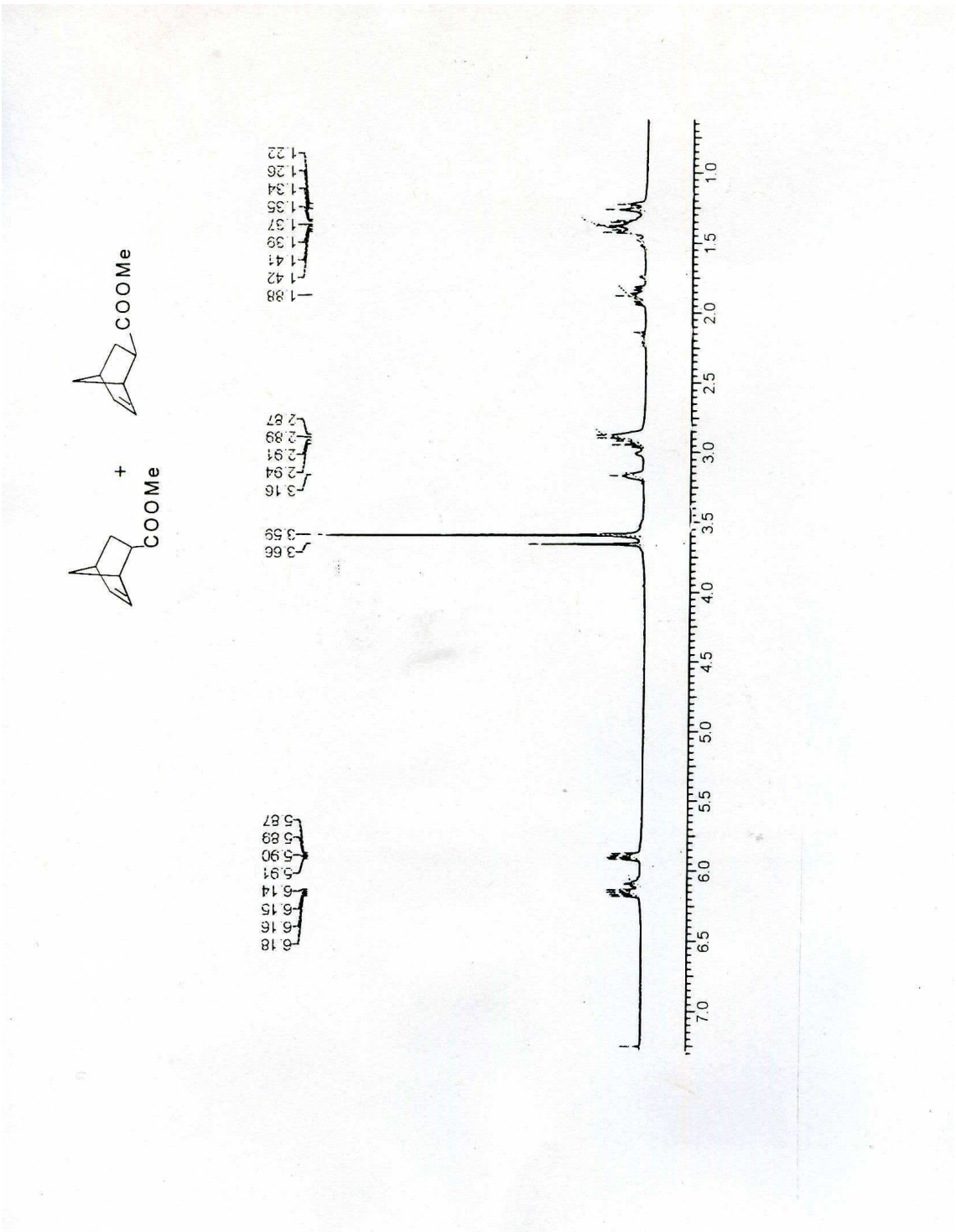

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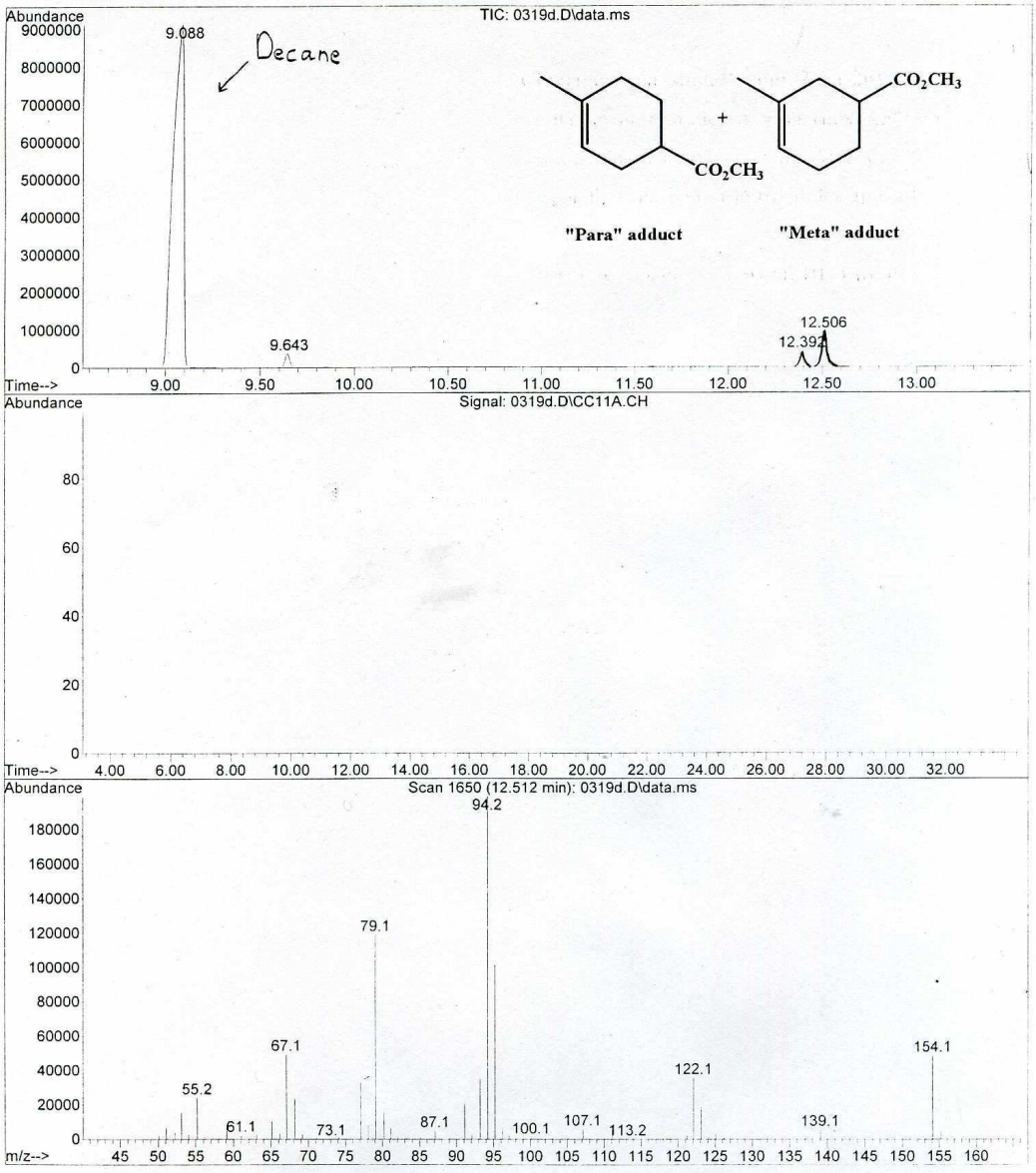

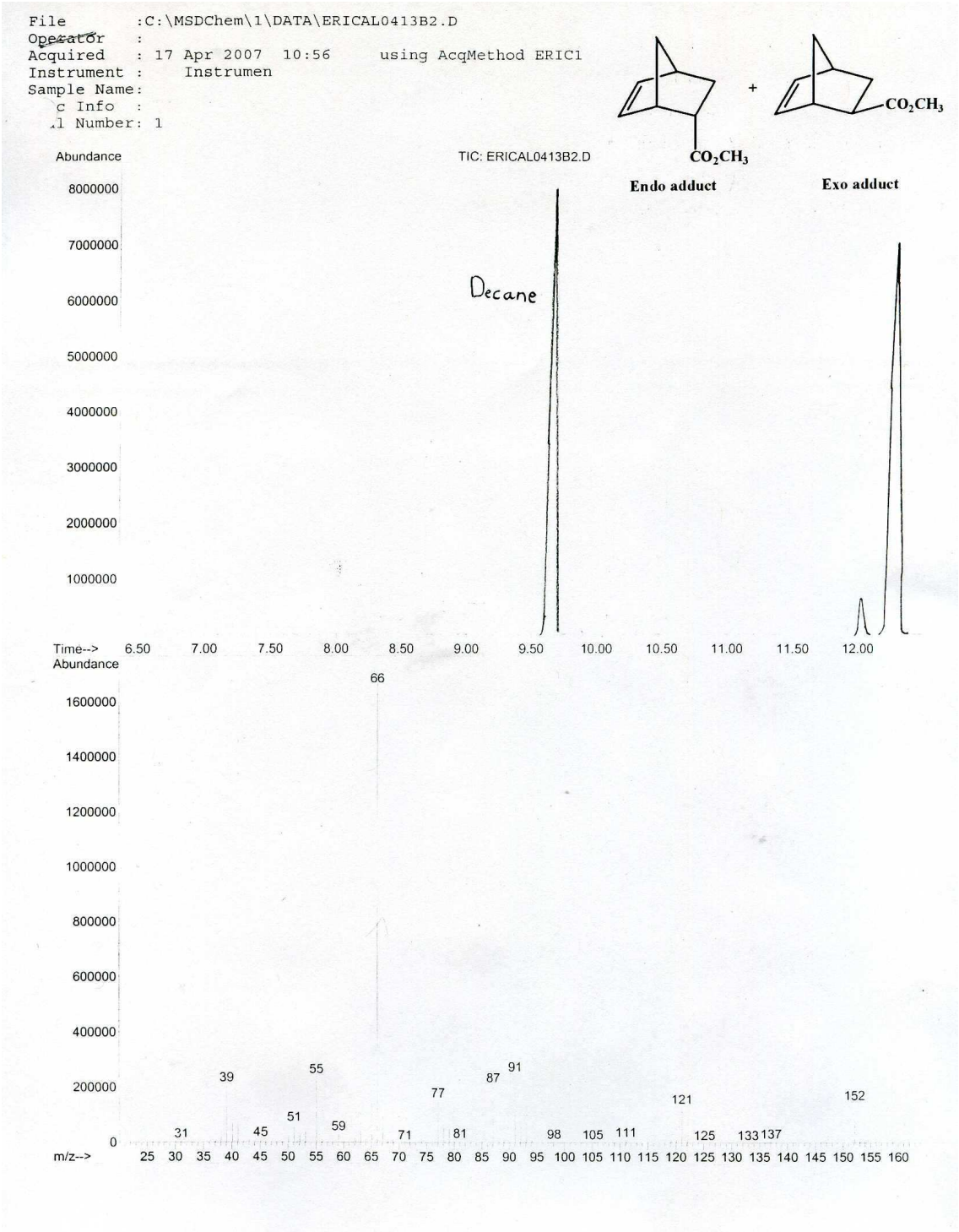

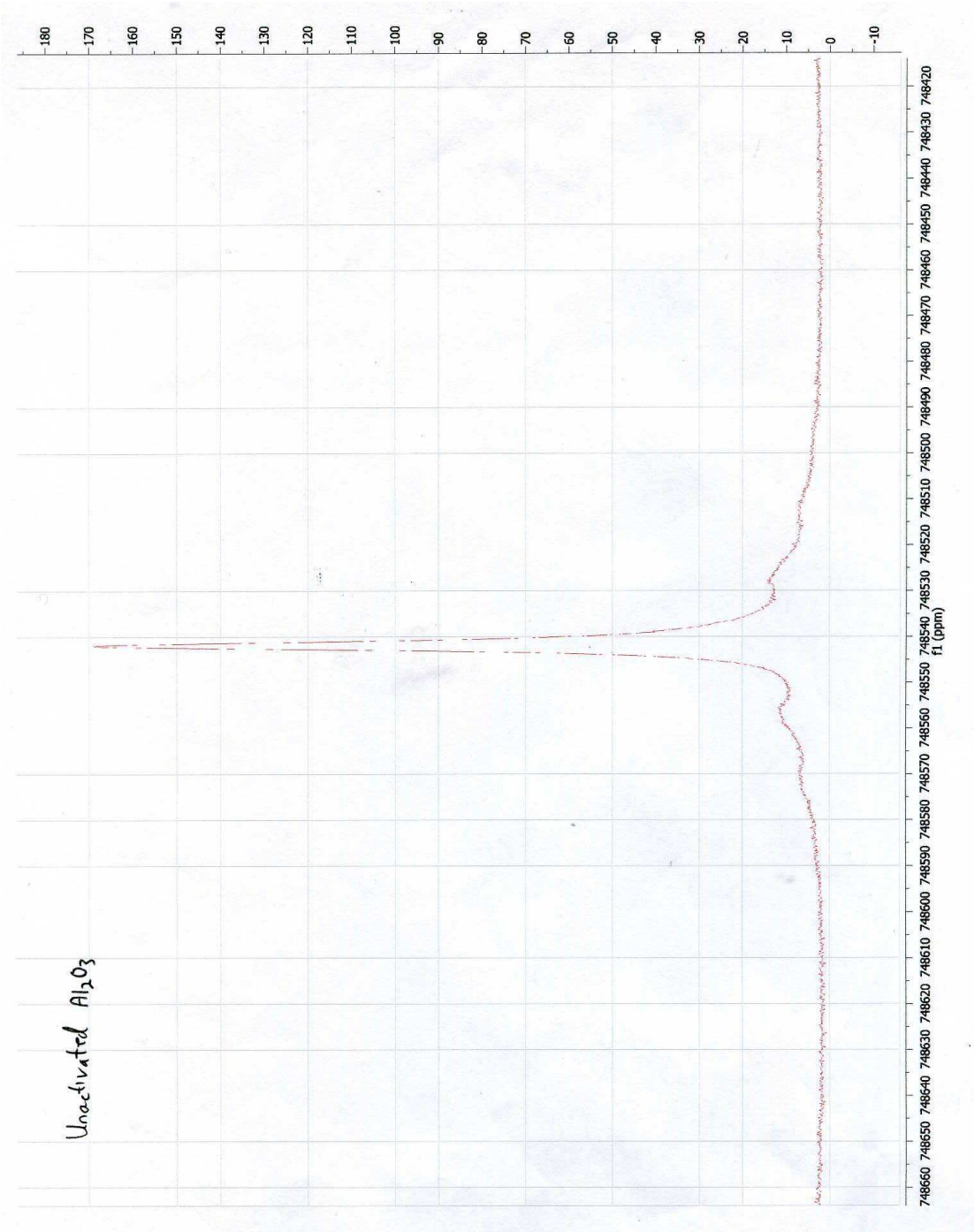

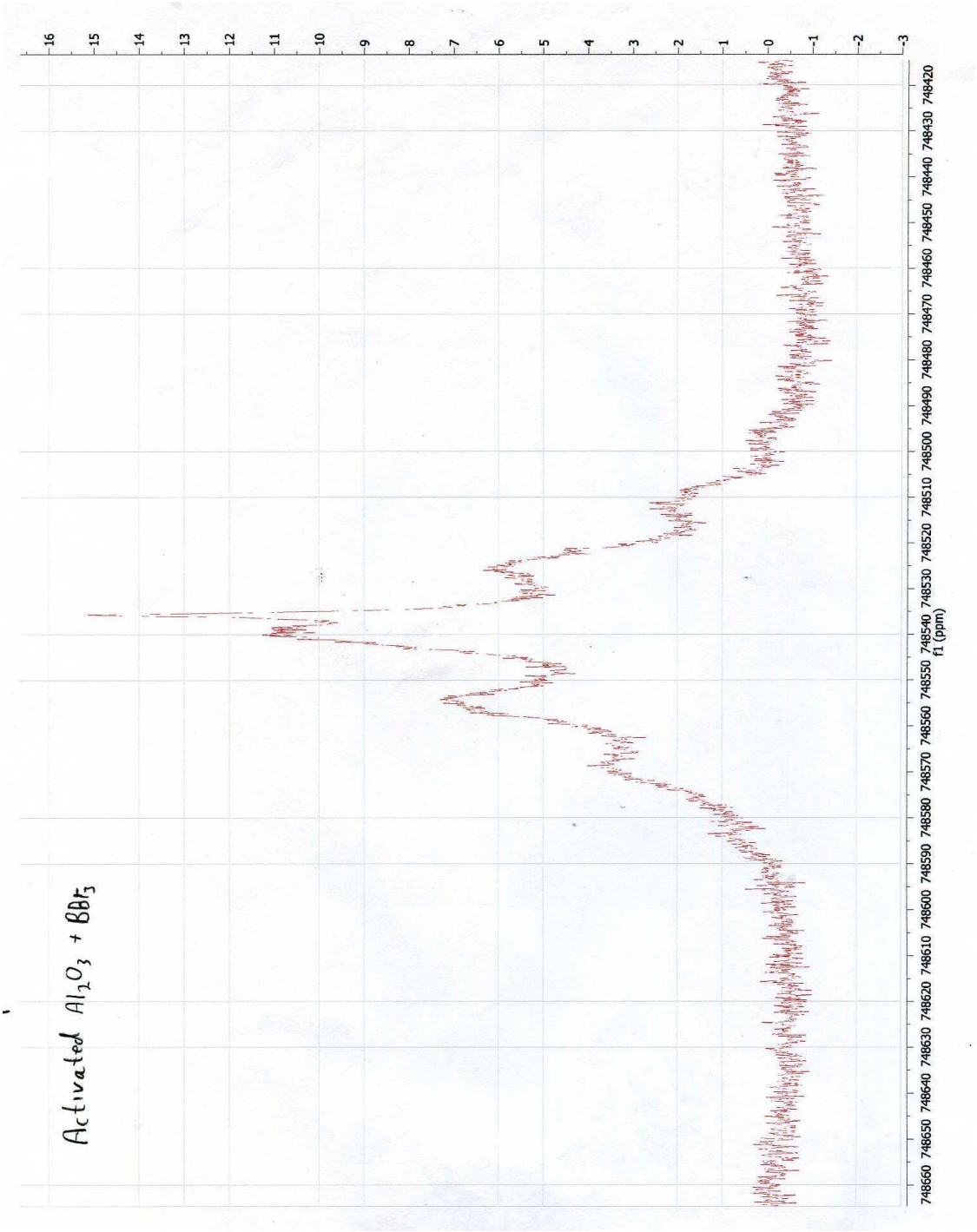

VITA

Eric (Arie) A. Dadush was born in Netanya, Israel on February 20, 1977. Eric graduated from Yeshiva High School in June 1995. Upon graduating he joined the Israeli Defense Force until his release in 1998. In 1999, he joined Tracks where he worked for two years as a group leader/facilitator for providing leadership skills in the expansion of adventure-based experiential programming. In 2001, Eric started his undergraduate studies in Chemistry and Biology at Lincoln Memorial University until his graduation. In 2004, he joined the University of Tennessee for his graduate studies in organic/medicinal chemistry under the direction of Dr. George W. Kabalka. In the final year of his graduate studies, Eric explored the utilization of Microwave in polymer chemistry. Upon his graduation from U.T.K. Eric joined St. George University to obtain his medical degree.