To the Graduate Council:

I am submitting herewith a thesis written by Kristy Lynn Homburger entitled "An Investigation Into A Microwave-Enhanced Solvent-Free Mannich Condensation Reaction." I have examined the final paper 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 W. Kabalka, Major Professor

We have read this thesis and
recommend its acceptance:

Richard Pagni

Acceptance for the Council:

Vice Chancellor and Dean of
Graduate Studies

An Investigation Into A Microwave-Enhanced Solvent-Free Mannich Condensation Reaction

A Thesis
Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Kristy Lynn Homburger
August 2006

DEDICATION

To my parents, Joe and Kathy Quick, grandparents, Kenneth and Earlene Pickett, and twin sister, Misty Pickett. Thank you for all of the love and support you have given me over the years. Thank you for never giving up on me. I would never have made it this far without all of you.

To my husband, Albert Thomas Homburger, Jr. Thank you for your love and support. Thank you for putting up with all you have this past year. I would have never finished this thesis without your support and help. I love you.

Words will never express how grateful I am to all of you. I love you all.

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Thank you to my family and friends, whose support and love made it possible for me to do this work. All of you have played such an important part in my life that I cannot even begin to put it in words. Lastly, but most important, thank you to Jesus Christ, my Savior and Lord, whose unending love and grace makes it possible for me to live on a daily basis. It is His love and grace that gets me through the day. Thank you for all you have provided and done for me. I am so undeserving, but You still love me. Thank you!

ABSTRACT

Microwave irradiation has gained in popularity in recent years since it has been found to accelerate various chemical reactions. Microwaves are generally considered to be more environmentally friendly than traditional methods for activating chemical reactions. An investigation into a microwave-enhanced, solventless Mannich condensation was performed. The efficiency of a standard household microwave was compared to that of an industrial microwave, with the industrial microwave proving to be more effective. The advantages of using microwave irradiation for a Mannich condensation include milder reaction conditions, the absence of solvent, less waste, and shorter reaction times. The reaction between terminal alkynes, secondary amines, and paraformaldehyde on CuI-doped alumina, to yield β-aminoalkynes, was investigated. Cuprous iodide and alumina were both required for successful reactions. The microwave reactions produced good yields of the β-aminoalkynes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SYMBOLS AND ABBREVIATIONS

Symbol	Description
β	Beta
^{13}C	Carbon-13
^{1}H	Hydrogen-1
δ	Parts per million

Abbreviation	Description
$CDCl_3$	Deuterated chloroform
Hz	Hertz
MHz	Megahertz
Mmol	Millimoles
NMR	Nuclear magnetic resonance

Chapter 1 Introduction

1.1 THE MICROWAVE

Microwave ovens have been used for almost fifty years to heat food. In the last few decades, scientists have utilized microwave energy as a means to accelerate chemical reactions. Inorganic chemists have used microwave technology since the late 1970's, and organic chemists began using the technology in the mid-1980's.[1,2] The increased use of microwaves has occurred for a variety of reasons including decreased cost, and more accurate control of temperature, pressure, and power. The use of microwave chemistry allows for shorter reactions times, an expanded range of reactions that can be achieved, and increased yields when compared to the traditional heating methods such as oil baths.[2] A wide array of reactions has been achieved using microwave chemistry. These chemical reactions include, but are not limited to, the Diels-Alder reaction,[3] Suzuki,[4,5] and Sonogashira coupling,[6] acid hydrolysis, oxidation, and esterification.[1]

In traditional reactions, heat has to pass through the reaction vessel in order to reach the reactants and solution. This results in heating of the reaction vessel to higher temperatures than the reactants which resulted in longer reaction times and energy loss. In microwave heating, the reaction times are shorter because the microwaves directly heat the reactants.

Even though microwave irradiation shortens the reaction times, it does not affect the activation energy. The microwaves provide the necessary energy to overcome the activation barriers. Microwaves are able to do this because they transfer heat faster than the molecules in the reactions relax. This allows for the temperature to rise faster and stay

higher than they do in using traditional heating techniques. The increase in temperature also allows for more collisions of the molecules leading to shorter reaction times.[7]

Microwave assisted reactions can occur in the presence or absence of solvents. Depending on the type of reaction medium, the microwave will heat the reaction mixture differently. The initial application of microwaves in organic synthesis involved solution phase reactions. The solvents that were used had high dielectric constants. As the solvents in the reaction were heated in the microwave, the dielectric constants decreased allowing for the temperature of the reaction to increase.[2] The decrease in reaction time has also been credited to a phenomenon called superheating, a phenomenon in which the solvents are heated above their boiling points during the reaction.[8]

Due to the fact that reactions were dependent on the ability of the solvent to interact with the microwave irradiation, only polar solvents, such as dimethyl sulfoxide and dimethylformamide, could be used. Non-polar solvents are inert to microwave dielectric loss.[9,10] They can be used only if they are combined with a small amount of polar solvents.[2] The main problem associated with the solution phase reactions was that the reactions had to be performed in sealed vessels in order to keep the reagents from damaging the microwave. These sealed vessels led to high pressure and resulted in potentially dangerous reaction conditions. Some solution-phased microwave assisted reactions can be performed in open-vessels. When a reaction is performed in an open-vessel flammability and volatility become potential hazards.[8]

Due to the limitations and dangers of microwave solution-phase reactions, investigations into solvent-free reactions increased. Solvent-free microwave reactions have many advantages over solution-phase reactions. In solvent-free reactions, the

reactions can be performed in open-containers eliminating many concerns related to pressure build-up in the reaction vessel. Since no solvent is used, there is less chance of losing product during the work-up after the reaction resulting in higher reaction yields. Also since no solvent is used, there is less reagent waste. Some of the solid supports that are used have the ability to be recycled and reused in future reactions.[11]

The solvent-free reactions use solid supports to absorb the reactants. In general, there are two types of microwave assisted dry reactions: a microwave inactive surface or a microwave active surface. Using a microwave inactive surface, one of the reagents must be microwave active. Using microwave active surfaces, the reagents do not have to be active toward microwaves.[8] Occasionally, it is necessary to mix the surface with a solvent to aid in coating it on the surface.[12]

Generally, inorganic oxides are used as the supports, and they do not absorb microwave irradiation, allowing the organic reactants to absorb most of the energy.[9] Various inorganic oxides have been used throughout the past years, with some being pure, and others being "doped" with another reagent. These supports include clays,[13,14] silica gel,[15] silica gel doped with indium (III) chloride,[16] silica gel supported on Lewis acids,[17] potassium fluoride doped alumina[18-21], and alumina.[22]

1.2 MANNICH REACTION

The traditional Mannich reaction is a three-component condensation reaction.[23] The reaction mixture contains at least one compound containing an active hydrogen that condenses with formaldehyde (or *para*-formaldehyde) and a primary or secondary amine or ammonia to generate a product known as the Mannich base. Under further heating, the base eliminates an amine hydrochloride to yield the desired product. Examples of active

hydrogen-containing molecules include ketones, alkynes, nitroalkanes, β-ketoesters, β-cyano-acids, indoles, furans, or pyrroles.[24]

Traditional Mannich reactions require drastic reaction conditions, including high temperatures and prolonged reaction times. These conditions often cause unwanted side reactions, lowering the product yields.[25] Also, solvents, such as dioxane, are traditionally used in the reaction, and the removal of these solvents can be a waste-handling problem.

1.3 APPROACH TO THE STUDY

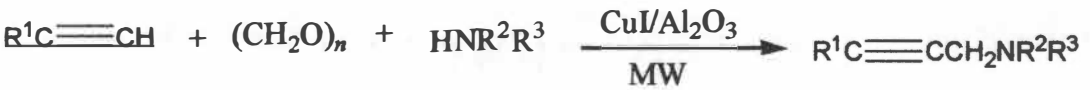
This study focused on the application of microwave activation to Mannich reactions. The reactions investigated were solvent-free, eliminating waste-handling problems associated with the traditional Mannich reaction. Alumina combined with copper(I) iodide was used as the solid surface.

Chapter 2 Results and Discussion

The synthesis of β-aminoalkynes using terminal alkynes, secondary amines, and *para*-formaldehyde via microwave irradiation is outlined in **Scheme 1**. Various terminal alkynes and secondary amines were used to obtain the desired Mannich condensation products. **Table 1** contains the results from the reactions of various alkynes and amines.

When the study was commenced, a standard household microwave was used to perform the syntheses. There were problems associated with the reactions carried out using the household microwave, these included uneven heating, long reaction times and unwanted side products. The household microwave created hotspots, which was observed by darkened spots on the reaction mixture after microwave irradiation. The hotspots resulted in non-uniform heating of the sample. This resulted in uneven heating and lower yields of the desired products. Also these reactions required a longer reaction time than what was thought to be safe when using the household microwave. The reactions required at least twenty minutes, and in the household microwave, anything longer than five minutes was deemed dangerous due to overheating. Thus reactions utilizing the household microwave required irradiating the mixture, letting it cool, and irradiating it again.

Another problem that resulted from the uneven heating was the formation of unwanted side products. Using the household microwave, it was discovered that the order of addition of the reactants made a difference in the yields of product formed. If all the reactants were combined and then microwaved, the desired β-aminoalkyne was not formed (**Scheme 1**). Instead, the tetrabenzylmethylenediamine product was formed



Scheme 1. General Reaction Pathway for the Synthesis of β-Aminoalkynes

Table 1. Mannich Condensation Reaction of Terminal Alkynes with Secondary Amines

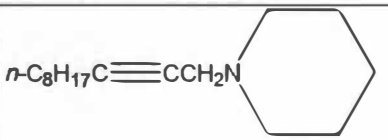
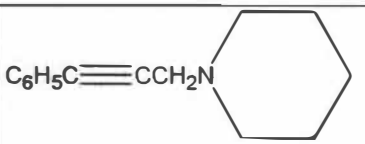
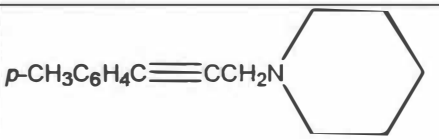
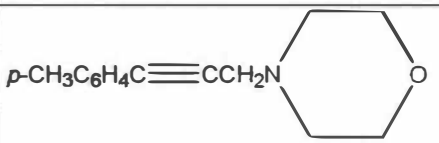
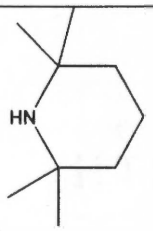
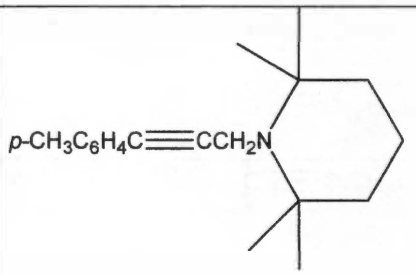
Terminal Alkynes	Secondary Amines	Product
$C_8H_{17}C{\equiv}CH$	$(n\text{-}C_4H_9)_2NH$	$C_8H_{17}C{\equiv}CCH_2N(C_4H_9)_2$
$C_8H_{17}C{\equiv}CH$		
$C_8H_{17}C{\equiv}CH$	$C_6H_5CH_2NHCH_3$	$n\text{-}C_8H_{17}C{\equiv}CCH_2N(CH_3)CH_2C_6H_5$
$C_8H_{17}C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$C_8H_{17}C{\equiv}CCH_2N(CH_2C_6H_5)_2$
$C_6H_{13}C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$C_6H_{13}C{\equiv}CCH_2N(CH_2C_6H_5)_2$
$p\text{-}BrC_6H_4C{\equiv}CH$	$(n\text{-}C_4H_9)_2NH$	$p\text{-}BrC_6H_4C{\equiv}CCH_2N(n\text{-}C_4H_9)_2$
$p\text{-}BrC_6H_4C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$p\text{-}BrC_6H_4C{\equiv}CCH_2N(CH_2C_6H_5)_2$
$C_6H_5C{\equiv}CH$	$(n\text{-}C_4H_9)_2NH$	$C_6H_5C{\equiv}CCH_2N(n\text{-}C_4H_9)_2$
$C_6H_5C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$C_6H_5C{\equiv}CCH_2N(CH_2C_6H_5)_2$
$C_6H_5C{\equiv}CH$		
$p\text{-}CH_3C_6H_4C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$p\text{-}CH_3C_6H_4C{\equiv}CCH_2N(CH_2C_6H_5)_2$
$p\text{-}CH_3C_6H_4C{\equiv}CH$		
$p\text{-}CH_3C_6H_4C{\equiv}CH$		

Table 1 Continued

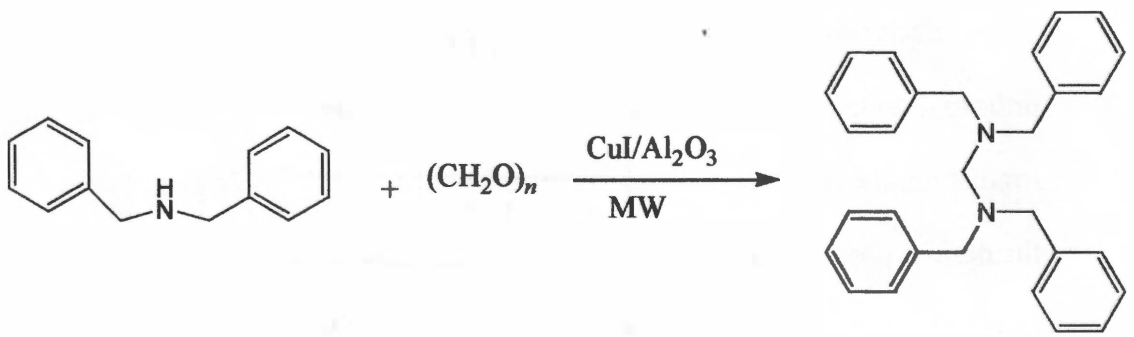
Terminal Alkynes	Secondary Amines	Product
p-$CH_3C_6H_4C{\equiv}CH$		
m-$FC_6H_4C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	*m*-$FC_6H_4C{\equiv}CCH_2N(CH_2C_6H_5)_2$

preferentially. Presumably the intermediate imine reacted with another molecule of dibenzylamine as opposed to the desired alkyne (**Scheme 2**). To overcome this problem, it was necessary to irradiate the terminal alkyne, *para*-formaldehyde, copper (I) iodide and alumina first, and then add the secondary amine; the mixture was then microwaved further. To overcome all of these problems an industrial microwave was purchased.

With the new microwave, the synthesis of the compounds was straightforward. Many functional groups were tolerant of the reaction conditions. The more hindered groups produced lower yields.

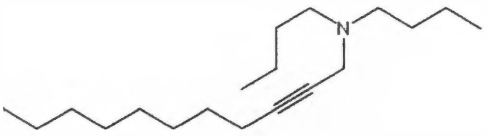
Each reaction mixture was stirred at room temperature for at least thirty minutes prior to irradiation to ensure that the reactants were mixed sufficiently. After microwave irradiation, the reaction mixture was stirred in ether and then vacuum filtered to separate the desired product from the surface. Additional ether was then added to the solid mixture and the procedure repeated. This process was repeated five times to ensure that all of the desired product was removed from the surface. After the product was isolated, the surface was recovered.

Column chromatography was required for purification of each product. The columns were run quickly to achieve the best isolation. **Figure 1** is representative and contains the desired products with their yields. Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained for each compound and are presented in Appendix 1. The ^{1}H NMR assignments are presented in **Figure 2**; the ^{13}C NMR assignments are summarized in **Figure 3**.



N,N,N',N'-Tetrabenzylmethylenediamine

Scheme 2. Reaction Scheme for the Production of Tetrabenzylmethylenediamine



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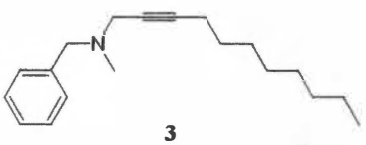

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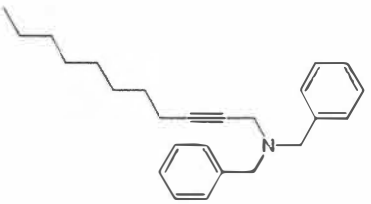

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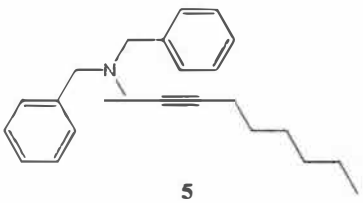

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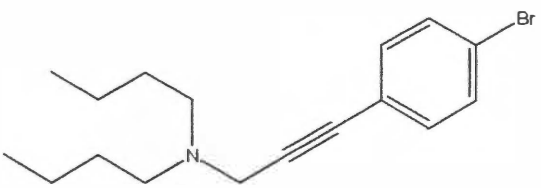

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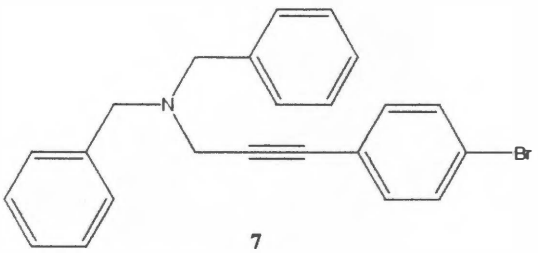

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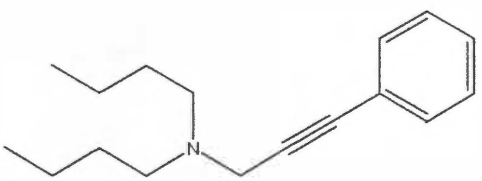

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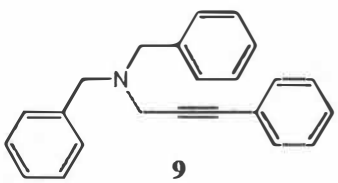

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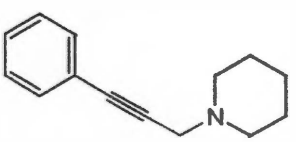

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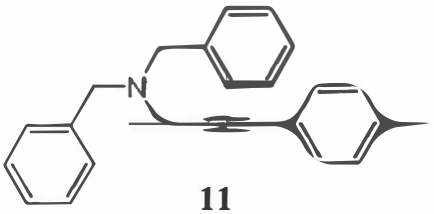
Figure 1. Desired Products With Yields



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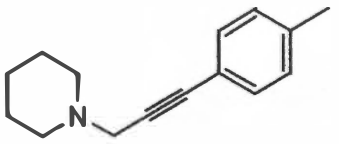

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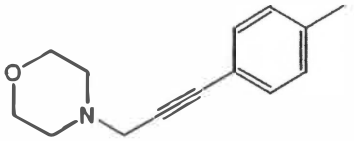

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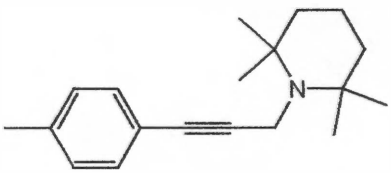

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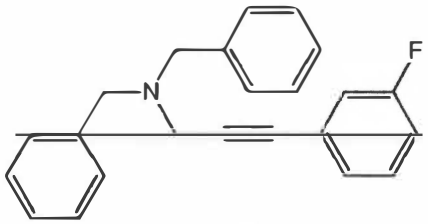

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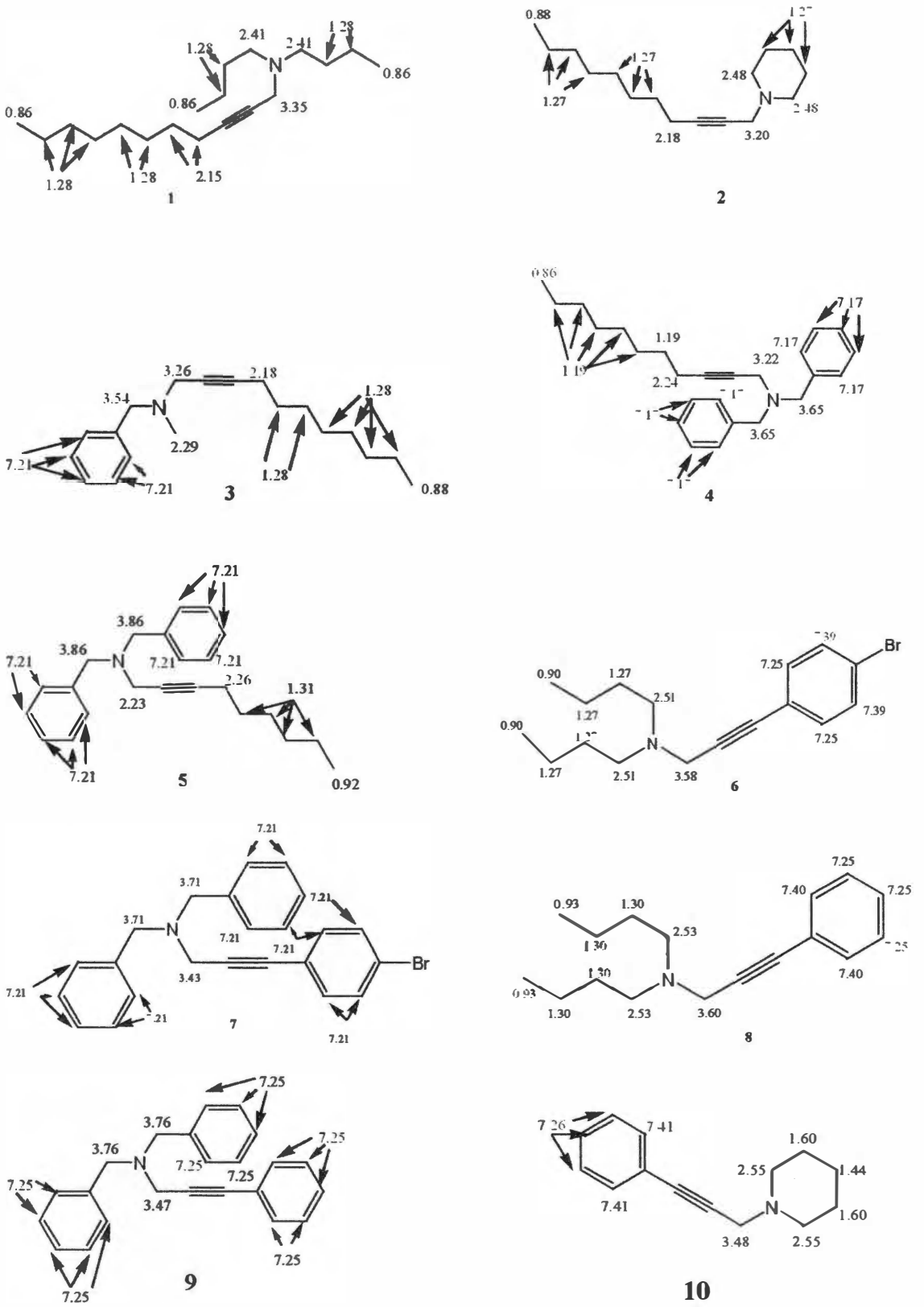
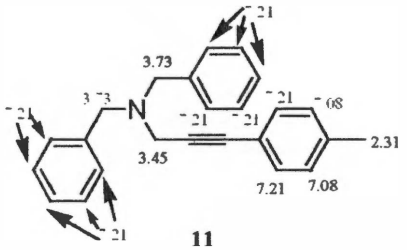


Figure 2. ^{1}H NMR Assignments



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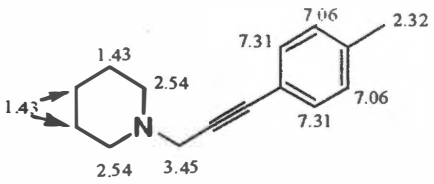

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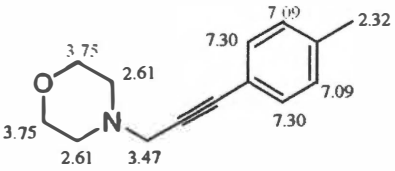

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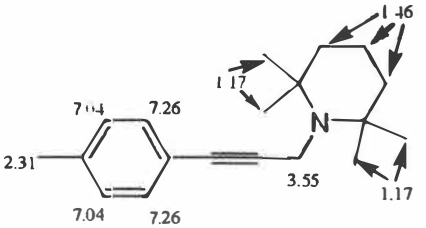

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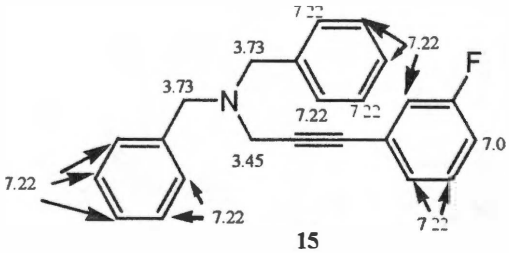

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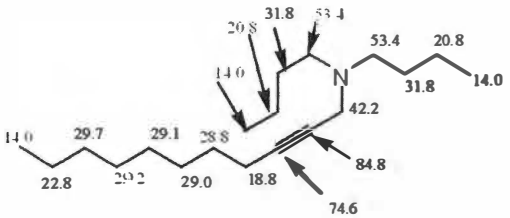
Figure 2 Continued



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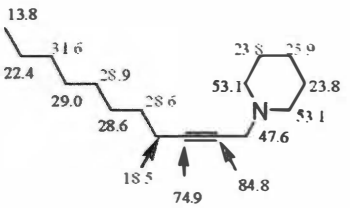

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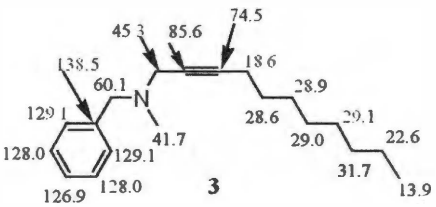

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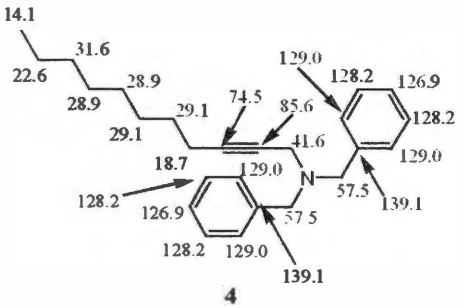

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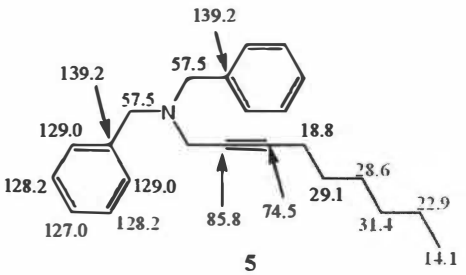

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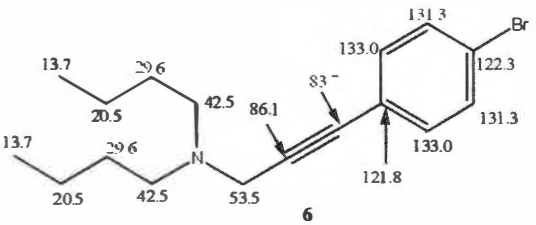

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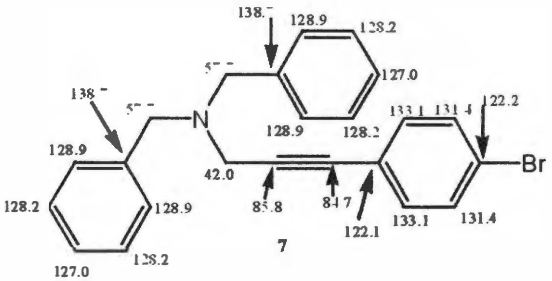

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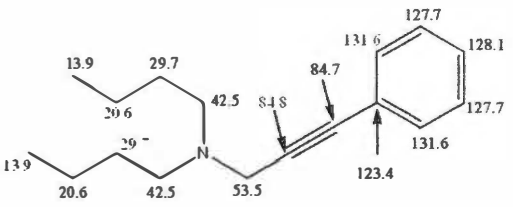

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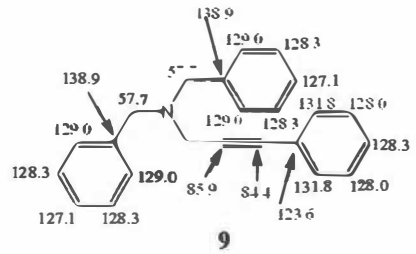

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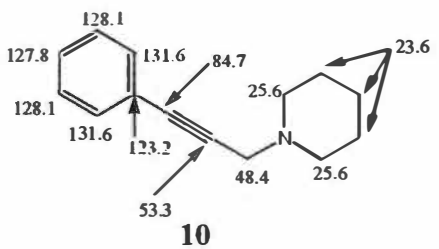

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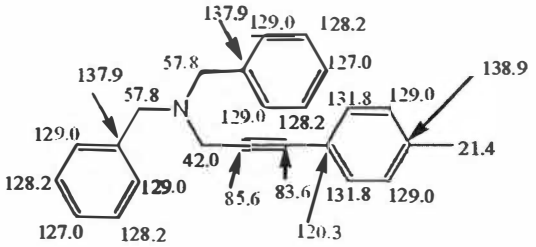
Figure 3. ^{13}C NMR Assignments



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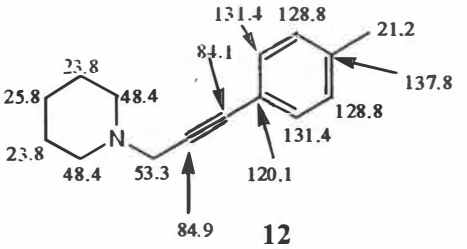

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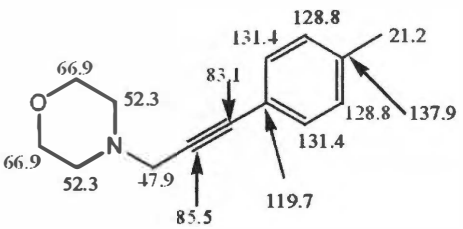

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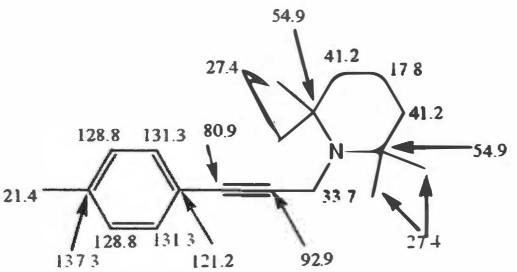

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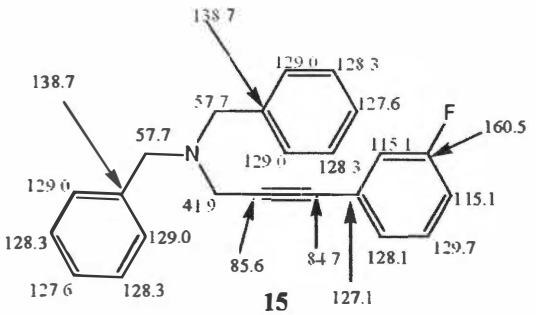

15

Figure 3 Continued

Chapter 3 Experimental Section

3.1 GENERAL METHODS

A Sharp Carousel R-4A38 household microwave was used in the initial investigations. A Milestone Ethos E Touch Control microwave was then purchased and all reactions were repeated using this microwave.

All commercial reagents were purchased from Aldrich Chemical Co., Milwaukee, WI, or Acros Organics, a subdivision of Fischer Scientific. Column chromatography was performed using silica gel (60 Å, 32-63 mesh) obtained from Bodman Chemical Co., Aston, PA. Analytical thin layer chromatography (TLC) was performed using 250 μm silica gel plates obtained from Analtech, Newark, DE. The plates were visualized with ultraviolet illumination at 254 nm and developed in an iodine chamber.

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were acquired either on a Bruker AC250 at 250.13 and 62.89 MHz, or on a Varian Mercury 300 at 300.09 and 75.46 MHz respectively. Chemical shifts are reported in parts per million (ppm) referenced to trimethylsilane (TMS) using residual protons in deuterated solvents for measurement. Splitting patterns are abbreviated as follows: s = singlet, d = doublet, t = triplet, and m = multiplet. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

3.2 EXPERIMENTAL PROCEDURE

3.2.1 General Procedure for the Mannich Condensation of Terminal Alkynes with Secondary Amines and *para*-Formaldehyde

A terminal alkyne (1.0 mmol) and secondary amine (1.0 mmol) were added to a mixture of *para*-formaldehyde (0.09 grams, 3.00 mmol), cuprous iodide (0.57 grams,

3.00 mmol), and alumina (1.00 grams) in a clean, dry, 25-mL round-bottomed flask (Scheme 1). This mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum that was pierced with a small capillary tube. A part of the capillary tube was left in the septum to serve as a pressure release valve. The flask was then fitted in the microwave oven and irradiated at 30% power for twenty minutes. After cooling, ether (4-mL) was added, and the slurry stirred at room temperature to remove the product from the surface. The mixture was then vacuum filtered using a sintered glass funnel. This procedure was repeated a total of five times. The product was then purified to yield the desired product. Table 1 contains a listing of the terminal alkynes and secondary amines used, as well as the desired products.

3.2.2 Experimental Data for Dibutyl(undec-2-ynyl)amine, 1.[26]

1-Decyne and dibutylamine were used to produce dibutyl(undec-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (1:9). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (m, 9H), 1.28 (m, 9H), 2.15 (t, J= 4.7 Hz, 3H), 2.41 (t, J=9.5 Hz, 4H), 3.35 (s, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 14.0, 18.8, 20.8, 22.8, 28.8, 29.0, 29.1, 29.2, 29.7, 31.8, 42.2, 53.4, 74.6, 84.8. Yield: 64.0%.

3.2.3 Experimental Data for 1-(Undec-2-ynyl)piperidine, 2.

1-Decyne and piperidine were used to produce 1-(undec-2-ynyl)piperidine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (4:6). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, J= 6.6 Hz , 3H), 1.64 (m, 18H), 2.18 (t, J= 5.0 Hz, 2H), 2.48 (s, br, 2X2H), 3.20 (t, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 13.8, 18.5, 22.4, 23.8, 25.9, 28.6, 28.9, 29.0, 31.6, 47.6, 53.1, 74.9, 84.8.

Anal. Calcd for $C_{16}H_{29}N$: C, 81.63; H, 12.42; N, 5.95. Found: C, 81.45; H, 12.55; N, 6.02. Yield: 85.1%

3.2.4 Experimental Data for Benzyl Methyl(undec-2-ynyl)amine, 3.

1-Decyne and benzyl methylamine was used to produce benzyl methyl(undec-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (1:9). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, J= 6.6 Hz, 3H), 1.28 (m, 12H), 2.18 (t, J= 2.5 Hz, 2H), 2.29 (s, 3H), 3.26 (s, 2H), 3.54 (s, 2H), 7.21 (m, 5H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 13.9, 18.6, 22.6, 28.6, 28.9, 29.0, 29.1, 31.7, 41.7, 45.3, 60.1, 74.5, 85.6, 126.9, 128.0, 129.1, 138.5. Anal. Calcd for $C_{19}H_{29}N$: C, 84.07; H, 10.77; N, 5.16. Found: C, 84.21; H, 10.88; N, 5.23. Yield: 84.9%

3.2.5 Experimental Data for Dibenzyl(undec-2-ynyl)amine, 4.

1-Decyne and dibenzylamine were used to produce dibenzyl(undec-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (2:8). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (t, J= 6.7 Hz, 3H), 1.19 (m, 12H), 2.24 (t, J=6.7 Hz 2H), 3.22 (s, 2H), 3.65 (s, 2H), 7.17 (m, 10H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 14.1, 18.7, 22.6, 28.9, 29.1, 31.6, 41.6, 57.5, 74.5, 85.6, 126.9, 128.2, 129.0, 139.1. Anal. Calcd for $C_{25}H_{33}N$: C, 86.40; H, 9.57; N, 4.03. Found: C, 86.34; H, 9.68; N, 4.09. Yield: 54.6%.

3.2.6 Experimental Data for Dibenzyl(non-2-ynyl)amine, 5.

1-Octyne and dibenzylamine were used to produce dibenzyl(non-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (2:8). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, 3H), 1.31 (m, 8H), 2.26 (t, 2H), 3.23 (s, 2H), 3.86 (s, 2X2H), 7.21 (m, 10H); ^{13}C NMR (250 MHz, $CDCl_3$): δ

14.1, 18.8, 22.9, 28.6, 29.1, 31.4, 41.7, 57.5, 74.5, 85.8, 127.0, 128.2, 129.0, 139.2. Anal. Calcd for $C_{23}H_{29}N$: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.24; H, 9.22; N, 4.41. Yield: 59.4%

3.2.7 Experimental Data for [3-(4-Bromophenyl)-prop-2-ynyl]-dibutylamine, 6.

1-Bromo-4-ethynylbenzene and dibutylamine were used to produce [3-(4-bromophenyl)-prop-2-ynyl]-dibutylamine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (1:9). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, J=7.1 Hz, 2X3H), 1.27 (m, 8H), 2.51 (t, J= 7.3 Hz, 2X2H), 3.58 (s, 2H), 7.25 (d, J= 8.4 Hz, 2H), 7.39 (d, J= 8.4 Hz, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 13.7, 20.5, 29.6, 42.5, 53.5, 83.7, 86.1, 121.8, 122.3, 131.3, 133.0. Anal. Calcd for $C_{17}H_{24}NBr$: C, 63.36; H, 7.51; N, 4.35. Found: C, 63.31; H, 7.53; N, 4.37. Yield: 55.9%.

3.2.8 Experimental Data for Dibenzyl-[3-(4-bromophenyl)-prop-2-ynyl]amine, 7.

1-Bromo-4-ethynylbenzene and dibenzylamine were used to produce dibenzyl-[3-(4-bromophenyl)-prop-2-ynyl]amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (1:9). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.42 (s, 2H), 3.71 (s, 2X2H), 7.21 (m, 14H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 42.0, 57.7, 84.7, 85.8, 122.1, 122.2, 127.1, 128.2, 128.9, 131.4, 133.1, 138.7. HRMS calculated: 390.0857. Found 390.0858. Yield: 76.9%

3.2.9 Experimental Data for Dibutyl-(3-phenyl-prop-2-ynyl)amine, 8.[27]

Ethynylbenzene and dibutylamine were used to produce dibutyl-(3-phenyl-prop-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (0.5:9.5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.93 (t, J= 7.2 Hz, 2X3H), 1.30 (m,8H) 2.53 (t, J= 7.3 Hz, 2X2H), 3.60 (s, 2H), 7.25 (m, 3H),

7.40 (m, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 13.9, 20.6, 29.7, 42.5, 53.5, 84.7, 84.8, 123.4, 127.7, 128.1, 131.6. Yield: 45.3%.

3.2.10 Experimental Data for Dibenzyl(3-phenyl-prop-2-ynyl)amine, 9.[27]

Ethynylbenzene and dibenzylamine were used to produce dibenzyl(3-phenyl-prop-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (0.3:9.7). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (s, 2H), 3.76 (s, 4H), 7.25 (m, 15H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 41.9, 57.7, 84.4, 85.9, 123.6, 127.1, 128.0, 128.3, 129.1, 131.8, 128.9. Yield: 74.5%.

3.2.11 Experimental Data for 1-(3-phenyl-prop-2-ynyl)piperidine, 10.[27]

Ethynylbenzene and piperidine were used to produce 1-(3-phenyl-prop-2-ynyl)piperidine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (5:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.44 (t, J= 5.3 Hz, 2H), 1.60 (m, 2X2H), 2.55 (s, 2X2H), 3.48 (s, 2H), 7.26 (m, 3H), 7.41 (m, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 23.6, 25.6, 48.4, 53.3, 84.7, 123.2, 127.8, 128.1, 131.6. Yield: 65.0%.

3.2.12 Experimental Data for Dibenzyl(3-*p*-tolyl-prop-2-ynyl)amine, 11.

Ethynyltoluene and dibenzylamine were used to produce dibenzyl(3-*p*-tolyl-prop-2-ynyl)amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (0.5:9.5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.45 (s, 2H), 3.73 (s, 2X2H), 7.08 (d, J= 8.0 Hz, 2H), 7.21 (m, 12H); ^{13}C NMR (250 MHz, $CDCl_3$): 21.4, 42.0, 57.8, 83.6, 85.6, 120.3, 127.0, 128.2, 129.0, 131.8, 137.9, 138.9. Anal. Calcd for $C_{24}H_{23}N$: C, 88.57; H, 7.12; N, 4.30. Found: C, 88.45: H, 7.21; N, 4.27. Yield: 73.8%.

3.2.13 Experimental Data for 1-(3-*p*-tolyl-prop-2-ynyl)piperidine, 12.[28]

Ethynyltoluene and piperidine were used to produce 1-(3-*p*-tolyl-prop-2-ynyl)piperidine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.43 (m, 2H), 2.32 (s, 3H), 2.54 (t, J=4.9 Hz, 3H), 3.45 (s, 2H), 7.06 (d, J=7.9 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 21.2, 23.8, 25.8, 48.4, 53.3, 84.1, 84.9, 120.1, 128.8, 131.4, 137.8. Yield: 70.4%

3.2.14 Experimental Data for 4-(3-*p*-Tolyl-prop-2-ynyl)morpholine, 13.

Ethynyltoluene and morpholine were used to produce 4-(3-*p*-tolyl-prop-2-ynyl)morpholine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.61 (t, J= 4.6 Hz, 2 X 2H), 3.47 (s, 2H), 3.75 (t, J= 4.6 Hz, 2 X 2H), 7.09 (d, J= 7.9 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): 21.2, 47.9, 52.3, 66.9, 83.1, 85.5, 119.7, 128.8, 131.4, 137.9. HRMS calculated: 216.1388. Found: 216.1383. Yield: 69.8%.

3.2.15 Experimental Data for 2,2,6,6-Tetramethyl-1-(3-*p*-tolyl-prop-2-ynyl)piperdine, 14.

Ethynyltoluene and 2,2,6,6-tetramethylpiperdine were used to produce 2,2,6,6-tetramethyl-1-(3-*p*-tolyl-prop-2-ynyl)piperdine. The final product was a solid (m.p. 178-180°C) and was purified by column chromatography using an ethyl acetate/hexane mixture (0.5:9.5). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.17 (s, 12H), 1.46 (m, 6H), 2.31 (s, 3H), 3.55 (s, 2H), 7.04 (d, J= 7.9 Hz, 2H), 7.26 (d, J= 8.0 Hz, 2H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 17.8, 21.4, 27.4, 33.7, 41,2, 54.9, 80.9, 92.2, 121.2, 128.8, 131.3, 137.3. Anal.

Calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.56; H, 10.23; N, 5.11. Yield: 44.6%

3.2.16 Experimental Data for Dibenzyl-[3-(3-fluoro-phenyl)-prop-2-ynyl]amine, 15.

Dibenzylamine and 1-ethynyl-3-fluorobenzene were used to produce dibenzyl-[3-(3-fluoro-phenyl)-prop-2-ynyl]amine. The final product was an oil that was purified by column chromatography using an ethyl acetate/hexane mixture (1:9). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.45 (s, 2H), 3.73 (s, 2X2H), 7.0 (m, 1H), 7.23 (m, 13H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 41.9, 57.7, 84.7, 85.8, 115.1, 116.4, 127.1, 127.6, 128.2, 129.0, 129.7, 138.8. HRMS calculated: 330.1658. Found: 330.1648. Yield: 42.6%.

Chapter 4 Conclusions and Future Work

4.1 CONCLUSIONS

In conclusion, microwave chemistry is an efficient way to perform the Mannich condensation reaction. The β-aminoalkynes were produced in good yields. Furthermore, the reaction times were short and the amount of waste was kept to a minimum. When comparing the reaction conditions of the microwave assisted Mannich condensation reaction to the traditional methods, the microwave-assisted method is preferred.

4.2 FUTURE WORK

Future work on the Mannich reaction could involve investigating the reaction between primary amines and terrminal alkynes, or between primary or secondary amines and ketones. In addition to the Mannich reaction, a variety of traditional organic synthesis still have not been explored in the area of microwave chemistry.

LIST OF REFERENCES

1. Gedye, R.; Smith, F.; Westaway, K; Ali, H.; Baldisera, L.; Laberge, L. Rousell, J. *Tetrahedron Lett.*, **1986**, *27(3)*, 279.

2. Lidström, P.; Tierney, J; Wathey, B.; Westman, J. *Tetrahedron*, **2001**, *57*, 9225.

3. Giguere, R.J.; Namen, A.M.; Lopez, B.O.; Arepally, A.; Ramos, D.E. *Tetrahedron Letters*, **1987**, *28(52)*, 6553.

4. Blettner, C.G.; König, W.A.; Stenzel, W.; Schotten, T. *J. Org. Chem.*, **1999**, *64*, 3885.

5. Kabalka, G.W.; Pagni, R.M.; Hair, C.M. *Org. Lett.*, **1999**, *1(9)*, 1423.

6. Kabalka, G.W.; Wang, L.; Pagni, R.M. *Tetrahedron*, **2001**, *57*, 8017.

7. Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: North Carolina, **2002**, p.11-24.

8. Caddick, S. *Tetrahedron*, **1995**, *51(38)*, 10403.

9. Varma, R.S. *Green Chem.* **1999**,*1*, 43.

10. Gabriel, C.; Gabriel, S.; Grant, E.H.; Halstead, B.S.J.; Mingos, D.M.P. *Chem. Soc. Rev.*, **1998**, *27*, 213.

11. Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, **2002**, p.181-219.

12. Wang, W.B.; Roskamp, E.J. *Tetrahedron Lett.*, **1992**, *33*, 7631.

13. Cornelis, A.; Laszlo, P. *Synthesis*, **1985**, *(10)*, 909.

14. Varma, R.S. *Tetrahedron*, **2002**, *58*, 1235.

15. Kotsuki, H.; Ohishi, T.; Araki, T.; Arimura, K. *Tetrahedron Lett.*, **1998**, *39*, 4869.

16. Ranu, B.C.; Hajra, A.; Dey, S.S.; Jana, U. *Tetrahedron*, **2003**, *59*, 813.

17. de la Hoz, A.; Díaz-Ortiz, A.; Gómez, M.V.; Mayoral, J.A.; Moreno, A.; Sánchez-Migalló, A.M.; Vázquez, E. *Tetrahedron*, **2001**, *57*, 5421.

18. Alloum, A.B; Villemin, D. *Synthetic Comm.*, **1989**, *19(13&14)*, 2567.

19. Kabalka, G.W.; Wang, L.; Pagni, R.M. *ARKIVOC*, **2001**, *(iv)*, 5.

20. Kabalka, G.W.; Wang, L.; Pagni, R.M. *Green Chem.*, **2001**, *3*, 261.

21. Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett*, **2001**, *1*, 108.

22. Kabalka, G.W.; Pagni, R.M. *Tetrahedron*, **1997**, *53*, 7999.

23. Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett*, **2001**, *5*, 676 and references cited therein

24. Ahluwalia, V.K.; Parashar, R.K. *Organic Reaction Mechanisms*; CRC Press: Boca Raton, FL, **2002**, p. 352-356.

25. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.*, **1998**, *37*, 1044.

26. Andreev, V.P.; Vuks, E.M.; Kochetkova, E.V.; Remizova, L.A.; Favorskaya, I.A. *Zh. Org. Khim*, **1979**, *15*, 464.

27. Sharifi, A.; Farhangian, H.; Mohsenzadeh, F.; Naimi-Jamal, M.R. *Monatshefte für Chemie*, **2002**, *133*, 199.

28. Chukhadzhyan, El.O.; Chukhadzhyan, E.O.; Babayan, A.T. *Zh. Org. Khim*, **1974**, *10*, 46.

APPENDIX

APPENDIX 1

^{1}H and ^{13}C NMR Spectra of Products

4.5
4.0
3.5
3.0
2.5
PPM
2.0
1.5
1.0
.5
0.0

120
110
100
90
80
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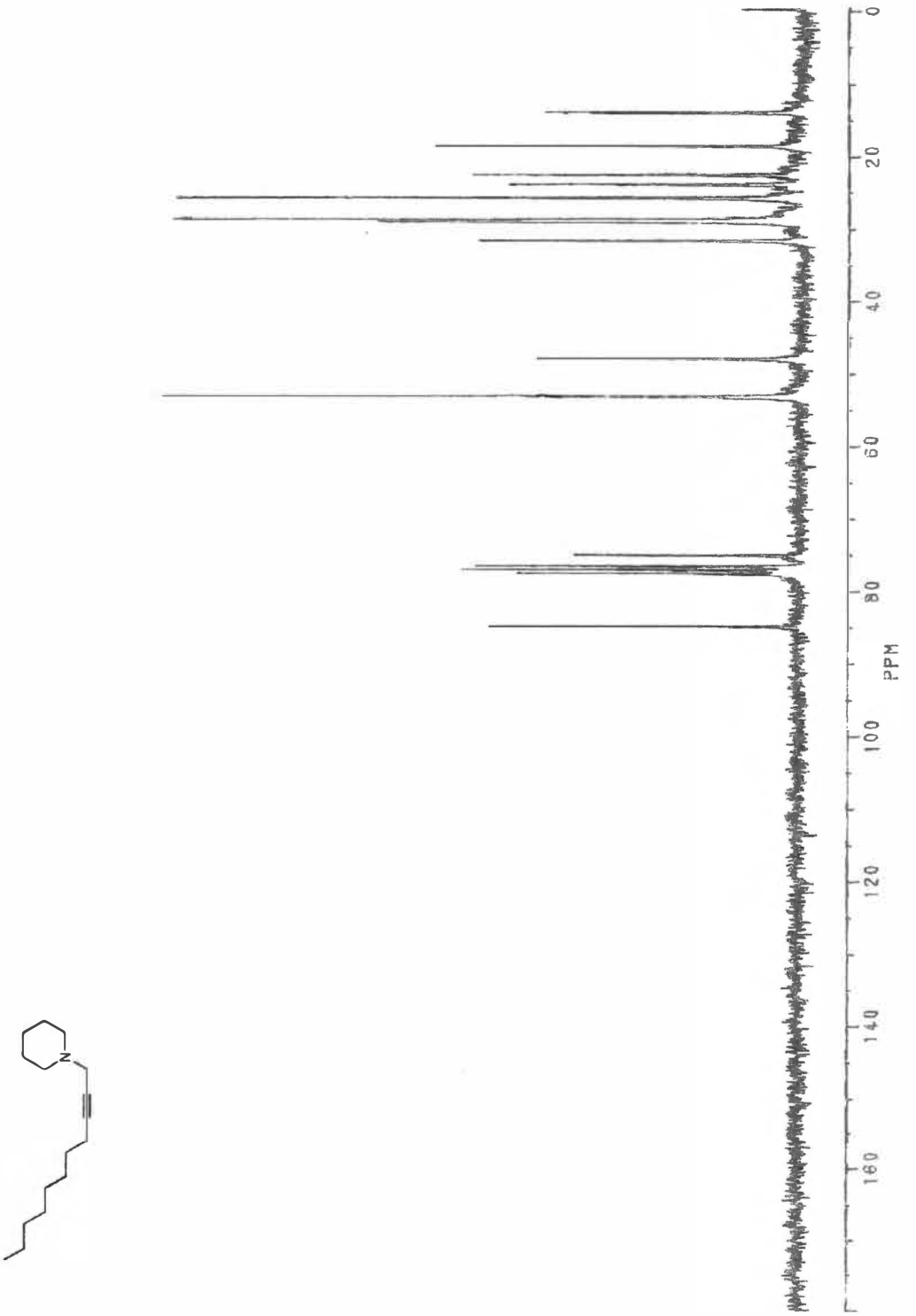
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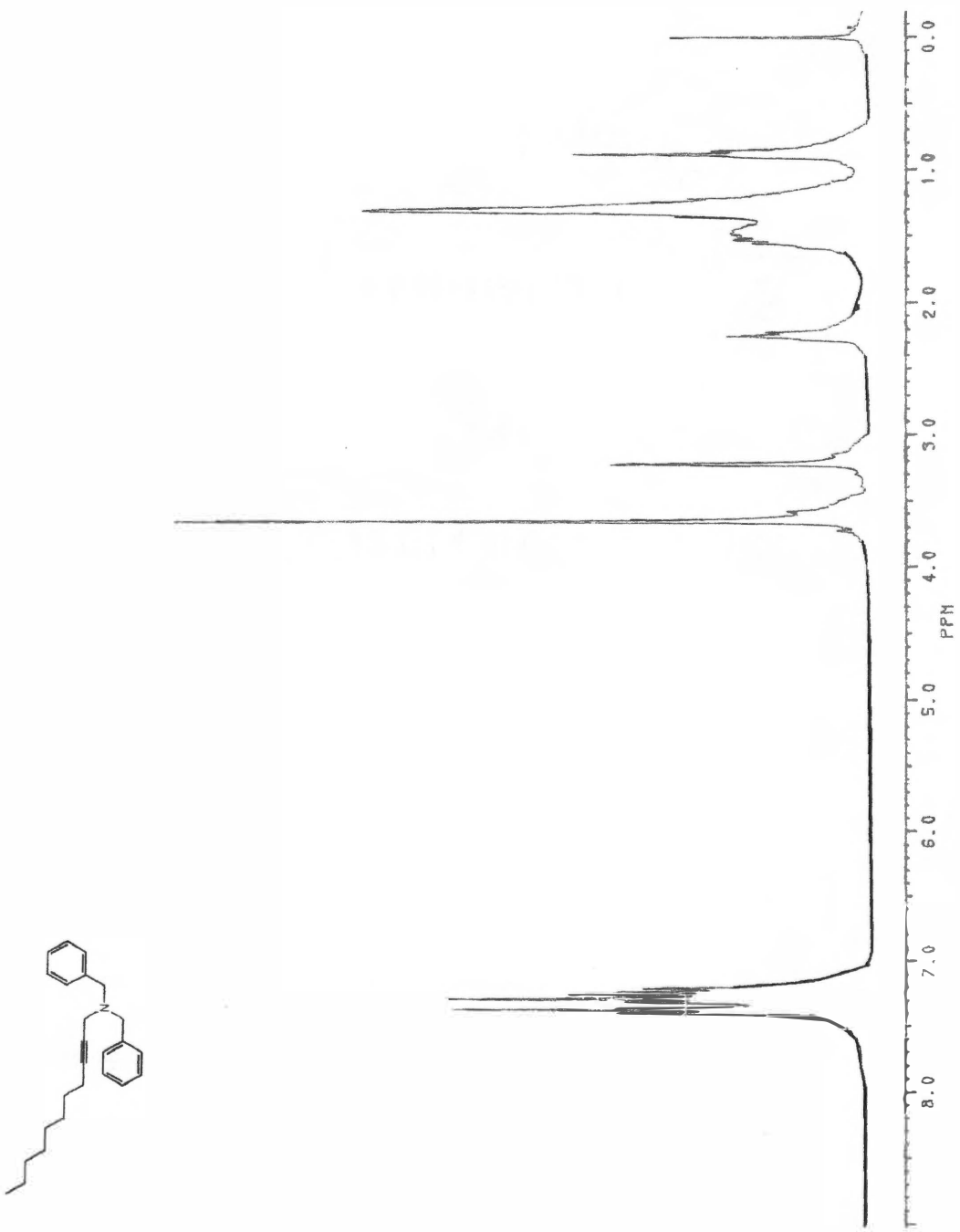
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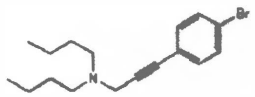
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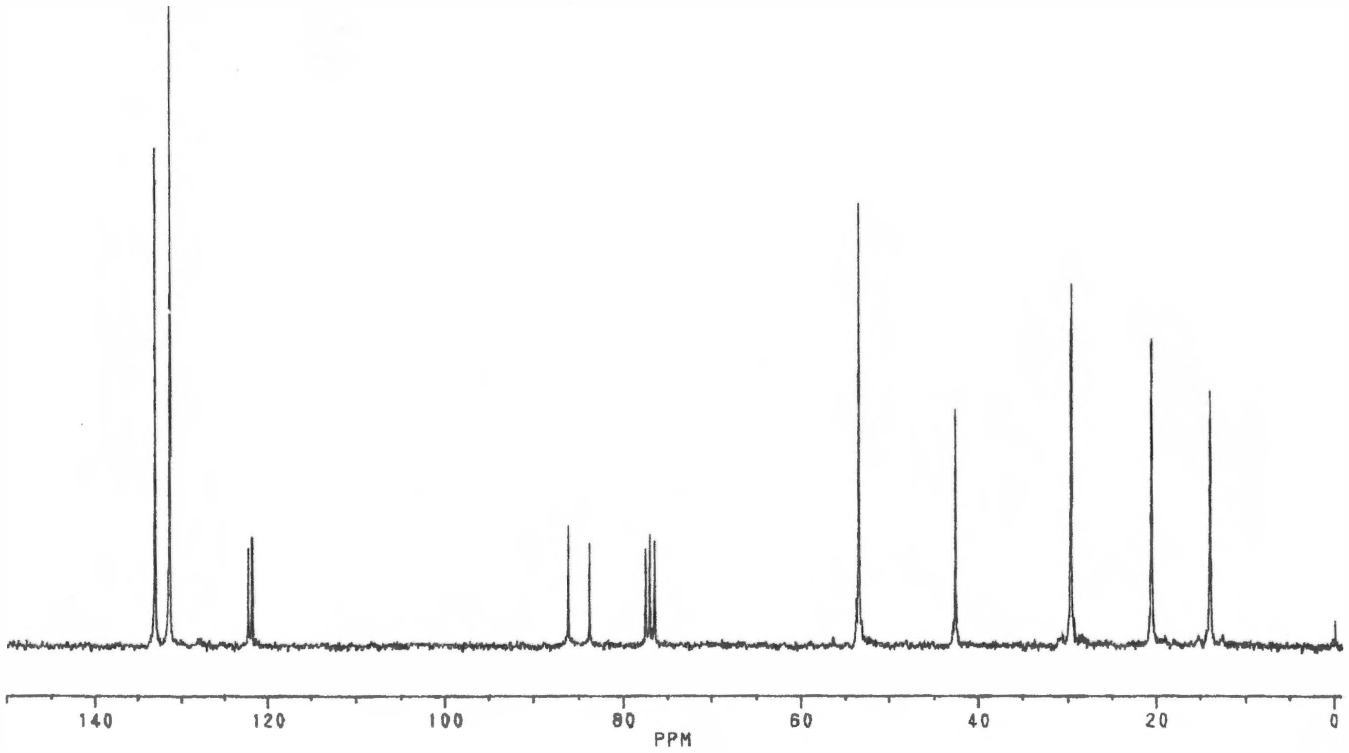
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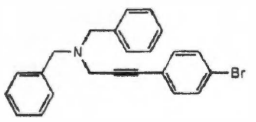
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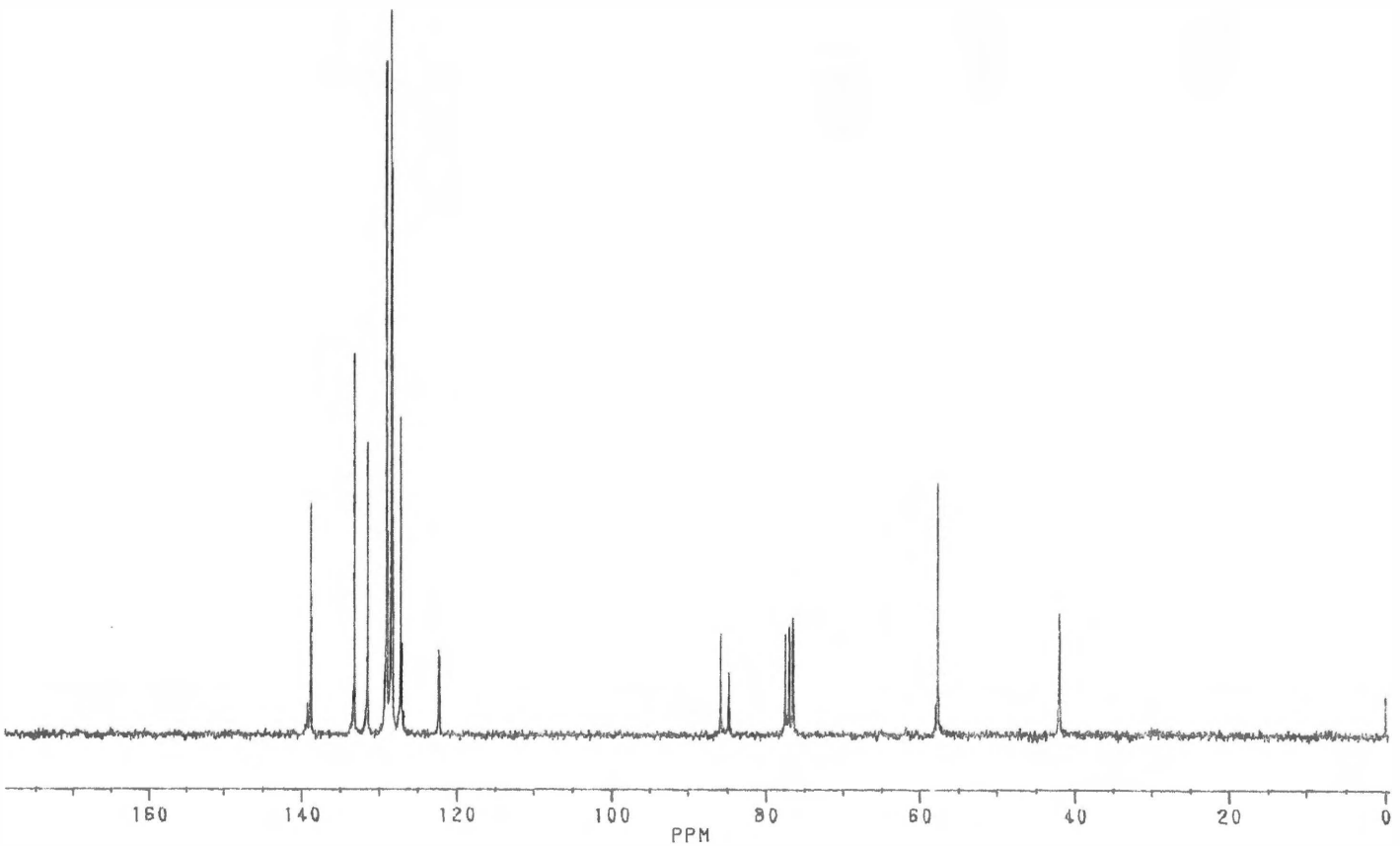
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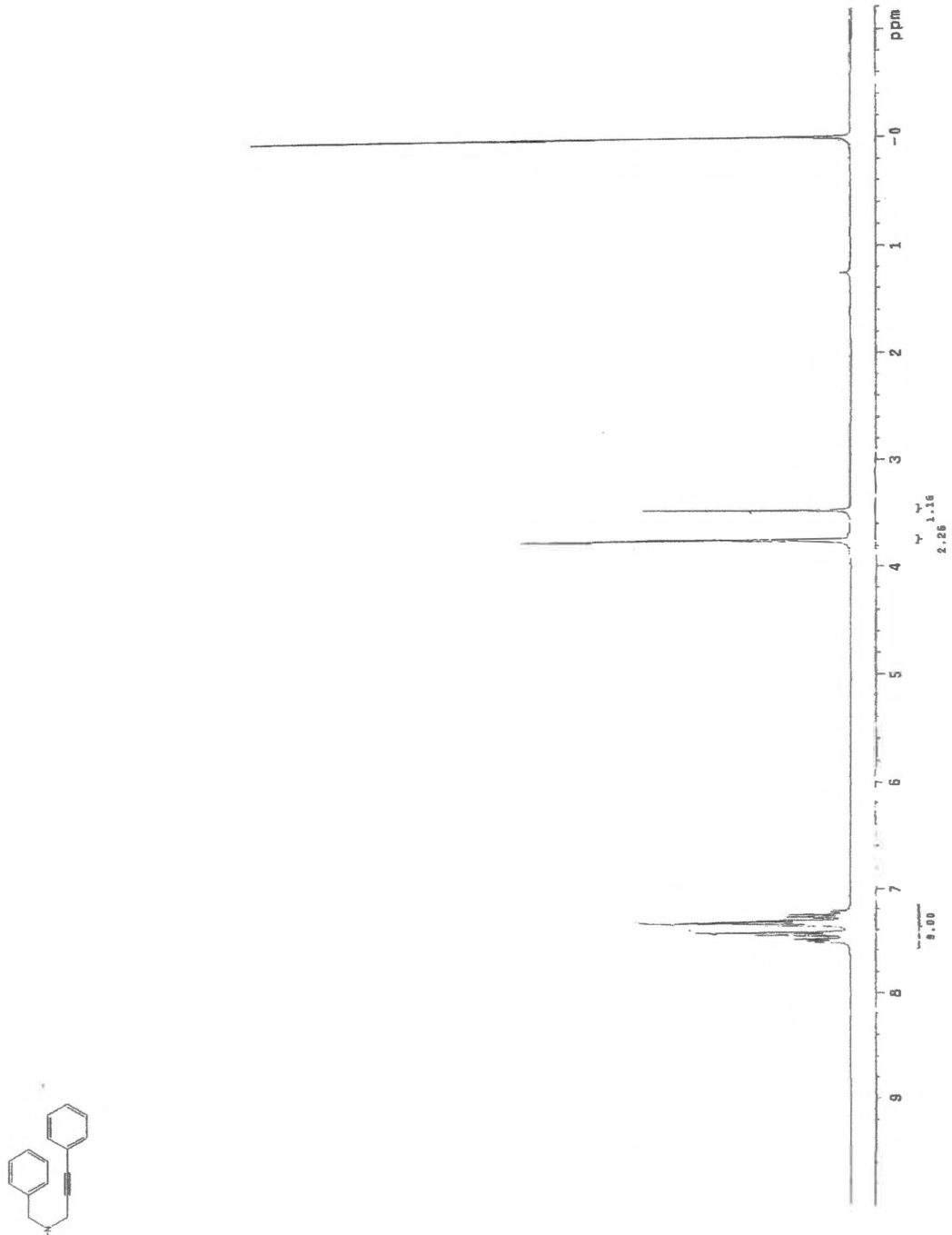
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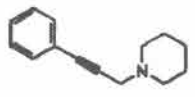

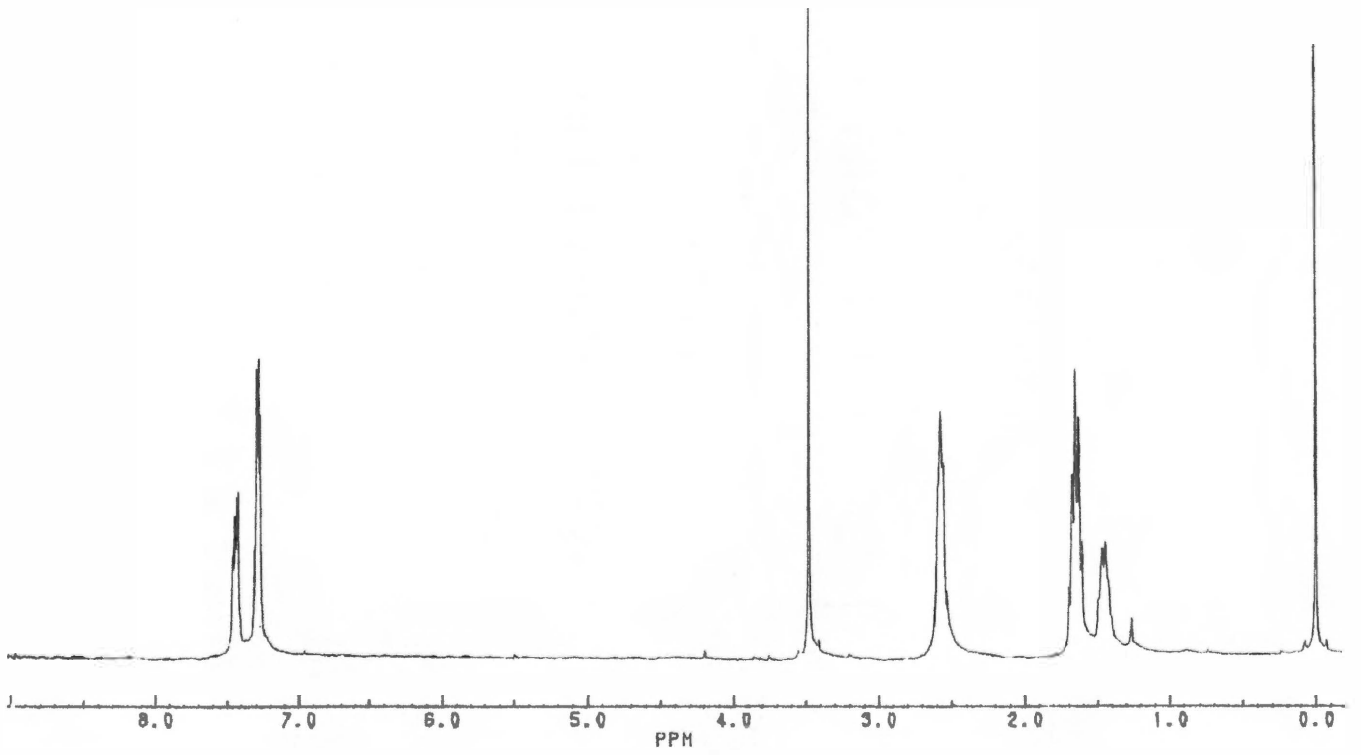
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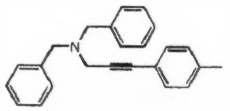

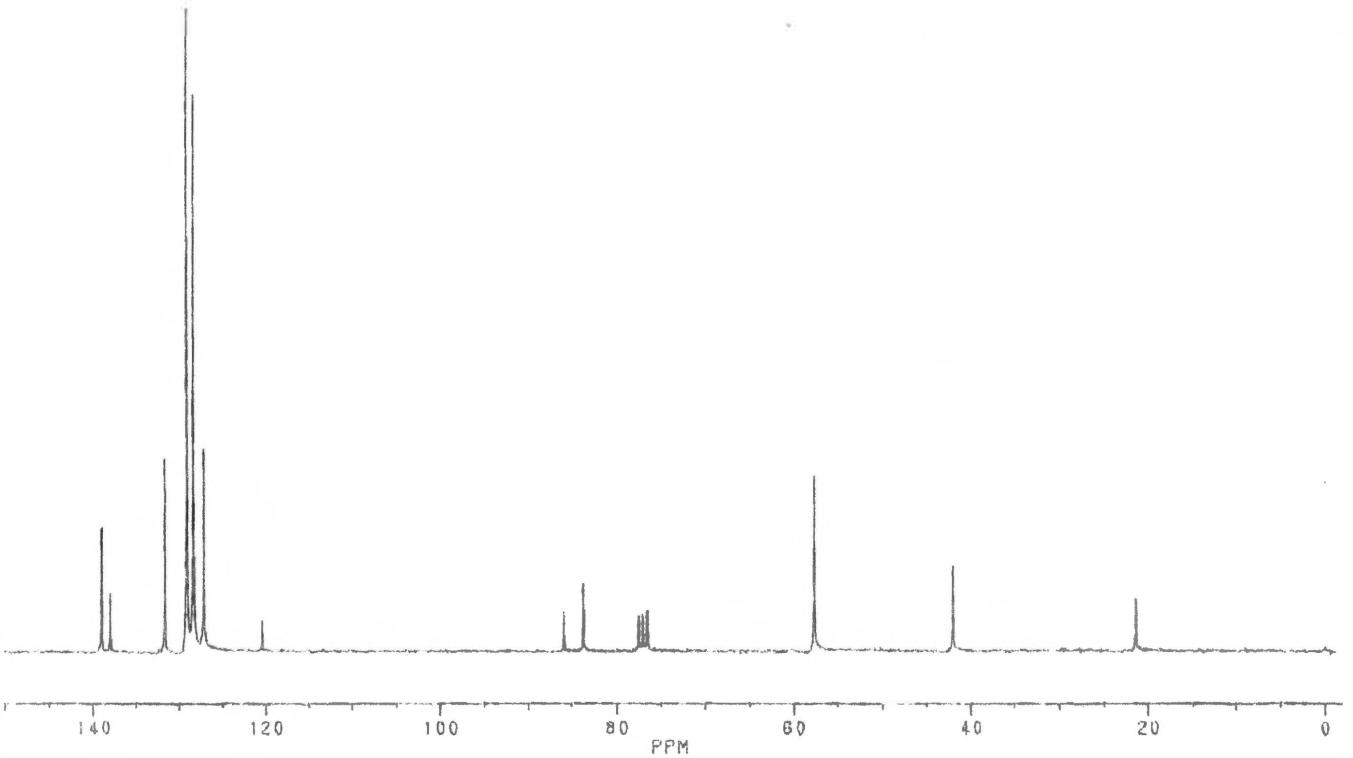
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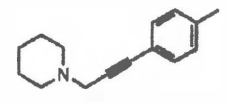
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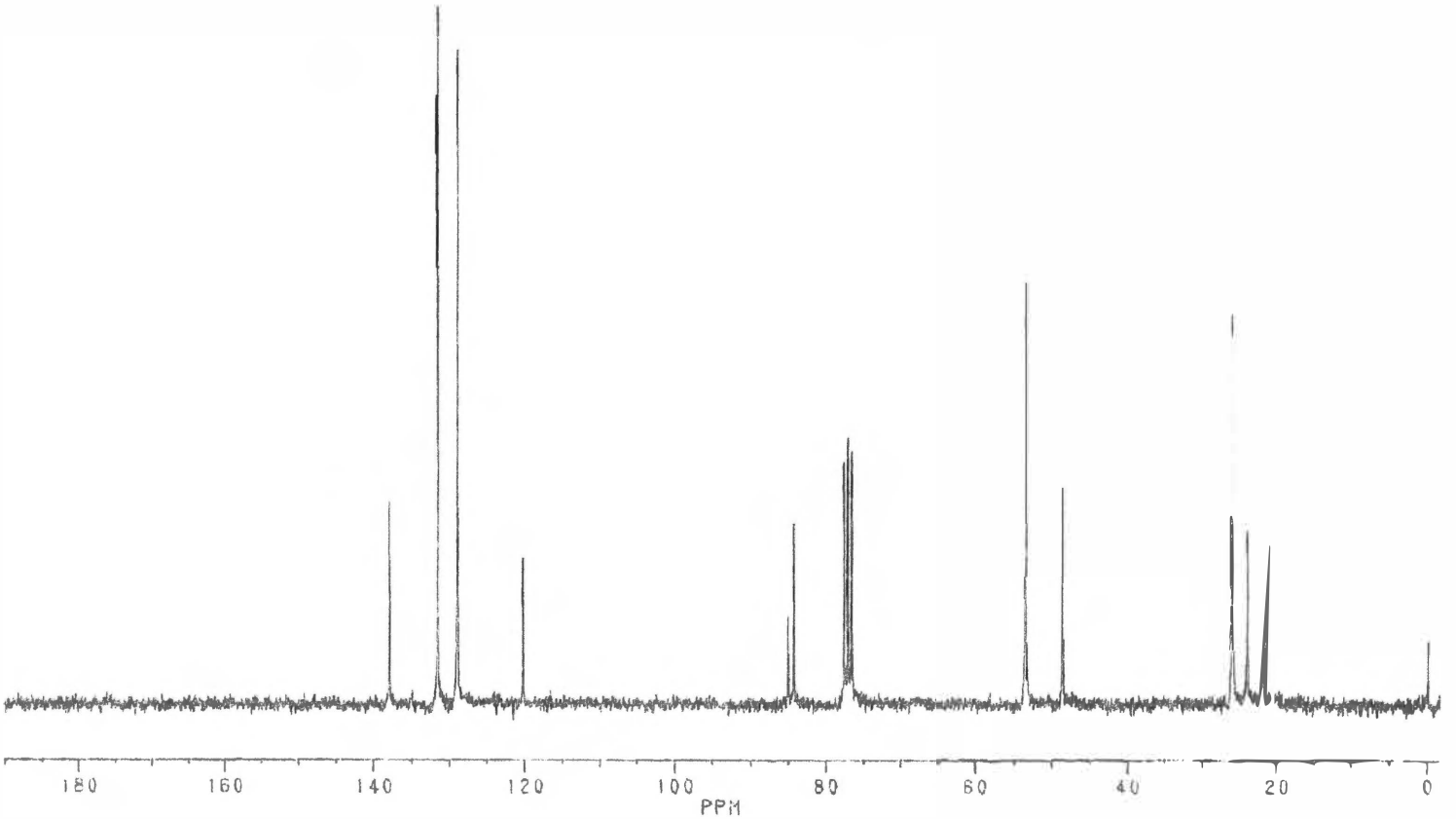
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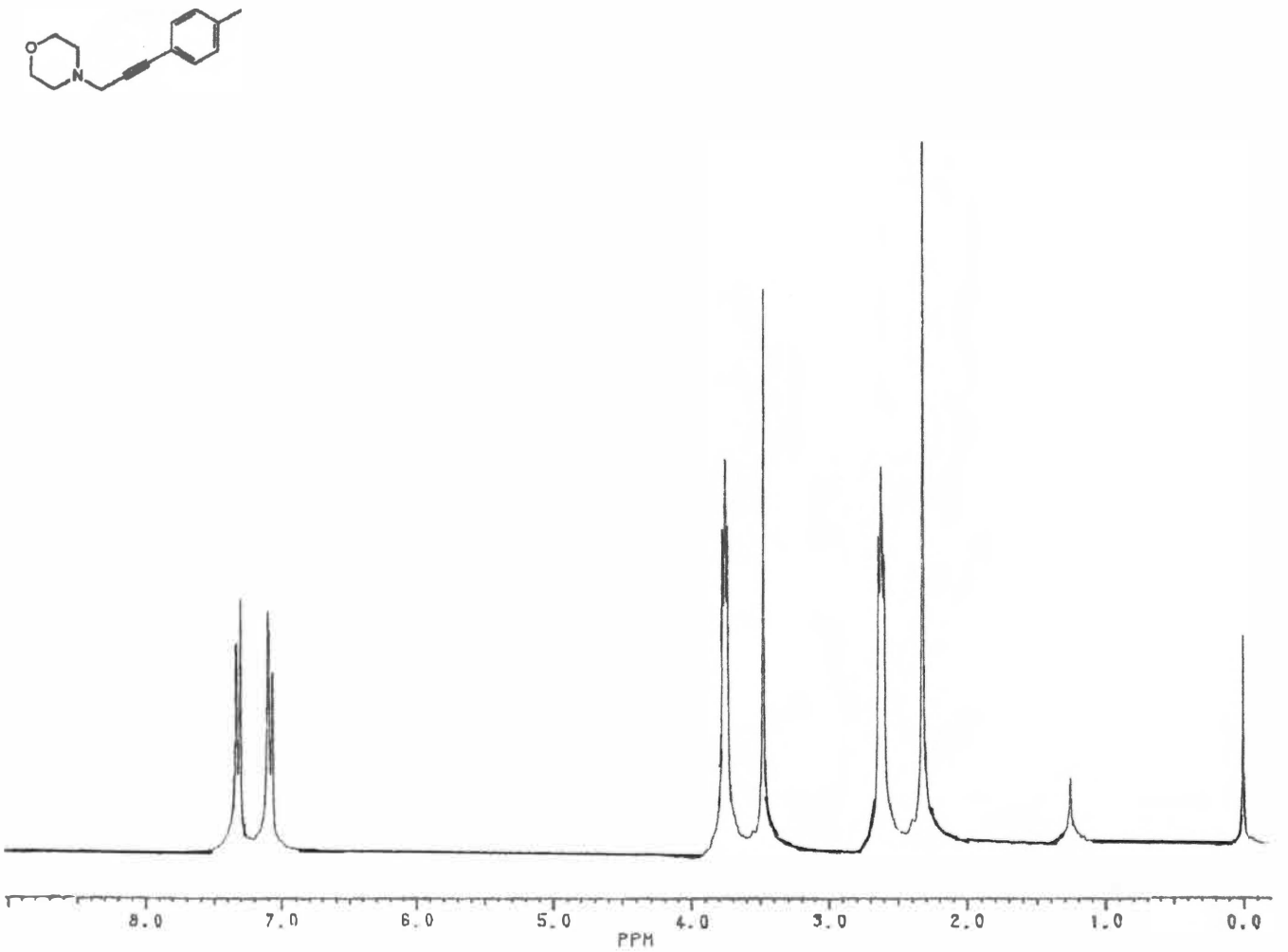
PPM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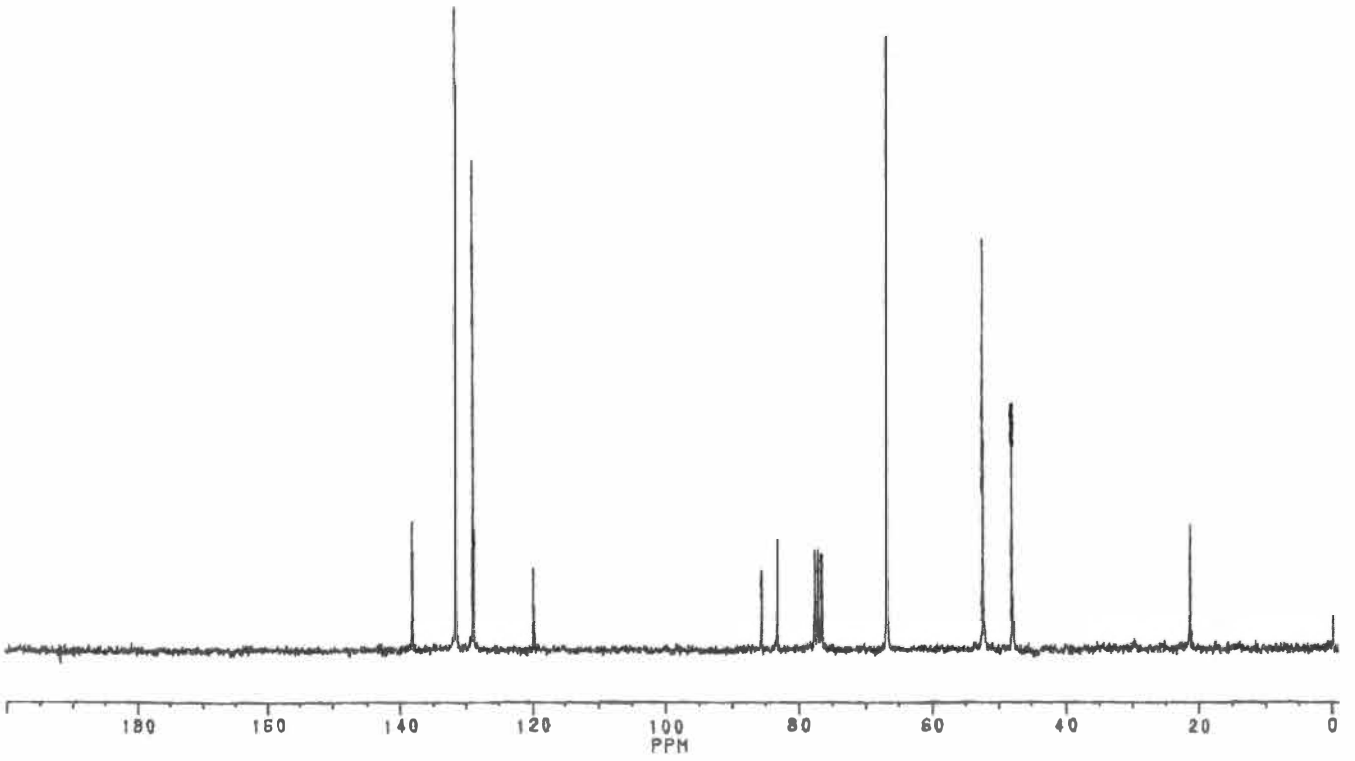
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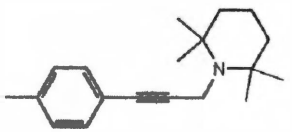

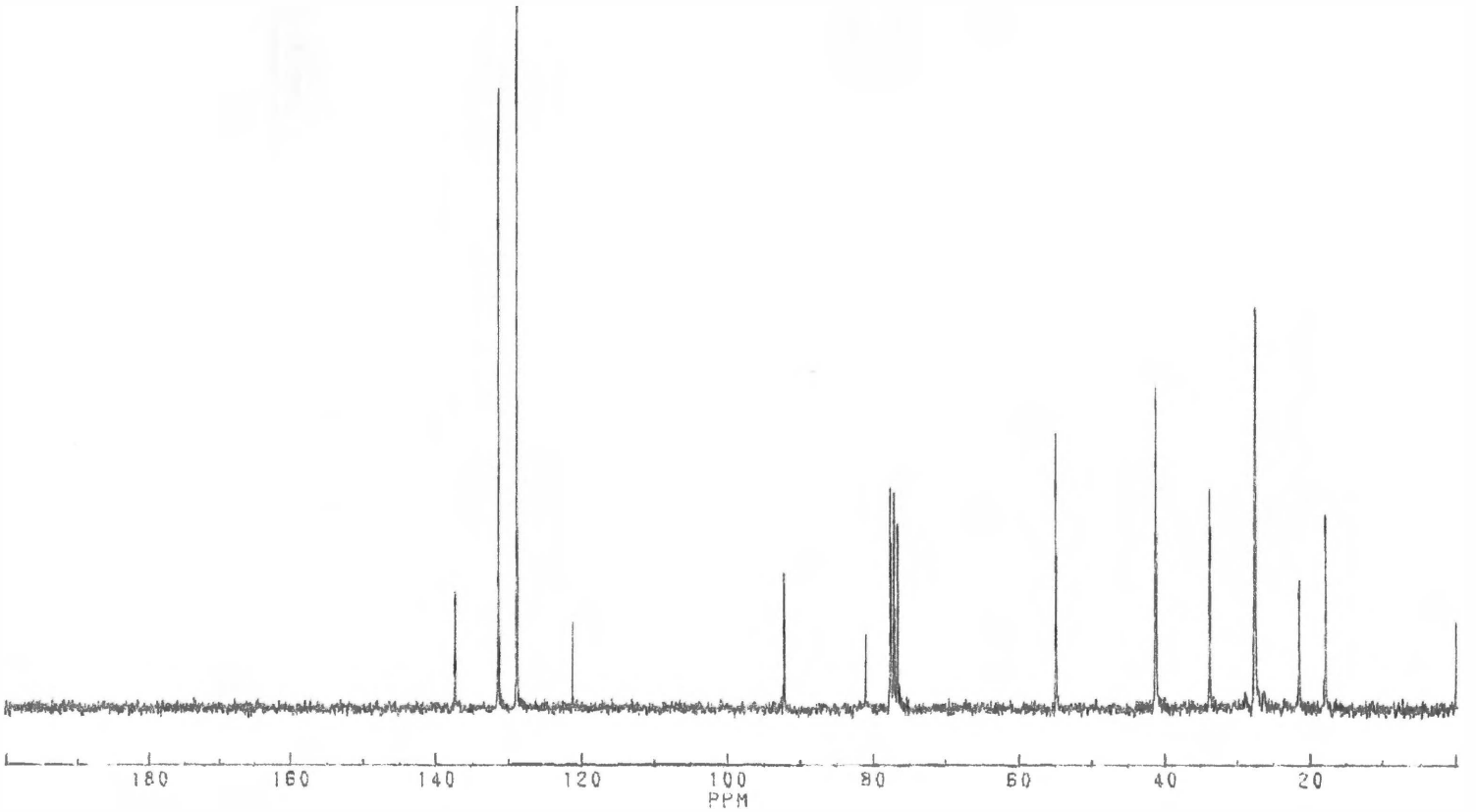
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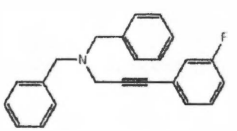
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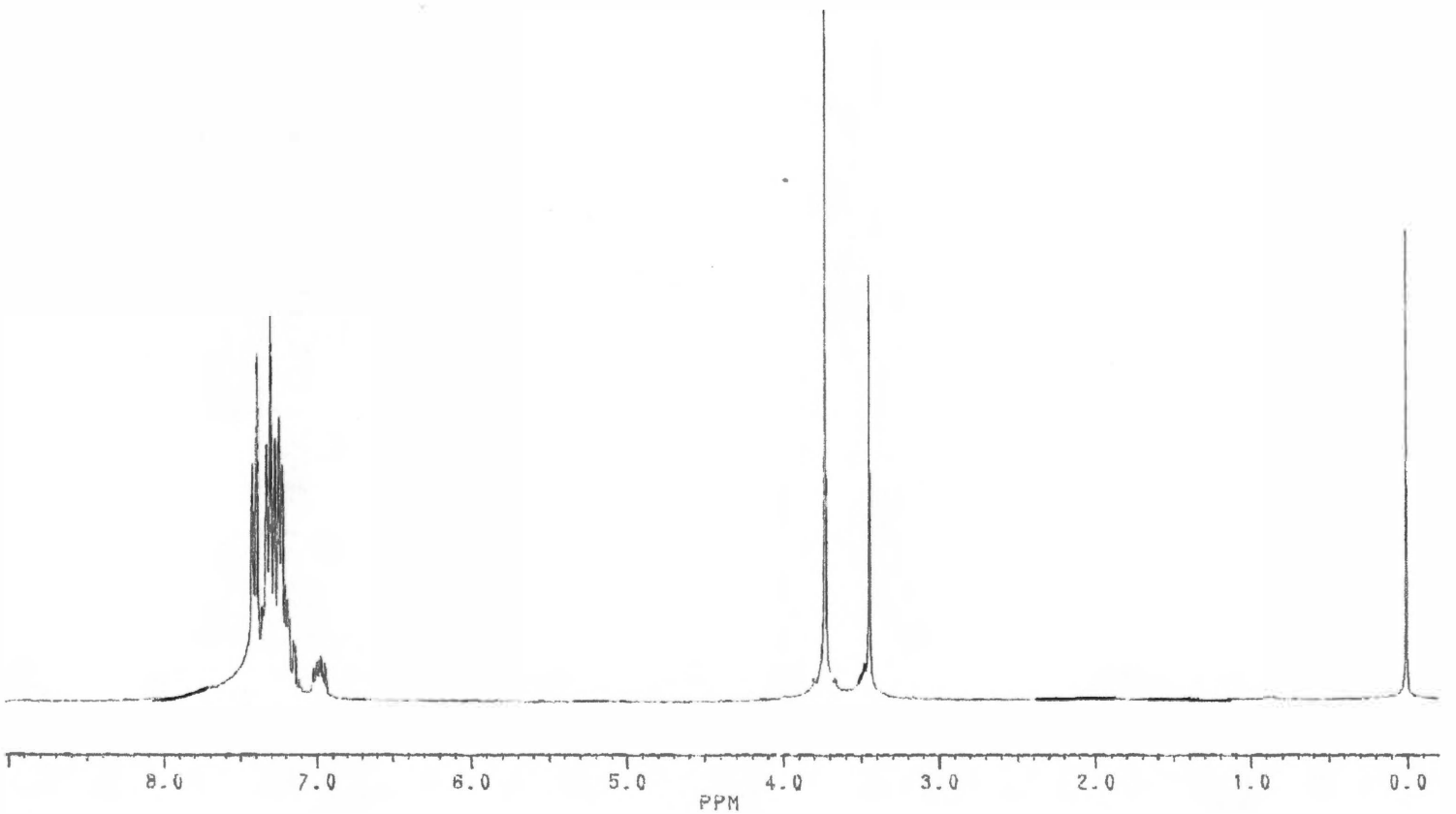
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PPM

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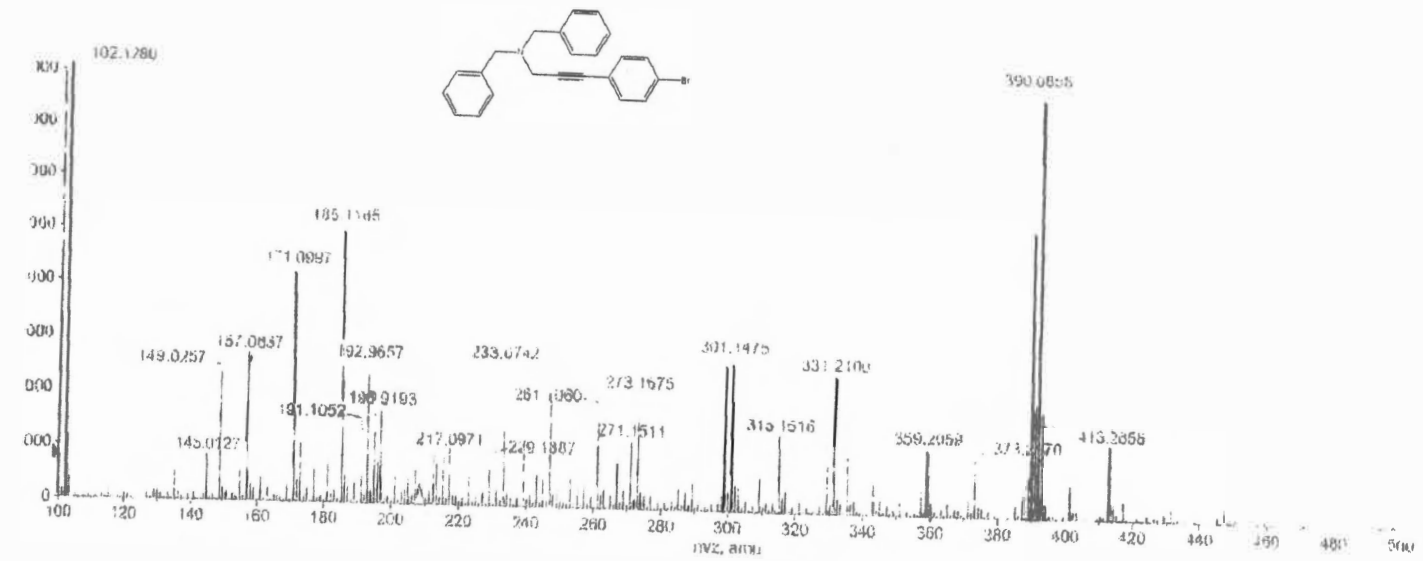
40
20
PPM

APPENDIX 2

HRMS Spectra of Selective Products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233.0742
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273.1575
271.1511
315.1516
359.2058
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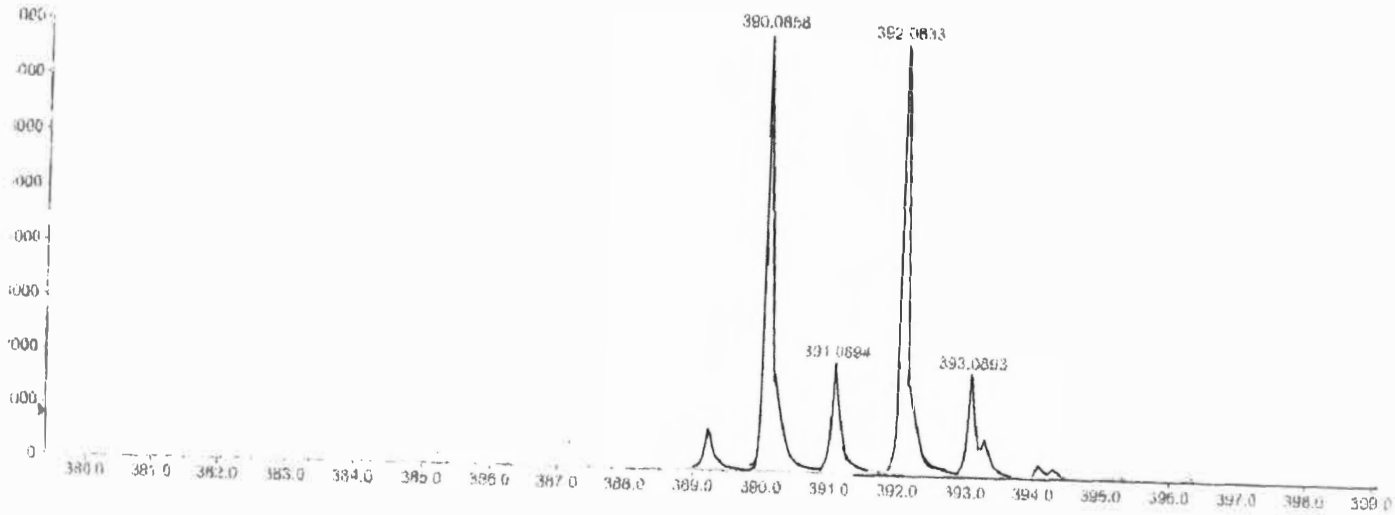
413.2855
m/z, amu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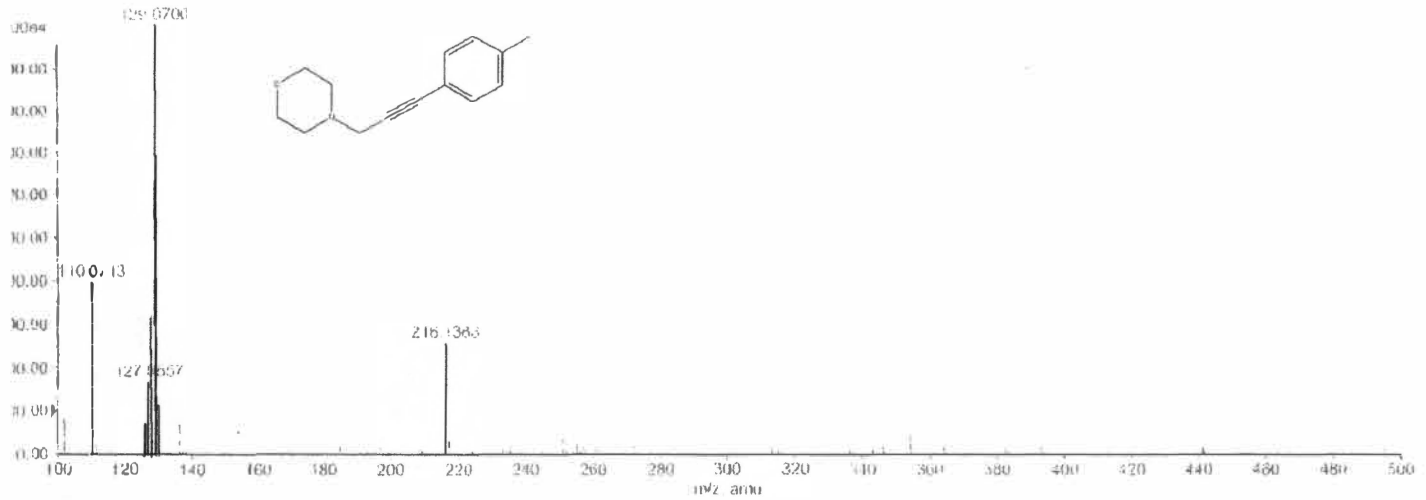
m/z, amu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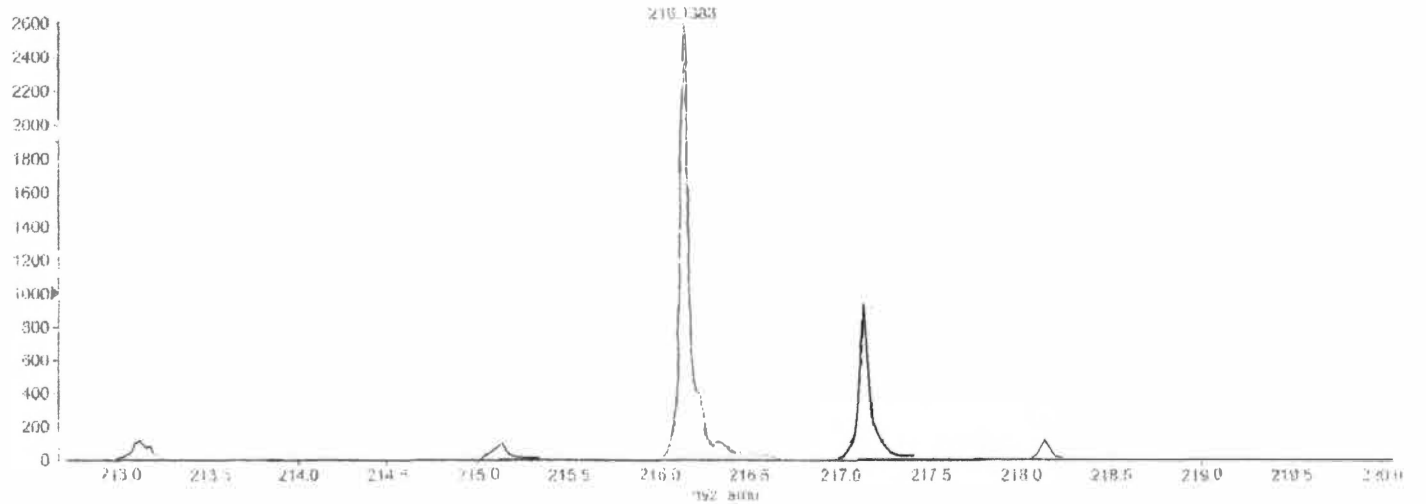
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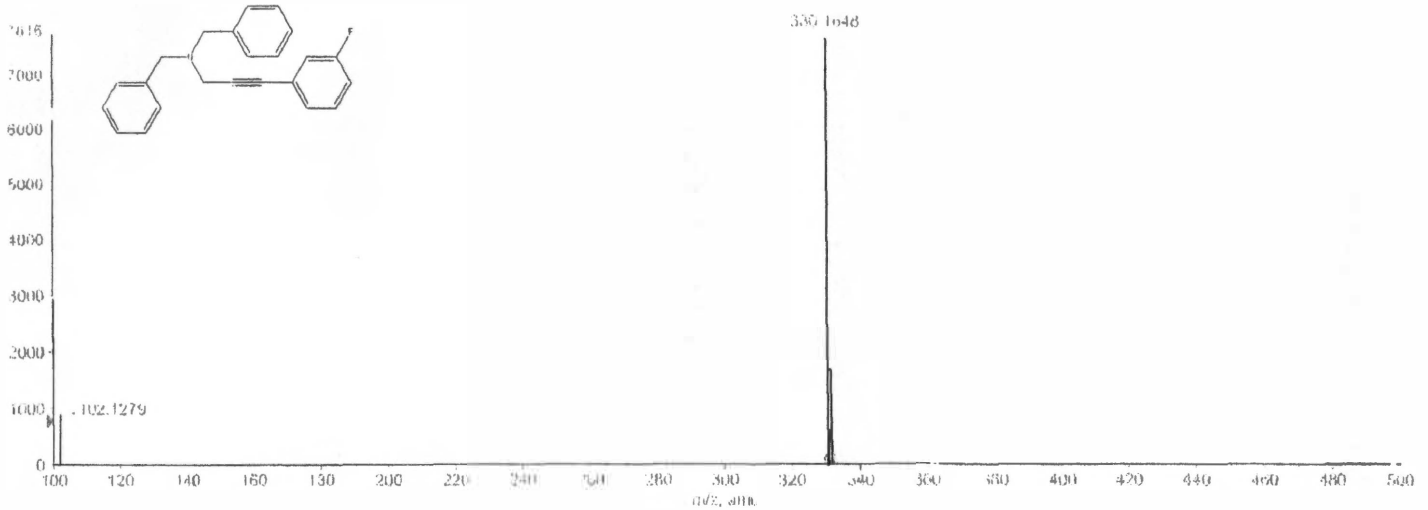
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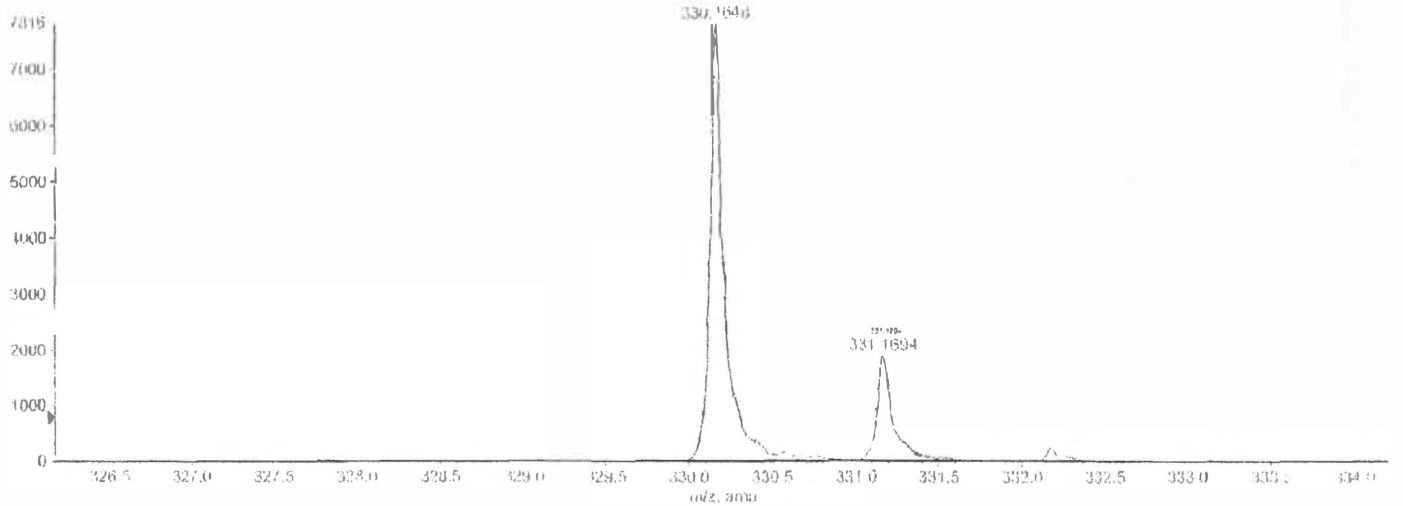
500
m/z, amu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331.0
331.5
332.0
332.5
333.0
m/z, amu

Vita

Kristy Lynn (Pickett) Homburger was born in Kokomo, IN on March 24, 1979. She was raised in Gary, IN until the age of 5, when her family moved to Fayetteville, TN, where she resided until the age of 18. She attended high school at Lincoln Country High School where she graduated in May 1997 with an honors diploma and twelth in her class out of three hundred. From there, she went to Austin Peay State University in Clarskville, TN, and received a Bachelor of Science in Chemistry, American Chemical Society certified, with a minor in Biology in May 2001. She received her Master of Science degree in Organic Chemistry from the University of Tennessee, Knoxville in August 2006.

Kristy is currently teaching at a private school in Knoxville, where she teaches middle school science, ecology, and chemistry.