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SYNTHETIC UTILITY OF PHENYL RADICALS GENERATED *IN SITU* AND A MECHANISTIC STUDY OF THE UNUSUAL REACTIVITY OF 2-OXAZOLINES WITH ALDEHYDES

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

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Degree of

DOCTOR OF PHILOSOPHY

By

ZHE JIANG
Norman, Oklahoma
2007

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SYNTHETIC UTILITY OF PHENYL RADICALS GENERATED *IN SITU* AND A MECHANISTIC STUDY OF THE UNUSUAL REACTIVITY OF 2-OXAZOLINES WITH ALDEHYDES

A DISSERTATION APPROVED FOR THE
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

BY

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TABLE OF CONTENTS

Chapter I: Phenyl Radicals in the Literature and Their Formation *in situ* from Nitrosamides……....1

1.1 General Introduction to Free Radical Reactions…….…..1

1.2 Methods to Generate Phenyl Radicals……..……2

1.3 A Brief History of Nitrosamide Formation……..……..……...6

1.4 Mechanistic Studies on Nitrosamide Decomposition…….....7

1.5 Synthetic Utility of Nitrosamides……..….13

1.6 Biphenyl Synthesis in the Literature……..…….....15

1.7 Goals of the Work……...20

Chapter II: Coupling Reactions of Phenyl Radicals Generated *In Situ*……..……27

2.1 General Methodology for Coupling Reactions Using Phenyl Radicals.27

2.2 Formation of Biphenyls from Acetanilides in Aromatic Solvents…..…28

2.3 Attempted Synthesis of Biphenyls from Oxamides……..….35

2.4 Attempted Synthesis of 6H-dibenzopyran…….……38

2.5 Summary and Future Work……44

Chapter III: 2-Oxazolines in the Literature and Their Unusual Reactivity with Aldehydes……..……59

3.1 2-Oxazolines in Modern Chemistry……...59

3.2 General Reactivity of 2-Oxazolines and Unusual Reaction with Ketones/aldehydes……59

3.3 Potential Use of Imine Products Generated……...66

3.4 Goals of This Work……68

Chapter IV: Results and Discussion on Ring Opening Reactions of 2-Oxazolines...73

4.1 Reaction Results with Aldehydes and Ketones……73

4.2 Mechanistic Studies……78

4.3 Potential Synthetic Utility……93

4.4 Conclusion and Future Work……103

Appendix……112

ABSTRACT

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Phenyl radicals are very reactive intermediates in organic chemistry but there is not a large body of literature on the subject. It has been discovered in our research group that such radicals could be generated in a mild way from the decomposition of nitrosamides generated *in situ* from aromatic amides using sodium nitrite in 2:1 acetic anhydride and acetic acid. The phenyl radicals generated *in situ* can participate in various reactions including coupling reactions which occur in reactive aromatic solvents (such as benzene) to form biphenyl products in up to 80% yield, which is comparable to yields from of Suzuki Couplings.

2-Oxazolines, as typical cyclic imino ethers (CIEs), have a broad range of applications in organic synthesis as well as polymer chemistry. When 2-oxazolines react with compounds that can be considered as electrophile/nucleophile pairs, the electrophile will first be attacked by the nitrogen in 2-oxazolines, followed by the attack on the 5-position on the oxazoline by the nucleophile. However, reactions of 2-oxazolines with aldehydes are unusual in that 2-oxazolines react with aldehydes (R'CH=O) without alpha enolizable hydrogens to give imine esters of ethanolamine ($R'CH=NCH_2CH_2O_2CR$). Ketones are observed to react much more slowly with 2-oxazolines compared to aldehydes.

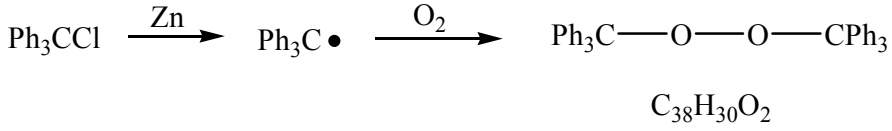
There are few references to this unusual reaction in the literature and no mechanistic studies. Therefore, a mechanistic study has been carried in order to provide a better understanding of the reaction. These studies revealed that the reaction is catalyzed by acid. Hammett and Bronsted correlation studies on acids indicate α=0.74 and ρ=0.93 while Hammett correlation studies on aldehydes indicate ρ=0.71, suggesting an acid pre-equilibrium. Thermodynamic studies have shown $\Delta H^{\neq}$= 3.5 kcal/mol and $\Delta S^{\neq}$= -70 cal/mol.K suggesting a concerted transition state including aldehydes, acid (benzoic acid or oxazolinium) and oxazoline. The rate determining step is believed to be an nucleophilic attack from the 2-oxazoline to the carbonyl group during the proton transfer process in the acid equilibrium. The results of all studies are summarized and a putative mechanism is presented which has some similarity to enzymatic reactions. Attempts to carry out metal-free Aldol reactions based on these reactions, along with other studies of the potential synthetic utility of the imine ester products, are also discussed in this dissertation.

Chapter I: Phenyl Radicals in the Literature and Their Formation *in situ* from Nitrosamides

1.1 General Introduction to Free Radical Reactions

Free radicals are defined as molecules or atoms with an unpaired electron, which generally makes them highly reactive species in organic chemistry. The discovery of organic free radicals dates back to the nineteenth century when Gomberg, as a postdoctoral fellow, tried to synthesize hexaphenylethane from the reduction of chlorotriphenylmethane using zinc powder. Instead of the desired product, he isolated a compound identified as $C_{38}H_{30}O_2$, rather than $C_{38}H_{30}$ (which is consistent with the molecular formula of hexaphenylethane, Scheme 1-1). This observation can be explained by formation of triphenylmethyl radicals, which once formed will react rapidly with oxygen in the air to form the observed product, bis(triphenylmethy) peroxide. Gomberg's subsequent synthesis of tetraphenylmethane by heating phenylazotriphenylmethane further demonstrated the existence of organic free radicals. [1]

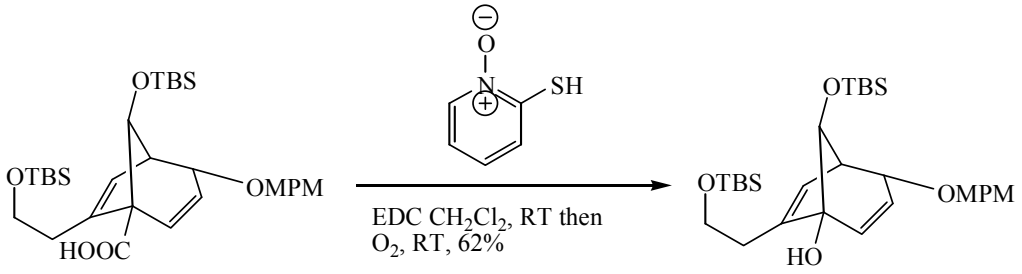
Scheme 1-1 Gomberg's Observed Result from the Attempted Synthesis of Hexaphenylethane [1]



Based on their electronic nature, free radicals can be categorized as neutral radicals, cation radicals or anion radicals. Based on the type of orbital where the unpaired electron is located, free radicals are either σ or π radicals: a t-butyl radical is a typical π radical while phenyl and vinyl radicals are σ radicals. With regard to reactivity, while π radicals can be stabilized by hyperconjugation or resonance effects, σ radicals are very reactive due to the lack of stabilization (The bond dissociation energy of $(CH_3)_3C$-H is about 91 kcal/mol, compared with 112 kcal/mol for C_6H_5-H). [2]

Organic free radicals can participate in a variety of reactions, which include radical cyclization, decarboxylation, chain reactions, and addition to unsaturated systems. One recent approach was Ito and his coworkers' use of cyclization/Barton decarboxylation in the total synthesis of Calvubicyclone (Scheme 1-2). [3]

Scheme 1-2 A Recent Example of Barton Decarboxylation [3]



1.2 Methods to Generate Phenyl Radicals

Given their highly reactive nature (along with the difficulty in generating them),

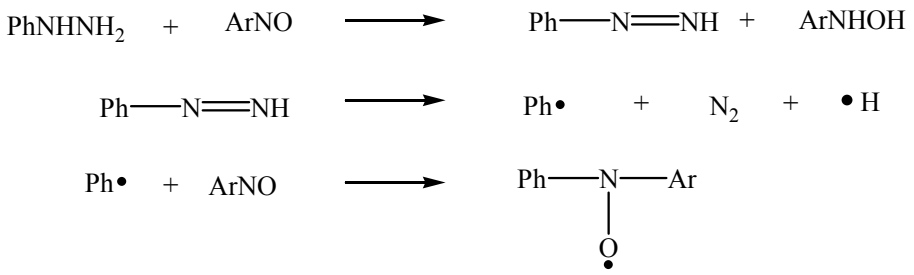
phenyl radicals are species of significant interest, and various studies of them date back to the beginning of the last century. Not only are people interested in their properties, such as their heat of formation and infrared spectra at low temperature, [4] but also their reactivity and synthetic potential which are to be covered in the following contents.

Phenyl radicals can be formed in a variety of ways. The most common is to generate them at high temperature using electronic ionization or laser photolysis, usually in the gas phase. Under such circumstances the radicals generated are generally used for thermodynamic studies [5-7] such as determination of heats of formation. This method is becoming more popular in recent years. However, such analyses are often carried out in mass spectrometers, making them of limited synthetic utility.

Phenyl radicals can also be formed during various reactions. Minato and Kusuoka had demonstrated the presence of phenyl radicals during the oxidation of phenylhydrazine by nitrosobenzene (Scheme 1-3). [8] Although the existence of phenyl radicals was confirmed, the isolation and further reaction of the phenyl radical seemed impossible as it was a reactive intermediate and does not exist for a long time. Similar radicals were also detected in the decomposition of N-phenyl-N'-benzoyldiimide. [9] However, they normally lead to the formation of benzene.

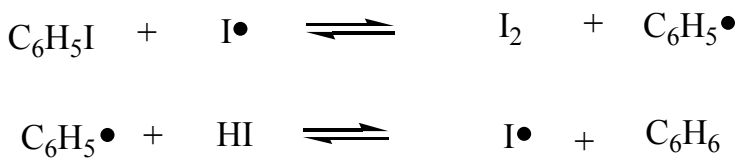
Scheme 1-3 Formation of Phenyl Radical from Phenylhydrazine and its Further Reaction

8



In 1967 Rodgers, A and colleagues did kinetic studies on the reaction of phenyl iodide and hydrogen iodide during which phenyl radicals were believed to have formed (Scheme 1-4). [10] Besides the fact that the reactions were performed at a high temperature (375~500 °C), the fast formation of benzene hindered use of the phenyl radicals in further reaction.

Scheme 1-4 Generation of Phenyl Radical from Iodobenzene and Hydrogen Iodide [10]



Another common way to generate such radicals is the decomposition of dibenzoyl peroxide derivatives. In 1970 it was shown that photolysis of single crystals of dibenzoyl peroxide could yield the phenyl radicals, which were used for ESR studies.[11] Although

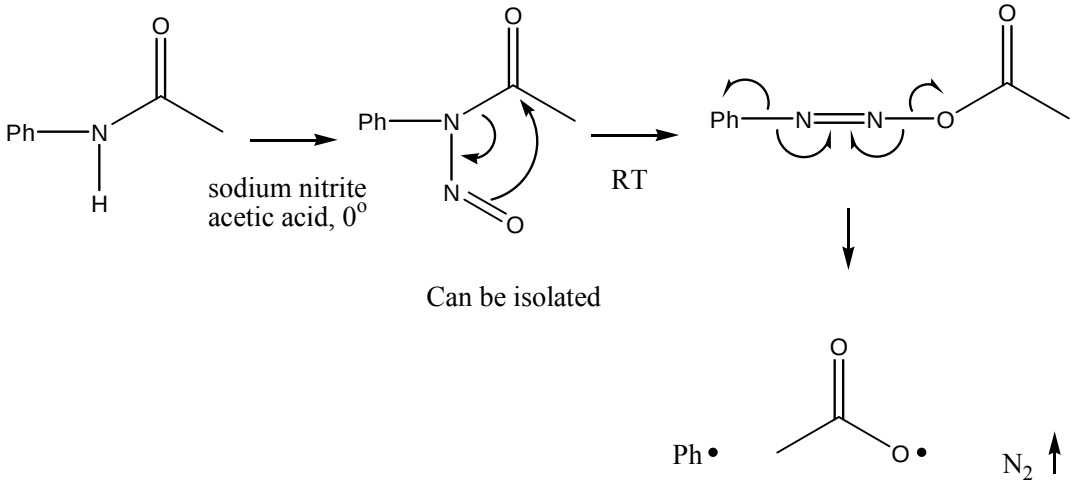
the reactions could be carried out at low temperatures, the process of slow evaporation of benzene solutions of peroxides was laborious, and the recombination of radical pairs tended to lead to unexpected results.

There are several other ways to prepare phenyl radicals, such as the decomposition of aromatic nitro or trifluoromethyl compounds,[12, 13] decompostion of benzene on hot metal surfaces,[14] or enzymetic reactions.[15] All of these reactions require either harsh reaction conditions such as high temperature, or, more importantly, have problems preventing the immediate reaction of phenyl radicals. In summary, there are few satisfactory ways to generate phenyl radicals under mild conditions to explore their potential synthetic utility. This is not surprising given the previous discussion indicating that the σ radicals are reactive and unstable.

In 2002 it was shown that phenyl radicals could be generated from the rearrangement of N-aromatic nitrosamides formed *in situ* (Scheme 1-5).[16] The presence of phenyl radicals was confirmed in two ways: 1) the nitrosamides generated and isolated were used as initiators for methyl methacrylate polymerization, which will occur by a radical mechanism but not by cationic initiation, and the aromatic moieties were incorporated into the polymer as confirmed by UV-Vis spectroscopy; and 2) when a large excess of toluene was added to the nitrosamides, significant amounts of dibenzyl were identified as reaction products, resulting from the coupling of two benzyl radicals

generated from hydrogen extraction by the phenyl radicals. This proves to be a simple way to generate highly reactive phenyl radicals under mild conditions.

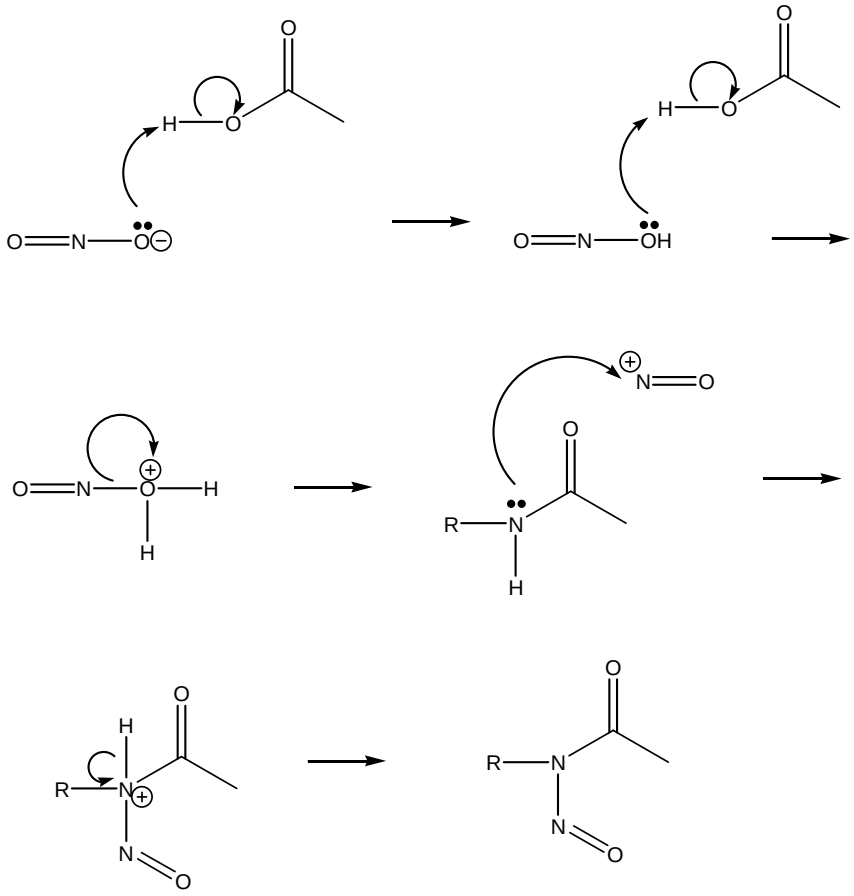
Scheme 1-5 Conversion of N-Aromatic Amides to O-Aromatic Esters [16]



1.3 A Brief History of Nitrosamide Formation

Studies of the formation of nitrosamides have had a long history since their first synthesis back in 1876, [17] when Chancel carried out the transformation by adding acid to an aqueous mixture of sodium nitrite and amide. The method was modified by Grieve and Hey in the 1930's by using nitrosyl chloride or fuming nitric acid. [18, 19] In 1954 White carried out the conversion by passing N_2O_4 gas through a CCl_4 solution of an amide, [20] and the next year he published work on a new method using 2:1 acetic anhydride/acetic acid at 0 °C in lieu of N_2O_4 gas. [21] An outline of this reaction is shown in Scheme 1-6.

Scheme 1-6 Nitrosamide Formation using Sodium Nitrite and Acetic Acid [21]



There have been several similiar methods applied, and recently Darbeau synthesized nitrosamides using sodium acetate, sodium sulfate and a methylene chloride solution of N_2O_4 at -78 °C. [22] It should be noted that most of the previous methods require harsh reagents such as fuming nitric acid, and careful handling of the carcinogenic nitrosamides.

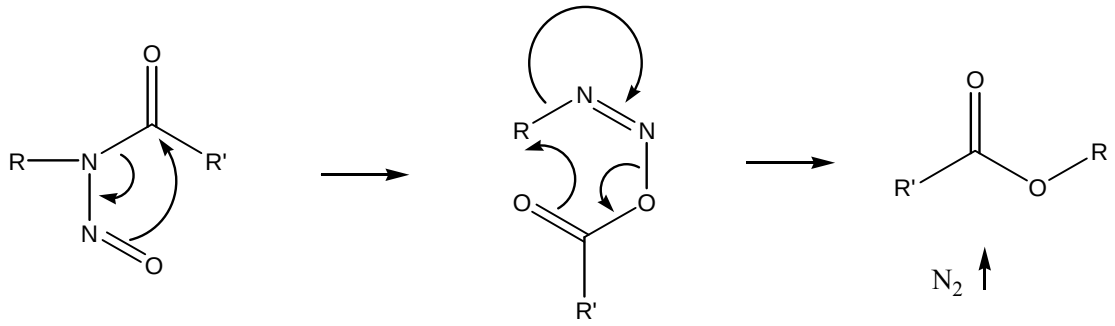
1.4 Mechanistic Studies on Nitrosamide Decomposition

There is a debate over the exact decomposition mechanism of N-nitrosamides which

has been mainly divided into two possible pathways: ionic and radical.

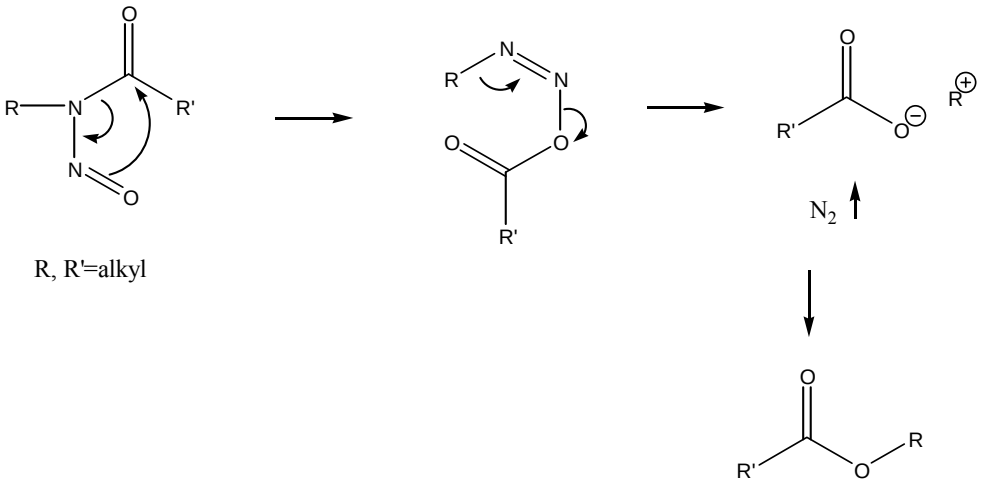
The ionic mechanism seems to be more straightforward and attracts less debate. White first suggested that ester formation proceeded through a concerted cyclic mechanism as shown in Scheme 1-7. [20]

Scheme 1-7 Cyclic Mechanism Proposed by White [20]



In a later work [23] White suggested that the rearrangement of N-alkyl-N-nitrosamide is likely undergoing a two-stage process: 1) the formation of a diazo ester and 2) nitrogen elimination from the diazo ester. Although the results were unclear, he claimed that the reaction proceeded through an ion pair pathway instead of the previous cyclic pathway (Scheme 1-8).

Scheme 1-8 Carbocation/carbanion Mechanism Proposed by White [23]

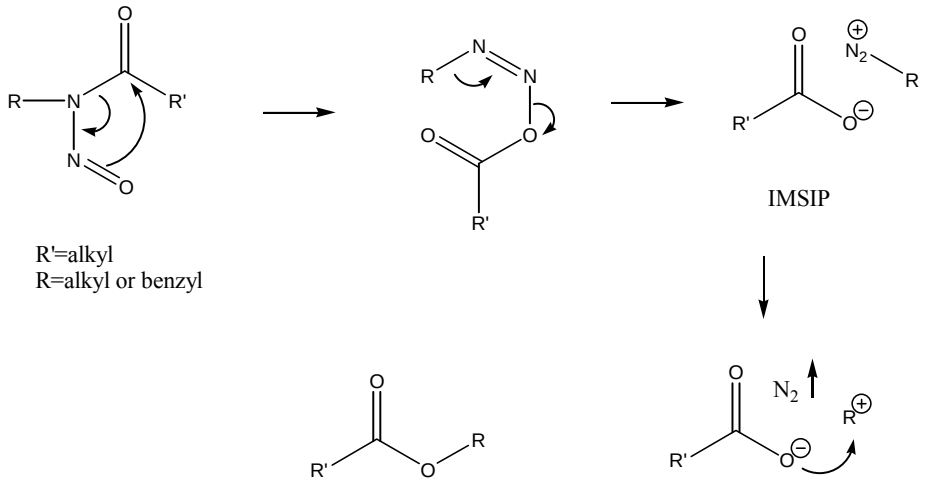


In 1973, White and his coworkers studied the deamination reactions of bridgehead amines such as 1-norbornylamine. The substrates were selected in order to reduce the chance of the olefin-formation as a side reaction, thus enhancing the stability of the carbocation to be studied. The authors concluded that although a small part of the cations/anions remained closely associated, the majority of carbocations escaped association with the anions and can account for the generation of a range of species.

In 1992, White and coworkers developed the hypothesis of inert-molecule-separate ion pairs (IMSIP), [25] which was to account for major observations such as intramolecular inversion and inefficient capture of counterions. According to White, the nitrogen-separated ion pairs were intimate ion pairs which were generated from the solvolytic route. [25] Although this did not change the fundamental mechanism, it is

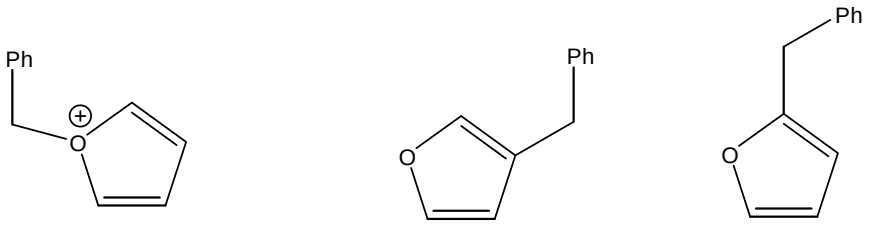
important to point out that it further explains the role of nitrogen in the reaction: "The nitrogen…., has an important role to play with respect to competing reaction modes-allowing a carbocation-solvent interaction to not only compete, but to dominate the reaction. " [25] A modified mechanism including IMSIP is shown in Scheme 1-9.

Scheme 1-9 Mechanism Including IMSIP Concept [25]



In 1997, Darbeau attempted to trap benzyl cations formed by adding furan to the system as he explored the activities of benzylic systems. [26] Although the desired O-benzylfuranonium ion was not observed due to a possible detection issue, benzylfuran was observed as a demonstration of the formation of benzyl cations during the decomposition, (Figure 1-1) and Darbeau did use such cations, generated as initiators, for polymerization in some of his later work. [27]

Figure 1-1 O-benzylfuranonium Ion and benzylfuran(s) [26]

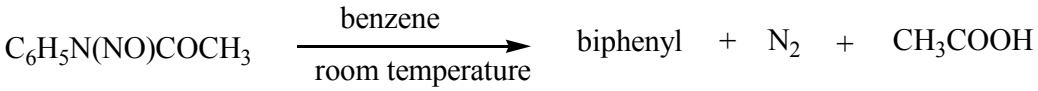


The O-benzylfuranonium Ion Benzylfuran

Although the mechanistic studies have shown support for ion-pair theory, it was valid only for aliphatic or benzylic nitrosamides rather than aromatic nitrosamides. In the case of formation of an aromatic carbocation, the positive charge formed would be orthogonal to the π system of the ring instead and not to be stabilized by the electron density of the system. Such carbocations result in the positive charge being close to the positive nucleus and are energetically very unfavorable. A brief literature search also confirms the low stability of phenyl cations and the difficulty in their formation. [28, 29]

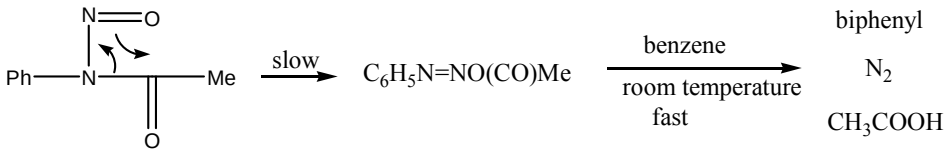
There has been more debate about the details of a radical mechanism. In 1897 Bamberger discovered the decomposition of N-nitrosoacetanilide in benzene at room temperature to give biphenyl and acetic acid, which was the focus of much later work (Scheme 1-10). [30]

Scheme 1-10 Bamberger's Discovery in 1897 [30]



Grieve and Hey were the first to suggest that the biphenyl was generated from phenyl radicals. [31] The transient existence of phenyl radicals was shown by the fact that the ratios of isomeric nitrobiphenyls formed in nitrobenzene using N-nitrosoacetanilide were close to those using more typical phenyl radical-generation methods. [32] The radicals were believed to be the products of homolysis of the benzenediazo acetate formed from N-nitrosoacetanilide, which was further suggested by Huisgen and Herold to be the rate determining step going through an intramolecular four-member ring transition state (Scheme 1-11). [33]

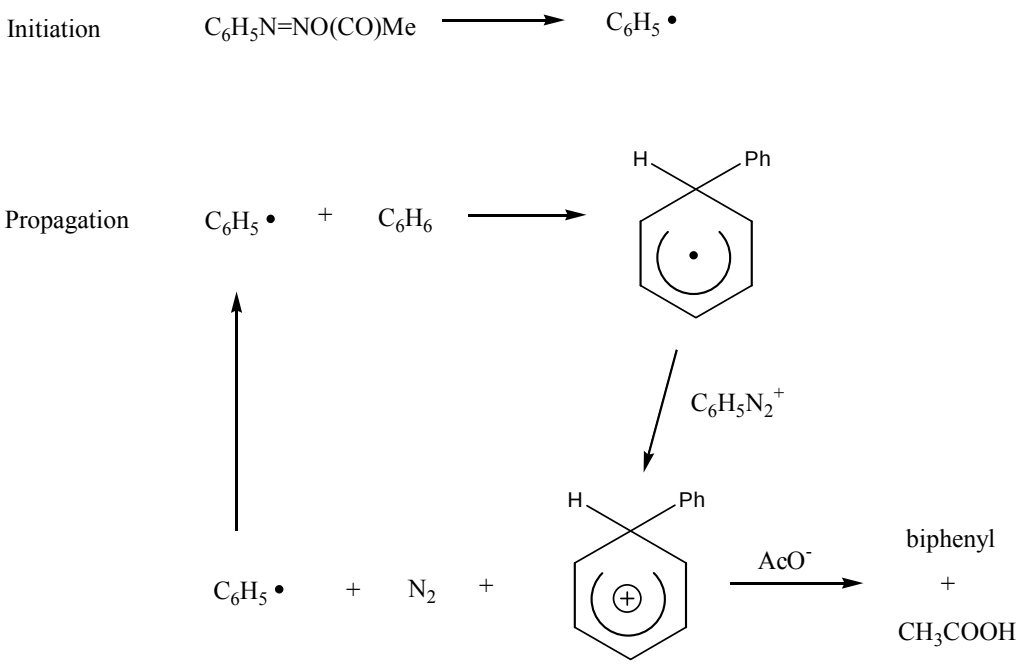
Scheme 1-11 Rearrangement Suggested by Huisgen and Herold [33]



There have been different views on the details of the mechanism: Freudenberg and Ruchardt believed that the key step involved the stable phenyldiazoxyl radical (PhN=NO •), [34] given the presence of arenediazonium acetate ion pairs ($PhN_2^+MeCOO^-$)

discovered by Suschitzky and his coworkers. [35] Although Chalfont and Perkins proposed another chain mechanism claiming a different oxidizing radical as the key step, [36] there was a general agreement that the formation of phenyl radical was the initiation step. Given the previous mechanisms and subsequent extensive ESR studies upon the subject, Cadogan, Paton and Thomson finally managed to provide a simple and more accurate mechanism (Scheme 1-12), [37] which was supported by evidence from Nonhebel and his coworkers. A more detailed mechanism was also reviewed by Cadogan, [38] and now there is general agreement that phenyl radicals are formed during the decomposition of aromatic nitrosamides.

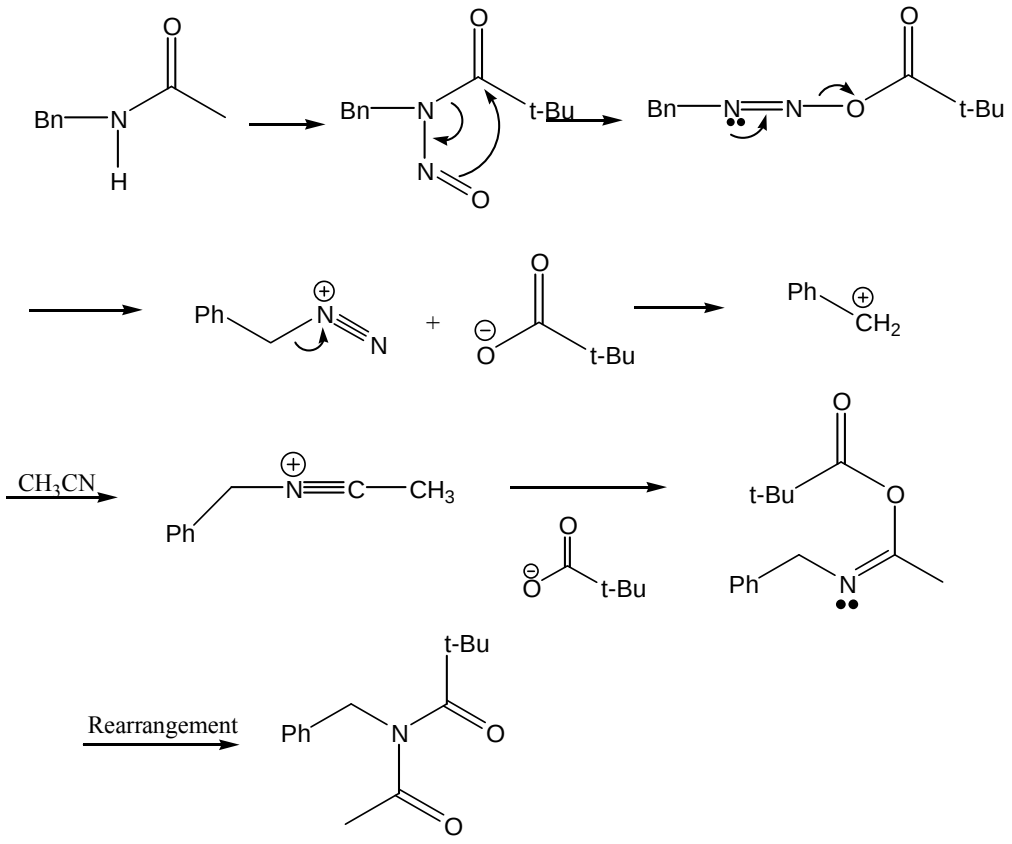
Scheme 1-12 Mechanism for the Second Step [37]



1.5 Synthetic utility of nitrosamides

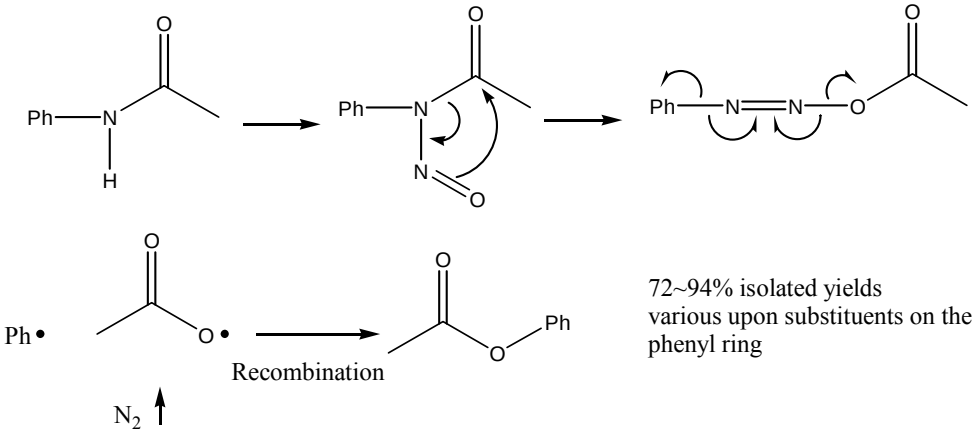
In 1997 Darbeau attempted to use the benzyl cations generated from nitrosamides as an intiator for the polymerization of styrene. [27] In his work, the author mentioned that it was the first demonstration of polymerization using carbocations generated via deamination. Later in his work, he explored the potential application of this method of benzyl cation formation for the synthesis of diacylamines (Scheme 1-13). [22]

Scheme 1-13 Synthesis of Diacylamines [22]



With regard to the radical pathway of decomposition, it was discovered that the phenyl radicals could be used to form O-aromatic esters in good yields. [16] The nitrosamides were generated from N-aromatic amides and reacted *in situ* to form the products. An obvious advantage of this methodology is that it is not necessary to isolate such nitrosamides, which are identified as carcinogens. An outline of the reaction is shown in Scheme 1-14.

Scheme 1-14 Conversion of N-aromatic Amides to O-aromatic Esters and Reaction Mechanism [16]

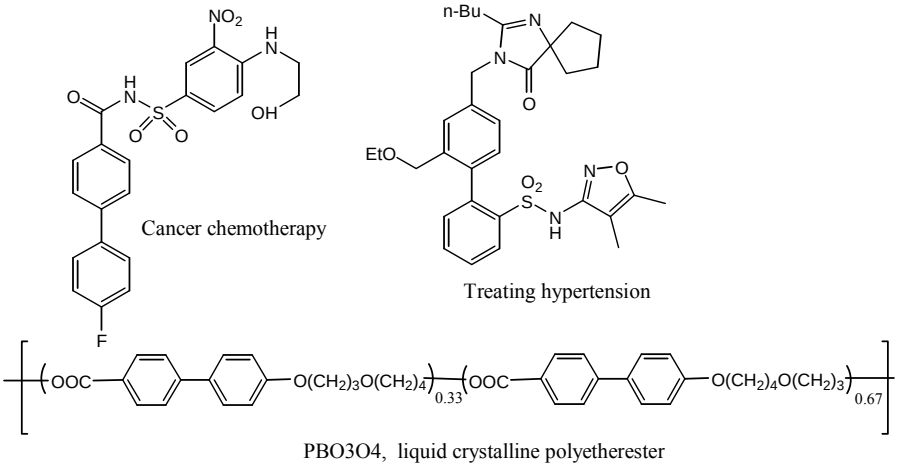


1.6 Biphenyl Synthesis in Literature

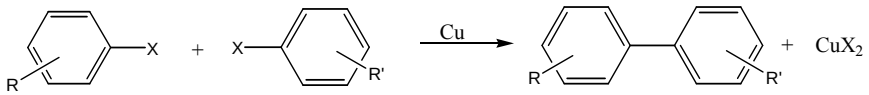
The formation of biphenyls is an important synthetic procedure; many compounds containing the structure of biphenyls are useful in industry (Figure 1-2). [39-41] One classic method for formation of biaryls is the Ullmann reaction. In the Ullmann reaction aryl

halides are coupled to form biaryls by heating them with copper.[42] The general reaction is shown in Scheme 1-15.

Figure 1-2 Compounds Containing Biphenyl Structure [39-41]



Scheme 1-15 Ulmann Reaction [42]

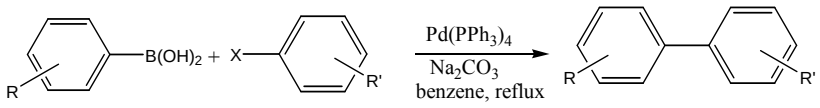


The Ullmann reaction has certain drawbacks. The first is that it generally forms symmetrical biphenyls, which limit its potential synthetic utility. The second is that reaction yields can be highly variable. The third is the need to synthesize the halides if they are not commercially available. Iodo compounds are the most reactive toward the Ullmann coupling, but they can be unstable. [43] Although a number of recent approaches

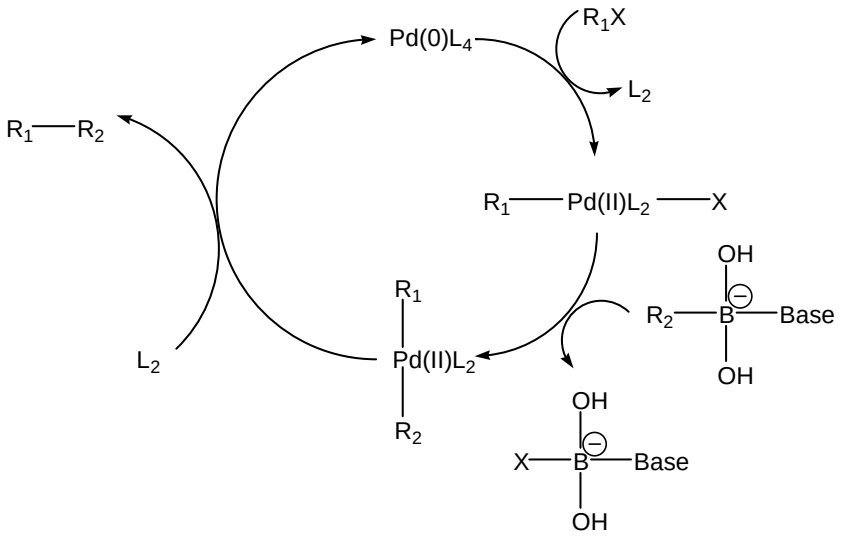
employing Ni(0) catalysts have been developed, [44] nickel tetracarbonyl [$Ni(CO)_4$] is still commonly used. Due to the toxicity of nickel tetracarbonyl, such procedures will always cause health concerns. Modifying methods involving $Ni(COD)_2$ in more recent years have improved results greatly. [45]

The most common modern method for the synthesis of biaryls is the Suzuki coupling which generally involves the use of an aryl bromide, an arylboronic acid and a palladium catalyst (Schemes 1-16 and 1-17). [46]

Scheme 1-16 A General Suzuki Coupling [46]



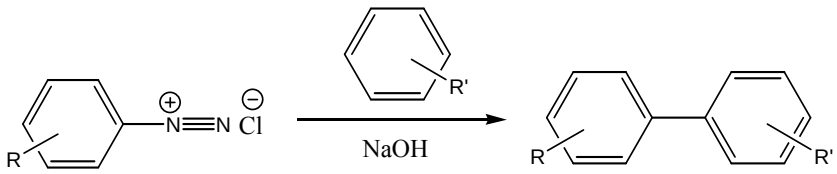
Scheme 1-17 A Proposed Catalytic Cycle for the Suzuki Reaction [46]



Once again the main issue for the Suzuki coupling is the need to, in some cases, synthesize the arylboronic acid. An additional problem is the expense of using palladium catalysts while reaction yields can depend on the substituents attached to the aromatic ring. Common catalysts used in the Suzuki coupling can have air-sensitivity problems and require special handling. Novel catalysts in more recent years have achieved better results. [47]

An older method for the formation of biaryls is the Gomberg-Bachmann reaction. [48] In this method the corresponding aromatic diazonium salts are formed from the corresponding aromatic amines, followed by coupling to other aromatic compounds in the presence of a base (Scheme 1-18). The major problems with this methodology are: 1) the need to isolate the diazonium salts, which can be explosive; 2) functional group compatibility under the harsh reactive conditions; and 3) yields are not as good as expected from such reactions.

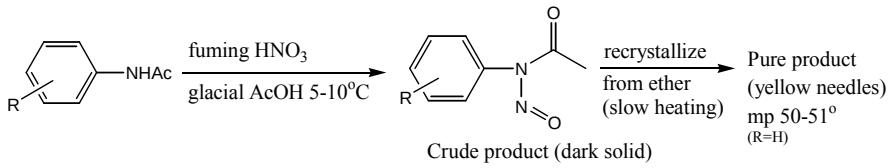
Scheme 1-18 Gomberg-Bachmann Reaction [48]



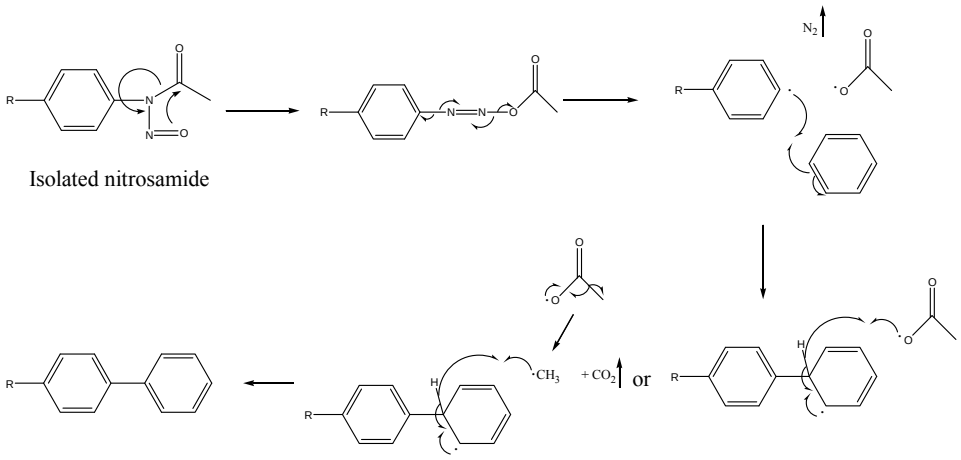
10-44% yields

Several decades ago, Grieve and Hey developed a method in which secondary N-aromatic acetamides were converted to biaryls through aromatic nitrosamides (Scheme 1-19). [14, 15] After isolation, the aromatic nitrosamides were allowed to decompose to synthesize biaryls in benzene. As discussed earlier, the mechanism is believed to proceed through rearrangement of the aromatic nitrosamide to the acetoxyazoaromatic compound, followed by homolytic cleavage to form the phenyl radical intermediate. This radical intermediate combines with benzene to form a phenyl cyclohexadienyl radical. Abstraction of hydrogens by either the acetoxy radical or a methyl radical formed by the decarboxylation of the acetoxy radical, will result in the formation of the biaryl (Scheme 1-20).

Scheme 1-19 Grieve and Hey's Synthesis of Nitrosamides [14, 15]



Scheme 1-20 Decomposition of Isolate Nitrosamides in Benzene [14, 15]



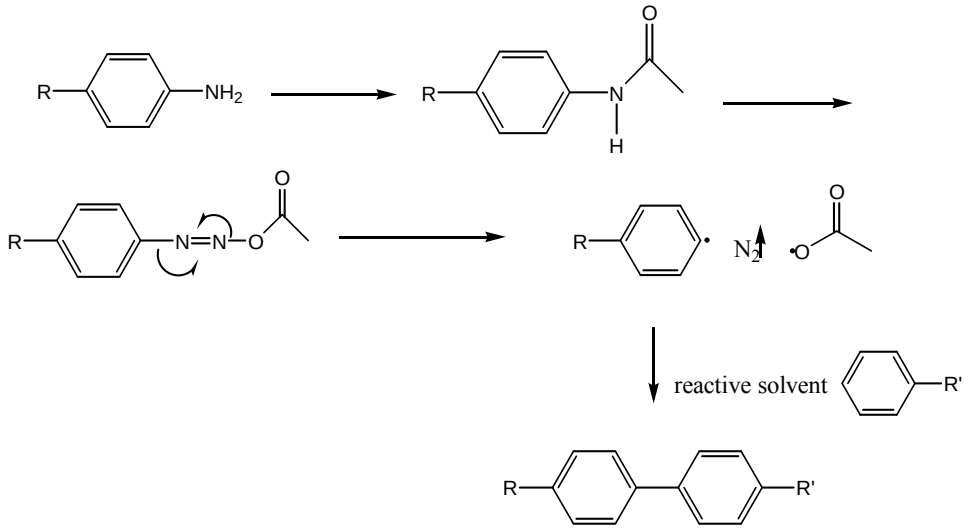
Yields for this method range from moderate to good. However, the use of nitrosyl chloride, concentrated nitric acid or nitrous fumes makes it difficult to monitor the completion of the reaction and results in functional group intolerance. Isolation of the nitrosamides also aroused safety concerns due to their known instability and carcinogenic issues. [49]

Recently there have been other publications upon the subject, such as thermo decomposition of phenyl-aryl-sulfamoylcarbamates. [50] However, these approaches are laborious and do not provide a simple synthesis of biphenyls under mild conditions.

1.7 Goals of the work

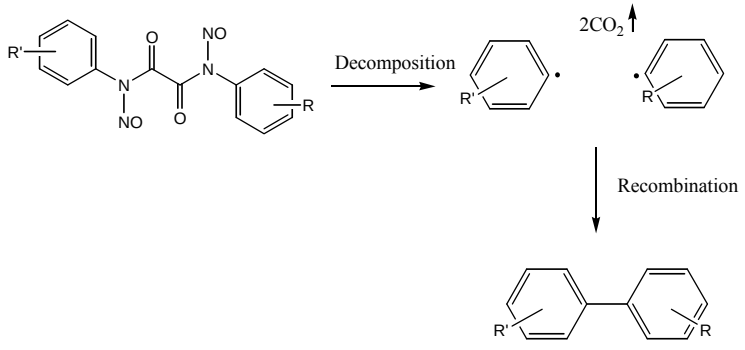
Given the success of ester synthesis using formation and decomposition of aromatic N-nitrosamides *in situ*, it seems plausible that by adding a reactive aromatic solvent after 2 hours at 0 °C before phenyl radicals form and allowing the solution to slowly warm to room temperature, the formation of "solvent-trapped" products would be possible (Scheme 1-21). The direct use of aromatic solvents as extracting solvents can also simplify the workup process, making the method more convenient for the synthesis of simple biphenyls compared to Suzuki coupling.

Scheme 1-21 Decomposition of Nitrosamides in Reactive Solvents and the Expected formation of Biphenyls



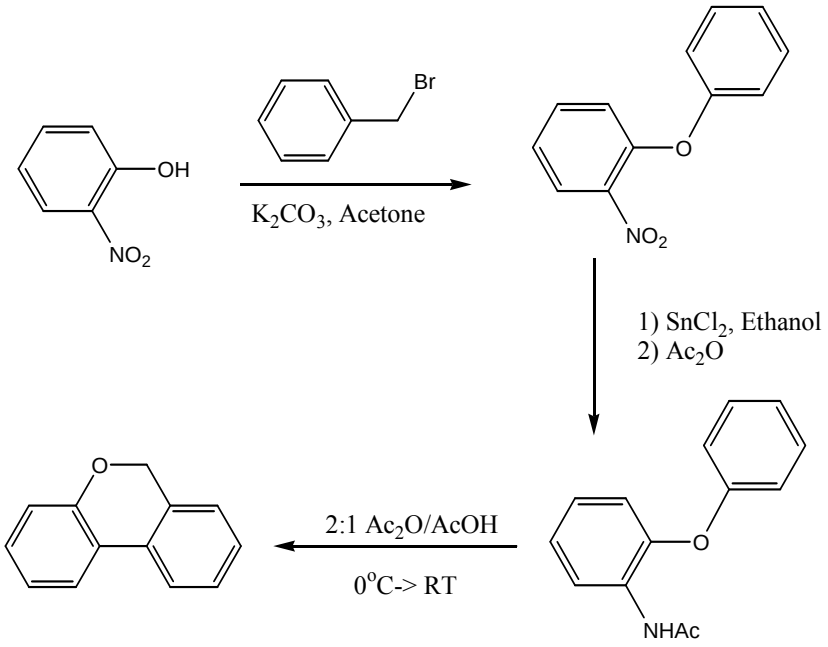
Secondly, it was proposed that oxamides with different substituted groups on both ends could be formed from a stepwise reaction by reacting oxalate esters with two different anilines, and asymmetric biphenyls could be formed by nitrosation, rearrangement and extrusion, and combination of two phenyl radicals (Scheme 1-22), thus directing the position of two different functional groups in the coupling product.

Scheme 1-22 Possible Synthesis of Asymmetric Biphenyls from Oxamides



Finally, the synthetic utility of this method could be extended to intramolecular coupling (such as the example shown in Scheme 1-23). The detailed results of the approaches above will be covered in Chapter 2.

Scheme 1-23 Attempted synthesis of 6H-Dibenzopyran



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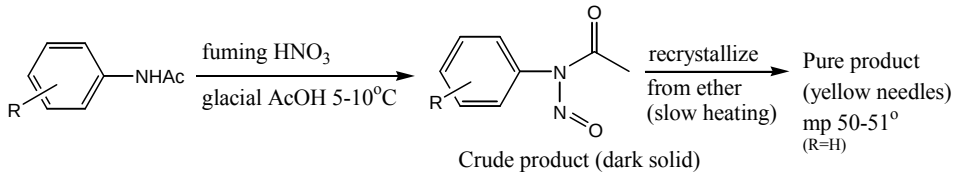
Chapter II Coupling Reactions of Phenyl Radicals Generated *in situ*

2.1 General Methodology for Coupling Reactions Using Phenyl Radicals

Given previous success for the synthesis of various O-aromatic esters, [51] it was thought that the decomposition of aromatic nitrosamides is a mild and safe way to generate phenyl radicals *in situ* for use in further reactions (Chapter 1.5). As indicated in Chapter 1, there have been several general methods to generate aromatic nitrosamides which will further form phenyl radicals. In the 1930's Grieve and Hey carried out this reaction using fuming nitric acid (Scheme 2-1). [52] The major flaw of this method is the difficulty in monitoring the completion of the reaction, as well as the tolerance of certain functional groups. Moreover, the unstable, carcinogenic nitrosamides must be isolated for further purification and use.

Scheme 2-1 Grieve and Hey's work [52]

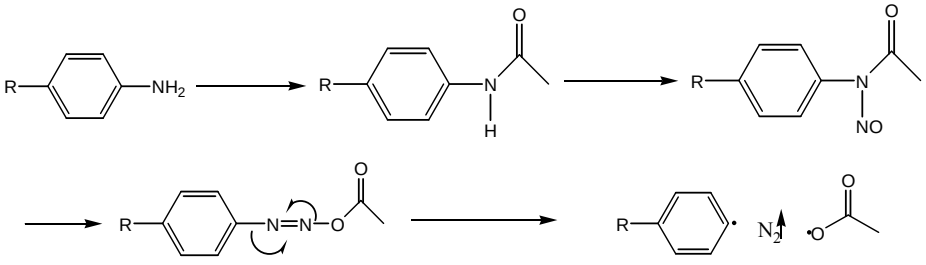


On the other hand, White and Darbeau have applied various methods to the formation of the benzyl nitrosamides. Having N_2O_4 bubbling into a methylene chloride

or carbon tetrachloride solution of the amide is the most common method; [53, 54] though White did show that sodium nitrite in 2:1 acetic anhydride/acetic acid had the same effect. [55a]

Although the benzyl nitrosamides formed using White and Darbeau's methods were believed to decompose through the ion pathway, our group has shown that treating N-aromatic amides with sodium nitrite in 2:1 acetic anhydride/acetic acid at 0 ˚C for 2 hours will allow the nitrosamides to rearrange to the azoacetoxy compounds which will be relatively stable at 0 ˚C. Allowing such compounds to warm up to room temperature will promote fragmentation to the phenyl radicals and the acetoxy radicals with loss of nitrogen gas (Scheme 2-2).

Scheme 2-2 Generation of Phenyl Radicals [51]



2.2 Formation of Biphenys from Acetanilides in Aromatic Solvents

With the addition of excess aromatic solvents and further stirring of 24 hours, the phenyl radicals formed will be converted into the desired biphenyl products. After the

acid was neutralized by sodium bicarbonate solution, the products were extracted directly using the aromatic solvents. After washing with water and drying, the solvent was removed to yield the crude products. If the product was a solid, it was generally recrystallized from corresponding solvents unless the purity was deemed sufficient, and its identity verified by melting point and NMR spectroscopy; if the product was a liquid, it was analyzed using GC-MS semi-quantitative analysis techniques (by comparing the area of the major peaks). The results of earlier reactions run in our research group are summarized in Table 2-1.

Table 2-1 Conversion of Various N-Aromatic Amides to Biphenyls using Two Equivalents of Sodium Nitrite in 2:1 Ac_2O/AcOH [56]

Example	R	Aromatic solvent	Yield %	mp, °C	Lit mp, °C	Purity %
1	phenyl	Benzene	60	68-69	69-71	
2	*p*-phenylphenyl	Benzene	62	212-214	212-213	
3	*p*-nitrophenyl	Benzene	81	112-113	113.8	
4	*o*-*t*-butylphenyl	Benzene	53	32-34	31-34	
5	2-pyridyl	Benzene	54	-	-	72
6	1,3,5-triazyl	Benzene	63	63-65	63-65	
7	*p*-bromophenyl	Benzene	71	90-92.5	91.2	
8	*p*-phenylphenyl	Nitrobenzene	53	208.5-211	209-213	

Although it can be seen from Table 1 that several of the entries have similar or even better results compared with those of Grieve and Hey while not having the need to isolate carcinogenic nitrosamides, the method can still be improved in several ways: 1)

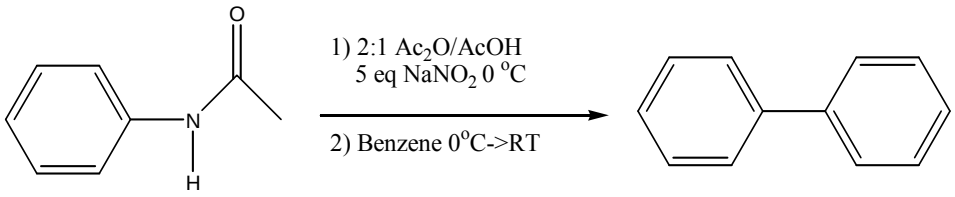
reproducibility, as several members of our research group were experiencing inconsistent reaction yields; 2) addition of several important substrates which were not used before; and 3) expansion of the methodology by replacing benzene with different aromatic solvents such as trifluorotoluene.

Although the optimized reaction conditions used by Roy were 2 equivalents of sodium nitrite to 1 equivalent of amide, several group members were later having difficulties running new reactions or even repeating reactions already done. Considering the fact that White in his work [57] used as many as 20 equivalents of sodium nitrite, it was expected that changing the amount of sodium nitrite could improve the reaction yields in individual attempts.

The first attempt to improve upon the previous results was in the synthesis of biphenyl (Scheme 2-3). Commercially obtained acetanilide was dissolved in 2:1 acetic anhydride/acetic acid and kept at 0 ˚C for thirty minutes, at the end of which period five equivalents of sodium nitrite was added. The color of the mixture changed from colorless to light blue, then to light green in the presence of brown gas (N_2O_4). After two more hours at 0 ˚C, 70 mL of benzene was added and the mixture was allowed to slowly warm to room temperature with stirring overnight. The mixture was light brown when reaction was done, and the solid formed was removed by filtration. The solution was neutralized by 5% sodium bicarbonate solution, the benzene phases were combined, dried with

anhydrous sodium sulfate and benzene was removed under reduced pressure. Unfortunately, under such conditions sublimation was observed from the expected product biphenyl and the actual yield was unable to be calculated. The sublimation product was collected and verified as biphenyl by melting point and ^{1}H-NMR.

Scheme 2-3 Synthesis of Biphenyl from Acetanilide

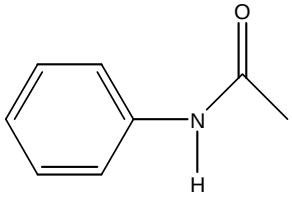
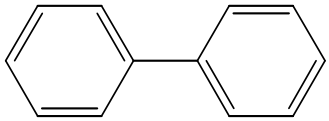
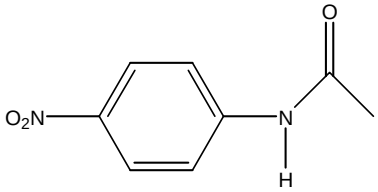
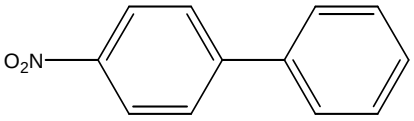
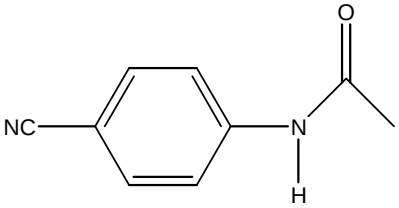
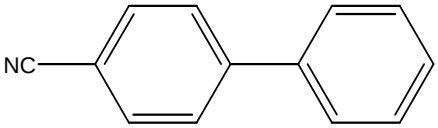


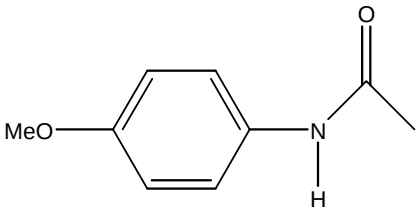
1

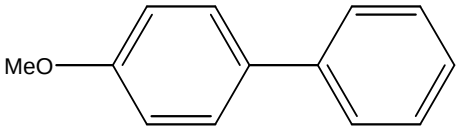
Although the precise yield was not obtained for the reaction, it was very clear that the desired product was formed. Since the previous results showed that the reaction using 2 equivalents of sodium nitrite will give 60% yield, it can be assumed that the purification/isolation was the key factor for the relative low yield. A series of substrates, including several new substrates which were not done before, were converted to biphenyls using two possible procedures: those starting with acetanilides were carried out using the procedure described above, and those starting with anilines using the method described as follows: 2 mmol commercially obtained anilines were added to a flask with 10 mL acetic anhydride and the mixture was heated to reflux solvent for 30 minutes. After the solution was cooled to room temperature, another 5 mL of acetic acid was added and the acetanilides, without isolation, were allowed to be converted to biphenyls

using the method described before. The results of all the entries are listed in Table 2-2.

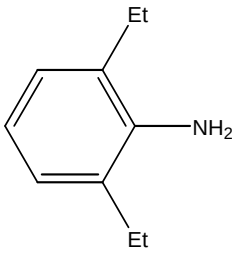
Table 2-2 Results on the Conversion of Various Acetanilides to Biphenyls Using A Large Excess of Benzene and 5 Equivalents of Sodium Nitrite in 2:1 Ac_2O/AcOH

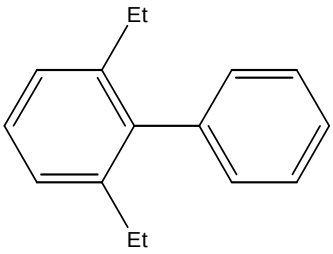
Starting Materials	Biphenyls Formed Yields
	 **1** Not Available (sublimation)
	 **2** 43%
	 **3** 70%



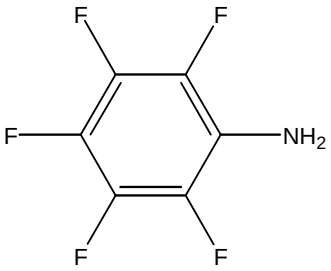


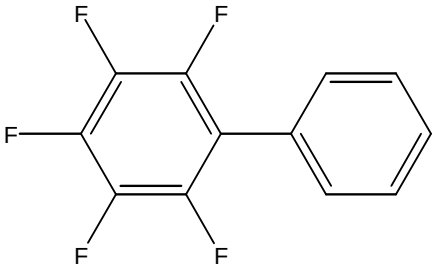
4
20%





0% (Acetanilide not formed)



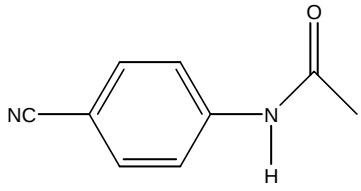


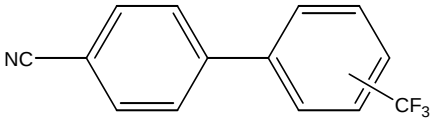
0% (Acetanilide not formed)

It can be concluded from Table 2 that the majority of the entries that worked gave moderate to good yields, with the exception of p-methoxybiphenyl, which can be explain as the activated phenyl ring is more susceptible to nitrosastion and nitration reactions. The synthesis of 4-cyanobiphenyl showed result comparable to those obtained from the Suzuki coupling,[55b] while the other two new entries failed because the corresponding acetanilides, based on NMR spectra, do not form and therefore the formation of biphenyl will be unlikely.

Attempts using α, α, α-trifluorotoluene instead of benzene also gave good yields. These attempts aroused the concern of selectivity of such reactions for possibly generating more than one product, but also indicated the potential of synthesizing asymmetric biphenyls using various aromatic solvents, although a good isolation method would be necessary (Table 2-3). It is notable that for the last reaction listed below the coupled biphenyls are the minor products, and this is probably due to the fact that the phenyl radical is less stable; thus the ester formation, which will eventually lead to phenol, occurs faster than the coupling reactions. More details about the procedure and analysis of these reactions can be found in the experimental section of this chapter.

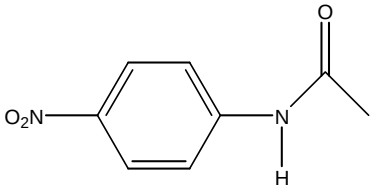
Table 2-3 Coupling Reactions Using An Excess of Trifluorotoluene and Five Equivalents of Sodium Nitrite in 2:1 Ac_2O/AcOH

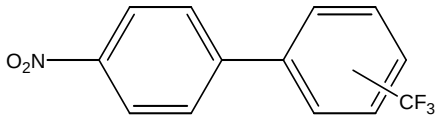




5

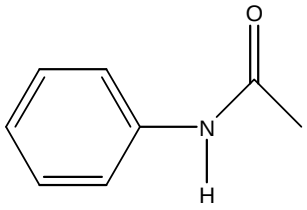
80% (Mixture of isomers)

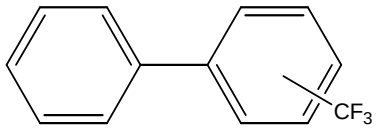




6

71% (Mixture of isomers)





7

<10% (Mixture of isomers)

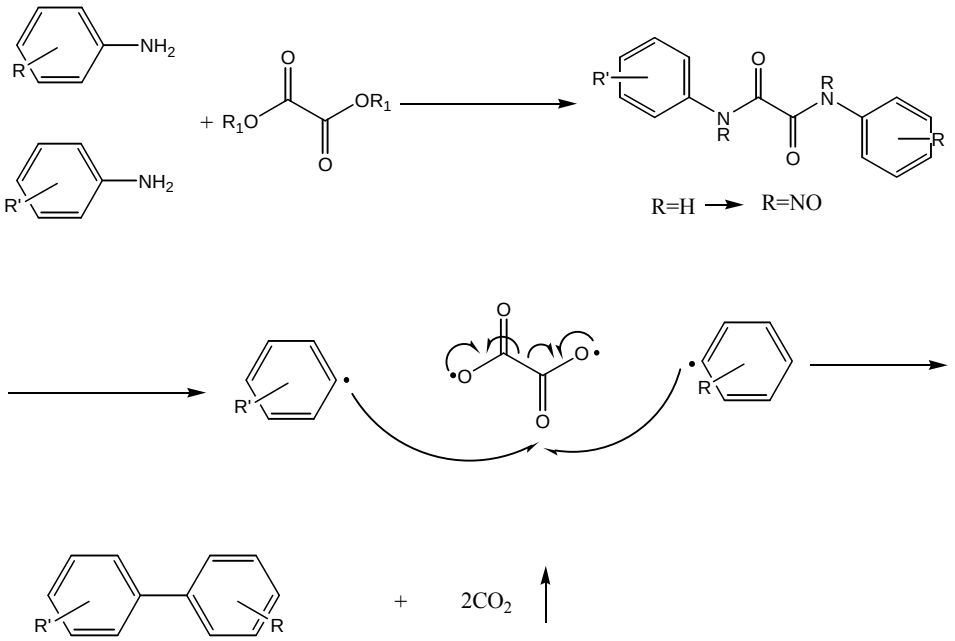
2.3 Attempted Synthesis of Biphenyls from Oxamides

Another approach was proposed for the synthesis of biphenyls from substituted oxamides given their abundance in nature. In this approach, after being prepared from dialkyl oxalate and anilines, the oxamides were allowed to be converted to N-aromatic nitrosamides before being treated by the standard procedure. If the reaction underwent rearrangement to form two phenyl radicals, they could couple with each other to form the desired product (Scheme 2-4).

To have these reactions able to proceed, there will be several requirements to be met: first, the nitrosamide must be able to be generated under the conditions used. Second, as the system is allowed to warm up to room temperature the phenyl radicals generated must recombine, which is very likely given the similar situation in Darbeau's IMSIP theory and the belief that the oxalyl direadical should decompose very fast to generate carbon dioxide, which would be thermodynamically very favorable. Last, the phenyl radicals must be formed simultaneously-it is not easy to predict, but it is possible, given Roy's observation that perylene was isolated from similar reaction from

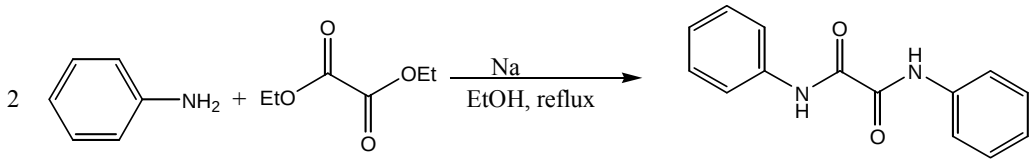
N,N'-(1,8-naphthylene)diacetamide. [56b]

Scheme 2-4 Formation of Biphenyls from Dialkyl Oxalates



The first diamide tested was N, N'-bisphenylethanediamide **(8)**. The amide was prepared from freshly distilled aniline/ethyl oxalate, sodium and pure ethanol (Scheme 2-5).

Scheme 2-5 Synthesis of N, N'-bisphenyldiamide

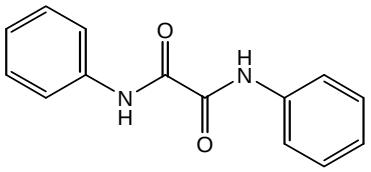
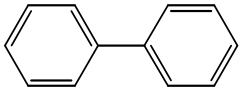
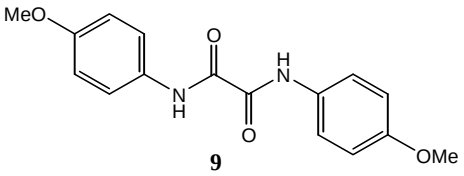
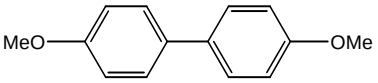
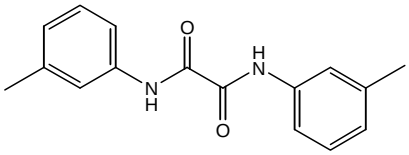
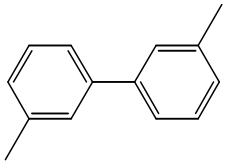
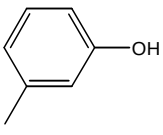


44%

8

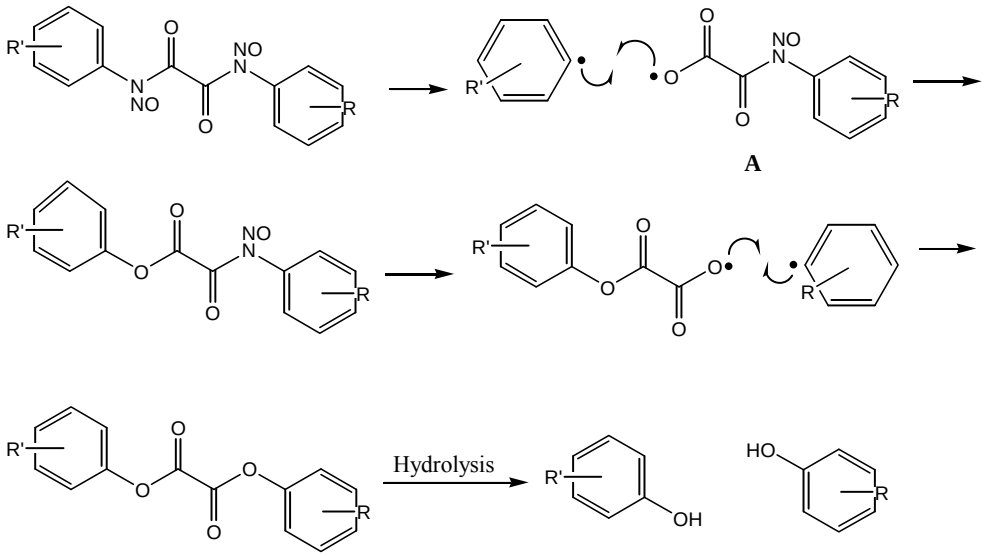
The oxamide was treated with sodium nitrite in 2:1 acetic anhydride/acetic acid for two hours to form the nitrosamides, then slowly allowed to warm up to room temperature. However, the reaction did not form the desired product by GC-MS detection, probably due to the fact that the poor solubility of the ethanediamide in the solvents used, but mostly giving undecipherable results.

Table 2-4 Synthesizing Biphenyls from Ethanediamides

Amide	Biphenyls Formed	Yields
 **8**		0%
 **9**		0%
 **10**		0%
	 **11**	Detected

The oxamide N,N'-bisphenyl(m-methyl)ethanediamide has relatively good solubility in 2:1 acetic anhydride/acetic acid and the results of the last attempt revealed the existence of m-cresol, which indicated that the rearrangement on both sides does not occur simultaneously, but in stepwise fashion. In other words, the formation of ester on one side is completed before the nitrosamide on the other side starts to rearrange (followed by the formation of the phenyl radicals), and the radical A was not able to go through decomposition by itself under the conditions used. A modified mechanism is shown in Scheme 2-6.

Scheme 2-6 Modified Mechanism of Decomposition of Ethanediamides

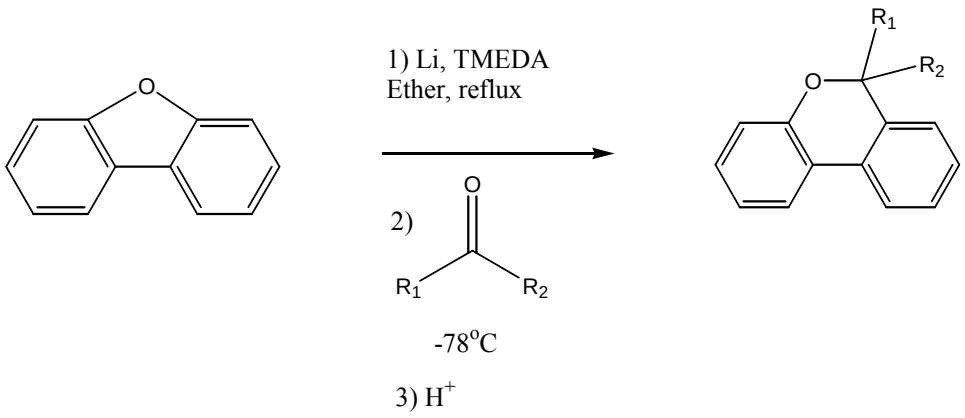


2.4 Attempted synthesis of 6H-dibenzopyran

6H-Dibenzopyran structures exist in a large number of natural products and can be very important precursors/intermediates for their syntheses. [58-60] There have been a

number of methods developed for the syntheses of 6H-dibenzopyran derivatives, recently among which are the works of Wang, et al [61], in which case a dilithiated intermediate was prepared from treating dibenzofuran with lithium, base in dry ether. The dilithiated intermediate was reacted with aldehydes/ketones to yield the desired products after dehydration. (Scheme 2-7) Such reactions could also be carried out using palladium catalysts, [58] but most of them require activated substrates. [62a]

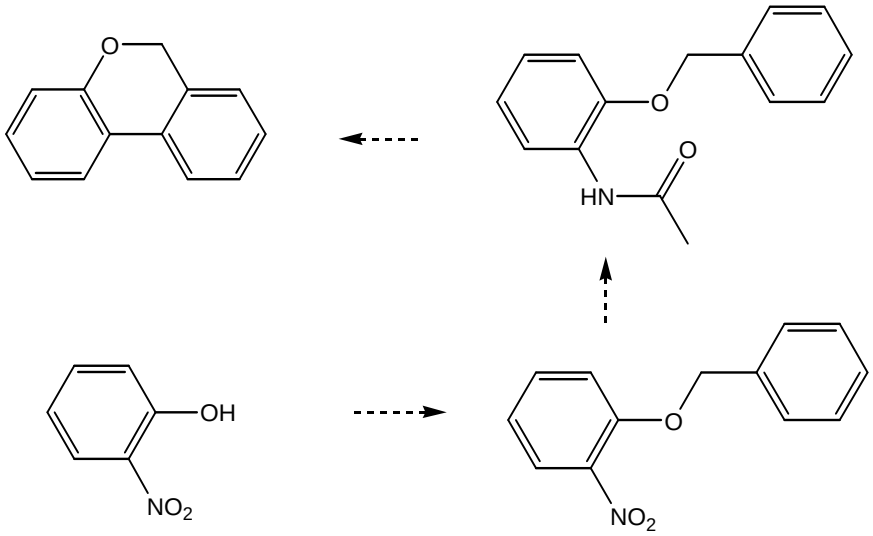
Scheme 2-7 Synthesis of Substituted 6H-Dibenzopyran Derivatives through Dilithiated Intermediates [61]



Given the importance of 6H-dibenzopyran derivatives, we proposed an approach to synthesize them (Scheme 2-8). Benzyl ortho-nitrophenyl ether can be prepared from o-nitroaniline followed by reduction using stannous chloride in ethanol. The benzyl o-aminophenyl ether formed was converted to the amide, it was hoped would undergo the transformation to the desired product (Scheme 2-8) in a similar fashion to the method

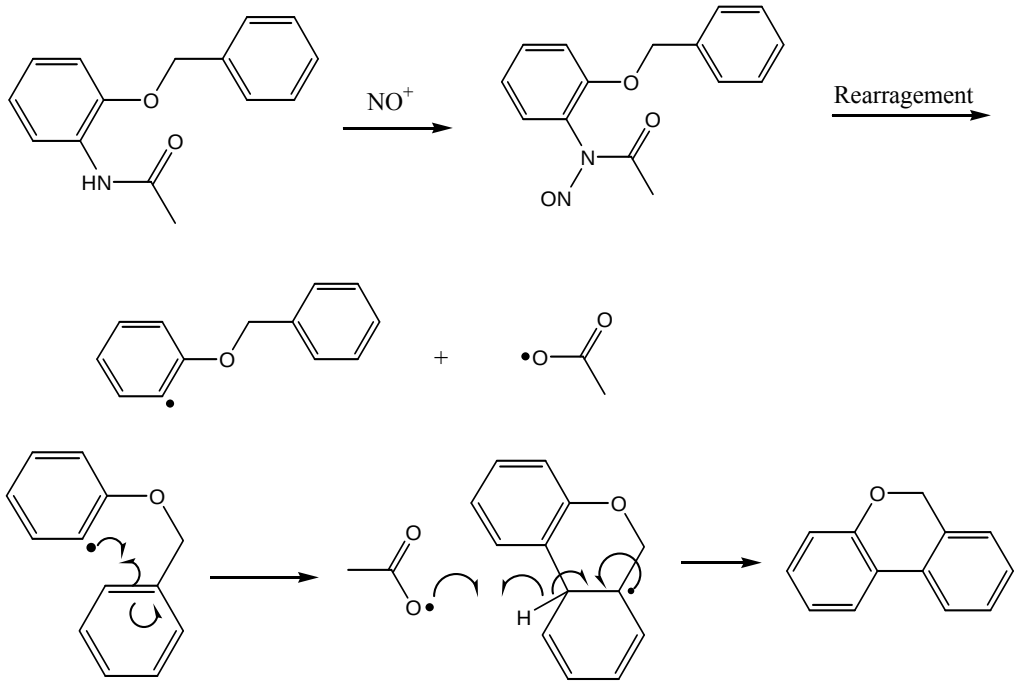
used in Chapter 2.2, with the exception of an intramolecular reaction rather than an intermolecular one.

Scheme 2-8 Retrosynthesis of 6H-Dibenzopyran

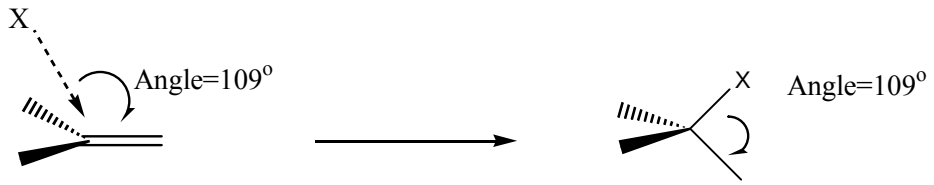


In the Bürgi-Dunitz trajectory [62b] the angle of attack of the phenyl radical (X) on the other aromatic ring should be close to 109° and should be coming from the top or the bottom of the double bond (Scheme 2-9). In the desired reaction, the radical, once formed, could attack the phenyl ring from a similar angle (Scheme 2-10), this indicates that the conformation is already preset well and the reaction should proceed smoothly.

Scheme 2-9 Mechanism of the reaction proposed

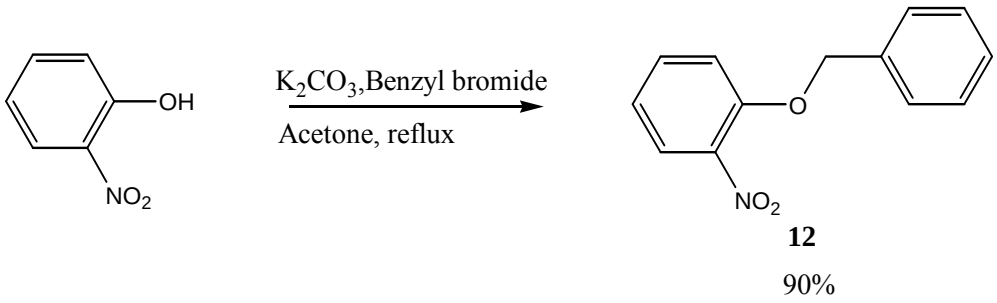


Scheme 2-10 Bürgi-Dunitz Trajectory [63]



The whole synthesis was fairly straightforward. In the first step, o-nitrophenol was deprotonated by potassium carbonate in acetone and allowed to react with allybromide to form the ether (Scheme 2-11). Without purification, the nitro group of the ether was reduced to the amine using stannous chloride in absolute ethanol at 70 °C (Scheme 2-12).

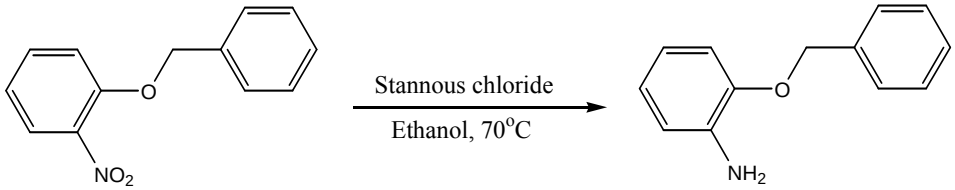
Scheme 2-11 Synthesis of Benzyl o-Nitrophenyl Ether



12

90%

Scheme 2-12 Reduction of Benzyl o-Aminophenyl Ether

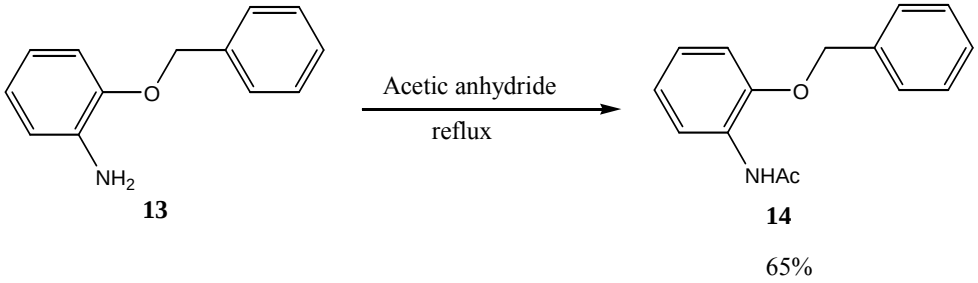


12 **13**

74%

The amine formed (**13**) was converted into aromatic amide using an excess of anhydride under refluxing conditions (Scheme 2-13) and the amide was treated with standard procedure in expectation of the desired product. Unfortunately, as indicated by the mass spectrum, the reaction did not give the 6H-dibenzypyran as the major product, but the ester of benzyl (orthahydroxy)benzyl ether (Scheme 2-14).

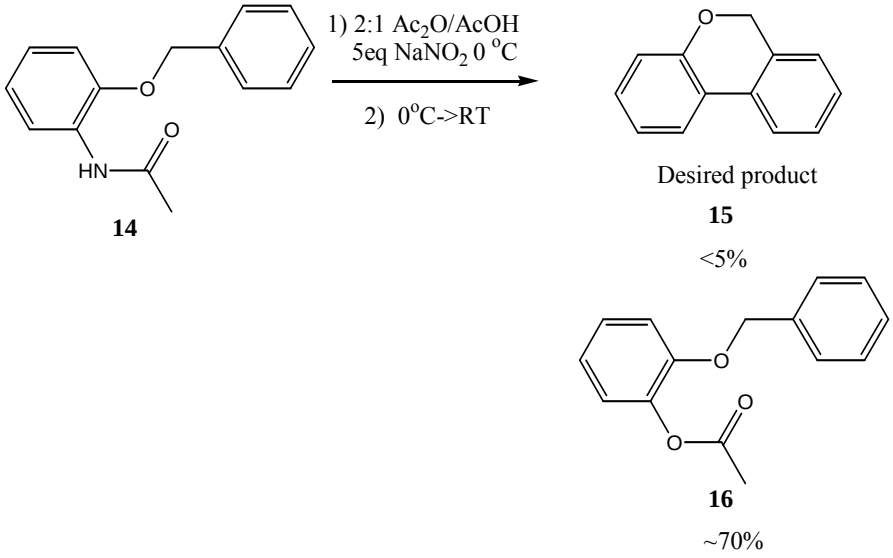
Scheme 2-13 Formation of the Amide **14**



13 **14**

65%

Scheme 2-14 Attempted Synthesis of **15** Using Amide **14**



14

Desired product

15

<5%

16

~70%

Although the fact that the reaction clearly showed the formation of the desired product, but only as the minor product, was not what we hoped, it was not unpredictable due to the short life of acetoxy radical generated, as well as possibly the fact that the combination of two radicals is much faster than the addition of phenyl radical to the other

benzene ring.

2.5 Summary and future work.

Several attempts have been carried out to explore the potential utility of the methodology by which phenyl radicals are generated under mild conditions. Although some attempts were unsuccessful, the results clearly elucidated certain notable issues regarding the methodology: first, it seems that changing the amount of sodium nitrite is needed to be able to reproduce, and sometimes even improve, the results on certain substrates. This can be seen from the fact that, when 2 equivalents of sodium nitrite are used (as per Roy [56b]) yields are generally 50%~70%, while when five equivalents are used yields will go up to 70%~80%. However, the drawback for using more sodium nitrite is the possible nitration/nitrosation of the substrates which are more active, such as p-methoxyacetanilide. Second, the coupling to form biphenyl could also be carried out using trifluorotoluene as solvent with moderate to good yields, although no specific o,m,p-selectivity is identified. Finally, each individual system must be approached independently rather than generally. This is clearly shown by the unexpected failure of the attempted syntheses of 2,4-diethylbiphenyl and 1,2,3,4,5-pentafluorobiphenyl, as well as the lower yield of p-nitrobiphenyl when more sodium nitrite is used. It should also be noted that the coupling of acetoxy radical and phenyl radical is much faster than the phenyl radical to a benzene ring, which is revealed by the results in Chapter 2. 3.

Currently, a potential solution to some of the problems presented in Chapter 2.4 would be trying to stabilize the acetoxy radical possibly by substitution, which would allow the phenyl radical to undergo intramolecular reaction to form the desired 6H-dibenzopyran. This might be achieved by using electron withdrawing groups such as trifluoroacetyl amides, although such modifications would not be useful for the reactions using oxamides in Chapter 2.3.

2.6 References to Chapter 2

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63. a) http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng

b)*Dictionary of Organic Compounds;* sixth edition; Chapman & Hall: London, UK, **1996.**

Experimental for Chapter 2

All materials/reagents/solvents were obtained from commercial resources and used without purification unless otherwise noted. Unless otherwise noted, all acetanilides were prepared by reacting freshly distilled anilines with acetic anhydride by heating to reflux for 30 minutes and recrystallizing the products from ethanol. ^{1}H-NMR samples were prepared by adding $CDCl_3$ to the product(s) and NMR spectra were obtained using a Varian 300MHz spectrometer, with residual solvent peaks as the reference unless otherwise noted. GC-MS samples were made by adding 0.5ml of chloroform to the product(s) and mass spectra were obtained using an electronic ionization technique, splitless injection, thermostat 70 electronic volts on a Trace GC 2000 and Thermoquest GCQ/Polaris mass spectrometer (ThermoQuest Finnigan, San Jose, CA) unless otherwise noted. The percentages of individual products in a mixture were determined by semi-quantitative GC/MS. Unless otherwise noted, NMR/MS spectra were correlated to the referenced data at the website of SDBS; [63a] Melting temperatures were determined using an uncorrected Mel-temp melting point apparatus and correlated to those in the dictionary of organic compounds [63b] unless otherwise mentioned.

Biphenyl (1)

Acetanilide (0.271 g, 2.00 mmol) was added to a 100 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed

to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored by a thermometer inside the flask. Sodium nitrite (0.694 g, 10.1 mmol) was slowly added to flask with mild stirring and the top of the flask was sealed by a piece of parafilm. The flask was kept in ice/water for an additional two hours, during which period red brown gas was observed, as was the color change from light blue to moderate green. At the end of two hours 50 mL of benzene was slowly added. The flask was removed from the ice/water and allowed to slowly warm up to room temperature with gentle stirring overnight. The color changed to yellow-brown. Benzene was removed under reduced pressure when a white solid was observed on the side of the flask, which was identified as biphenyl, mp: 58-60 ºC (lit. mp 68-70 ºC, see text in Chapter 2.2). ^{1}H-NMR: 7.65 (4H, d, Ha-see spectra in the appendix for more details), 7.45 (4H, m, Hb), 7.33 (2H, d, Hc). NMR spectrum located in A.1.

4-Nitrobiphenyl (2)

4-Nitroacetanilide (0.365 g, 2.00 mmol) was added to a 100 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored by a thermometer inside the flask. Sodium nitrite (0.690 g, 10.0 mmol) was slowly added to the flask with mild stirring and the top of the flask was sealed using a piece of parafilm. Red-brown gas was observed to form, as was a color change in the solution from light blue to moderate green. The flask

was kept in ice/water for two hours, after which period 70 mL of benzene was slowly added. The flask was removed from ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The color changed to yellow-brown. The acid was neutralized using 5% sodium bicarbonate solution, the organic phase was separated, washed with deionized water, dried with anhydrous sodium sulfate and benzene was removed under reduced pressure. The crude product achieved was recystallized from ethanol, and the crystals were isolated by filtration. The procedure gave 85 mg, 43% isolated yield of **2**, mp 107-112 ^{o} C (lit. mp 113 ºC); ^{1}H-NMR: 8.31 (2H, d, Ha), 7.80 (2H, d, Hb), 7.69-7.45 (5H, m, Hc). NMR spectrum located in A.2.

4-Cyanobiphenyl (3)

4-Cyanoacetanilide (0.272 g, 1.73 mmol) was added to a 100 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored using a thermometer inside the flask. Sodium nitrite (0.591 g, 8.56 mmol) was slowly added to the flask with mild stirring and the top of the flask was sealed using a rubber septum. Red-brown gas was observed, as was a color change from light blue to moderate green. The flask was kept in ice/water for two hours, after which 70 mL of benzene was slowly added. The flask was removed from the ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The color changed to yellow-brown. The acid was neutralized using

5% sodium bicarbonate solution, the organic phase was separated, washed with deionized water, dried with anhydrous sodium sulfate and benzene was removed under reduced pressure. The crude product achieved was recystallized from ethanol, and the crystals were isolated by filtration. The procedure gave 125 mg, 70% isolated yield of **3**, mp 81-83 ºC (lit. mp 84-85 ºC); ^{1}H-NMR: 7.80 (2H, d, Ha), 7.61 (2H, d, Hb), 7.50-7.40 (5H, m, Hc). NMR spectrum located in A.3.

4-Methoxybiphenyl (4)

4-methoxyacetanilide (0.497 g, 3.00 mmol) was added to a 250 mL Erlenmeyer flask together with 20 mL of acetic anhydride and 10 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored using a thermometer inside the flask. Sodium nitrite (0.995 g, 14.4 mmol) was slowly added to the flask with mild stirring and the top of the flask was sealed using a rubber septum. Red-brown gas was observed, as was a color change in the solution from light blue to moderate green. The flask was kept in ice/water for two hours, after which 70 mL of benzene was slowly added. The flask was removed from the ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The color was observed to change to yellow-brown. The acid was neutralized using 5% sodium bicarbonate solution, the organic phase was separated, washed with deionized water, dried with anhydrous sodium sulfate and benzene was removed under reduced pressure. The crude product was

recystallized from ethanol, and the crystals were isolated by filtration. The procedure gave 114 mg, 20% isolated yield of **4**, mp 88-90 ^{o}C (lit. mp 91-92 ºC).

2-, 3-, and 4-Trifluoromethyl-4'-cyanobiphenyls (5)

4-Cyanoacetanilide (1.0 mmol) was added to a 100 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored using a thermometer inside the flask. Sodium nitrite (0.391 g, 5.60 mmol) was slowly added to the flask under mild stirring and the top of the flask was sealed using a rubber septum. Red-brown gas was observed, as was a color change from light blue to moderate green. The flask was kept in ice/water for two hours, after which 70 mL of α,α,α-trifluorotoluene was slowly added. The flask was removed from ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The color was observed to change to yellow-brown. The acid was neutralized using 5% sodium bicarbonate solution, the organic phase was separated, washed with deionized water, dried with anhydrous sodium sulfate and α,α,α-trifluorotoluene was removed under reduced pressure. The crude products formed were analyzed by GC-MS without isolation. The procedure gave 201.0 mg, 80% crude yield of **5** (as a mixture of three isomers, while assignments of isomers were not carried out). GC: Retention time (min): 13.54, 14.01, 14.13; MS m/z(%) of the peak with retention time 13:54 min: 248(11), 247(100), 226(18), 208(4), 201(3), 126(3). Products

are identified by m/z=247 peak. GC-MS spectra located in A.4.

2-, 3-, and 4-Trifluoromethyl-4'-nitrobiphenyls (6)

4-Nitroacetanilide (0. 181 g, 1.00 mmol) was added to a 100 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0ºC for 30 minutes, monitored using a thermometer inside the flask. Sodium nitrite (0.381 g, 5.40 mmol) was slowly added to the flask under mild stirring and the top of the flask was sealed using a rubber septum. Red-brown gas was observed, as was a color change from light blue to moderate green. The flask was kept in ice/water for two hours, after which 70 mL of α,α,α-trifluorotoluene was slowly added. The flask was removed from the ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The color was observed to change to yellow brown. The acid was neutralized using 5% sodium bicarbonate solution, the organic phase was separated, washed with deionized water, dried with anhydrous sodium sulfate and α,α,α-trifluorotoluene was removed under reduced pressure. The crude products achieved were analyzed without isolation by GC-MS. The procedure gave 191.0 mg, 71% crude yield of **6** (as a mixture of three isomers). GC: Retention time (min): 14.23, 14.66, 14.81; MS m/z(%)of the peak with retention time 14.23 min: 268(14), 267(100), 237(55), 209(32), 201(26), 152(23). Products are identified by m/z=267 peak. GC-MS spectra located in A.5 and A.6.

2-, 3-, and 4-Trifluoromethylbiphenyls (7)

Acetanilide (0. 157 g, 1.00 mmol) was added to a 100 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored using a thermometer inside the flask. Sodium nitrite (0.390 g, 5.60 mmol) was slowly added to the flask under mild stirring and the top of the flask was sealed using rubber septum. Red-brown gas was observed, as was a color change from light blue to moderate green. The flask was kept in ice/water for two hours, after which 70 mL of α,α,α-trifluorotoluene was slowly added. The flask was removed from the ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The color was observed to change to yellow-brown. The acid was neutralized using 5% sodium bicarbonate solution, the organic phase was separated, washed with deionized water, dried with anhydrous sodium sulfate and α,α,α-trifluorotoluene was removed under reduced pressure. The crude products achieved were analyzed by GC-MS without isolation. The procedure gave less than 10% crude yield of **7** (as a mixture of three isomers) by using semi-quantitative analysis. GC: Retention time (min): 11.42, 11.84, 11.96. MS m/z(%) of the peak with retention time 11.42 min: 223(15), 222(100), 201(19), 153(55), 152(67), 151(25). Products are identified by m/z=222 peak. GC-MS spectra located in A.7 and A.8.

N, N'-diphenyloxamide (8)

Sodium metal (0.103 g, 4.50 mmol) was added to a 100 mL Erlenmeyer flask holding 10 mL pure ethanol. After the reaction was completed, ethyl oxalate (2.20 g, 15.0 mmol) and aniline (2.79 g, 30.0 mmol) were added to the flask and the solution was heated to reflux solvent for one hour. After cooling, the crude solid was filtered off, washed with water and crystallized from ethanol. This procedure gave 1.56 g, 44% isolated yield of **8**, mp 255-260 ^{o}C (lit. mp 255 ºC).

N, N'-di(p-methoxyphenyl)oxamide (9)

Sodium metal (0.106 g, 4.50 mmol) was added to a 100 mL Erlenmeyer flask holding 10 mL pure ethanol. After bubble formation had stopped, ethyl oxalate (2.20 g, 15.0 mmol) and p-anisidine (3.69 g, 30.0 mmol) were added to the flask and the solution was heated to reflux solvent for one hour. After cooling, the crude solid was filtered off, washed with water and crystallized from ethanol. This procedure gave 1.44 g, 32% isolated yield of **9**, mp 230-233 ^{o}C (lit. mp 235 ºC).

N, N'-di(m-methylphenyl)oxamide (10)

Sodium metal (0.10 g, 4.5 mmol) was added to a 100 mL Erlenmeyer flask containing 10 mL pure ethanol. After the reaction was completed, ethyl oxalate (2.20 g, 15.0 mmol) and aniline (3.21 g, 30.0 mmol) were added to the flask and the solution was heated to reflux solvent for one hour. After cooling, the crude solid was filtered off and washed with

water. This procedure gave 1.91 g, 46% crude yield of **10**, mp 132-135 °C (lit. mp 135 ºC).

m-Cresol (11)

N,N'-bis(m-methyl)phenyldiamide (0.538 g, 2.00 mmol) was added to a 100 mL Erlenmeyer flask together with 32 mL of acetic anhydride and 16 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored using a thermometer inside the flask. Sodium nitrite (2.75 g, 40.0 mmol) was slowly added to flask under mild stirring and the top of the flask was sealed using a piece of parafilm. The flask was kept in ice/water for four hours, during which period red-brown gas was observed, as was a color change from light blue to moderate green. At the end of the period the flask was removed from the ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. A water/methylene chloride mixture (1:1, 100 mL) was added, the organic phase was separated, and the aqueous phase was extracted two more times using 50 mL of methylene chloride each time. All the organic phases were combined, dried (anhydrous sodium sulfate), and solvent was removed under reduced pressure. The crude product **11** was identified by GC-MS (see text in Chapter 2.3). MS: m/z(%) 109 (10), 108(100), 107(90), 79(53), 77(58), 51(19). MS spectra located in A.9.

Benzyl o-nitrophenyl ether (12)

O-nitrophenol (6.26 g, 45.0 mmol) was added to a 250 mL flask and dissolved in 80 mL acetone. Anhydrous potassium carbonate (6.21 g, 45.0 mmol) was added to the flask and the color was observed to change to orange-red. Benzyl bromide (4.2 mL, 50 mmol) was added and the solution was heated to reflux solvent for 24 hours. When the reaction was done, the yellow solid which formed at the bottom of the flask over time was removed by filtration. The acetone was removed under reduced pressure to give a yellow liquid, which was used without purification. This procedure gave 9.27 g, 90% crude yield of **12**. ^{1}H-NMR: 7.80 (1H, d, Ha), 7.61-7.30 (6H, m, Hb), 7.15 (1H, d, Hc), 7.05 (1H, t, Hd), 5.30 (2H, s, He). Product is identified by the chemical shifts of hydrogens in NMR spectrum. NMR spectrum located in A.10.

Benzyl o-aminophenyl ether (13)

An oil bath was equilibrated at 70 ^{o}C. To a 100 mL flask was added **12** (2.29 g, 10.0 mmol) and stannous chloride (11.4 g, 50.0 mmol) in 20 mL pure ethanol. The flask was put into the oil bath and allowed to equilibrate for 40 minutes under argon. The yellow mixture was poured onto ice in a 250 mL beaker. The solution was neutralized using 5% sodium bicarbonate solution until pH was between 7 and 8. The solution was extracted three times using 100 mL ethyl acetate and 50 mL brine solution each time. The organic phases were combined and activated carbon and anhydrous sodium sulfate were added with gentle heating and stirring. Solids were removed by filtration through a funnel

covered in Celite to give a purple solution, and ethyl acetate was removed under reduced pressure to yield a red liquid. This procedure gave 1.47 g, 74% isolated yield of **13**. ^{1}H-NMR: 7.60-7.20 (5H, m, Ha), 6.90 (4H, m, Hb), 5.15 (2H, s, Hc). Product is identified by the chemical shifts of hydrogens in NMR spectrum. NMR spectrum located in A.11.

o-Benzyloxyacetanilide (14)

To a 100 mL flask was added benzyl(o-amino)phenyl ether (**13**) (1.01g, 5.00 mmol) and 25 mL acetic anhydride. The flask was heated to reflux solvent for three hours before the solution was poured on ice. The aqueous phase was extracted three times using 30 mL ether each time, the organic phases were combined, washed with water, dried (anhydrous sodium sulfate) and ether was removed under reduced pressure to produce a dark liquid. This procedure gave 0.84 g, 65% isolated yield of **14**. ^{1}H-NMR: 7.40 (5H, m, Ha), 7.05 (4H, m, Hb), 5.05 (2H, s, Hc), 2.31 (3H, s, Hd). Product is identified by the chemical shifts of hydrogens in NMR spectrum. NMR spectrum located in A.12.

6H-Dibenzopyran (15) and o-Benzyloxyphenyl acetate (16)

o-Benzyloxyacetanilide **(14)** (0.261 g, 1.00 mmol) was added to a 250 mL Erlenmeyer flask together with 10 mL of acetic anhydride and 5 mL of glacial acetic acid. The acetanilide was allowed to dissolve before the flask was placed into a mixture of ice and water. The solution was stirred at 0 ºC for 30 minutes, monitored using a thermometer

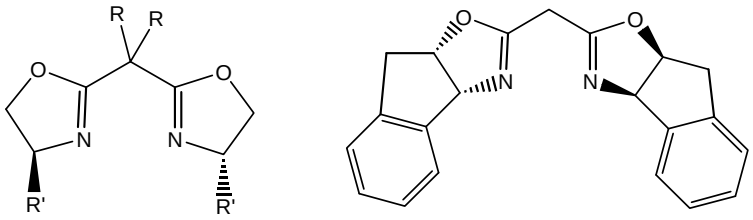
inside the flask. An excess of sodium nitrite was slowly added to the flask with mild stirring and the top of the flask was sealed using a piece of parafilm. The flask was kept in ice/water for two hours, during which period red-brown gas was observed, as was a color change from light blue to moderate green. The flask was removed from the ice/water and allowed to slowly warm to room temperature with gentle stirring overnight. The crude products in the solution were identified by GC-MS before the workup process. This procedure gave 0.181 g, 75% crude yield (~70% **16** and less than 5% of **15**, based on semi-quantitative analysis). GC Retention time (min): 14.05 (**15**) and 16.58 (**16**). MS m/z(%): **15**: 182(55), 181(100), 153(26), 152(77), 126(15), 91(25); **16**: 241(10), 223(20), 199(21), 108(35), 91(100). Products are identified by m/z=181 peak (**15**) and m/z=241 peak (**16**). GC and MS spectra located in A.13, A.14 and A.15.

Chapter III 2-Oxazolines in the Literature and Their Unusual Reactivity with Aldehydes

3.1 2-Oxazolines in Modern Chemistry

During the last few decades, 2-alkyl oxazolines have attracted increasing interest as good examples of cyclic imino ethers (CIEs). CIEs have a broad range of applications in organic synthesis as well as polymer chemistry [64-68] because they can, "provide hydrolysis, oxidation, and cycloaddition reactions and addition reactions with organic acids, phenols, thiols and anilines",[68] during which process ring-opening or cationic polymerization of 2-oxazolines is commonly observed. Oxazolines have also attracted considerable interest as ligands in the fields of enantioselective catalysis [69-71] in recent years (Figure 3-1).

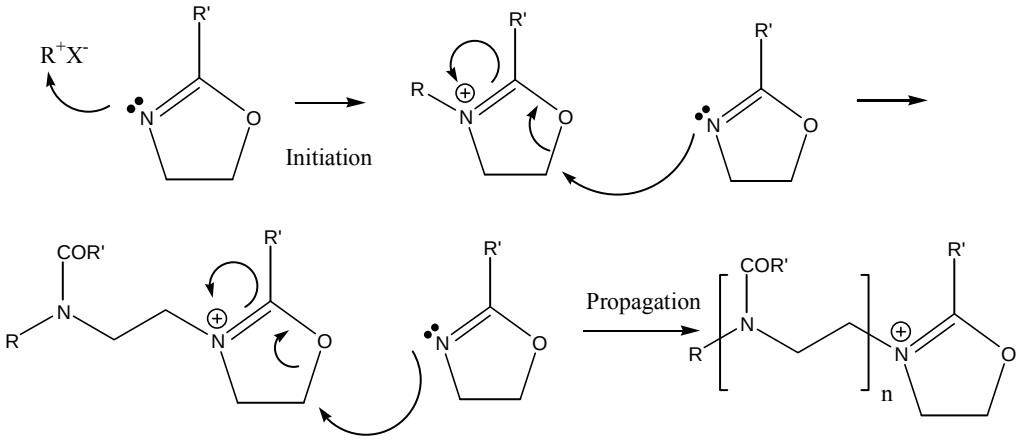
Figure 3-1 Some Oxazoline Ligands in Enantioselective Catalysis [69-71]



3.2 General Reactivity of 2-Oxazolines and Unusual Reaction with Ketones/aldehydes

Ring opening polymerization is a common type of reaction for 2-oxazolines. Typically, a Lewis Acid initiator is used for the process. The nitrogen atom on a 2-alkyl oxazoline will attack the initiator, make the carbon next to oxygen more susceptible to the nucleophilic attack from the nitrogen from another 2-oxazoline molecule (Scheme 3-1). A recent example is from Hoogenboom and his colleague's work towards the synthesis of amphiphilic copolymers. [72]

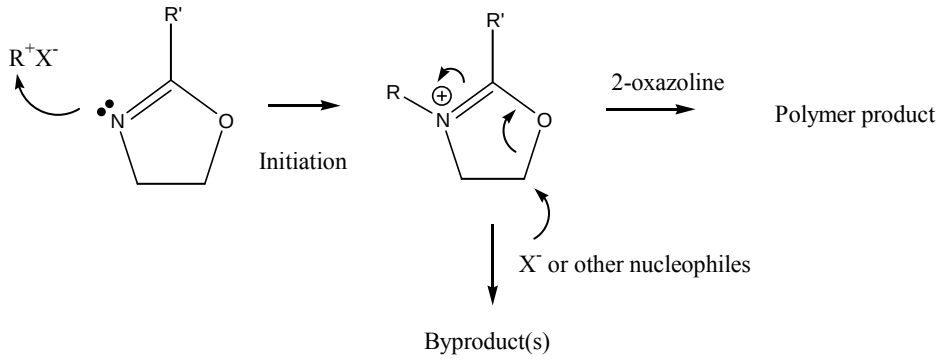
Scheme 3-1 Ring Opening Polymerization of 2-Oxazolines [72]



It has been noted that byproducts did occur during the process shown above. The byproducts are believed to be formed from the ring opening of 2-oxazolines as well. However, the nucleophilic attack was not from another 2-oxazoline molecule but rather

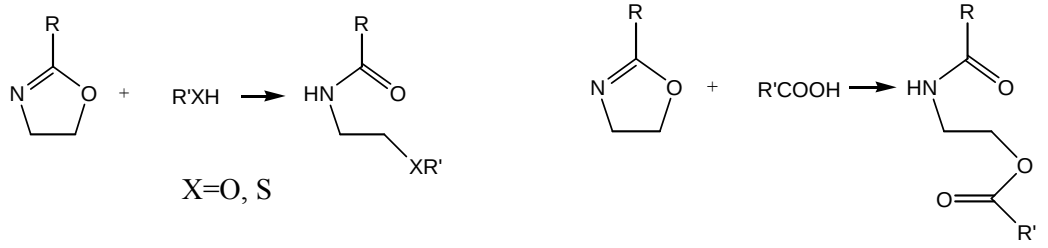
from the anion in the initiator or other nucleophiles in the system (Scheme 3-2)

Scheme 3-2 Formation of Byproduct(s) [72]



The reactions in which acids/phenols/thiols act as nucleophiles have already been reviewed in the literature.[73-75] In this process, the protonation on the nitrogen atom is followed by nucleophilic attack of the anion at the 5-position (Scheme 3-3).

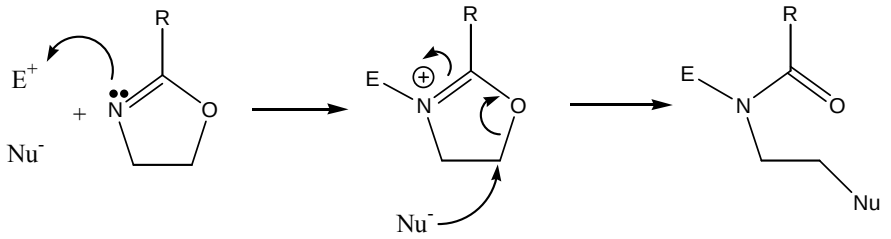
Scheme 3-3 Oxazolines Reacting with Acids/phenols/thiols [73-75]



It can be therefore concluded that in the general non-polymerization ring-opening pathway the compounds which force the ring to open can be considered as

electrophile/nucleophile pairs. In the first step of the reaction, the electrophile will be attacked by the nitrogen in 2-oxazoline, followed by the attack on the 5-position by the nucleophile. The mechanism is shown in Scheme 3-4.

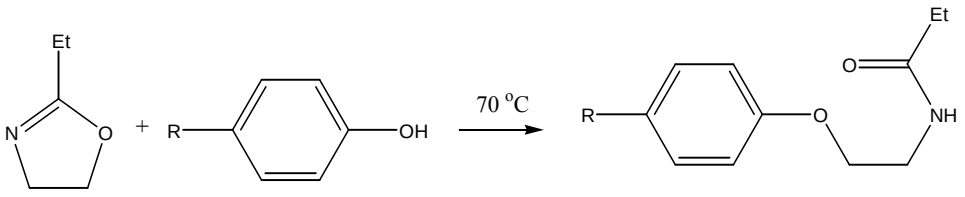
Scheme 3-4 General Non-Polymerization Ring-Opening Pathway [73-75]



In the past, we observed the formation of relatively large amounts of bromide byproducts when benzyl bromide was used as one of the catalysts used for the ring polymerization reaction of 2-alkyl oxazolines, as well as the slow reaction between water and 2-alkyl oxazolines. In order to carry out systematic studies, we wanted to have a better understanding of the reactions between phenols and 2-alkyl oxazolines, so a series of reactions were set up to study the reaction rate difference among various phenols. The reactions were carried out under a relatively high temperature (~70 ^{o}C) using the same amount of *p*-methylphenol, phenol, and *p*-nitrophenol, respectively. The relative rates of the reactions were determined by measuring the amount of the newly-formed ring opening product using NMR spectroscopy. The results indicated that the nitrophenol had the highest rate. Given the results, we concluded that the rate was determined by the pKa of the reactant (Scheme 3-5), because the nitrophenol has the lowest pKa value, and the

methylphenol the highest.

Scheme 3-5 Reactions of 2-Ethyl-2-oxazoline with Various Phenols for the Measurement of Relative Rates

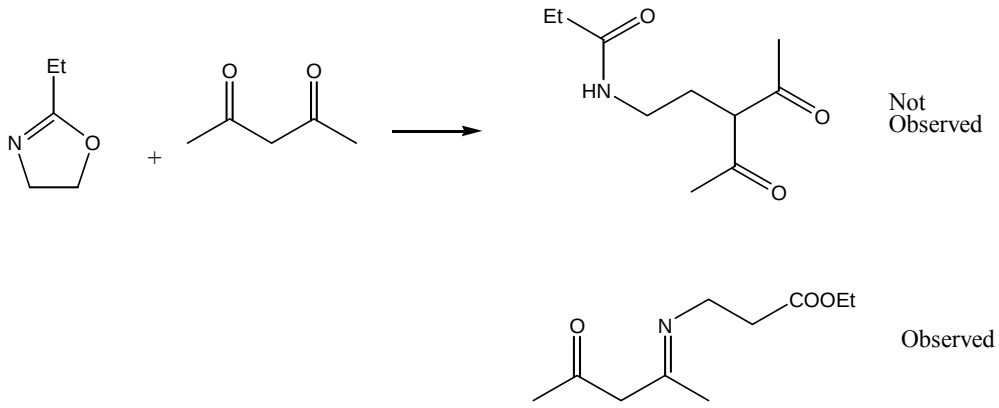


R=Nitro, H or Methyl

Rate: Nitro>H>Methyl

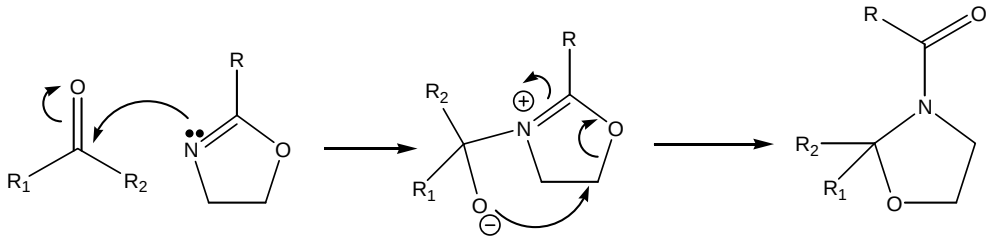
Since the reaction of 2-alkyl oxazolines with phenols is reasonably well understood, we wanted to explore the scope of the reaction. Therefore, our next step was to test compounds with pKa values similar to those of the phenols (pKa 8~12), and the first substrate we used was 2,4-pentadione whose pKa value for the central hydrogens is about 10. Given the experience with phenols, we had expected that it would go through a similar process (Scheme 3-6); however, the reaction proceeded very fast and formed an imine instead of the expected product. [76] The details of this work will be covered in Chapter 4.

Scheme 3-6 Reaction of 2-Ethyl-2-Oxazoline with 2,4-Pentadione [76]



This outcome led us to look differently at the reaction of oxazolines with different electrophiles. We thought it might be proceeding via another pathway in the presence of a carbonyl group (Scheme 3-7), which would start with the nitrogen atom on the oxazoline ring acting as the necleophile, followed by the back attack of the carbonyl oxygen to form a new five-member ring. However, models show that backside attack would require a highly strained transition state and would not account for the product when the diketone was used.

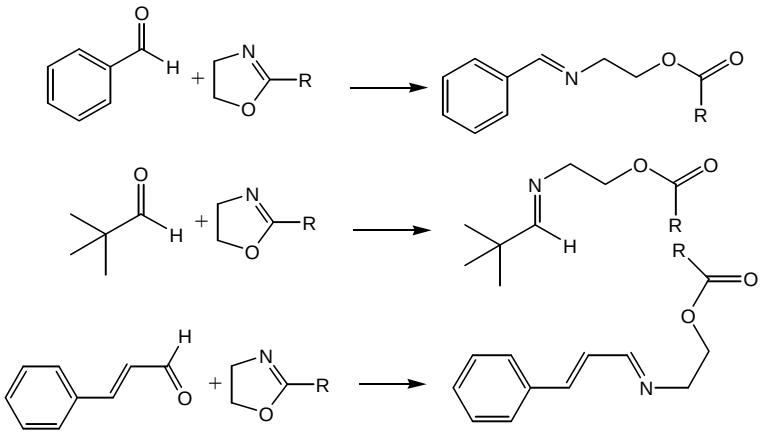
Scheme 3-7 Possible pathway with Aldehydes/Ketones



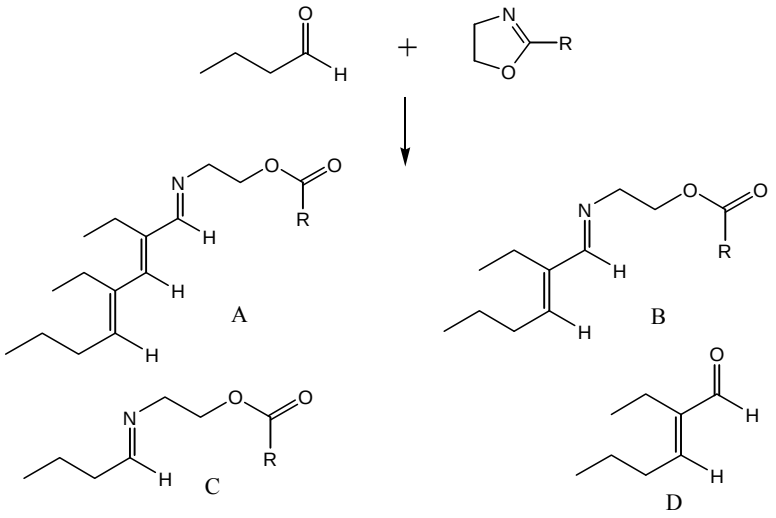
In order to explain this reaction further we reacted a variety of ketones and

aldehydes, with 2-oxazolines. According to the results, which will be discussed in more detail Chapter 4, when aldehydes without α-hydrogens were used, the major products were imines; and for aldehydes with α-hydrogens, the reaction became much more complicated and resulted in polycondensation products (Scheme 3-8). With regard to ketones, normal ketones did react similarly but, unlike the diketone, they did so at a much slower rate. What should also be noticed is that more "bulky" ketones, such as acetopheone, revealed no sign of reactivity, even after a long period of time. We were certainly very interested in these results but surprised to find out that there have been very few precedents in literature [77, 78] concering this kind of reaction and these only point out the imine as the final product of the ring opening reaction.

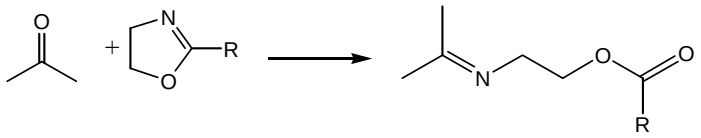
Scheme 3-8 Reactions of 1:1 Ratio of 2-Alkyl-2-oxazolines with Various Aldehydes/ketones at Room Temperature



Aldehydes without alpha enolizable hydrogens



Butyraldehyde (with alpha enolizable hydrogens)

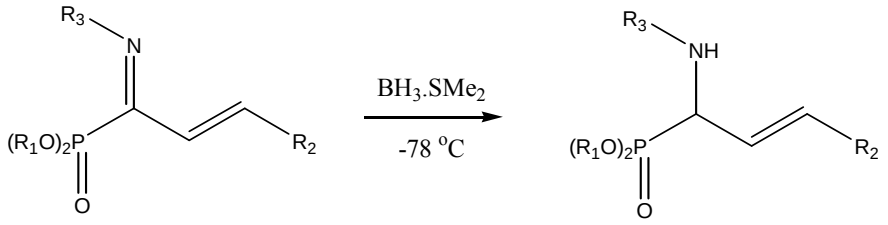


Acetone

3.3 Potential Use of Imine Products Generated

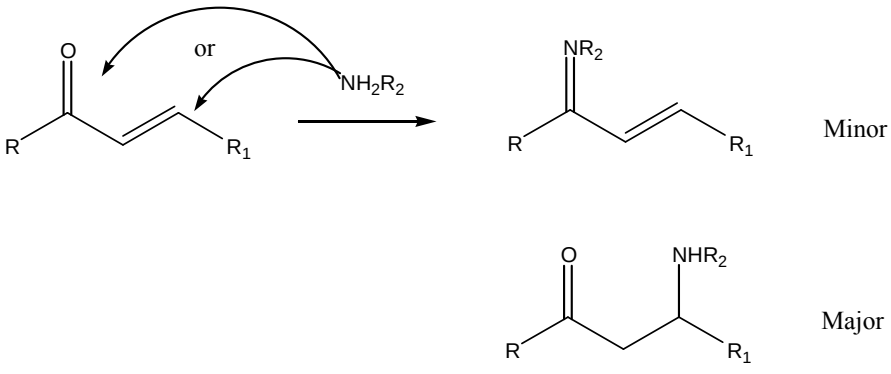
Imines are important intermediates in various transformations, and their roles in enantioselective reactions such as reductive alkylations and Mannich-type reactions have attracted much interest.[79-81] α,β-Unsaturated imines, in particular, are interesting precursors in organic synthesis. One recent example of such applications is Palacios's selective reduction of α,β-unsaturated imines to vinylogous and saturated α-aminophosphonates (Scheme 3-9). [82]

Scheme 3-9 Reduction of α,β-unsaturated imine [82]



Although imines are generally prepared by reacting amines with aldehydes and ketones, [83] α,β-unsaturated imines are not as easily prepared. The most obvious route to α,β-unsaturated imines would be condensation of α,β-unsaturated aldehydes or ketones with amines but conjugate addition dominates under such circumstances (Scheme 3-10). [84, 85]

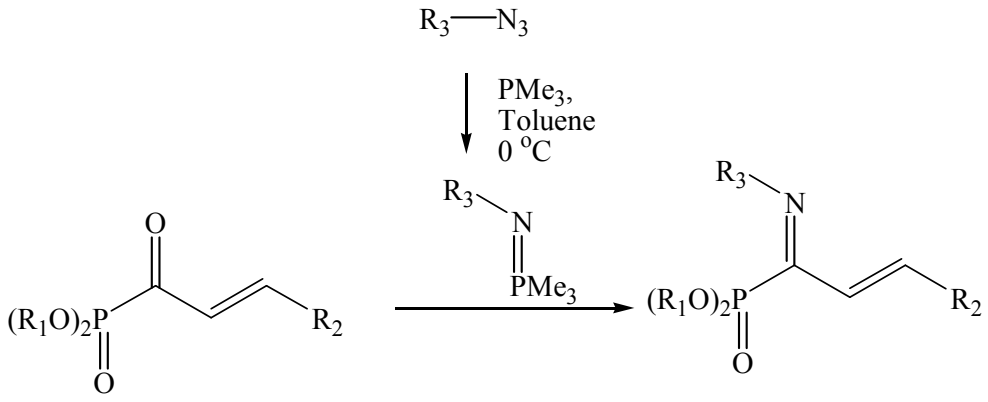
Scheme 3-10 Conjugate Addition to α,β-Unsaturated Aldehydes/Ketones [84, 85]



In Palacios's work mentioned above, an aza-Wittig reaction was used (Scheme 3-11),

[82] while there have also been some references using the aza-Michael type reactions. [86, 87] However, based on our findings (Scheme 3-8), the synthesis of α,β-unsaturated imines can be easily achieved by reacting 2-oxazolines with various aldehydes and ketones and mostly at room temperature, which makes it a potentially very useful method.

Scheme 3-11 Synthesis of α,β-Unsaturated Imines using Aza-Wittig Reactions [82]



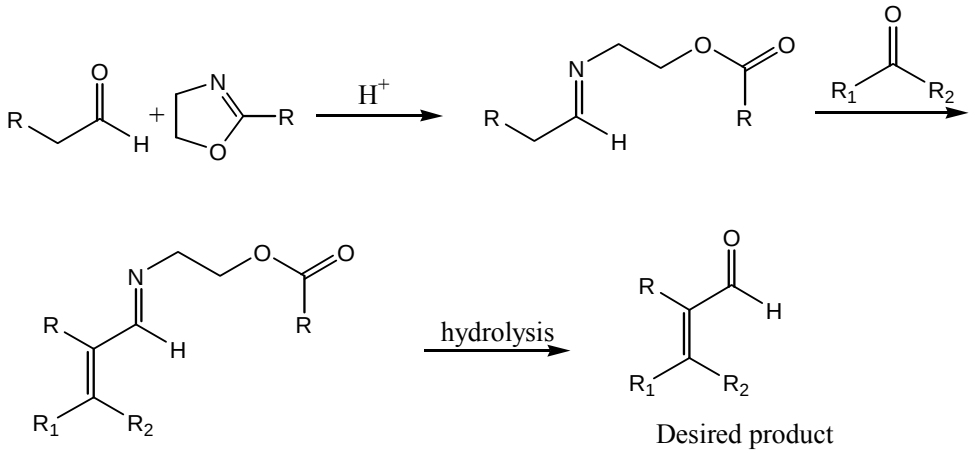
3.4 Goals of This Work

Although the reactions carried out on the alkyl group at the 2-position have been reviewed,[64] there have been few references to the ring-opening reaction with aldehydes and there hasn't been a mechanistic study on the process. All the results, both in the literature and from our work, have prompted us to first look deeper into the reaction to have a better understanding of this still unexplored reaction. To achieve this, first NMR kinetic experiments were carried out to derive reaction order and explore the possibility

of acid catalysis. Secondly, linear free energy relationships were probed using various substituted benzaldehydes; and finally, variable temperature experiments were carried out to obtain thermodynamic parameters for the reaction. The results of these studies are discussed in Chapter 4 of this thesis.

In addition to the mechanistic studies, we are also intrigued by the potential synthetic utility of such reactions. One possibility would be to use 2-oxazolines as metal-free catalysts for Crossed- Aldol reactions. On looking at Scheme 8, it can be proposed that the 2-alkyl oxazoline reacts at the beginning with only one equivalent of the aldehydes. If true, a crossed-Aldol reaction could be achieved by the addition of a second aldehyde (or ketone) after the initial reaction. (Scheme 3-12), resulting in an unusual metal-free reaction. We are also very interested in the possibility of applying such reactions towards the synthesis of long linear conjugate structures in natural products such as the polyene macrolides (antifungal) [88] and carotenoids (antioxidant). [89]

Scheme 3-12 A Possible Metal-Free Cross Aldol Reaction Using Different Aldehydes/Ketones and 2-Oxazolines



Desired product

Finally, it was desirable to further explore the synthetic utility of the α,β-unsaturated imines formed. Since Aza Diels-Alder reactions involving imines are important in the synthesis of natural products with nitrogen-containing heterocyclic rings such as tetrahydroquinolines, [90] it would be worthwhile to investigate the possibility of using the imines as reactants of such Aza Diels-Alder reactions. The reduction of the imine, which will lead to useful secondary amines, will also be examined. The results of these attempts will be covered in Chapter 4 of this thesis.

3.5 References to Chapter 3

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Chapter IV Results and Discussion on Ring Opening Reactions of 2-Alkyl Oxazolines

4.1 Reaction Results with Aldehydes and Ketones

A qualitative screening protocol was used to detect and identify the products of the reactions between 2-ethyl-2-oxazoline and various aldehydes/ketones. The basic procedure was to mix the oxazoline directly with the corresponding aldehyde or ketone, and let the reaction proceed slowly until an obvious color change in the mixture was observed (the products of these reactions tend to be colorful, possibly due to the conjugated structures generated). Most of the reactions observed formed a single major product by NMR spectroscopy, usually together with varying amounts of unreacted staring materials. In this chapter, all the reactions were carried out at room temperature unless otherwise noted.

The first aldehyde used to react with 2-oxazoline was benzaldehyde. When mixed with 2-ethyl-2-oxazoline, the reaction proceeded slowly over six days to produce the final product **(19)** which is identified without isolation by NMR spectroscopy taking the chemical shift of the imine hydrogen peak at 8.31 ppm as characteristic (Scheme 4-1 and Figure 4-1).

Scheme 4-1 Reaction of 1:1 Benzaldehyde and 2-Ethyl-2-oxazoline

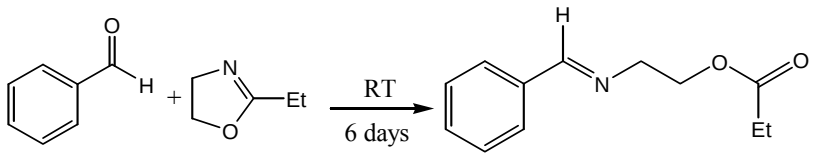

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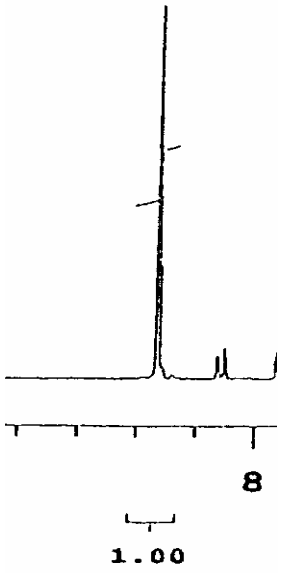
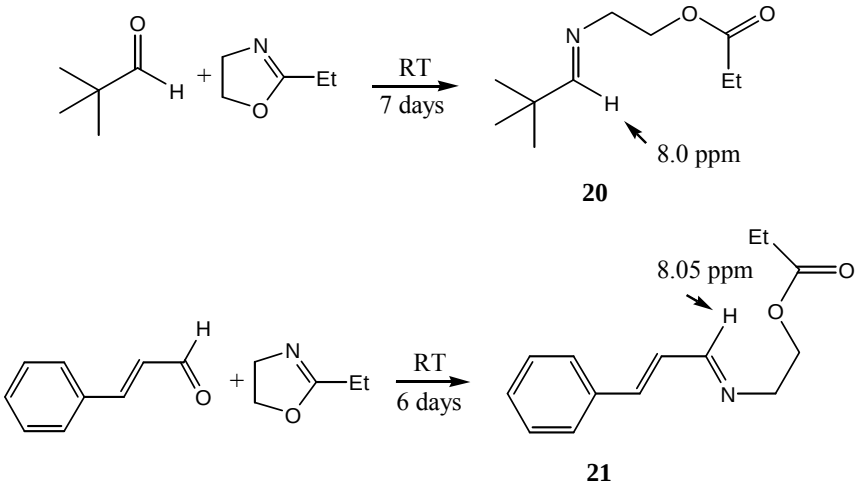
Figure 4-1 ^{1}H-NMR Spectrum of the Imine Peak in the Product from the Reaction of 1:1 Benzaldehyde with 2-Ethyl-2-Oxazoline at Room Temperature for Six Days



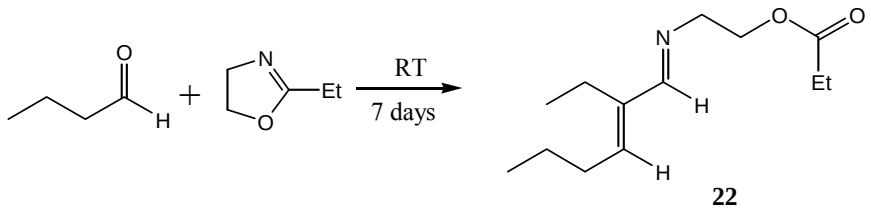
Pivaldehyde and cinnamaldehyde were then reacted with 2-ethyl-2-oxazline. Both reactions proceeded smoothly to imine by monitoring evolution of the imine hydrogen peak in the NMR spectra (Scheme 4-2).

Scheme 4-2 Reactions Using 1:1 Pivaldehyde/Cinnamaldehyde and 2-Ethyl-2-Oxazoline



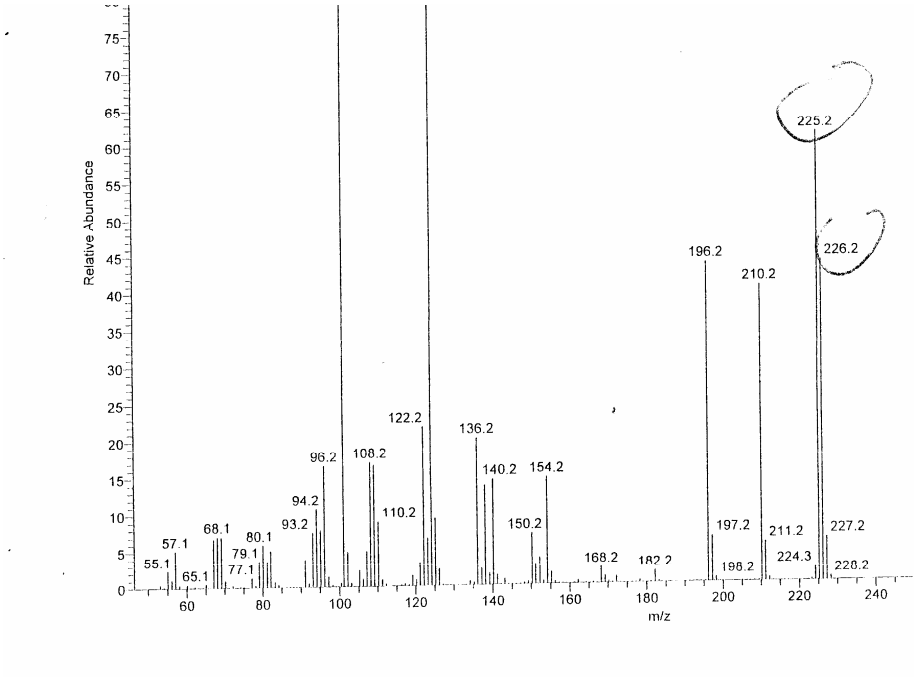
Given the success above, we expected that when butyraldehyde was used as the reactant the reaction would proceed smoothly as well to form a single imine. To our surprise, the NMR technique failed to identify the expected final product and it turned out to be a mixture of several compounds. Only through GC-MS was it shown that a minor product was formed from one equivalent of butyraldehyde and one equivalent of oxazoline, while one of the major products was formed from two equivalents of butyraldehyde and one of 2-oxazoline (identified by m/z=226 peak, see Figure 4-2), but with the loss of H_2O. More details concerning this reaction will be addressed later in this chapter.

Scheme 4-3 Reaction using 1:1 Butyraldehyde and 2-Ethyl-2-Oxazoline



22

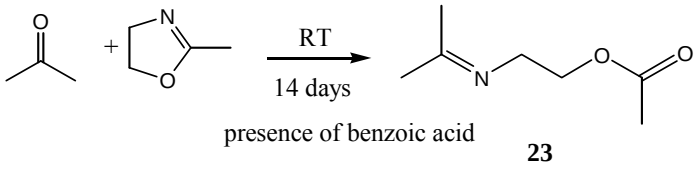
Figure 4-2 Mass Spectrum of Product **22**



One the other hand, analogous reactions of 2-ethyl-2-oxazolines with ketones proceed much more slowly in comparison to the aldehydes. Although several ketones have been tested, only acetone has shown significant reactivity (Scheme 4-4), but at a much slower rate compared to the aldehydes as the reaction required two weeks to accomplish (verified by m/z=144 peak, Figure 4-3). Acetophenone and chalcone have not

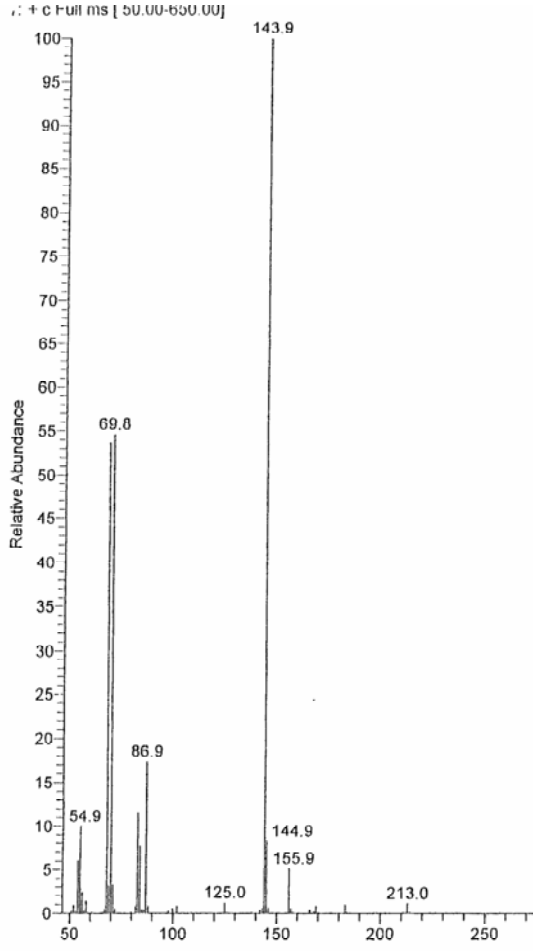
shown any signs of reactivity.

Scheme 4-4 Reaction using 1:1 Acetone with 2-Methyl-2-Oxazoline



23

Figure 4-3 Mass Spectrum of Product **23**



In summary, based on the results described above, certain conclusions can be drawn: 1) when aldehydes without α-hydrogens were used, the major products were imines as one single product; 2) when aldehydes with α-hydrogens were used, the reaction became much more complicated and can result in polycondensation products as well and 3) less bulky ketones did react similarly but at a much slower rate.

4.2 Mechanistic Studies

The result discussed in chapter 4.1 attracted our interest and prompted us to look deeper into the details of such reactions. After reviewing the literature, we discovered that the reactions carried out at the 2-position on the 2-alkyl group have been reviewed [91-93] but very few references exist concerning their ring-opening reactions with aldehydes and there hasn't been a mechanistic study on the process. Moreover, we were intrigued by the possibility of using 2-oxazolines as metal-free catalysts for Aldol reactions (see Chapter 3.4). Thus, a mechanistic study would be necessary to explore the reaction more thoroughly, and the first study done was on the reaction order.

In our case, various amounts of distilled benzaldehyde and 2-ethyl-2-oxazoline were added to a vial and mixed well in order to carry out studies on reaction order.. The solution was immediately transferred to a NMR tube and the reaction was monitored using ^{1}H-NMR at 21 ± 0.1 °C. Because shimming was difficult on the neat sample, a separate NMR tube with approximately the same volume of $CDCl_3$ was used to set up the

instrumental parameters first. The reaction process was monitored using the integration of –CHO peak of the starting material and newly formed imine peak. To assure that the kinetic studies were not affected by side reactions between 2-ethyl-2-oxazoline and water, since these reaction were not typically carried out under anhydrous conditions, a sample was prepared using large amounts of both 2-ethyl oxazolines and water and monitored by NMR, which revealed that in five to ten minutes (which is generally the time before the first data collection occurs) such side reactions were not observed.

Kinetic studies of reaction order have been a general topic in the past. Reaction orders are typically measured by keeping the concentration of one reactant constant while modifying that of the other reactant, as done by Lorenzini and Walling. [94] On looking at the reaction, our first thought was that the reaction would be first order in each reactant. To prove this, a series of reactions were carried out using four samples prepared with 1:1, 1:2, 2:1, 3:1 ratio(s) of benzaldehyde/2-ethyl-2-oxazoline and monitored over a period of ninety (90) minutes. The relative rates derived from the slopes in Figure 4-4 and relative rates were obtained using the rate for 3:1 ratio reaction as the standard. The relationship between relative rate and the ratio of [benzaldehyde]/ [2-ethyl-2-oxazoline] is shown in Figure 4-5. The fact that the reaction is zero order in each reactant is clearly suggested, since any change in the ratio of reactants only made very small changes upon the rates at the beginning.

Figure 4-4 Reactions Using Different Ratio of Aldehyde/2-Ethyl-2-oxazoline at 21 ± 0.1 °C in order to Measure Relative Rates

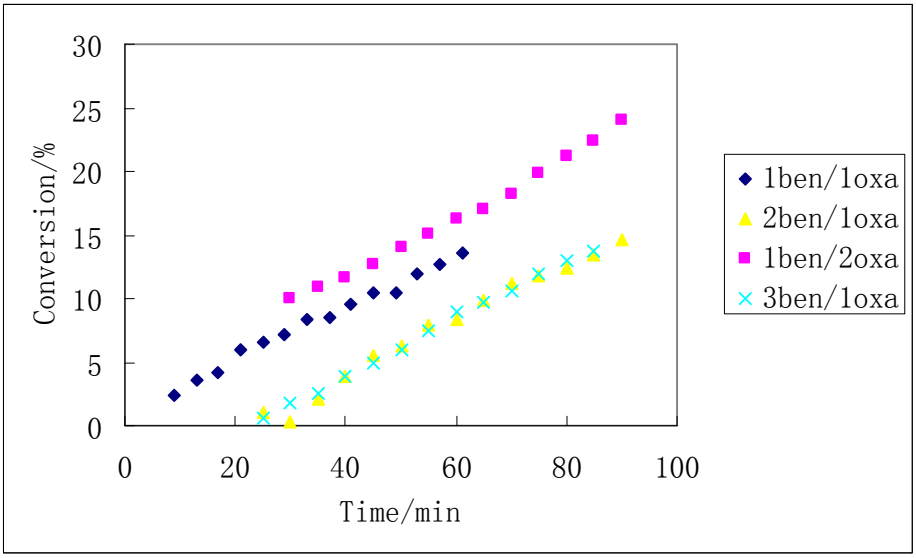
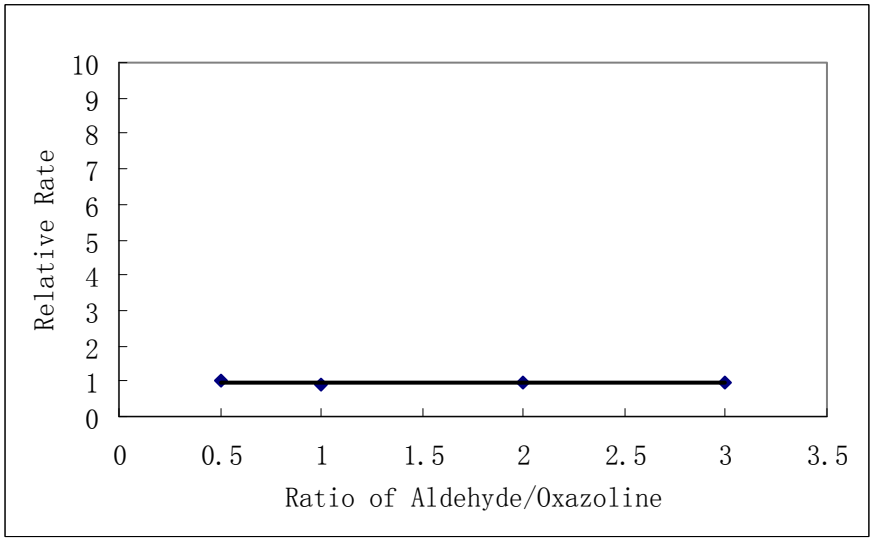


Figure 4-5 Effect of [Benzaldehyde]/ [2-ethyl-2-oxazoline] ratio on Relative Rates (with Regard to the Rate of the 2:1 Benzaldehyde/2-Ethyl-2-oxazoline Reaction)



There are, however, other points that have attracted our attention. The different intercepts from the plots (which suggest various degrees of reaction at the beginning), together with the apparent zero order dependence on both reactants, suggested an acid catalyzed mechanism, in which case the different intercepts may indicate differing amounts of acid (resulting from oxidation) present in the aldehydes. Such mechanisms are common for other condensation reaction involving carbonyl containing functional groups, such as the acid catalyzed esterification. [95]

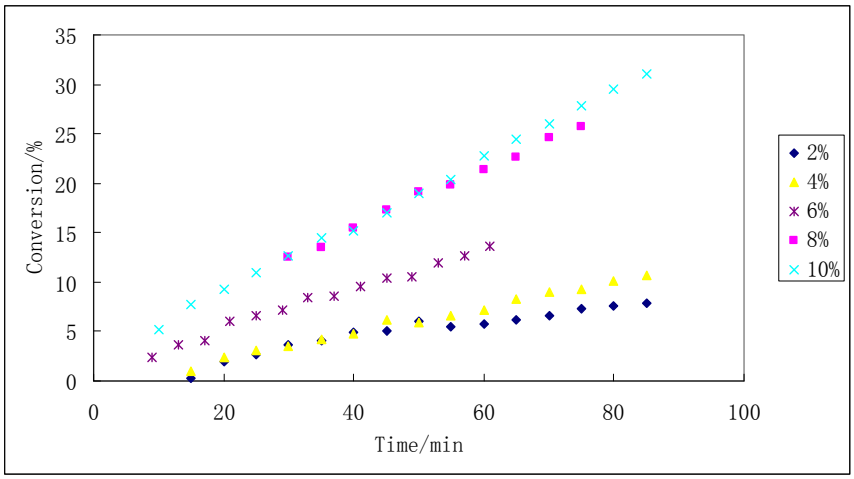
Our reaction has certain unique features compared to the one studied by Lorenzini and Walling. In their studies on the chlorination of aldehydes using cupric chloride, the "true" reaction order was studied in the absence of the acid catalyst. In our system, however, some acid is always present, even after the distillation of benzaldehyde, so it was not possible to follow their methods completely. Since our interest was to study the acid catalysis by comparing reaction rates rather than calculate rate constants, we decided to, by using their work as a reference, mix the two reactants together (aldehydes/ketones and 2-alkyl-2-oxazolines) and monitor the reaction by the appearance of the product. Another noteworthy point was that these reactions have to be carried out in a solvent-free environment to provide appropriate reaction times, and this caused problems for knowing the accurate concentrations of reactants which are both liquids on mixing. Due to the factors mentioned above, we decided to use the slopes obtained by plotting conversion of reactants against time and comparing slopes, if linear, to get k_{rel} values, which are used in

the discussions that follow in this chapter, unless noted otherwise.

After our literature search we were able to find very few references concerning this topic, and the only part related to the fact that the reaction was catalyzed by acids was a short sentence in a patent. [96a, 96b] As we suspected acid catalysis, a suppression experiment was run using triethylamine (pka=10.65 for the ammonium salt [97]). The reaction was run overnight at 318 K using 2 mmol benzaldehyde/2 mmol 2-ethyl-2-oxazoline, 0.12 mmol benzoic acid and 0.16 mmol of triethylamine. No color change was observed in comparison to the "blank" reaction. The absence of the product was also verified by the NMR spectroscopy. This work also suggested that the reaction is catalyzed by the acid, considering the fact that triethylamine is more basic than 2-ethyl-2-oxazoline (oxazolium ion pKa=5.5 [97]).

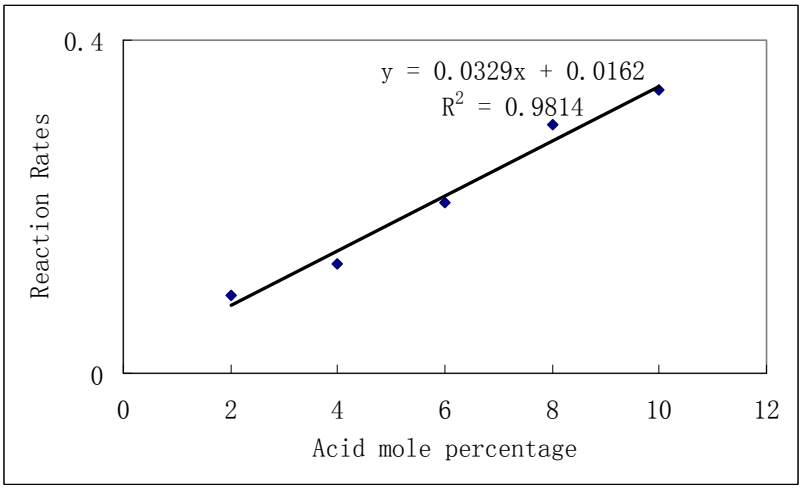
To provide a more solid proof for the acid catalysis, a series of reactions were run, all using 1:1 ratio of benzaldehyde/2-ethyl-2-oxazoline, but with different amounts of added benzoic acid (with respect to benzaldehyde). The results are shown in Figure 4-6. The amounts of benzoic acid were purposely selected so any trace amounts of acid in the benzaldehyde will be small in comparision. The rates derived from the plots are shown in Figure 6, and the new plot of rate against acid percentage was shown in Figure 4-7.

Figure 4-6 Addition of Different Amounts of Acid* to the reaction of 1:1 Benzaldehyde with 2-Ethyl-2-Oxazoline at 21 ± 0.1 °C in order to Measure Relative Rates



*With respect to Benzaldehyde

Figure 4-7 Effect of the Amounts of Acid on Rates



From the data in Figure 4-7, it can be seen that the rate varies linearly with acid amount with a very small intercept (Figure 4-4), confirming our hypothesis that the

reaction is indeed catalyzed by the acid in the system.

To further study the role of acids in this reaction, linear free energy correlation studies were carried out on samples with a 1:1 ratio of both reactants and 6 mol% of various benzoic acids as the catalyst. These reactions were monitored using the same technique and rates were derived from plotting conversion against reaction time. The data obtained were listed in Table 1; all acids used were substituted benzoic acids. Data in the $\log k_{rel}$ column were calculated using rates: k_{rel}=Rate measured using substituted benzoic acid/Rate measured using benzoic acid, and σ values were obtained from literature.

Table 4-1 Data Obtained by Using Various Benzoic Acids as Catalysts in the Reaction of 1:1 Benzaldehyde with 2-Ethyl-2-Oxazoline for Linear Free Energy Correlation Study

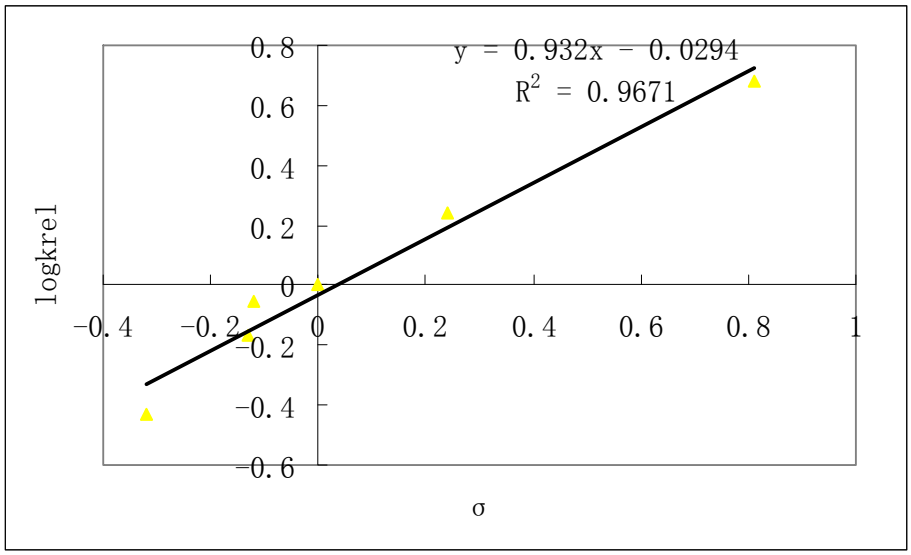
Acids	$\log k_{rel}$	Σ
p-nitro	0.682	0.81
p-hydroxy	-0.168	-0.13
p-dma	-0.431	-0.32
p-H	0	0
p-methoxy	-0.051	-0.12
p-chloro	0.239	0.24

dma=dimethylamino

The linear free energy correlation for the reactions of 2-ethyl-2-oxazolines with

aldehydes using different acids was done using the data in Table 4-1. As shown in Figure 4-8, a ρ value of 0.932 was obtained from the plot. The fact the best correlation was obtained using σ values, together with the ρ value itself, indicates the $[H^+]$ is the real crucial factor to affect the rates of such reactions. The ρ value being not exactly 1.00 indicates the possibility of protonation equilibrium in such reactions: this could be done on either the aldehydes or the 2-ethyl-2-oxazoline.

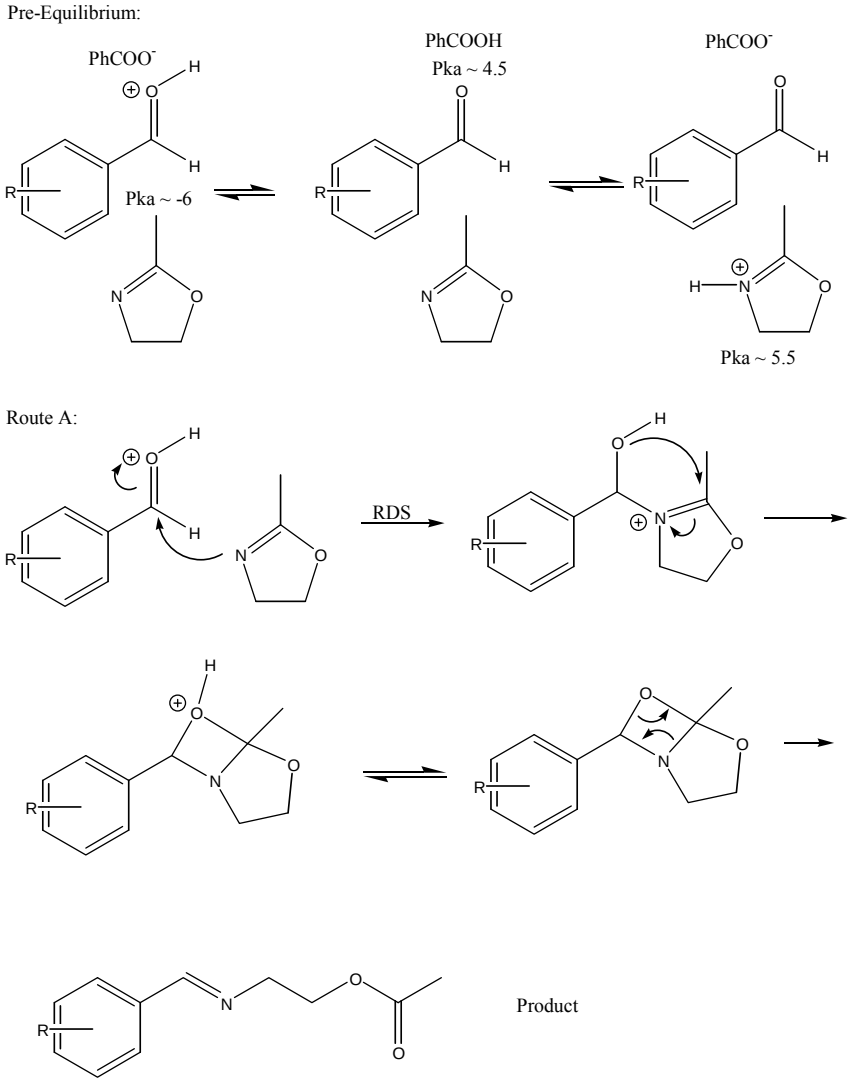
Figure 4-8 Linear Free Energy Correlation on Acid

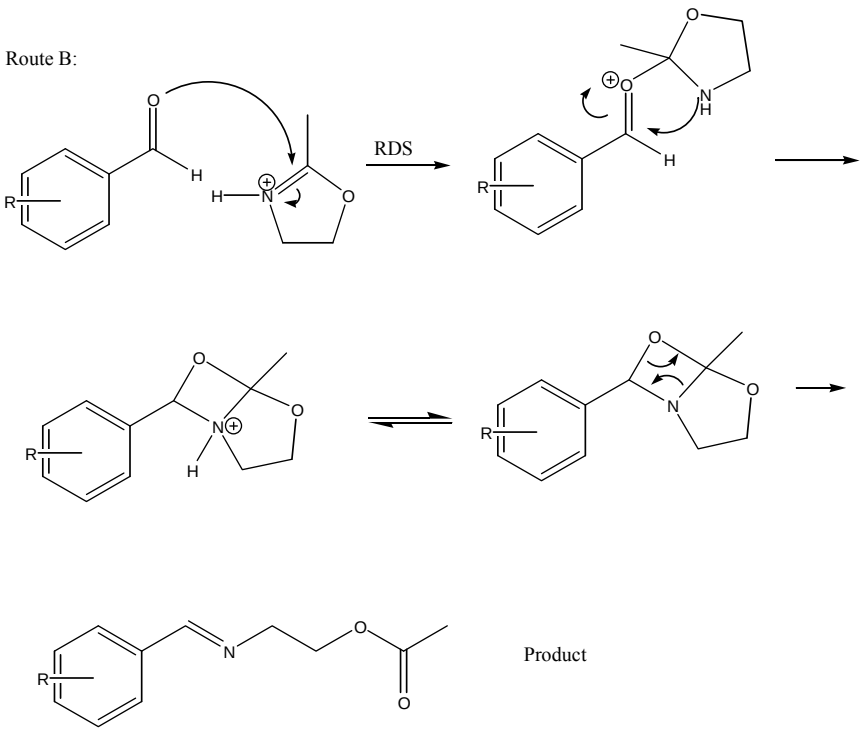


Given all the experimental data, we proposed two possible mechanistic routes (Scheme 4-5). We assumed an equilibrium to exist after the reactants were mixed with the acid, after which two different routes to the final product would be likely. When considering route A, given the big differences in pka between the tiny amount of

protonated aldehydes and oxazolinium ions, will have to react very fast once formed. In route B the protonated oxazoline is the electrophilie, which should be present in fair amounts but attack is from a carbonyl group in the aldehyde. Such attacks seem to be rare in the literature. Obviously more studies are needed to provide a better mechanistic understanding.

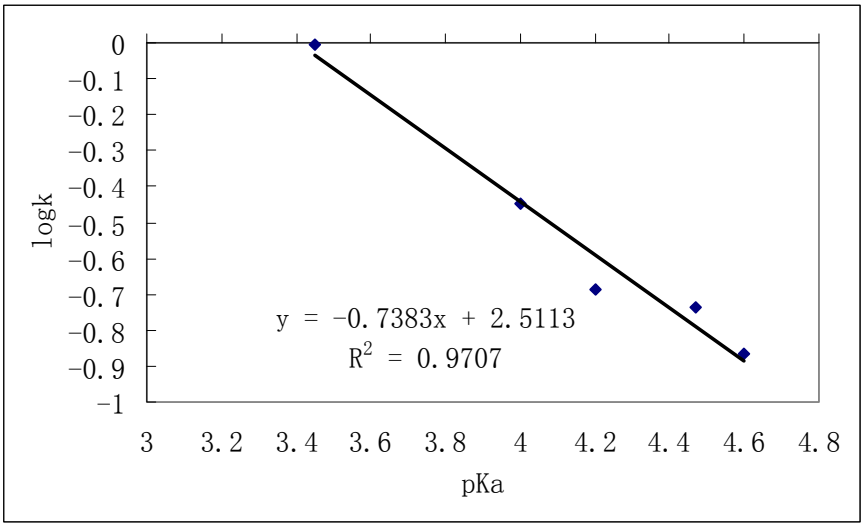
Scheme 4-5 Initial thoughts about Possible Reaction Pathways After Benzaldehyde, 2-Oxazoline and Benzoic acid were Mixed





A Bronsted plot based on pKa was therefore carried out and the result is shown in Figure 4-9. The α value being 0.74 suggests a specific acid catalysis. However, general acid catalysis can result in a high α value if the nucleophile is weak and would suggest that the transition state is late with regard to both the oxazoline and the aldehyde. [98] It has been shown that α will decrease as the nucleophilicity increases, which fits well with the 0.74 value when oxazoline, a weak nucleophile, is used.

Figure 4-9 Bronsted Correlation on Acid Using Reaction Rates Data in Table 4-1

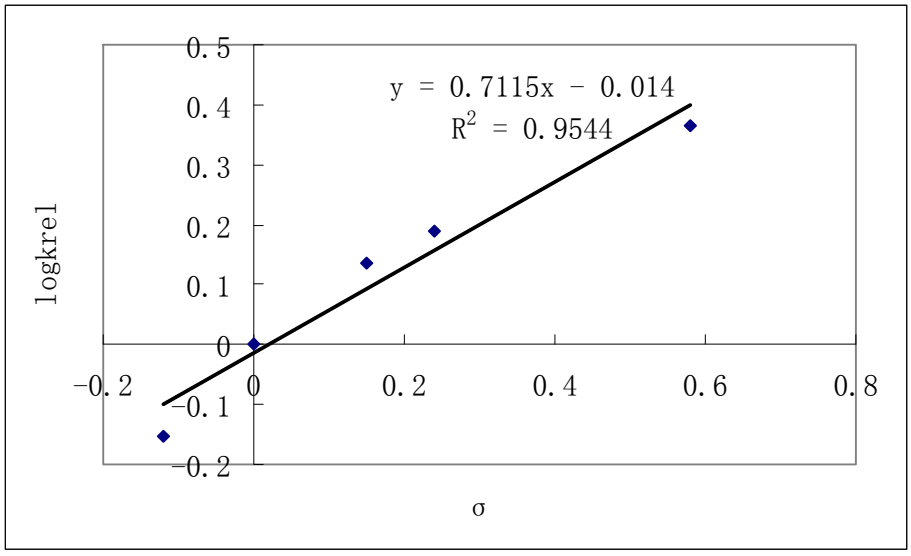


Linear correlation studies were therefore carried out using substituted aldehydes to study their roles in the reaction, and the results are shown in Table 4-2 and Figure 4-10. It should be noted that although all the reactions were carried out using 2:1 ratio of oxazoline/aldehydes instead of 1:1, due to the poor solubility of certain aldehydes. Figure 4-10 clearly shows that aldehydes also participate in the rate determining step, though the effects of functional groups were not outwardly as strong. Based on the correlation with the aldehydes, route B is unlikely because the electronic donating groups will certainly make the reaction favorable, which will lead to a negative ρ value. The magnitude of ρ value possibly indicates the decreasing of positive charge on the carbonyl oxygen during the transition state, which is similar to one of the examples shown in literature. [99]

Table 4-2 Data Obtained by Using Various Benzaldehydes in the Reaction of 1:1 Benzaldehyde with 2-Ethyl-2-Oxazoline with 6 mol% of Benzoic Acid as the Catalyst for Linear Free Energy Correlation Study

Aldehydes	$\log k_{rel}$	σ
p-H	0	0
p-MeO	-0.152	-0.12
p-chloro	0.188	0.24
p-fluoro	0.135	0.15
m-nitro p-methyl	0.364	0.58
p-hydroxyl	-0.481	-0.13

Figure 4-10 Linear Free Energy Correlation on Aldehydes



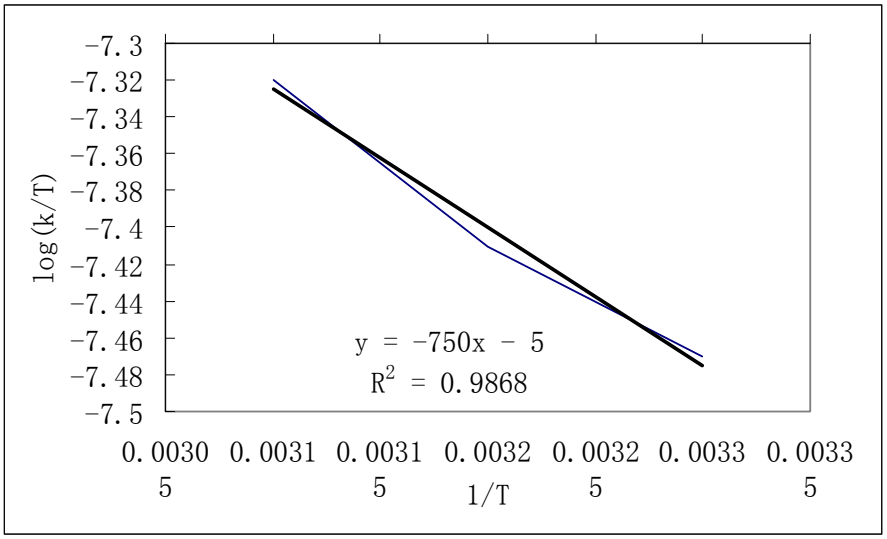
To further study the transition state, thermodynamic studies were carried out by measuring rates at different temperatures, which were used when plotting log(k/T) ~ 1/T

and logk ~ 1/T (Table 4-3). $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated using Figure 4-11: $\Delta H^{\neq}$= 3.4 kcal/mol and $\Delta S^{\neq}$= -70 cal/molK, and they suggest the reaction likely goes through a more concerted transition state.

Table 4-3 Data Obtained from Reactions of 1:1 Benzaldehyde/2-Oxazoline and 6 mol% Benzoic Acid as Catalyst under Various Temperatures for Thermodynamic Studies

k(mol^{-1}.L)	T (°K)	1/T	log(k/T)
1.03E-05	303	0.0033	-7.47
1.21E-05	310	0.0032	-7.41
1.51E-05	318	0.0031	-7.32

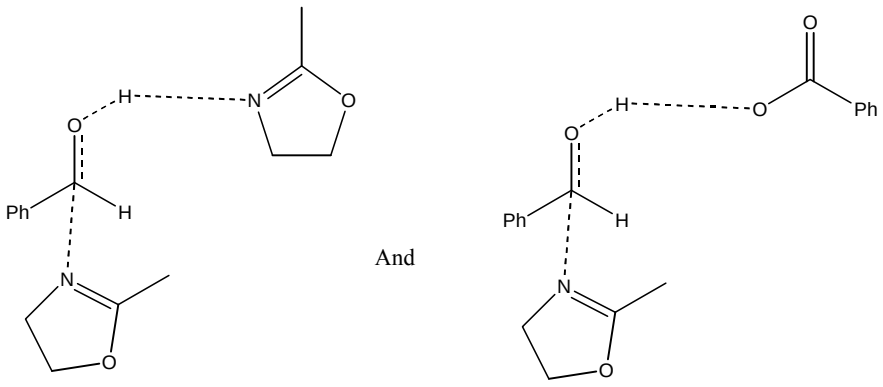
Figure 4-11 Thermodynamic Studies: log(k/T) ~ 1/T Plot



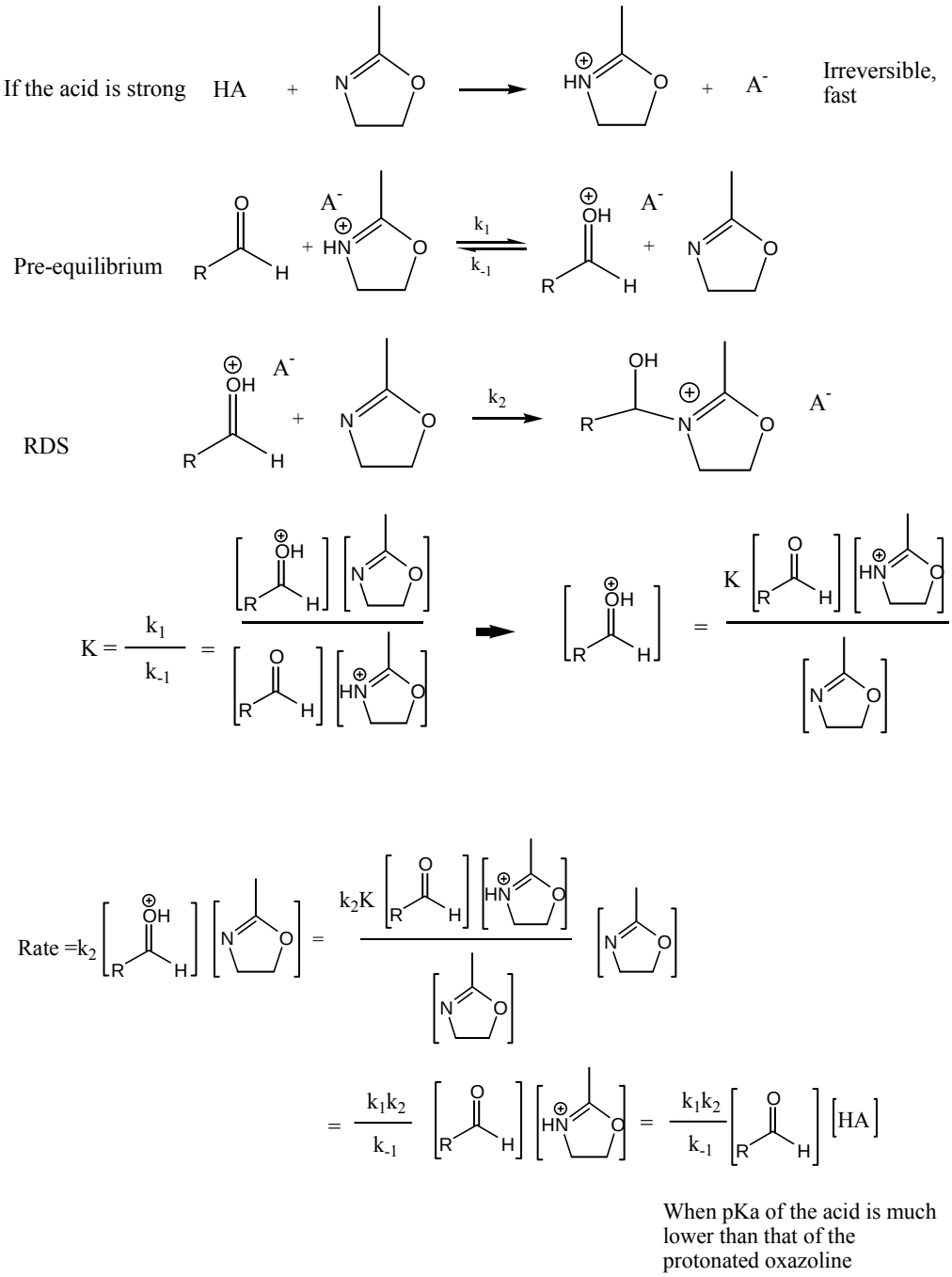
Based on the thermodynamic parameters and the earlier studies a modified reaction

pathway A was postulated. The reaction likely involves general acid catalysis and goes through a concerted transition state (Scheme 4-6). Since the acid generally is less than 10 mol% with respect to 2-alkyl-2-oxazoline and, given the pka values of benzoic acid and oxazoline, it can be expected that a small portion of the oxazoline will be protonated but most of it shall remain its neutral form. The reaction order can thus be explained that in the presence of the acid the catalytic effect reveals itself. Moreover, because of the neat reaction conditions and the fact that the nucleophile can be consider as "solvent", the unusual situation exists that the reaction would "approach" specific acid catalysis if strong acids were used (Scheme 4-7).

Scheme 4-6 Modified Rate Determining Step



Scheme 4-7 Deriving A Simplified Rate Equation



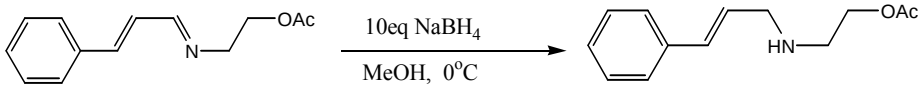
A rate equation was derived as shown in Scheme 4-7. This is done assuming that the

acid is strong, while we used benzoic acids which would add another equilibrium, and if the reaction is general acid catalyzed, would further complicate the situation. It can be seen that the rate is first order in both the aldehyde and the acid, though as the concentration of oxazoline decreases the reaction will likely get more complicated. It should be noted, however, that our focus has been the better understanding of the mechanism rather than determining the exact rate equation. Nonetheless, crude simulations of the reaction using the rate equation derived above fit reasonably well, while those based on aldehyde and oxazoline, or aldehyde, oxazoline and acid, do not.

4.3 Potential Synthetic Utility

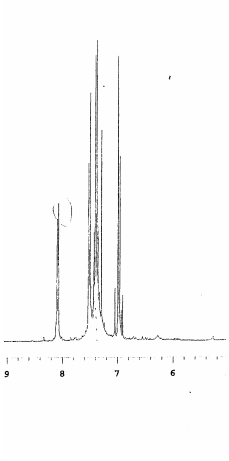
Given the importance of unsaturated imines (Chapter 3.3), we wanted to briefly explore the synthetic potential of the conjugate imines generated using our methodology. Our first thought was the reduction of the imine product (Scheme 4-8). The reduction of **21** using 10 equivalents of sodium borohydride in methanol gave a 85% crude yield and, given the NMR spectrum, the reaction was close to completion though there was still some imine left unreacted (Figure 4-12, indicated by the disappearing of the imine peak at 8.3 ppm: complete spectra are located in A.18 and A.21).

Scheme 4-8 Reduction of **21** using $NaBH_4$

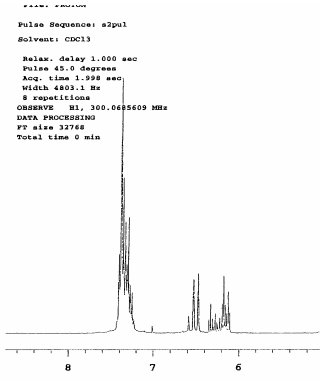


21 **24**

Figure 4-12 ^{1}H-NMR Proof for the Success of the Reduction (6-9 ppm Region)



Imine (before reduction)

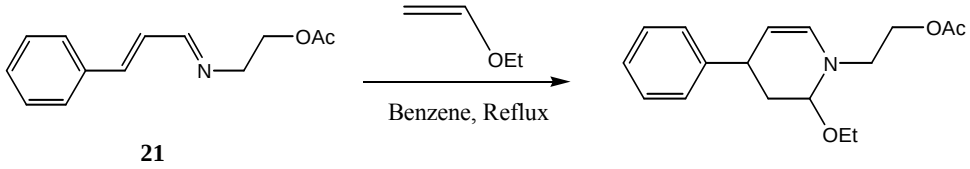


Amine (after reduction)

Encouraged by the result above, we moved on to investigate the possibility of using such imine products as reactants for aza Diels-Alder type reactions. The first reaction we tried was using ethyl vinyl ether: the newly formed imine product **21** was transferred to a 100 ml flask with five equivalents of ethyl vinyl ether in 30 ml benzene. The solution was heated to reflux solvent to allow for complete reaction (Scheme 4-9). Although the reaction was given four days to react, no desired product is observed based on both NMR

and GC-MS analysis. More attempts with other dienes/dienophiles (such as styrene) have given no success so far. Though the details are yet to be studies thoroughly, it is likely the results are caused by steric factors and the fact that aldehydes are generally more reactive than ketones.

Scheme 4-9 Reaction of **21** with Ethyl Vinyl Ether

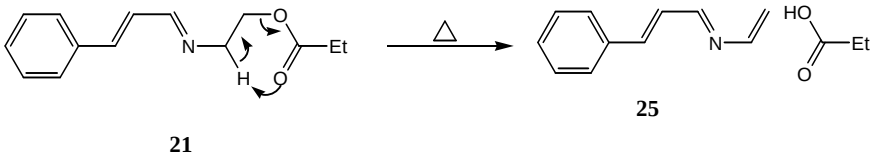


21

Not observed

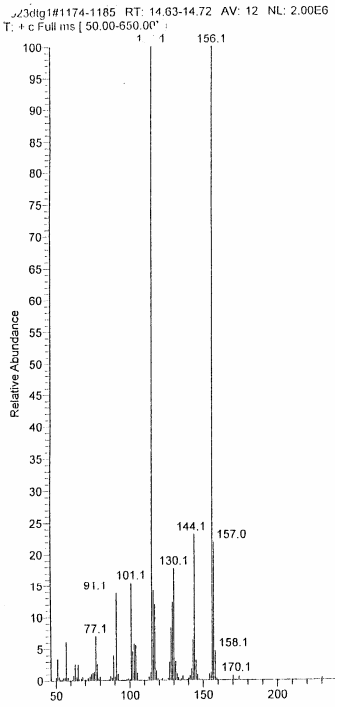
Although the expected Diels-Alder reaction did not occur, during the analyses of the crude products it was observed by GC-MS that the conjugate imine could go through pyrolysis-like transformation to form long conjugated systems. Decomposition of product **21** at high temperature (Scheme 4-10) gave product **25** as evidence by the peak m/z=156 in the GC-MS spectrum (Figure 4-13). The color was also observed to be darker than the corresponding imine, which can be explained by the extended length of the conjugate system. Similar phenomena have been observed from other substrates including **19**, however, such pyrolysis reactions resulting in dark, highly viscous liquid are generally not going to completion, and any attempt to isolate the desired product has yet to be successful.

Scheme 4-10 Thermodecompostion of **21** in Mass Spectrometer



21 **25**

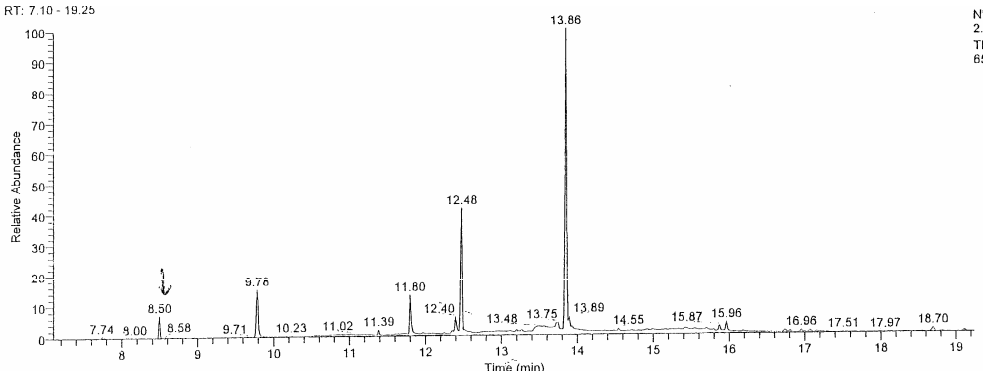
Figure 4-13 Mass Spectrum of the Observed Product **25**



Aside from the utilities of the unsaturated imine products, we were also very interested in the result from the reaction between butyraldehyde and 2-alkyl-oxazolines. Believing the reaction would form a single product (**29**) when a proper ratio of reactants was used; we mixed the oxazoline with two equivalents of butyraldehyde and expected

that given sufficient time the reaction would go to a completion. It was observed that the reaction was still giving a variety of products (Figure 4-14). What we also concluded from the outcome was the detection of individual product(s) in such systems generally tends to be difficult using NMR because of the number of possible products generated from the reaction. Therefore, the analyses were mostly carried out using GC-MS technique, which can identify each individual product, though the isolation still remains a problem for the future.

Figure 4-14 GC Chromatogram of the Reaction of 2:1 Butyraldehyde/2-Methyl-2-oxazoline with 6 mol% Benzoic Acid as Catalyst at 21 ± 0.1 °C

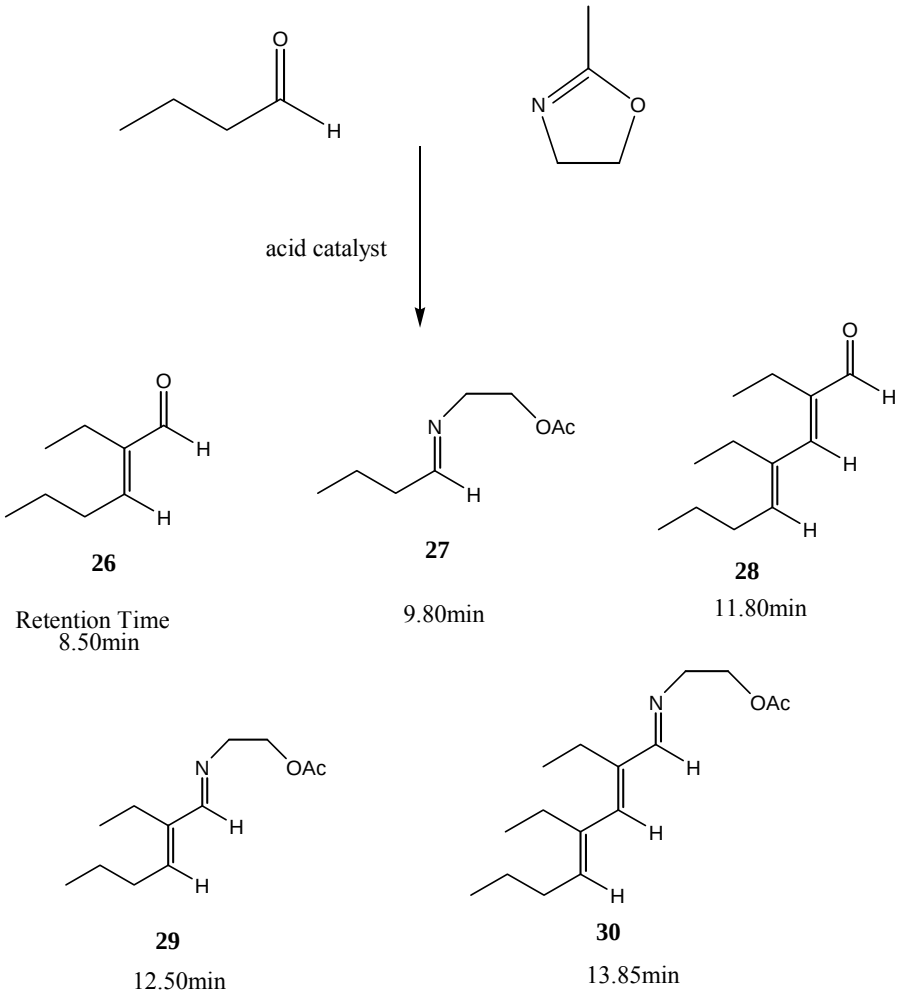


The arrow shows one of the five products.

By using GC-MS technique, at least five products have been identified (Scheme 4-11). It is noted that certain products, such as **26** and **28**, are most likely originating

from the hydrolysis of **29** and **30** since water is generated in condensation. Detailed information regarding each product can be found in the experimental section at the end of this chapter.

Scheme 4-11 Products from the Reaction(s) between 2-Methyl-2-oxazoline and butyraldehyde with 6 mol% Benzoic Acid as Catalyst at 21 ± 0.1 °C



The results from changing the amount of butyraldehyde are shown in Table 5. It is

possible that the reaction is thermodynamically controlled rather than kinetically, since the one using excessive aldehyde did not form product(s) with longer chains. It is generally believed that the addition of a large amount of butyraldehyde will favor the formation of product with longer conjugation but, it should be noted, **30** seems to be the most stable product, although its formation could be slow, given the result of line 1 (Table 4-4). It is also unclear if the formation of **29** is from the condensation of **27** with another molecule of butyraldehyde, or rather the condensation of two molecules of butyraldehydes catalyzed by the oxazoline. GC chromatographs of these attempts were located in appendix.

Table 4-4 Results with Various ratio of Butyraldehyde/2-Methyl-2-Oxazoline with 6 mol% Benzoic Acid (with Respect to 2-Methyl-2-Oxazoline) as Catalyst at 21 ± 0.1 °C

Equivalents	Major Product	Notes
1	**29**	**26, 27** and **28** in small amounts
2	**30**	-
3	**30**	**26, 27, 28** in small amounts
Excess	**30**	Product formed out of four butyraldehyde observed

It was also earlier mentioned in Chapter 3.4 that we proposed a possible metal-free Crossed-Aldol reaction using 2-alkyl-2-oxazolines as the catalysts (Scheme 4-12) which, if successful, could lead to the synthesis of long conjugated systems. To explore the possibility of such reactions, a mixture of 1:1:1 of 2-methyl-2-oxazoline/butyraldehyde/acetophenone was prepared and monitored by GC-MS. Further analysis showed that although the reaction with butyraldehyde was going smoothly, the expected Cross Aldol reaction did not occur (Figure 4-15): It can be clearly seen that the major peak with a retention time of 9.32 min stands for acetophenone, and the two minor peaks (retention time 12.50 min and 13.83 min) correspond to products **29** and **30** mentioned above.

Scheme 4-12 A Possible Metal-Free Cross Aldol Reaction

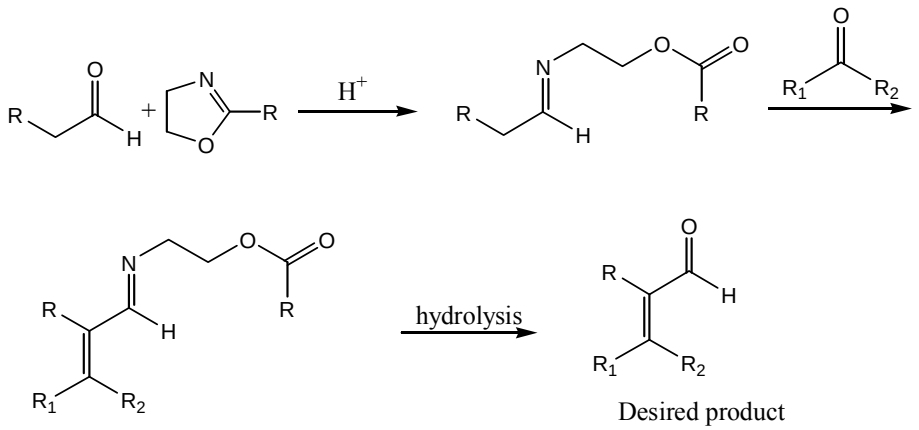
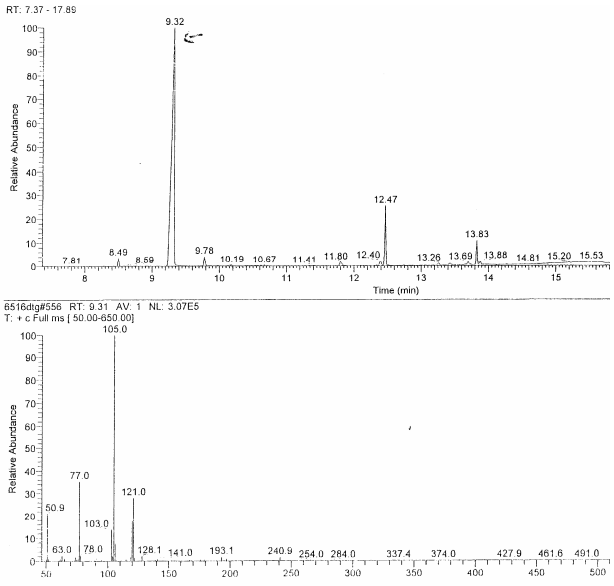


Figure 4-15 GC Spectrum of the Mixture of 1:1:1 Ratio of 2-Methyl-2-oxazoline/Butyraldehyde/Acetophenone after 72 Hours at 21 ± 0.1 °C Using 6 mol% Benzoic Acid as Catalyst



Attributing the unsuccessful result to the steric structure of acetophenone, we continued with another attempt using acetone instead (Scheme 4-13). The reaction was run under the same conditions as indicated above and did generate the desired Crossed product (retention time 7.63 min in Figure 4-16, identified by m/z=113 peak). However, due to both its small amount and the difficulty in isolation, **31** has yet been successfully isolated. The results, however, indicated that given the slow rates of reaction between the imine and ketones, it will be difficult to carry out these Cross Aldol reactions successfully under mild conditions.

Scheme 4-13 Attempted Cross Aldol Reactions (1:1:1 ratio)

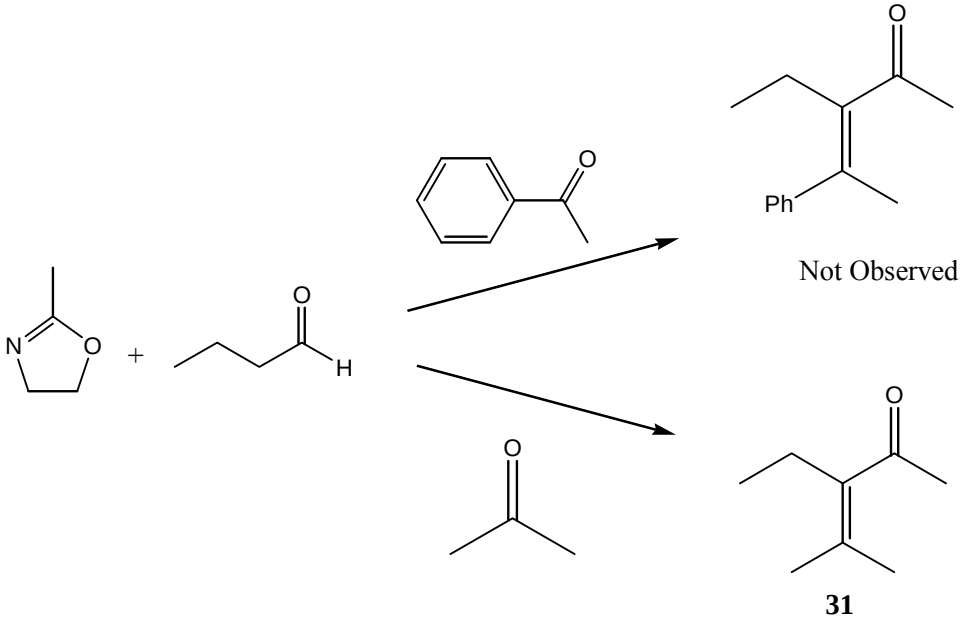
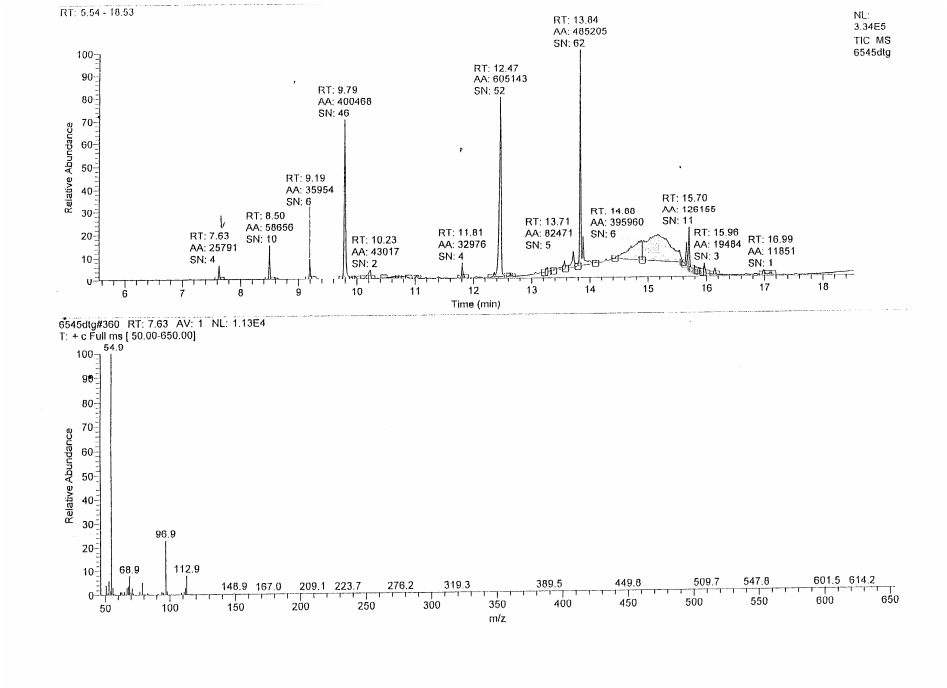


Figure 4-16 Mass Spectrum of **31** (the first peak in GC Spectrum)



4.4 Conclusion and Future Work

Several mechanistic studies have been carried out in the first part of this chapter to elucidate the details of the unique reactions between 2-alkyl-2-oxazolines and various ketones/aldehydes. Through these studies, it is clear that the reaction is catalyzed by acid and because of the basicity of oxazoline, the rate behavior is more complicated (Chapter 4.2, Scheme 4-7). The acid's role is to protonate the 2-alkyl-2-oxazoline which will further participate in the rate determining step, as shown by the linear free energy correlations of the acid and the aldehydes. 2-Alkyl-2-oxazoline, on the other hand, is believed to play both roles as reactant and catalyst in the reaction, which is also supported by the thermodynamic parameters derived. This kind of reaction is very intriguing because of its similarity to that of certain enzymes.

With the success of the mechanistic study, we have expected a broad synthetic utility in both the methodology itself and the unsaturated imine products. Although some of the initial probes of reactivity were not as successful as hoped, they are indicative of the focus of possible future work: 1) the unsaturated imine products can be reduced to amines or further hydrolyzed to amine alcohols, both of which are important synthetic precursors; 2) the reaction conditions, such as the ratio of ketones or temperature have to be modified to provide more successful aza Diels-Alder reaction or Cross Aldol reactions and 3) should the issues above be solved, an efficient way to isolate and identify individual products from the mixture will have to be established in order to make the

work in this chapter truly useful for the syntheses of natural products or certain drugs with long unsaturated structures. It can be expected that more time will be devoted to explore the reactions between 2-alkyl-2-oxazolines and functional groups similar to aldehydes, such as nitrosobenzenes.

4.5 References to Chapter 4

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Experimental for Chapter 4

2-ethyl-2-oxazoline/2-methyl-2-oxazoline and substituted benzoic acids were obtained commercially and used without further purification. All the aldehydes were also from commercial resources, distilled and stored in dry box for 24 hours prior to reaction unless mentioned otherwise. For mechanistic studies, all the reactions were carried out in solvent-free NMR tubes unless mentioned otherwise. All the amounts of acids indicated below are with respect to the amount of aldehyde in the reaction unless mentioned otherwise. NMR samples were prepared using the standard procedure unless mentioned otherwise: freshly distilled aldehyde and 2-ethyl-2-oxazoline or 2-methyl-2-oxazoline were added to a vial containing the acid and mixed well until all the acid dissolved. The solution was immediately transferred to a NMR tube and the reaction was monitored using a 300 Varian NMR instrument using periodical data collection technique; all the reactions were done in the NMR instrument at 21 ± 0.1°C unless noted otherwise. Because shimming was difficult on the neat sample, a separate NMR tube with approximately the same volume of $CDCl_3$ was used to set up the instrumental parameters first. Reaction conversion and relative rates were calculated using the integration of the –CHO peak of the starting material and newly formed imine peak, data storage and analyses were achieved using Microsoft Excel. GC-MS samples were made by adding 0.5 mL of chloroform or methylene chloride to the product(s) and mass spectra were obtained using an electronic ionization technique, splitless injection, thermostat 70 electronic volts on a Trace GC 2000 and Thermoquest GCQ/Polaris mass spectrometer

(ThermoQuest Finnigan, San Jose, CA) unless otherwise noted. Percentage of individual products in a mixture was determined by semi-quantitative GC/MS.

N-Benzylidene-2-aminoethyl propanoate (19)

Benzaldehyde (0.211 g, 1.99 mmol) was added to a 4 dram Kimble Stopper vial. 2-Ethyl-2-oxazoline (0.193 g, 1.95 mmol) was slowly added to the vial and mixed thoroughly. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for six days resulting in a dark orange liquid. The crude product **19** was analyzed directly by ^{1}H-NMR and completion was confirmed by the absence of the aldehydes peak. ^{1}H-NMR: δ8.32 (1H, d, Ha), 7.4-7.8 (5H, m, Hb), 3.74 (2H, t, Hc), 3.44 (2H, t, Hd), 2.25 (2H, q, He), 1.2 (3H, t, Hf). Product is identified by the chemical shifts of hydrogens in the spectrum. NMR spectrum located in A.16.

N-t-Butylmethylene-2-aminoethyl propanoate (20)

Pivaldehyde (0.152 g, 1.77mmol) was added to a 4 dram Kimble Stopper vial. 2-Ethyl-2-oxazoline (0.194 g, 1.96 mmol) was slowly added to the vial and mixed thoroughly. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for six days resulting in a dark red liquid. The crude product **20** was solely identified by the imine peak in ^{1}H-NMR at 8.0 ppm.

N-Cinnamylidene-2-aminoethyl propanoate (21)

Cinnamaldehyde (0.265 g, 2.02 mmol) was added to a 4 dram Kimble Stopper vial. 2-Ethyl-2-oxazoline (0.201 g, 2.03 mmol) was slowly added to the vial and mixed thoroughly. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for seven days resulting in a dark red liquid. The crude product **21** was analyzed directly by ^{1}H-NMR and completion was confirmed by the absence of the aldehydes peak. ^{1}H-NMR: δ8.05 (1H, d, Ha), 7.6-7.2 (5H, m, Hb), 7.0 (2H, d, Hc), 4.4 (2H, t, Hd), 3.78 (2H, t, He), 2.35 (2H, q, Hf), 1.2 (3H, t, Hg). Product is identified by the chemical shifts of hydrogens in the spectrum. NMR spectrum located in A.17.

N-(2-Ethyl)hex-2-enylidene-2-aminoethyl propanoate (22)

Butyraldehyde (0.285 g, 3.96 mmol) was added to a 4 dram Kimble Stopper vial. 2-Ethyl-2-oxazoline (0.195 g, 1.97 mmol) was slowly added to the vial and mixed thoroughly. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for six days resulting in dark yellow liquid. The crude product **22** was identified directly by GC-MS. MS: m/z(%) 226(40), 225(57), 210(37), 196(40), 124(100), 101(86). Product is identified by the m/z=226 peak. Mass spectrum located in A.18.

N-(2-Methyl)ethylidene-2-aminoethyl acetate (23)

To a 4 dram Kimble Stopper vial was added 2-ethyl-2-oxazoline (0.193 g, 1.95 mmol) and a large excess of dry acetone. Benzoic acid (12.1 mg, 0.992 mmol) was added to the vial and mixed thoroughly until dissolved. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for fourteen days resulting in a yellow liquid. The crude product **23** was analyzed directly by GC-MS and the completion was confirmed by a single major peak from GC chromatography. MS: m/z(%) 143(100), 87(17), 70(55). Product is identified by m/z=143 peak. GC-MS spectra located in A.19.

N-Cinnamyl-2-aminoethyl propanoate (24)

To a 100 mL Erlenmeyer flask was added **21** (42.1 mg, 0.201 mmol) and cooled at 0 ^{o}C for thirty minutes. 74.2 mg sodium borohydride (2.01 mmol) was added to the vial and stirred for thirty more minutes at 0° C. When the reaction was finished 5 mL of water was slowly added to the vial to quench the excessive sodium borohydride. Diethyl ether/water (1:1, 30 mL) was used to extract the product, the organic phase was separated and the aqueous phase was extracted using 15 mL of diethyl ether three times. The organic phase was combined, dried (anhydrous sodium sulfate) and ether was removed under reduced pressure resulting in a yellow oil. This procedure gave 40 mg (0.17 mmol), 85% crude yield of **24.** ^{1}H-NMR: 7.4-7.15 (5H, m, Ha), 6.5 (1H, d, Hb), 6.07 (1H, m, Hc), 4.2 (2H, t, Hd), 3.8 (2H, d, He), 3.4 (2H, t, Hf), 2.6 (1H, s, Hg), 2.45 (2H, q, Hh),

1.2 (3H, t, Hi). Product is identified by the chemical shifts of hydrogens in NMR spectrum. NMR spectrum located in A.20.

N-Cinnamylideneaminoethene (25)

To a 4 dram Kimble Stopper vial was added freshly prepared **21** (21.3 mg, 0.101 mmol) and heated in a drying oven for 24 hours. The color during the process was observed to change from orange to black. The crude product **25** was analyzed directly by Mass spectrometry. MS: m/z(%) 157(20), 156(100), 144(24), 130(19), 117(100), 101(15), 91(14), 77(9). Product is identified by m/z=156 peak. Mass spectrum located in A.21.

Reaction of 2-methyl-2-oxazoline with 2 equivalents of butyraldehyde for 72 hours

Butyraldehyde (0.572 g, 7.94 mmol) was added to a 4 dram Kimble Stopper vial. 2-Methyl-2-oxazoline (0.341 g, 4.01 mmol) was slowly added to the vial and mixed thoroughly. 0.2 mmol of benzoic acid was dissolved in the clear mixture as the acid catalyst. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for 72 hours resulting in a dark red liquid. The crude products **26** – **30** were identified directly by GC-MS. Retention time(min): 8.50 (**26**), 9.80 (**27**), 11.80 (**28**), 12.50 (**29**), 13.85 (**30**). MS: m/z(%): product **26**: 127(38), 111(42), 97(100), 91(33), 78(30), 67(40), 55(84); product **27**: 158(31), 130(15), 87(18), 69(52), 68(100); product **28**: 177(24), 162(48), 149(100), 148(93), 121(15), 106(10); product **29**: 211(36), 196(34), 182(31), 150(5), 138(11), 136(19), 124(100), 108(29), 87(60), 80(18);

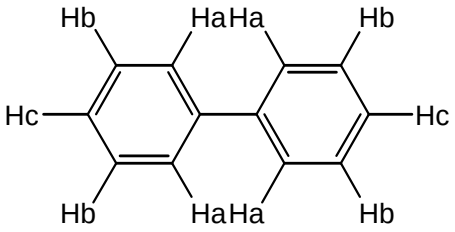
product **30**: 266(11), 223(12), 222(90), 178(8), 162(24), 136(85), 87(100). Mass spectrum located in A.22 (**26**); A.23 (**27**); A.24 (**28**), A.25 (**29**), A.26 (**30**)

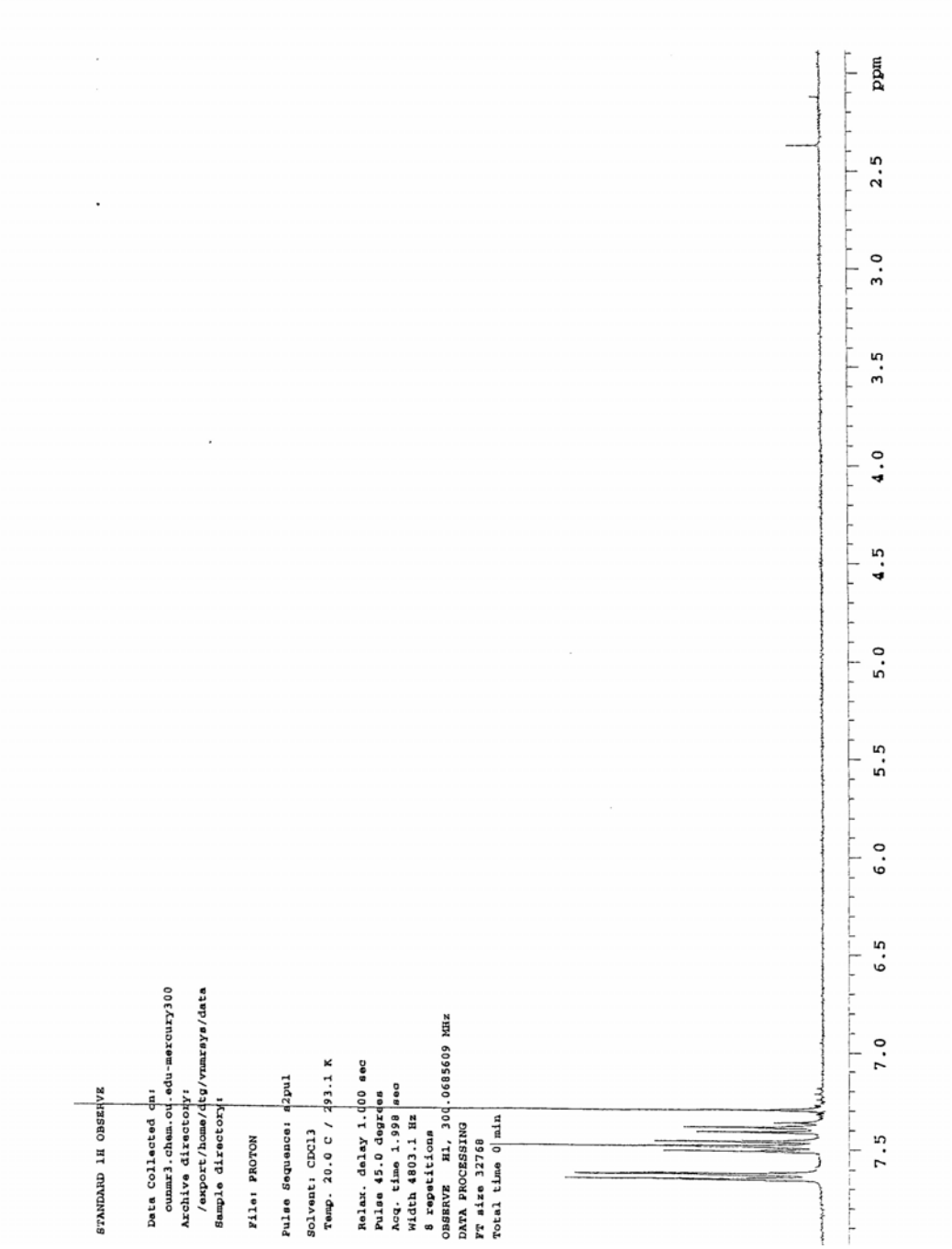
Attempted Crossed-Aldol Condensation

Butyraldehyde (0.144 g, 2.00 mmol) was added to a 4 dram Kimble Stopper vial. 2-Methyl-2-oxazoline (0.171 g, 2.00 mmol) and acetone (0.115 g, 1.98 mmol) were slowly added to the vial and mixed thoroughly. 0.1 mmol of benzoic acid was then dissolved in the clear mixture as the acid catalyst. The vial was capped, sealed with parafilm, and the reaction was allowed to be carried out at room temperature for 72 hours resulting in orange liquid. The crude product **31** was identified directly by GC-MS. MS: m/z(%) 113(11), 97(24), 69(10). Mass spectrum located in A.27.

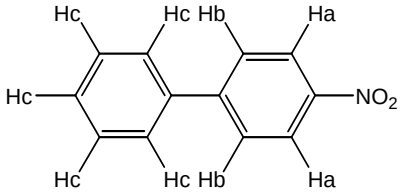
APPENDIX

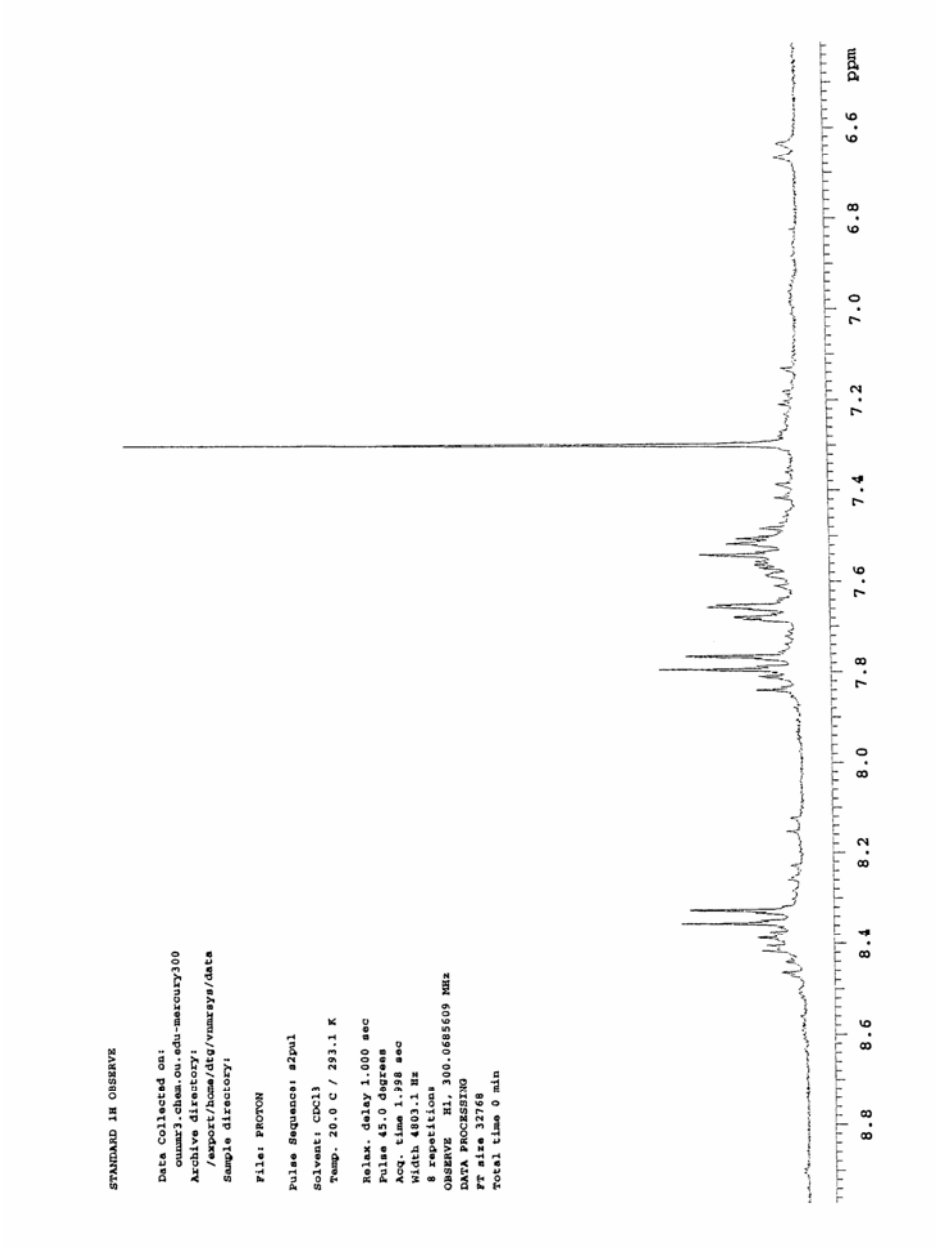
A.1 NMR Spectrum of Biphenyl



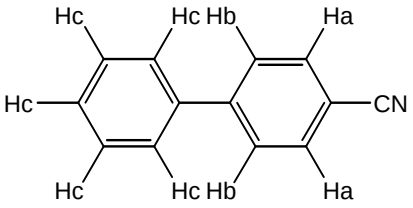


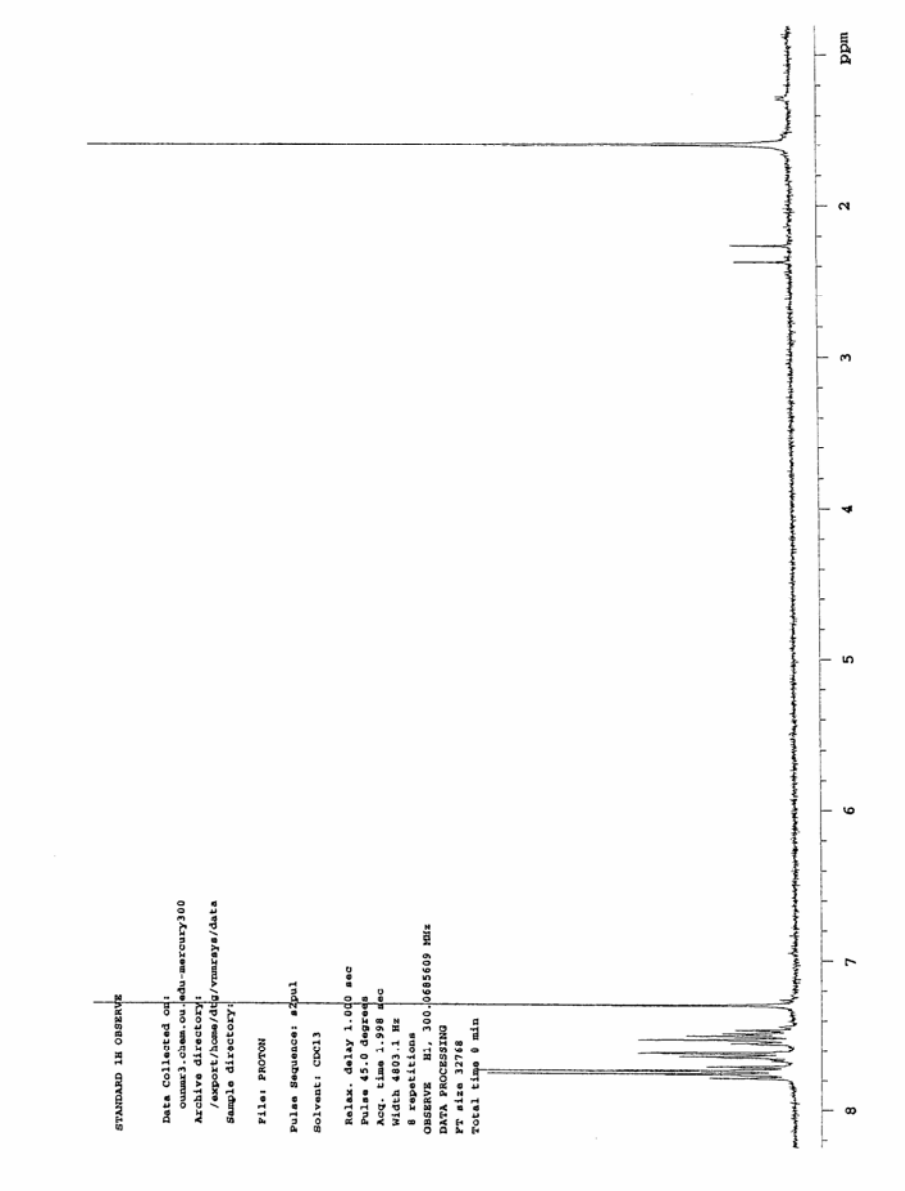
A.2 NMR Spectrum of 4-Nitrobiphenyl





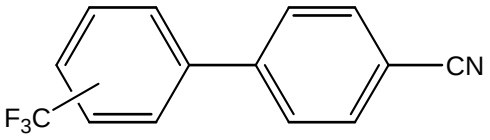
A.3 NMR Spectrum of 4-Cyanobiphenyl

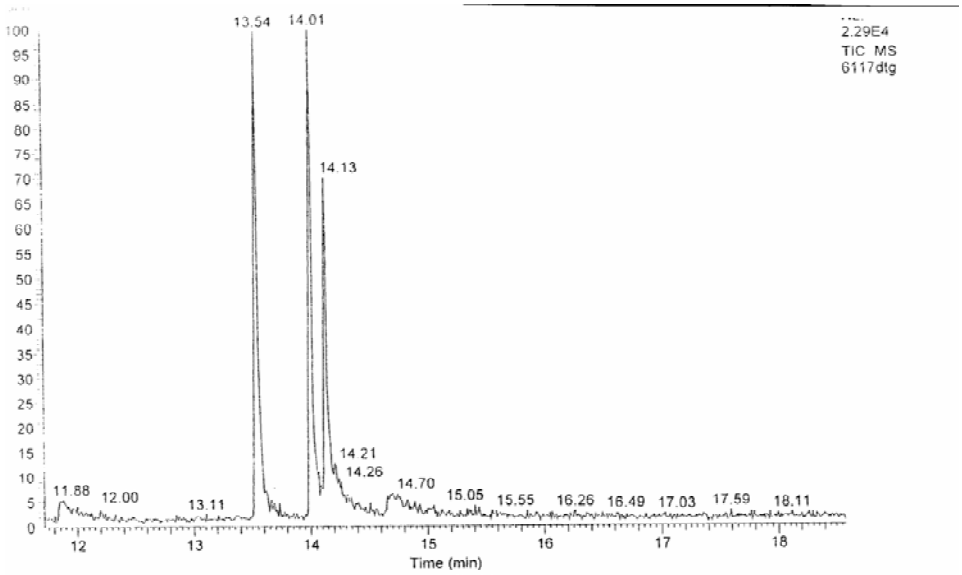


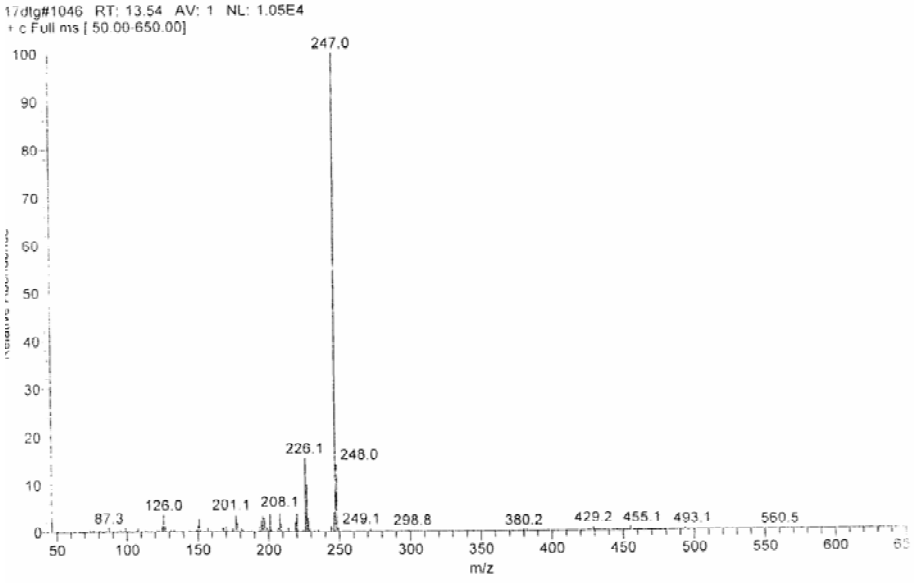


A.4 GC-MS Spectrum of 2-, 3-, and

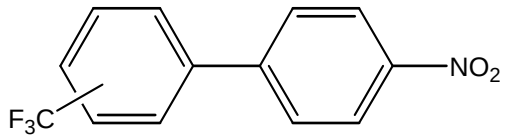
4-Trifluoromethyl-4'-cyanobiphenyls

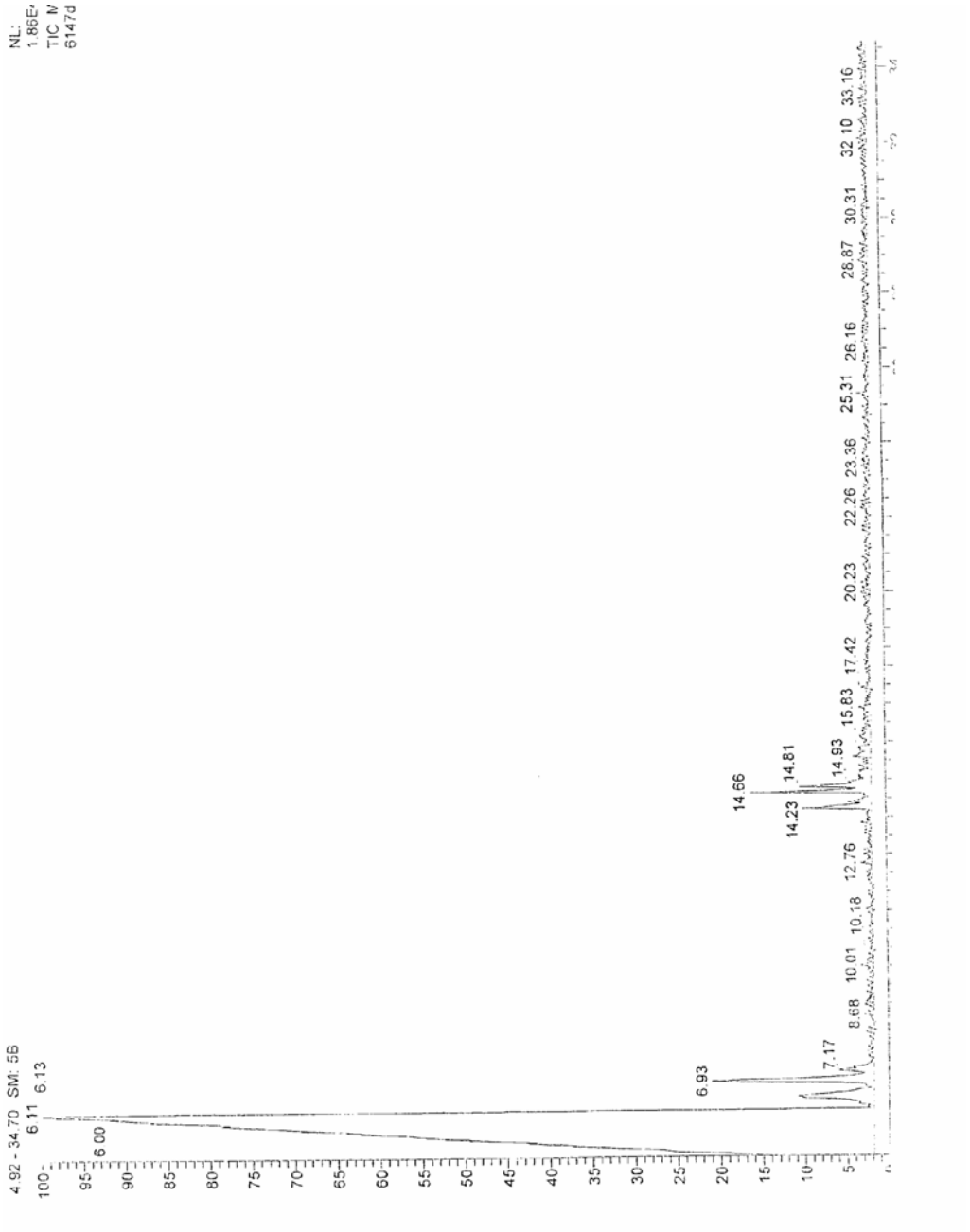




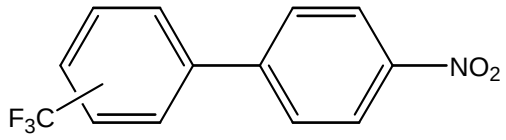


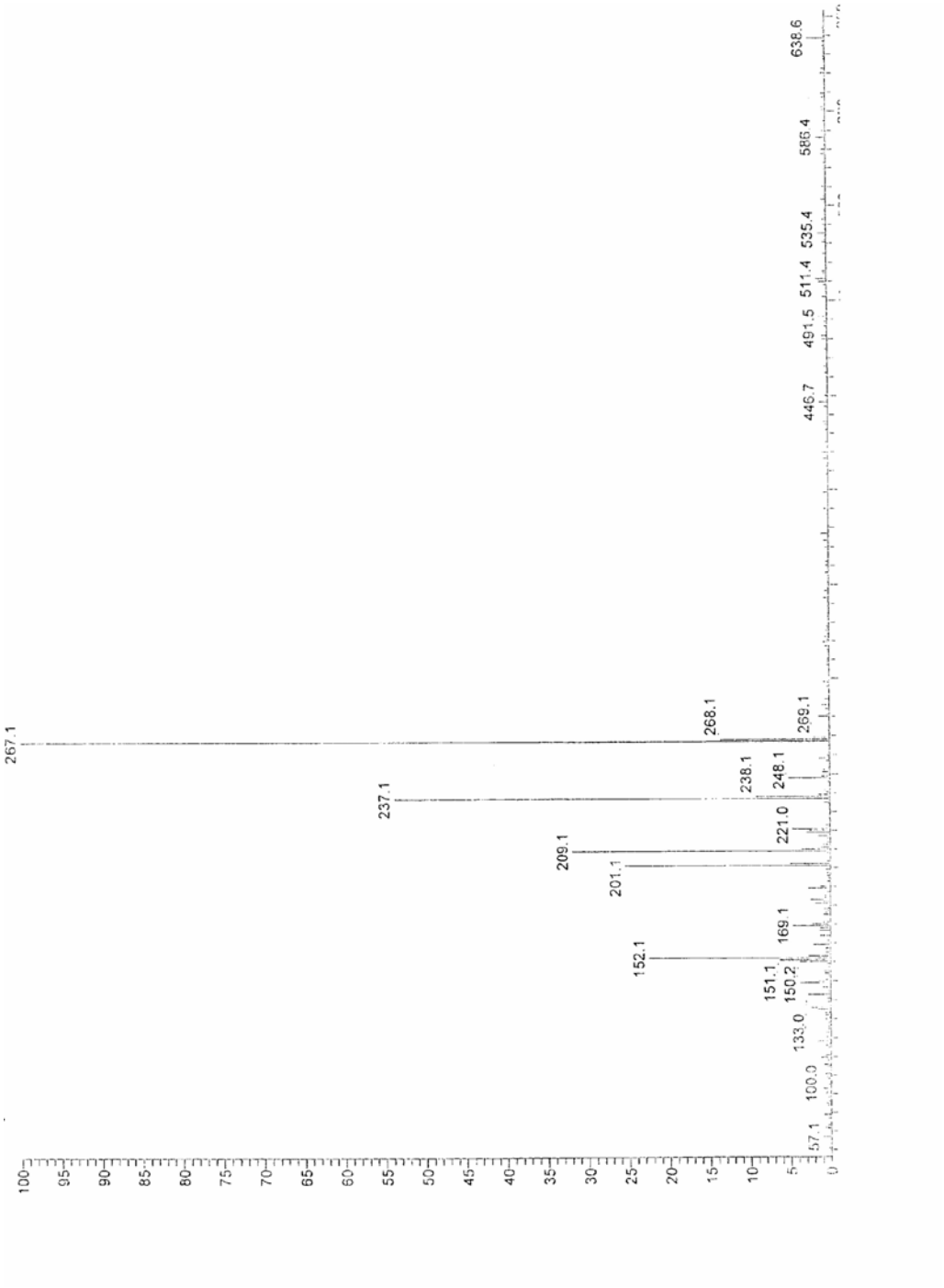
A.5 GC Spectrum of 2-, 3-, and 4-Trifluoromethyl-4’-nitrobiphenyls



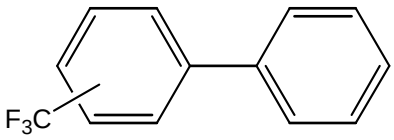


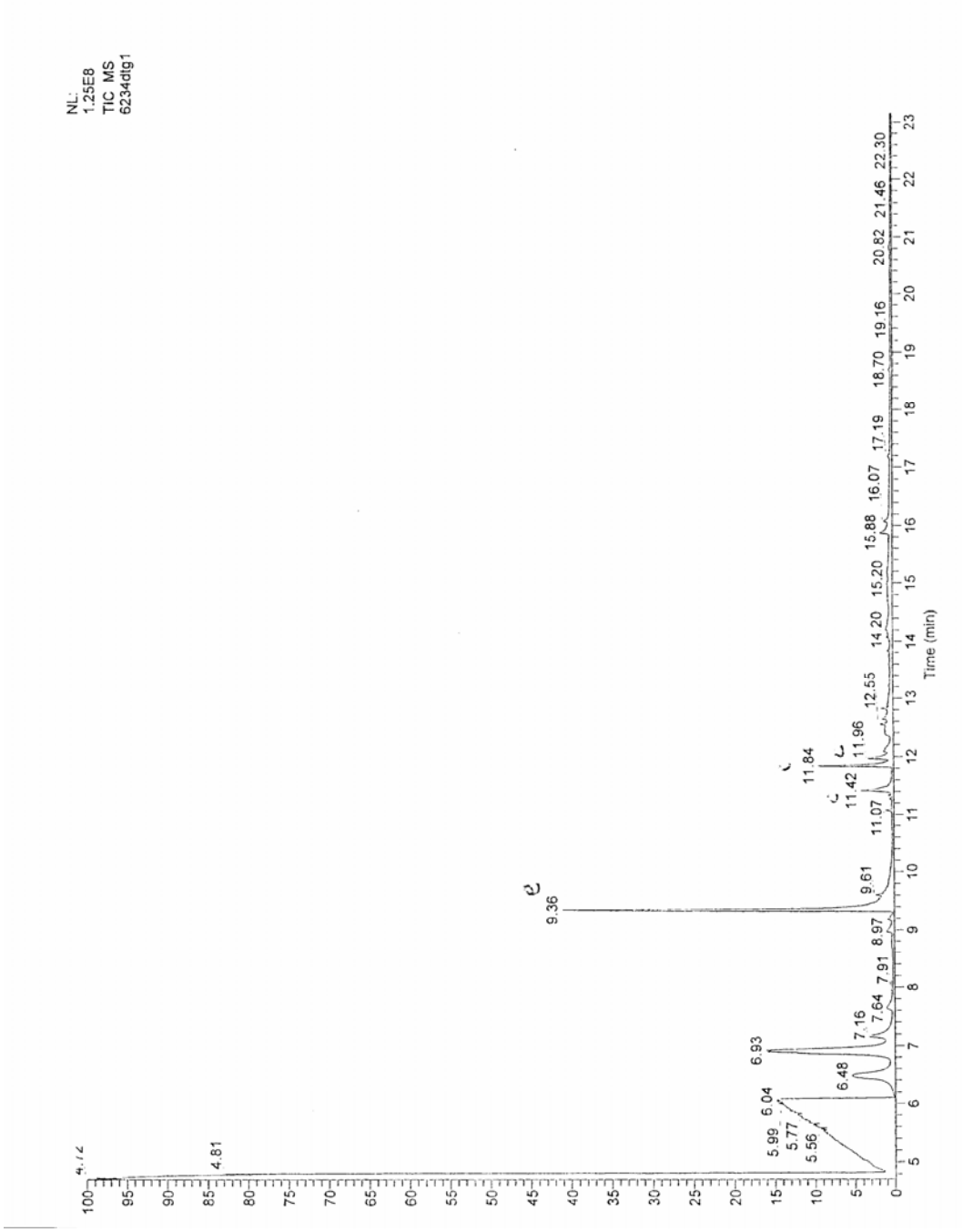
A.6 Mass Spectrum of 2-, 3-, and 4-Trifluoromethyl-4'-nitrobiphenyls



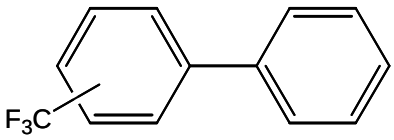


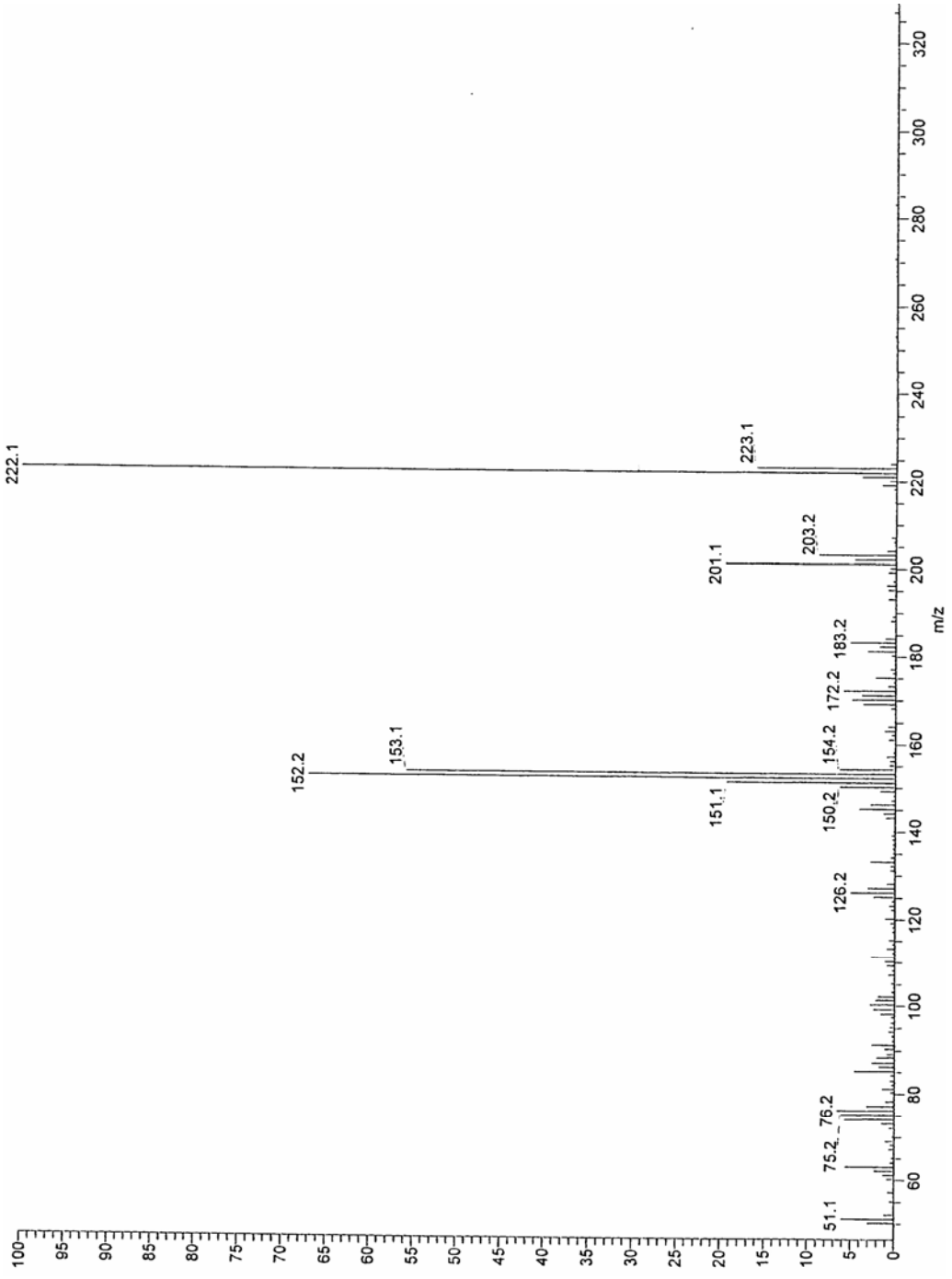
A.7 GC Spectrum of 2-, 3-, and 4-Trifluoromethylbiphenyls



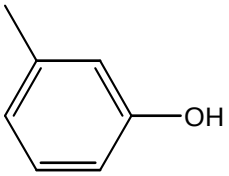


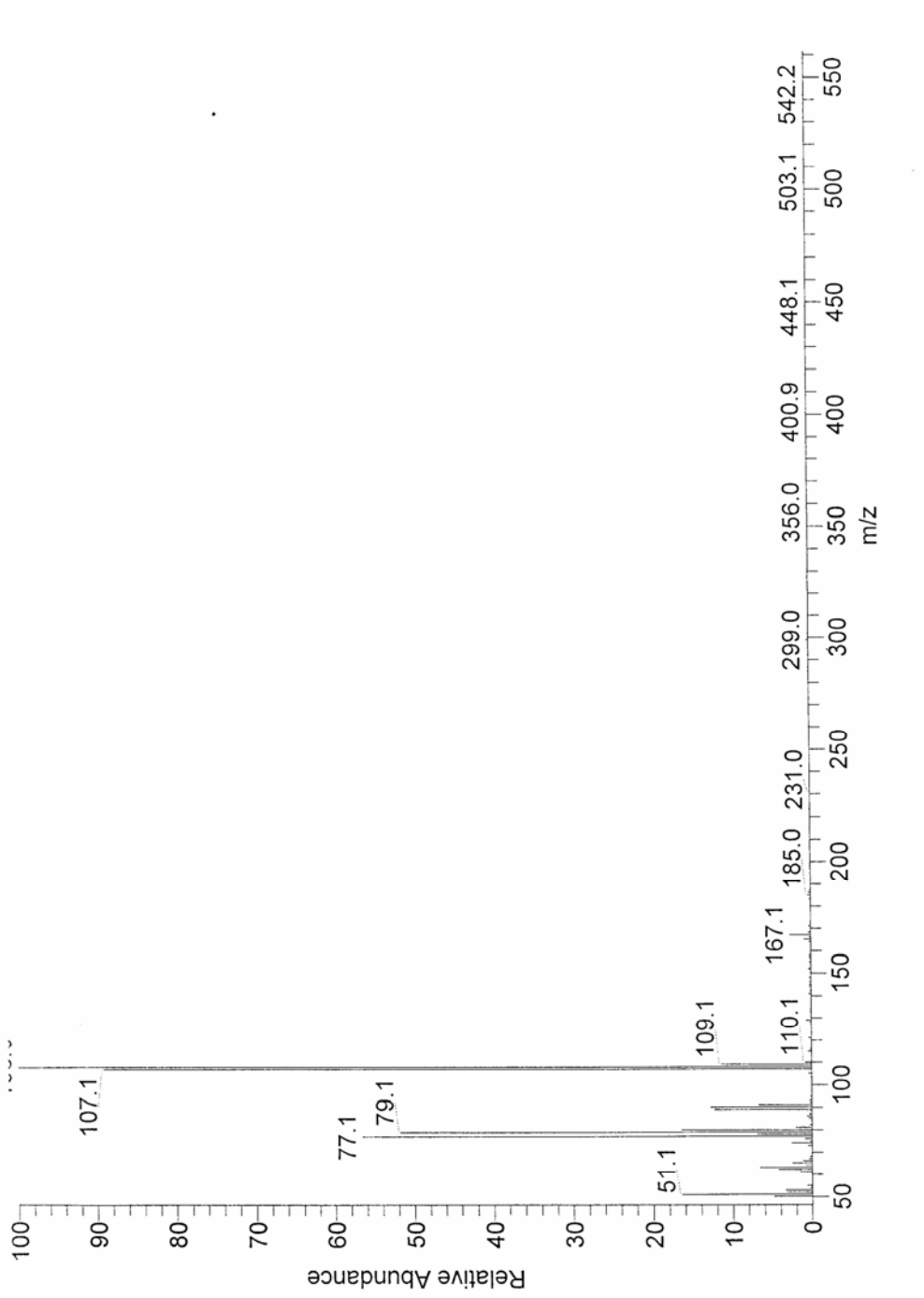
A.8 Mass Spectrum of 2-, 3-, and 4-Trifluoromethylbiphenyls



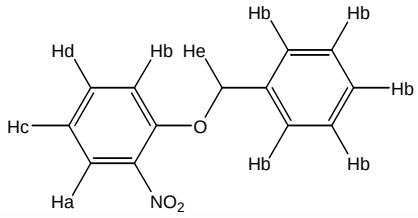


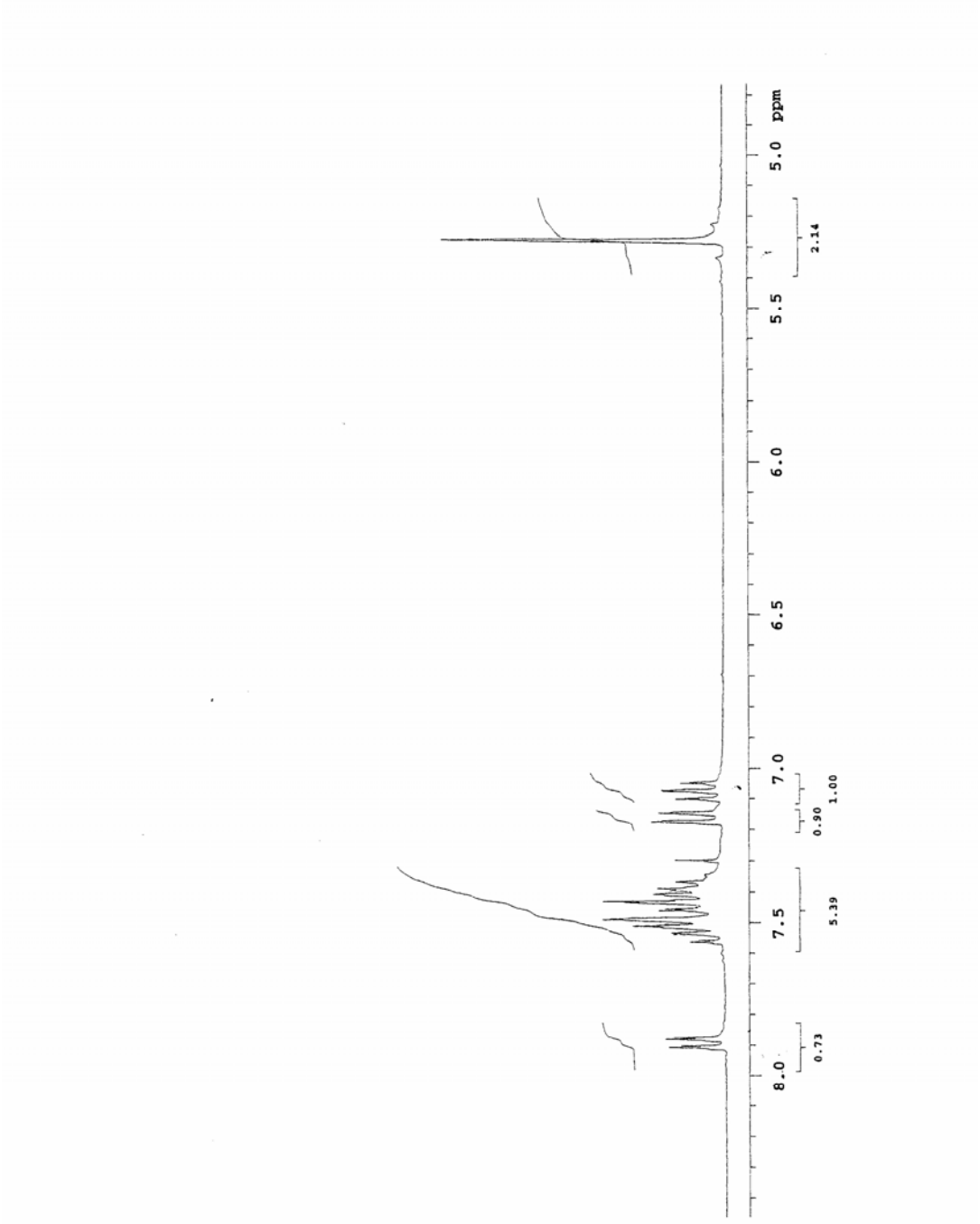
A.9 Mass Spectrum of 3-Cresol



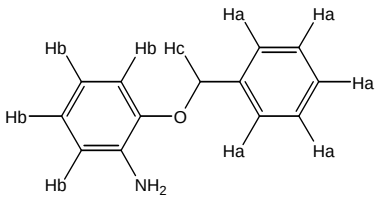


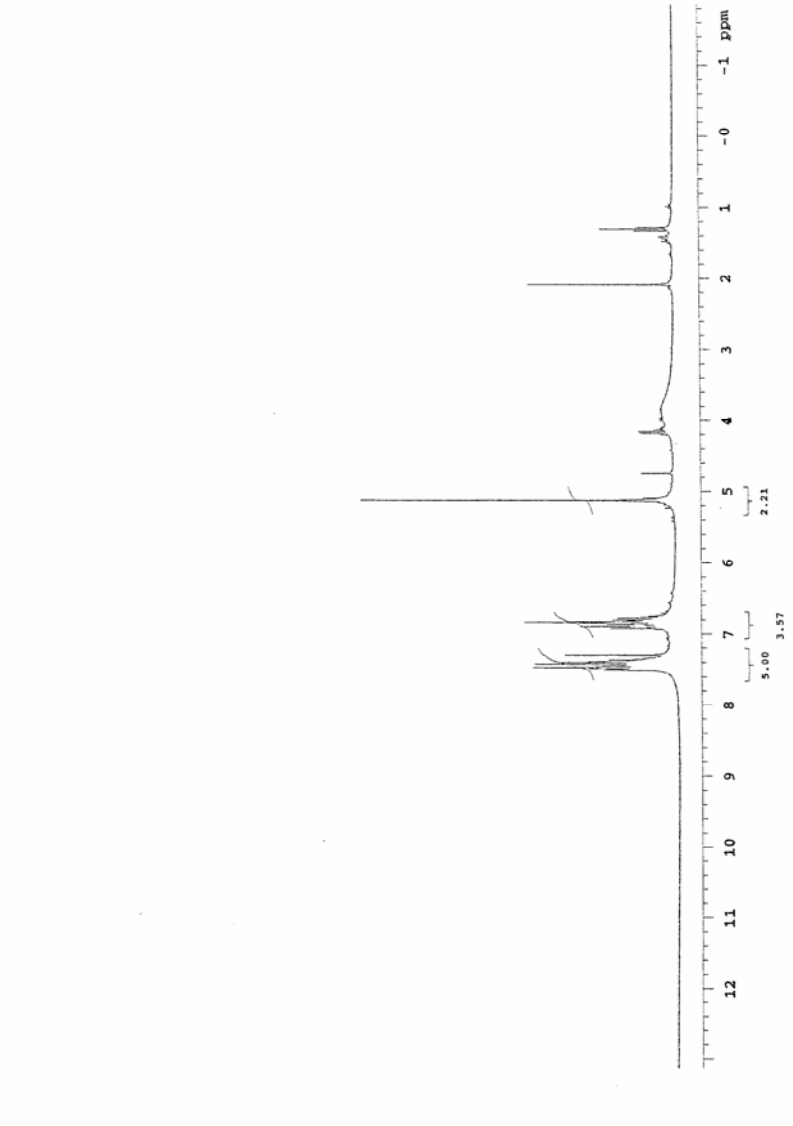
A.10 NMR Spectrum of Benzyl o-Nitrophenyl Ether



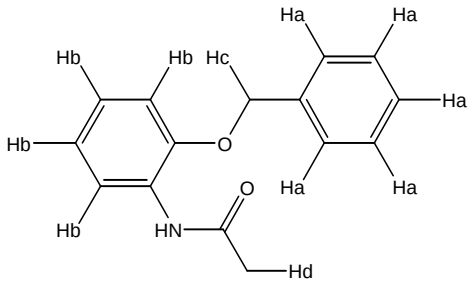


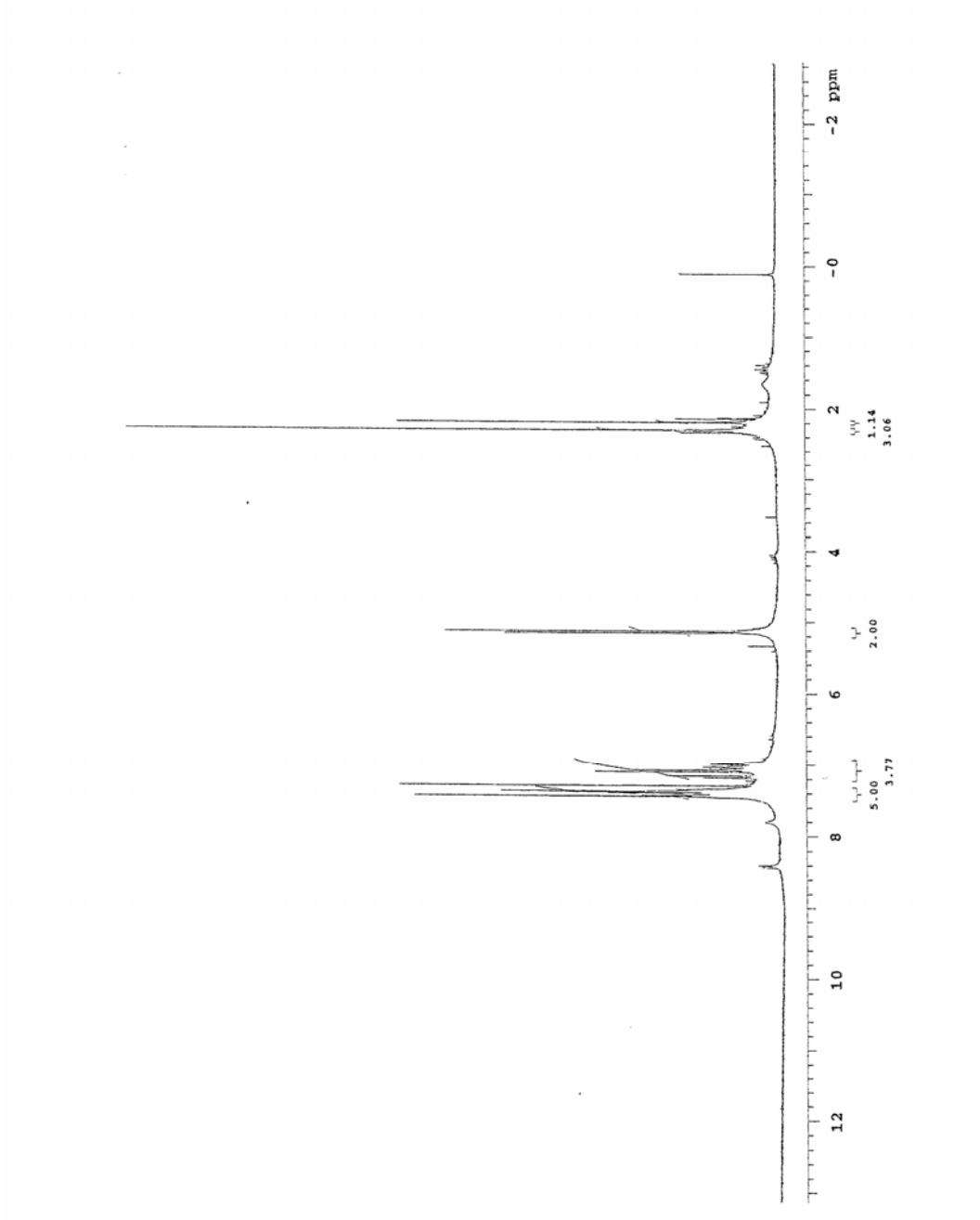
A.11 NMR Spectrum of Benzyl o-Aminophenyl Ether



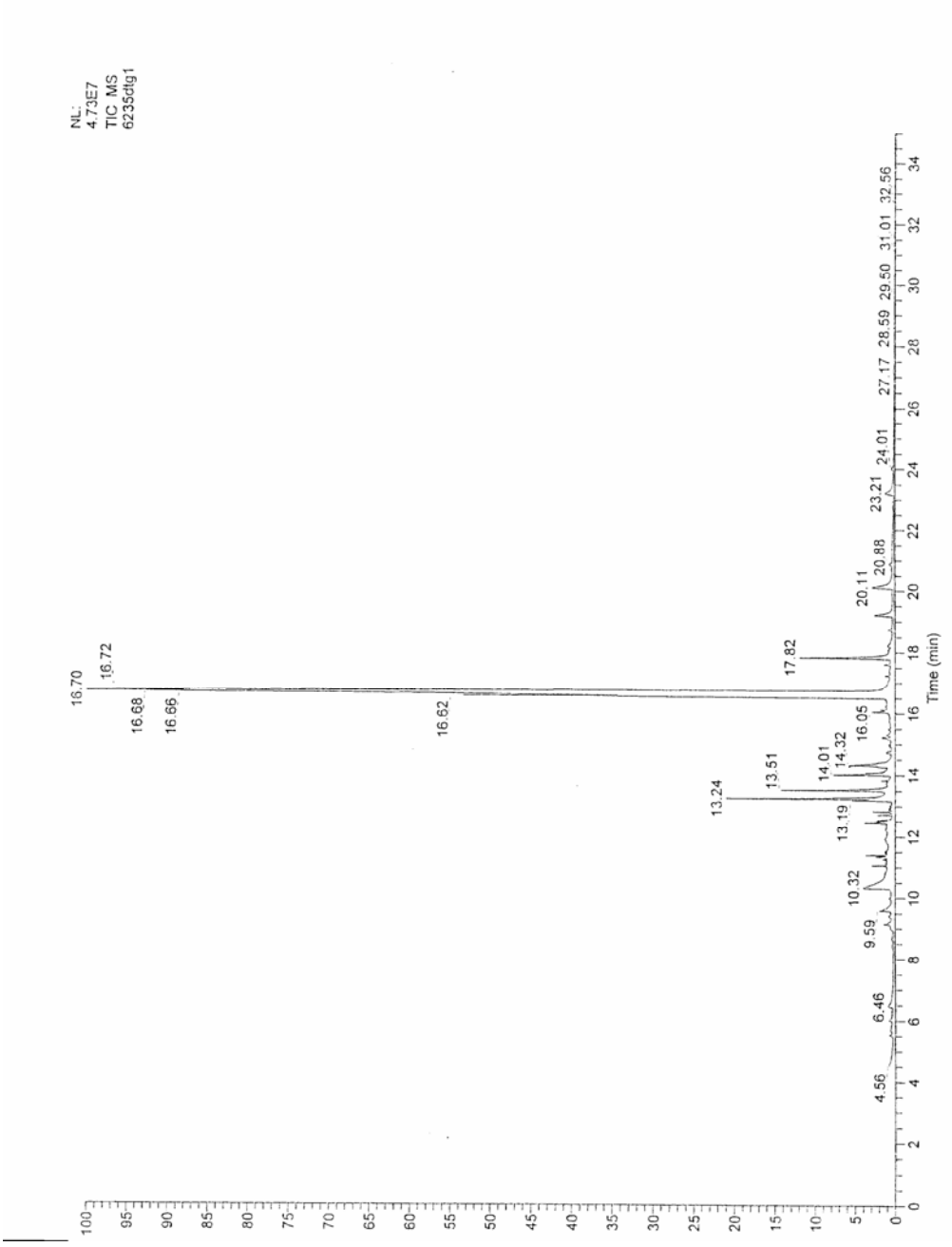


A. 12 NMR Spectrum of o-Benzyloxyacetanilide

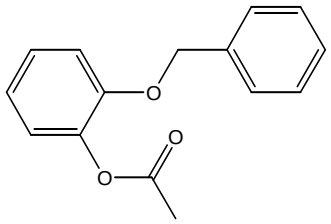




A. 13 GC Spectrum of Reaction Mixture Containing 6H-Dibenzopyran and o-Benzyloxyphenyl Acetate

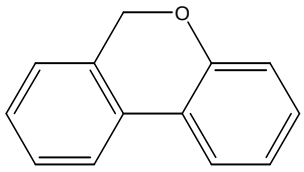


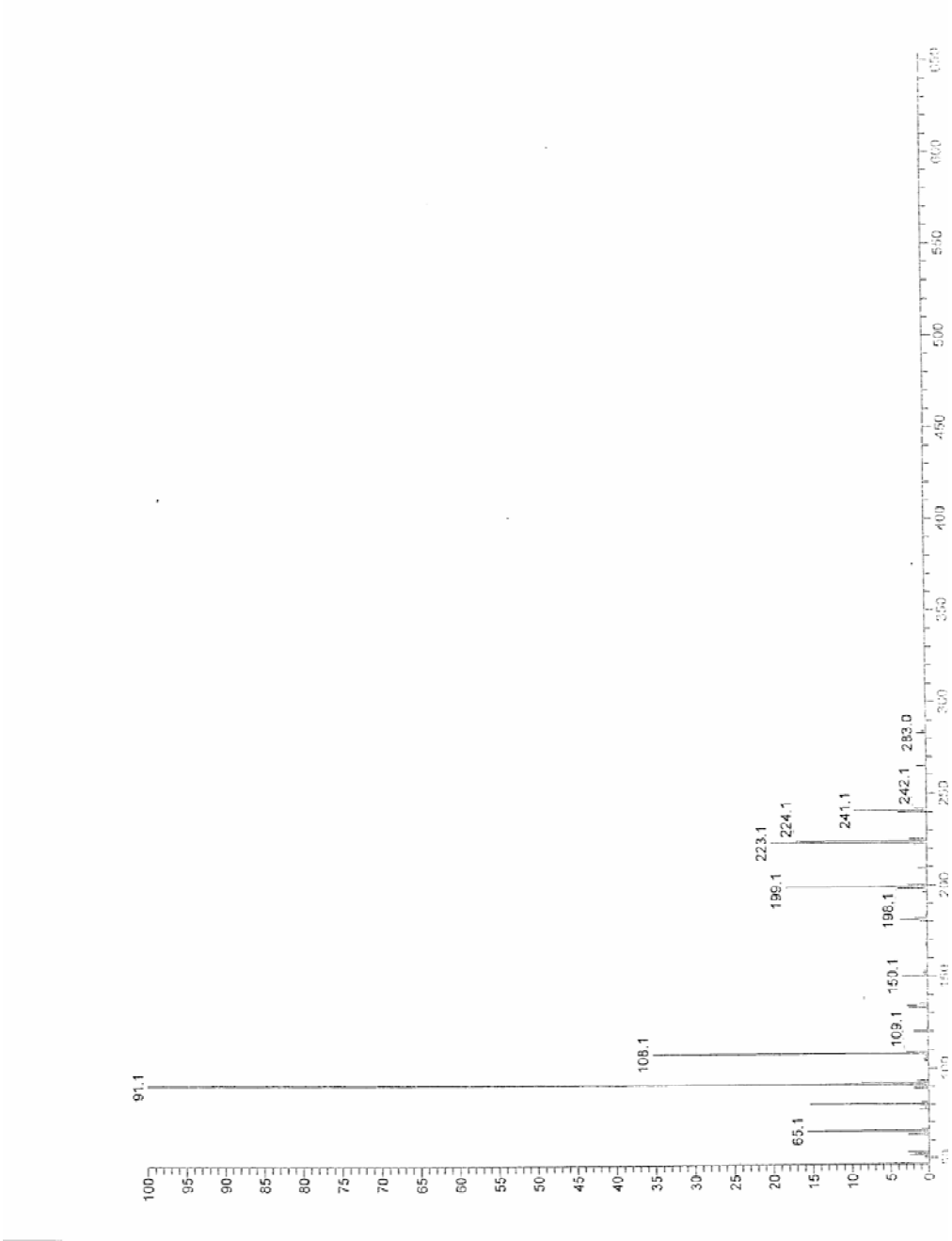
A. 14 Mass Spectrum of o-Benzyloxyphenyl Acetate



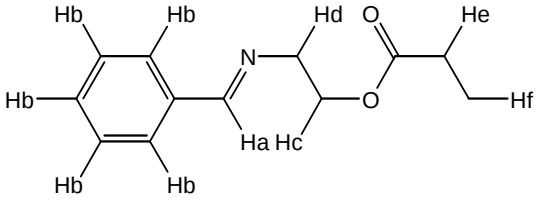


A. 15 Mass Spectrum of 6H-Dibenzopyran



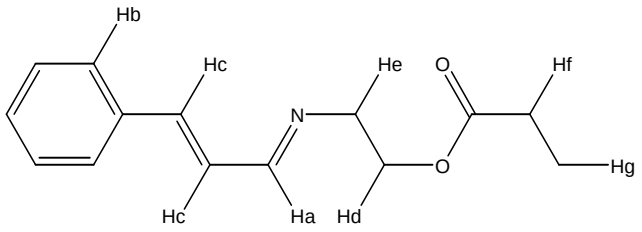


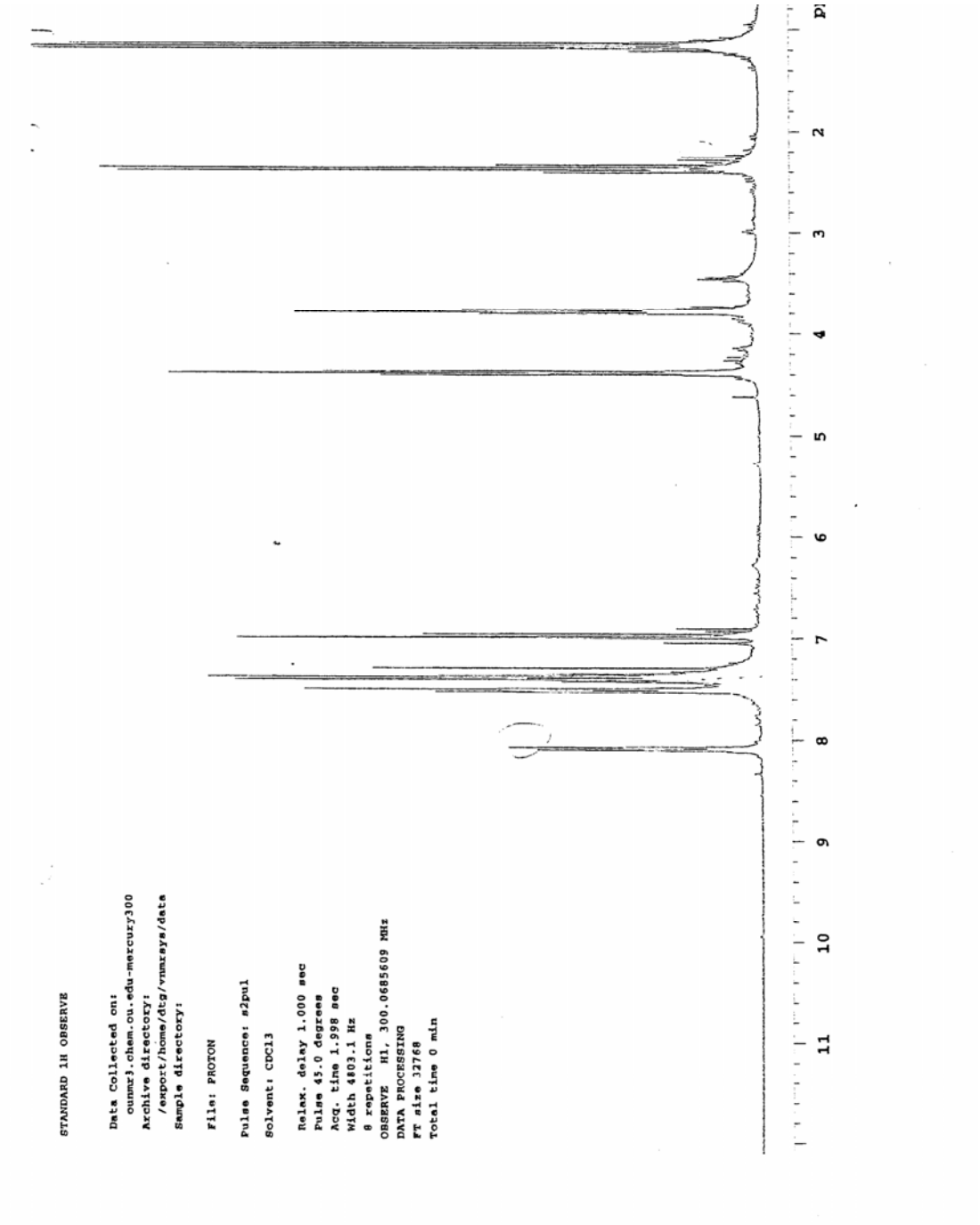
A.16 NMR Spectrum of N-Benzylidene-2-aminoethyl Propanoate



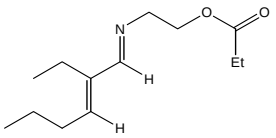


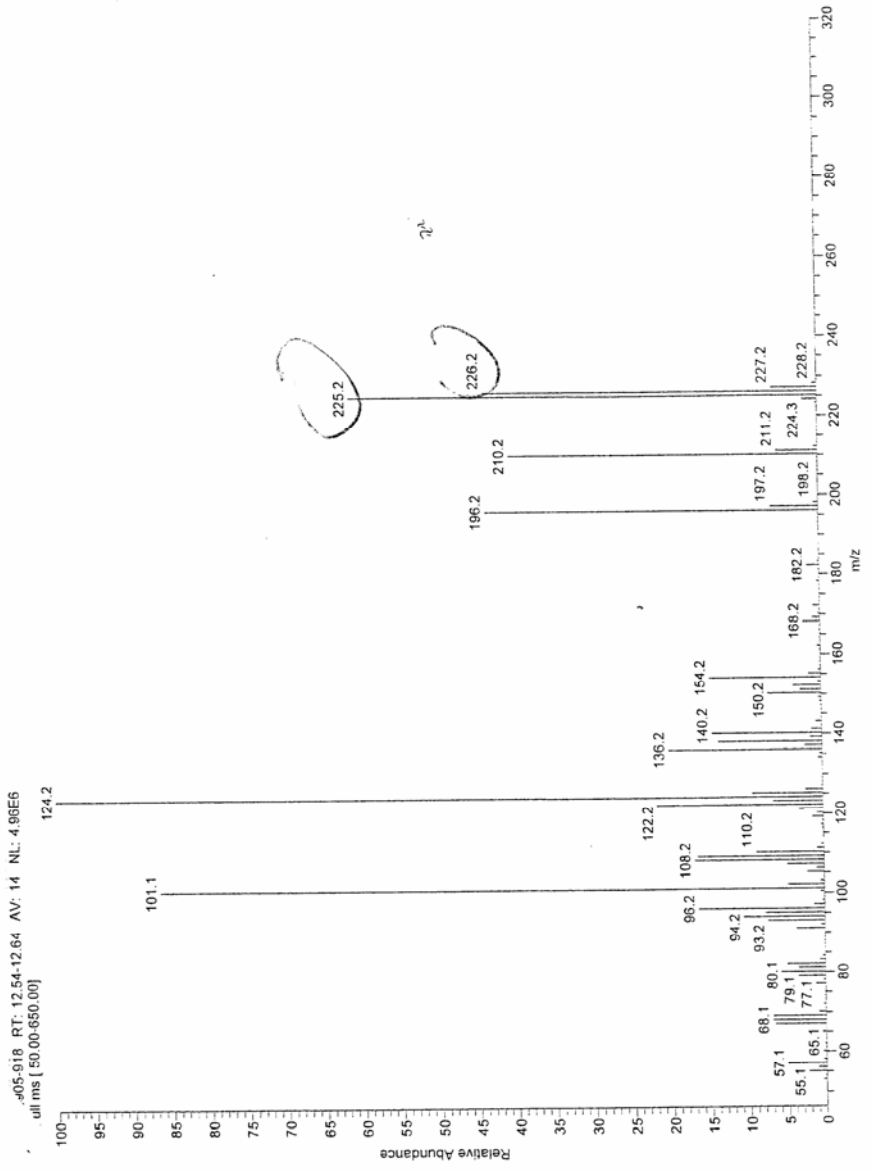
A.17 NMR Spectrum of N-Cinnamylidene-2-aminoethyl Propanoate



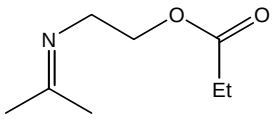


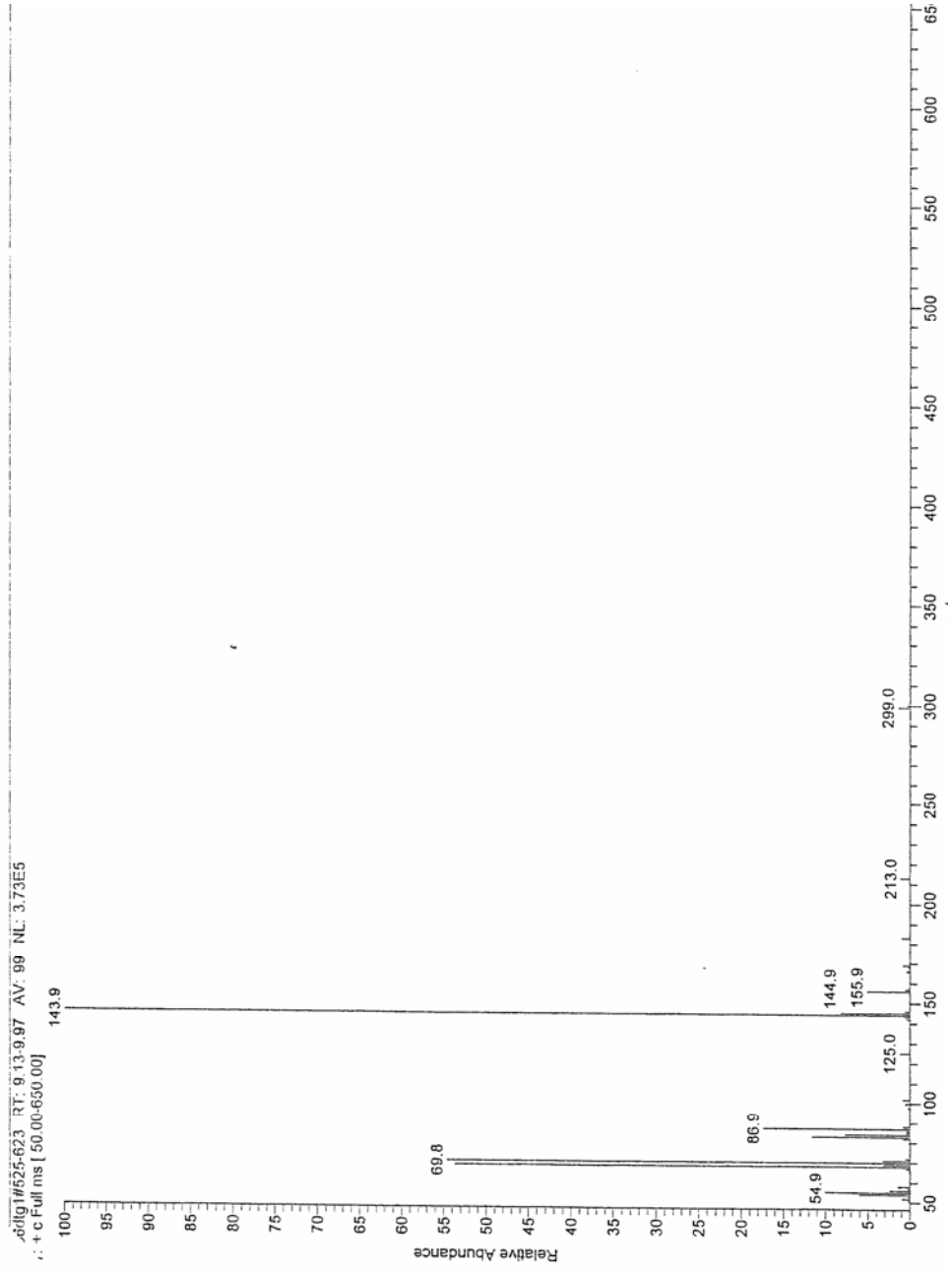
A.18 Mass Spectrum of N-(2-Ethyl)hex-2-enylidene-2-aminoethyl Propanoate



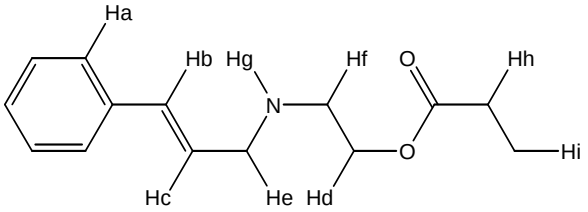


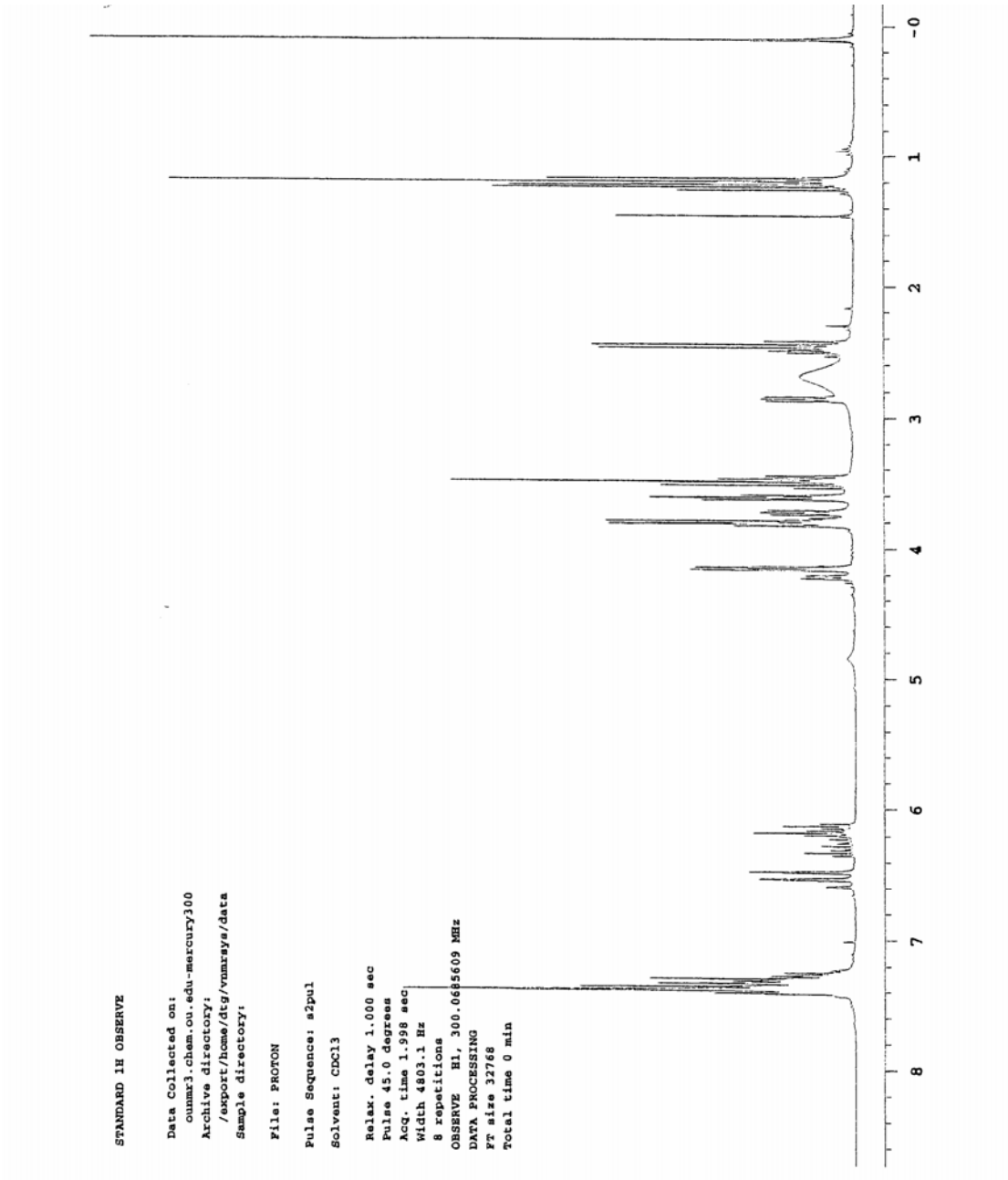
A.19 Mass Spectrum of N-(2-Methyl)ethylidene-2-aminoethyl Acetate



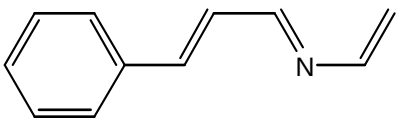


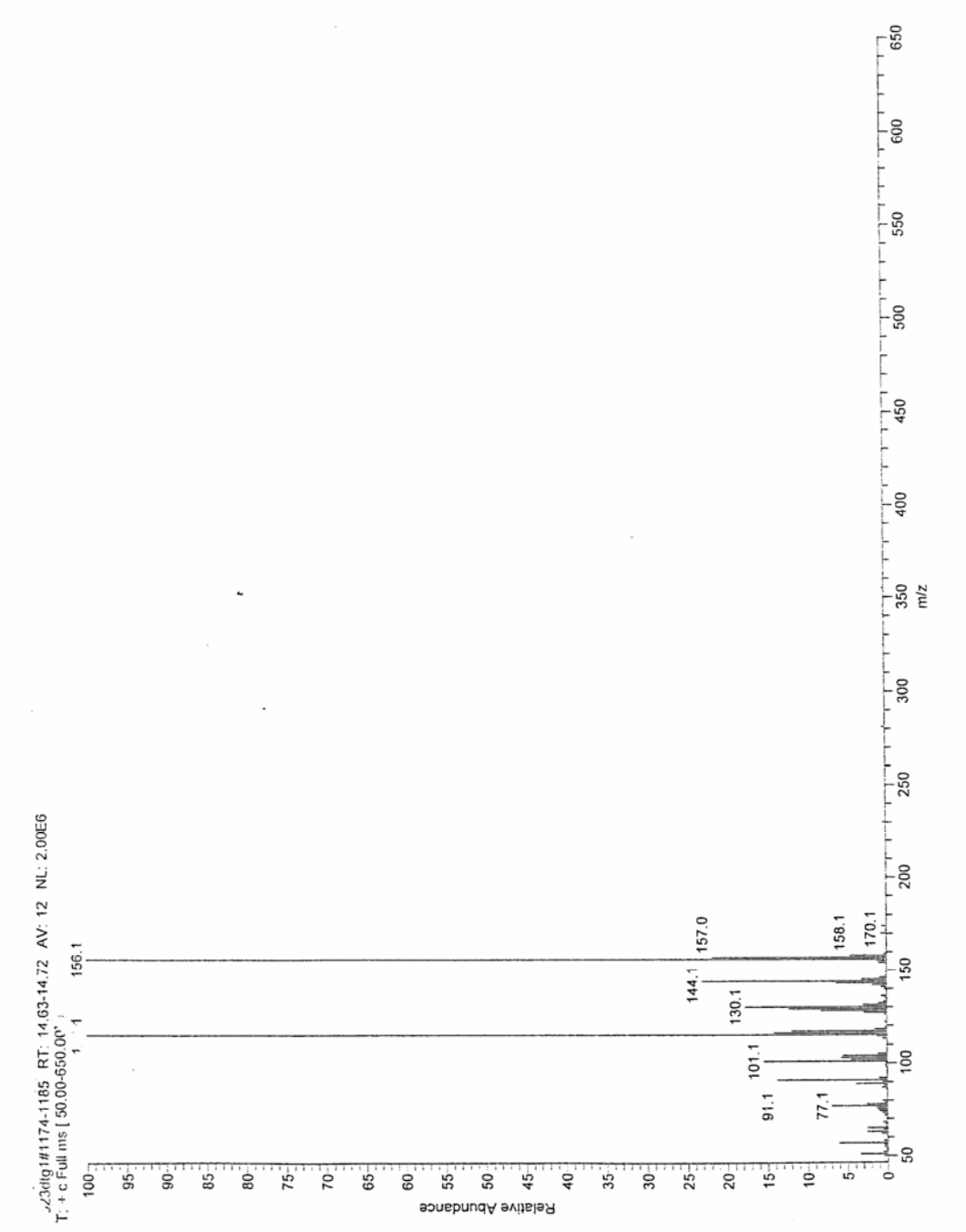
A.20 NMR Spectrum of N-Cinnamyl-2-aminoethyl Propanoate



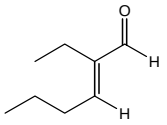


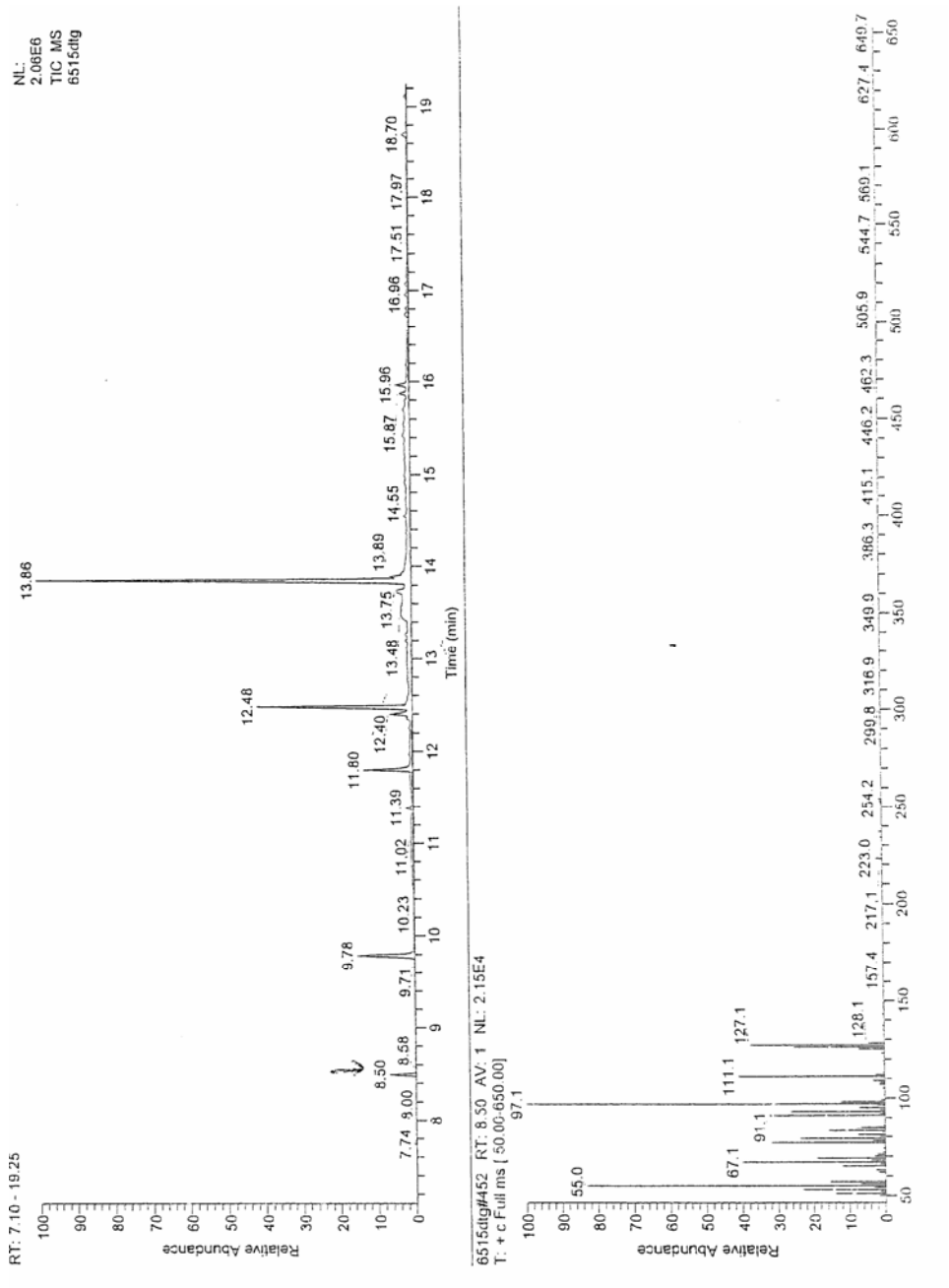
A.21 Mass Spectrum of N-Cinnamylideneaminoethene



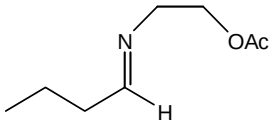


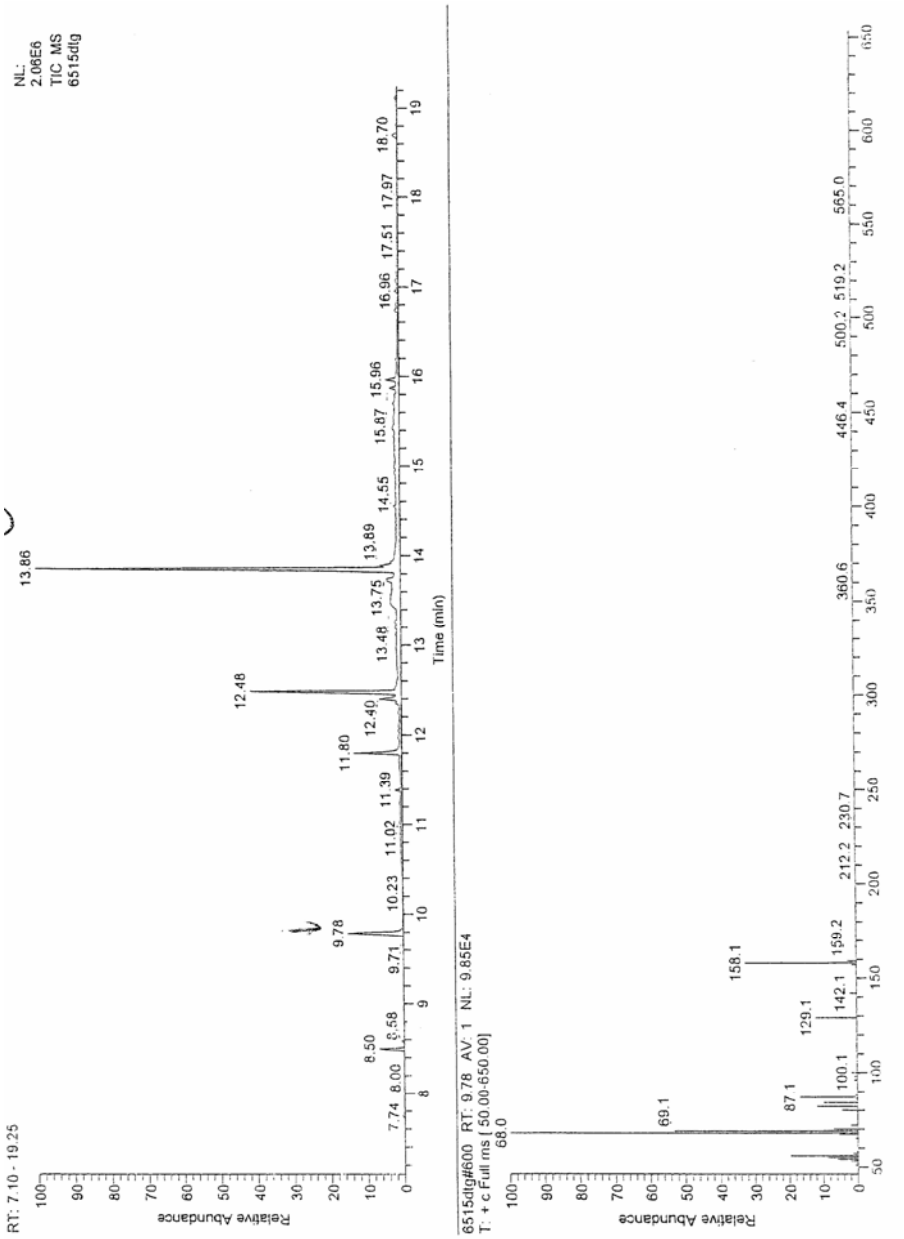
A. 22 Mass Spectrum of Product 26 from the Reaction of 2-Methyl-2-oxazoline with 2 Equivalents of Butyraldehyde for 72 Hours



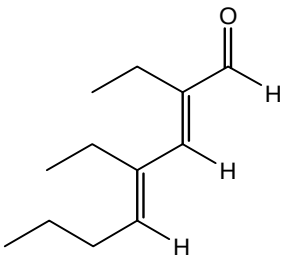


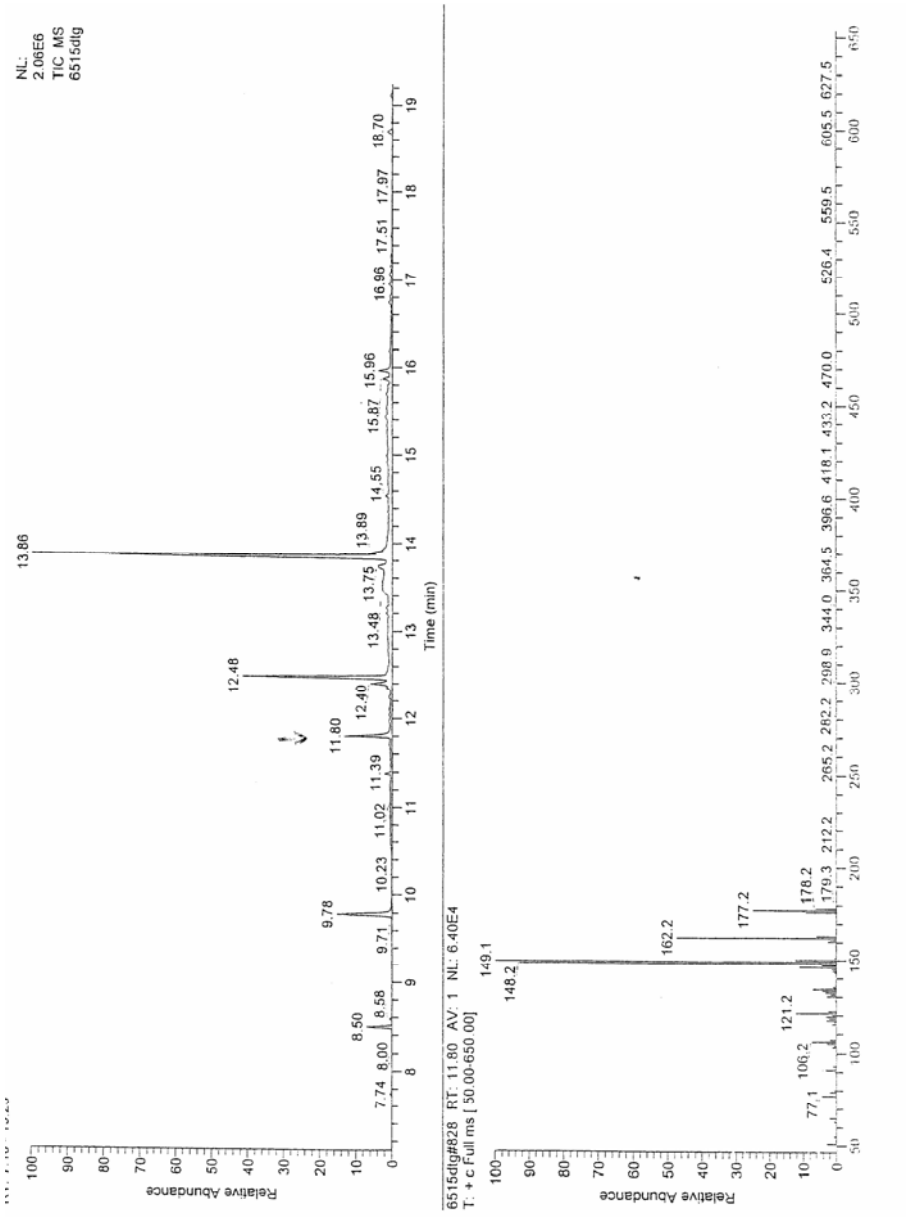
A. 23 Mass Spectrum of Product 27 from the Reaction of 2-Methyl-2-oxazoline with 2 Equivalents of Butyraldehyde for 72 Hours



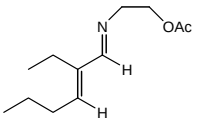


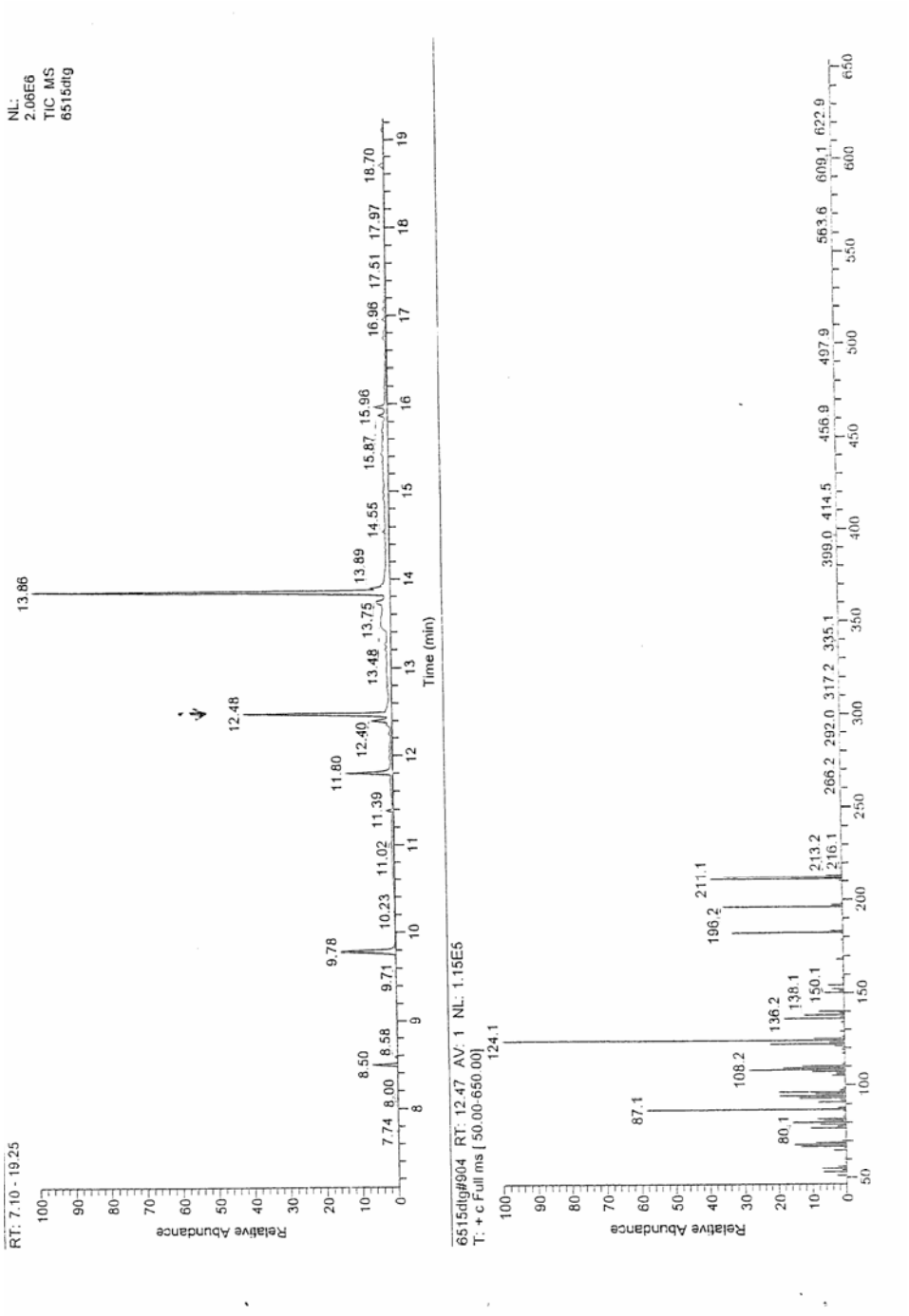
A. 24 Mass Spectrum of Product 28 from the Reaction of 2-Methyl-2-oxazoline with 2 Equivalents of Butyraldehyde for 72 Hours



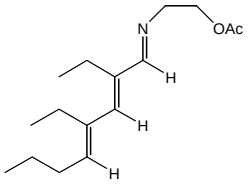


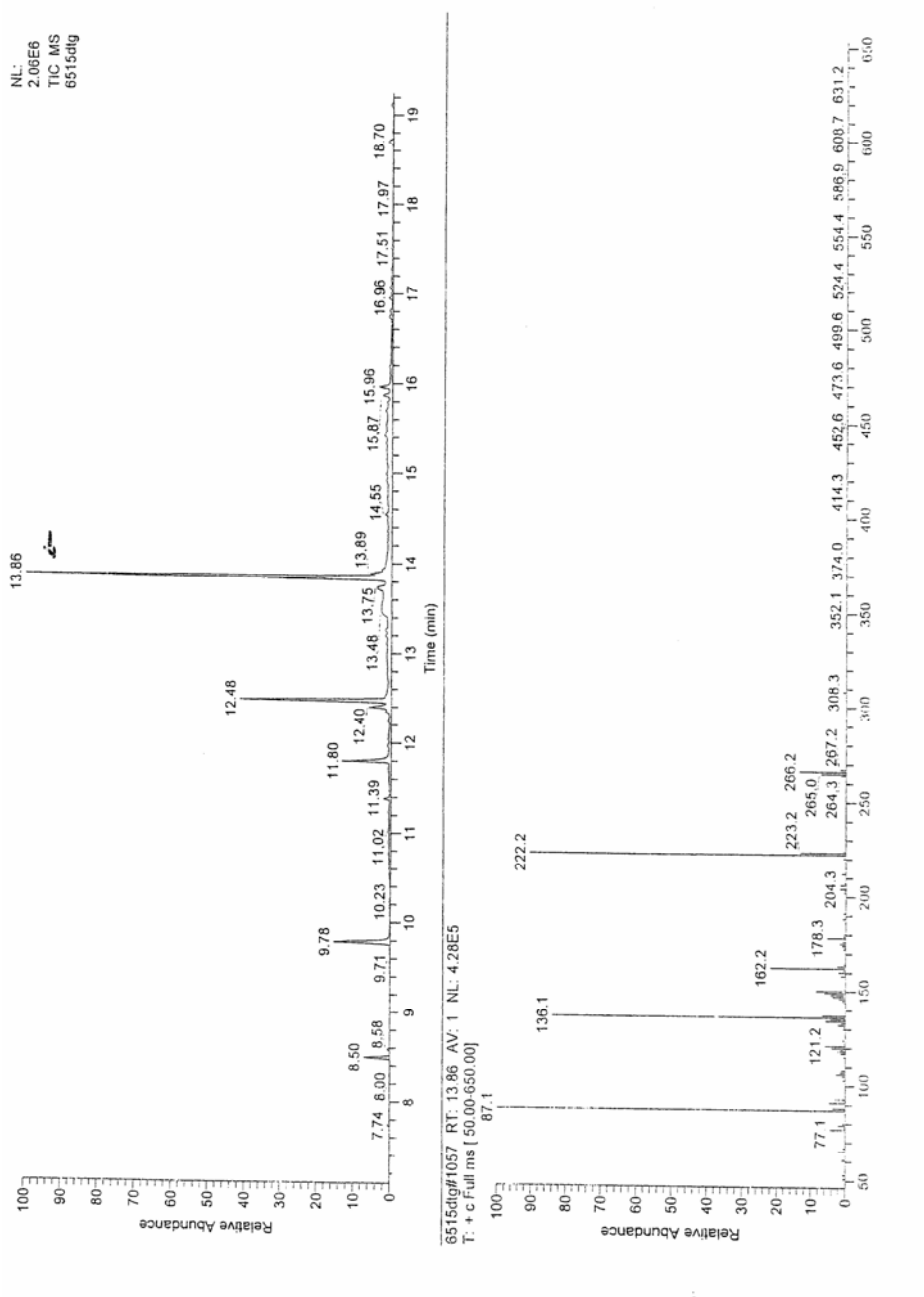
A. 25 Mass Spectrum of Product 29 from the Reaction of 2-Methyl-2-oxazoline with 2 Equivalents of Butyraldehyde for 72 Hours



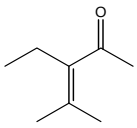


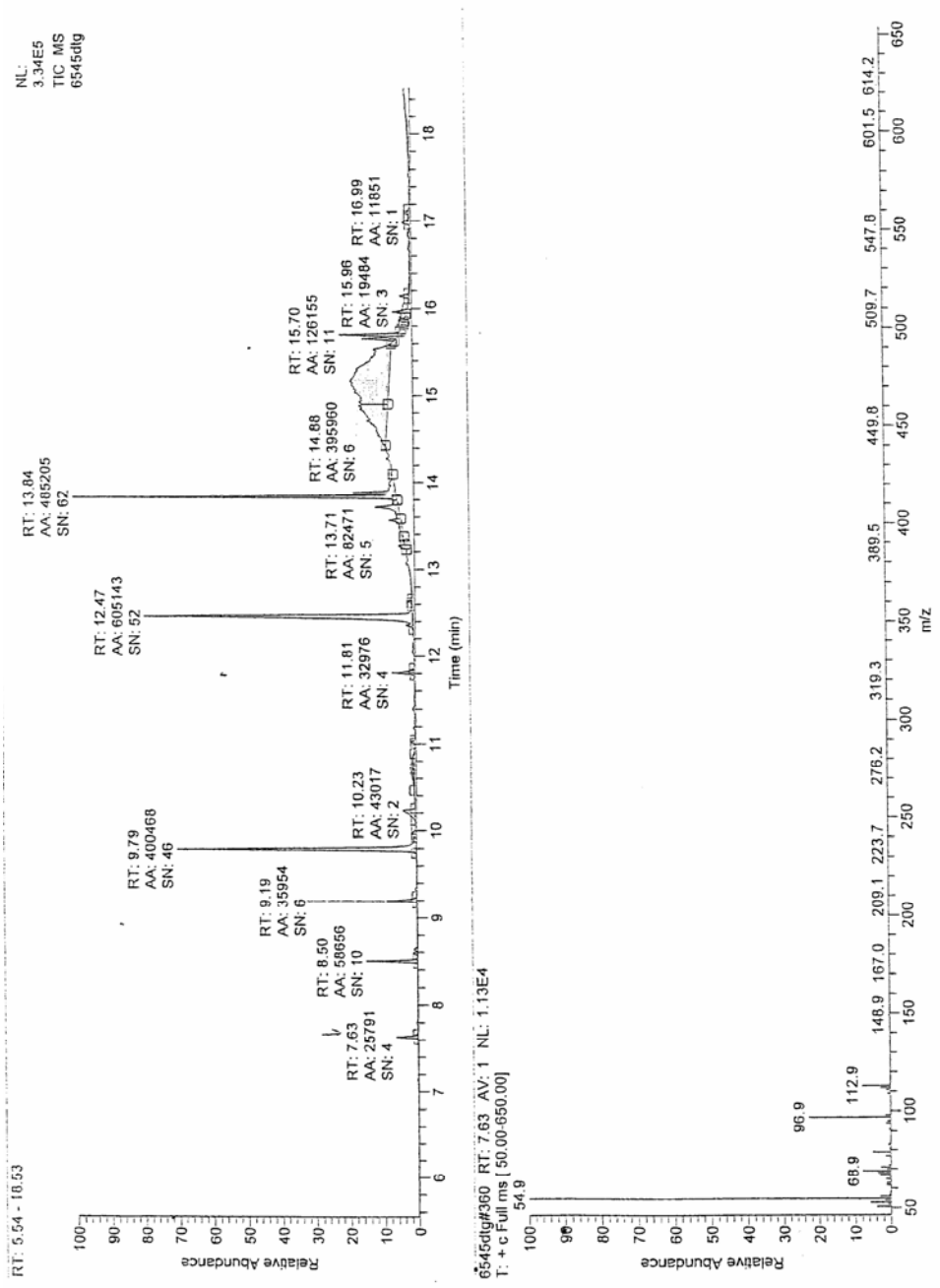
A. 26 Mass Spectrum of Product 30 from the Reaction of 2-Methyl-2-oxazoline with 2 Equivalents of Butyraldehyde for 72 Hours



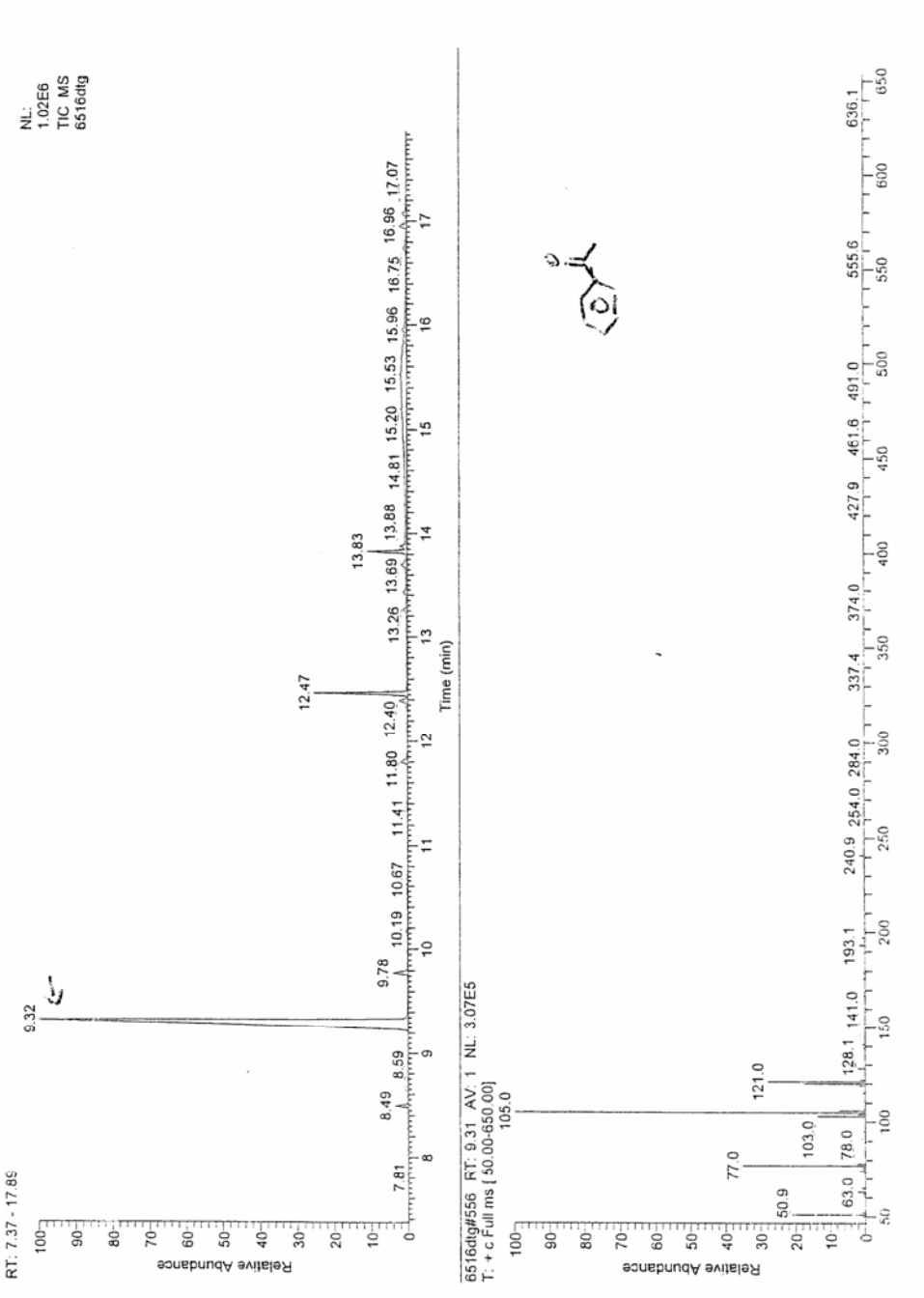


A. 27 Mass Spectrum of Product 27 from the Attempted Crossed-Aldol Condensation

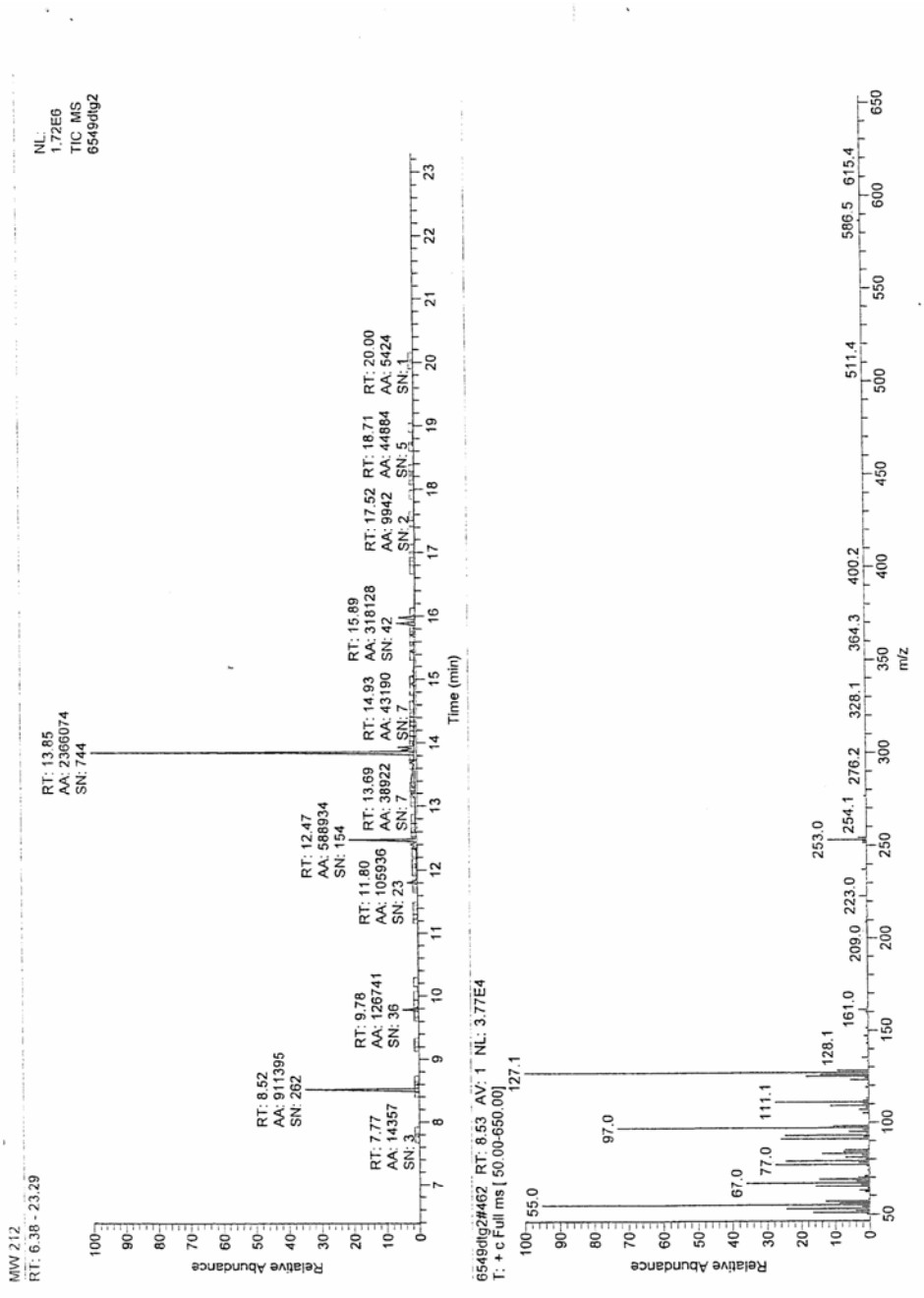




A.28 GC Chromatograph of the Mixture of 1:1:1 Ratio of 2-Methyl-2-oxazoline/Butyraldehyde/Acetophenone after 72 Hours



A.29 GC Chromatograph of the Mixture of 1:3 Ratio of 2-Methyl-2-oxazoline/Butyraldehyde after 20 Hours



A.30 GC Chromatograph of the Mixture of 2-Methyl-2-oxazoline and a Large Excess of Butyraldehyde after one week

