1-1-2011

Reactions of in Situ Generated Cyclic Ketene-N,N-,-N,O- and -N,S-Acetals: Acid Catalyzed Olefinations of Bio-Oil

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By

Sabornie Chatterjee

A Dissertation
Submitted to the Faculty of
Mississippi State University
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
in Chemistry
in the Department of Chemistry

Mississippi State, Mississippi

April 2011

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Title of Study: REACTIONS OF IN SITU GENERATED CYCLIC KETENE-N,N´-,-N,O- AND -N,S- ACETALS. ACID CATALYZED OLEFINATIONS OF BIO-OIL

Pages in Study: 240

Candidate for Degree of Doctor of Philosophy

This dissertation research is based on two reactions, including those of cyclic ketene acetals with acid chlorides and acid catalyzed olefination reactions in bio-oil. In first four chapters, reactions of *in situ* generated cyclic ketene acetals were explored.

Highly functionalized heterocycles such as pyrrollo-[1,2-*c*]imidazolediones, were synthesized in one-pot reactions of 2-alkylimidazoles or 2-methylbenzimidazoles with 1,3-diacid chlorides. Some reactions proceed through *in situ* generated cyclic-*N*,*N*′-ketene acetal intermediates. 2-Alkylimidazoles and 2-methylbenzimidazole can be considered as tridentate nucleophiles in these reactions that can give four consecutive attacks on electrophiles which ultimately generate new heterocycles.

Reactions of substituted oxazoles and thiazoles with different acid chlorides in the presence of different bases were explored. Arylvinyl esters of substituted benzoic acids

containing substituted oxazoles or thiazoles were formed when aroyl chlorides were used. Most reactions occurred through *in situ* generated cyclic ketene acetals.

Reactions of 2-methylbenzoxazole and 5-phenyl-2-methylbenzoxazole with acid chlorides and base in THF generated a series of *ortho*-amidoesters.

All of these reactions showed that aromatic heterocycles based *in situ* generated cyclic ketene acetals could be used to make highly functionalized heterocycles under mild conditions. These one-pot reactions generated various heterocycles, which might have useful bioactivities. For example, arylvinyl esters of substituted benzoic acids have been reported to show insecticidal activities.

The last two chapters describe the olefinations of bio-oil and model bio-oil compounds using acid catalysts. Two different branched olefins were used, representative of those available at petroleum refineries. Amberlyst-15 and Nafion NR-50 were used as heterogeneous acid catalysts.

The acid catalyzed olefination of bio-oil was explored using an excess of 1-octene. Some olefinations were performed in the presence of ethanol. Ethanol was used to make the olefin and bio-oil phases partially miscible.

Acid catalyzed olefination of raw bio-oil induced some changes in the resulting bio-oil by generating variety of alcohols, ethers and oligomeric mixtures of the starting olefin. Olefination with excess 1-octene showed the decrease of the water content and the acid value and increase of the heating value of the bio-oil. Thus, the acid catalyzed olefination of bio-oil can be considered as a potential bio-oil upgrading technique.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Dr. Charles U. Pittman, Jr. for his advices and suggestions in my dissertation research. I would also like to thank my major professor Dr. Keith T. Mead and committee members Dr. Andrzej Sygula, Dr. Steven Gwaltney, and Dr. William P. Henry for their valuable time, assistance and suggestions.

I am grateful to Dr. Paul von Rague´ Schleyer and Judy Wu of the University of Georgia, who helped me by performing a few NICS calculations on some molecules described in this dissertation.

Appreciation is also extended to my graduate coordinator, Dr. Stephen C. Foster for his guidance throughout my gradute career. I would also like to thank other professors in the Department of Chemistry for helping me to develop my basic knowledge in chemistry.

I sincerely thank Dr. Guozhong Ye, Yingquan Song, Ireshika De Silva, Sean Stokes, Chinni Yalamachilli and other colleagues for their help and friendship.

Finally, I wish to express special words of appreciation to the most important persons of my life: my son Nandik Chatterjee, my wife Priyanka Chatterjee, my parents Devasis Chatterjee and Esha Chatterjee and my brother Rajarshi Chatterji for their unconditional love and invaluable support.

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CHAPTER I

GENERAL INTRODUCTION AND RESEARCH GOALS

Chemistry of Cyclic Ketene Acetals

Ketene acetals have similar structural properties to acetals and vinyl ethers. They can also be viewed as the ethers of the enolic form of esters.

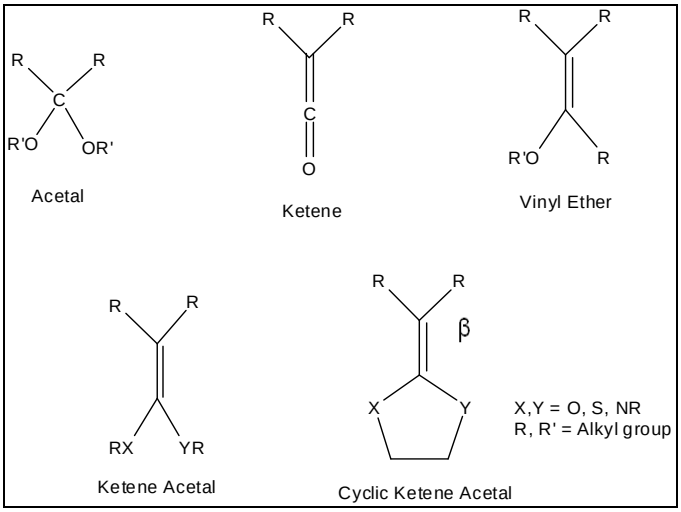


Figure 1.1 General Structures of an Acetal, a Ketene, a Vinyl Ether, a Ketene Acetal and a Cyclic Ketene Acetal (CKA)

Cyclic Ketene acetals (CKA) are a sub-class of ketene acetals. The resonance structures of different ketene acetals, depicting the highly polarized nature of the carbon-

carbon double bonds are shown in Figure 1.2 for -*O*,*O*-acetals, (**1**), -*N*,*O*-acetals, (**2**), -*N*,*S*- acetals, (**3**), and -*N*,*N'*-acetals (**4**). Commonly used cyclic ketene acetals contain five or five- or six-membered rings.

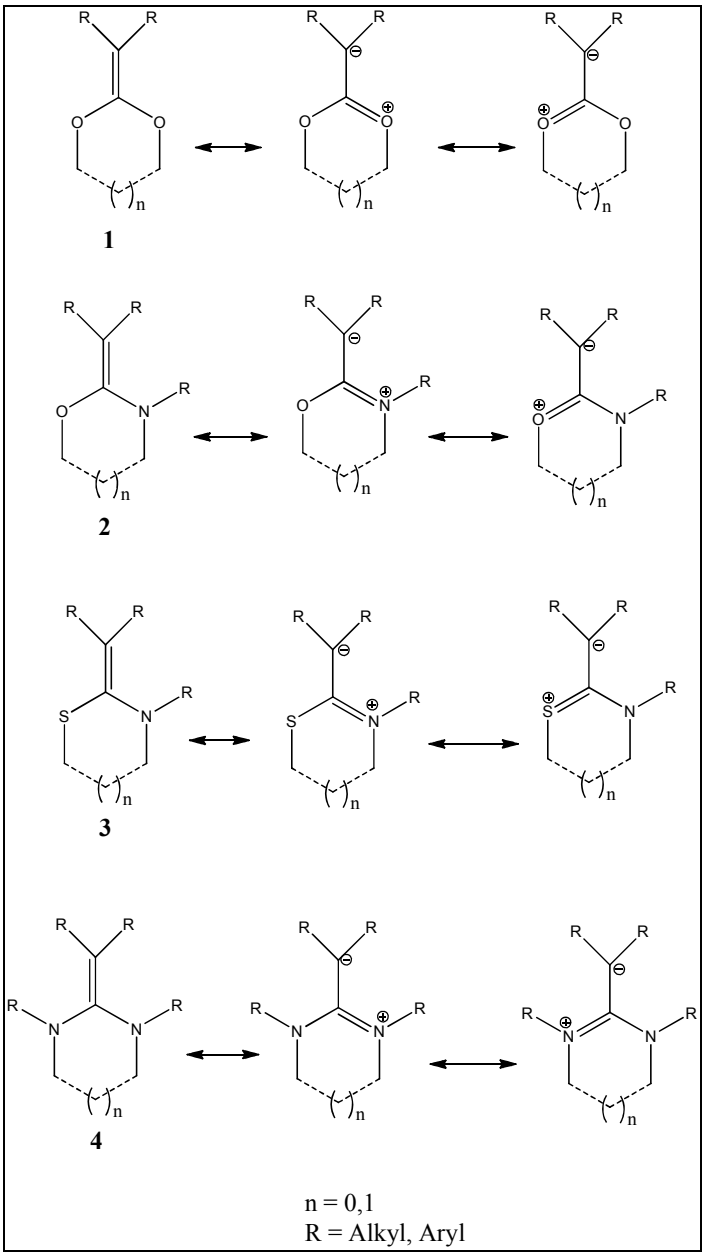
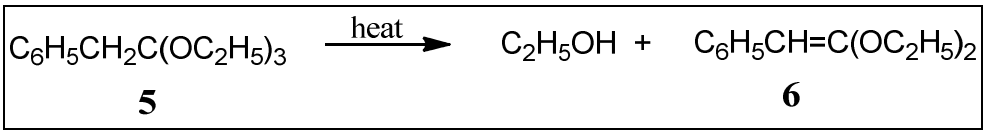


Figure 1.2 Resonance Structures of Cyclic Ketene Acetals

Cyclic ketene (-*O*,*O*-, -*N*,*O*-, -*N*,*N'*- and -*N*,*S*-) acetals are extremely nucleophilic because of the two electron donating hetaroatoms at the same end of the carbon-carbon double bond. The heteroatom lone-pair electrons are conjugated with the carbon-carbon double bond. This makes the carbon-carbon double bond highly polar and the *β*-carbon (defined in this Dissertation as the exocyclic carbon of this double bond, see Fig. 1.1) extremely nucleophilic. Nucleophilicity increases if the alkyl or aryl 'R' groups (Figure 1.2) are replaced with hydrogens. *O*,*O*-Ketene acetals are very reactive towards protic acids because of the high nucleophilicity of the *β*-carbon and the high stability of the resulting dioxonium-stabilized carbocation. Similar stabilization of -*O*,*S*-, -*N*,*O*-, -*N*,*S*- and -*N*,*N'*- systems promotes protonation of the *β*-carbon.

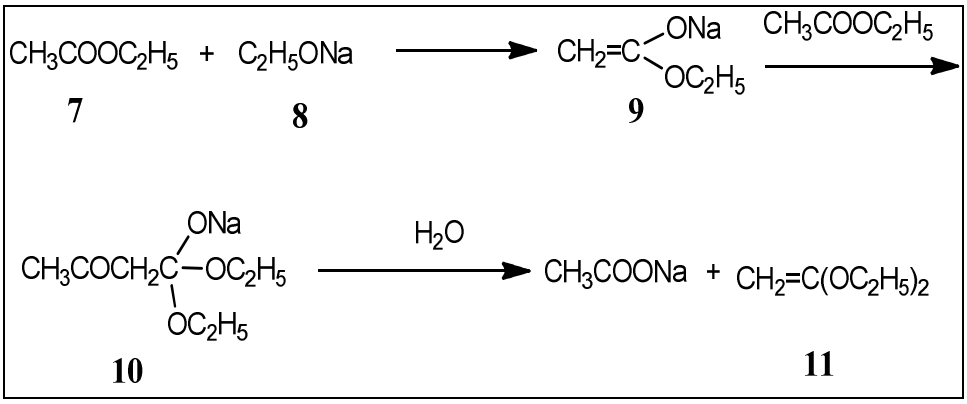
In 1891, Biginelli claimed the first synthesis of a ketene-*O*,*O*-acetal, which, later was proven wrong by Cope.[1,2] Cope found that the Biginelli reported structure was actually a diphenyl acetal of ethylene glycol. The credit for the first successful synthesis of a ketene-*O*,*O*-acetal goes to Reitter and Weindell in 1907 who synthesized *β*-diethoxyacrylic ester.[3]

In 1922, Staudinger and Rathsam reported the preparation of phenylketene diethylacetal (**6**), by a pyrolysis of 2,2,2-triethoxyethylbenzene (**5**) (Scheme 1.1).[4] They failed to extend this technique to make ketene acetals from other esters such as orthoacetic or orthopropionic esters. They also explored the properties of **6** and were the first to coin the term 'ketene acetal'.



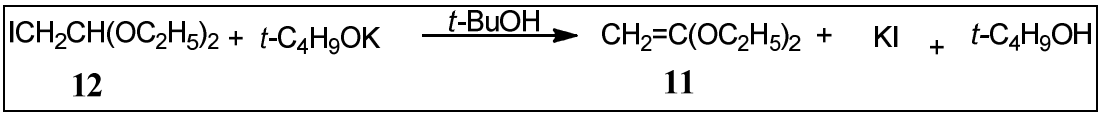
Scheme 1.1 Preparation of the Ketene-*O,O*-Acetal, 2,2-Diethoxyvinylbenzene (**6**), by Pyrolysis of 2,2,2-Triethoxyethylbenzene (**5**)[4]

In the same year, Scheibler and Ziegner reported the preparation of 1,1-diethoxyethene (**11**) (Scheme 1.2) while determining the course of the acetoacetic ester synthesis.[5] The hydrolysis of the primary product (**10**) of ethyl acetate addition to its sodium enolate resulted in the formation of sodium acetate and ketene diethylacetal (**11**) as the minor product. However, many groups could not duplicate this technique successfully.[6-8]



Scheme 1.2 Synthesis of 1,1-Diethoxyethene (**11**) from Ethyl Acetate (**10**)[5]

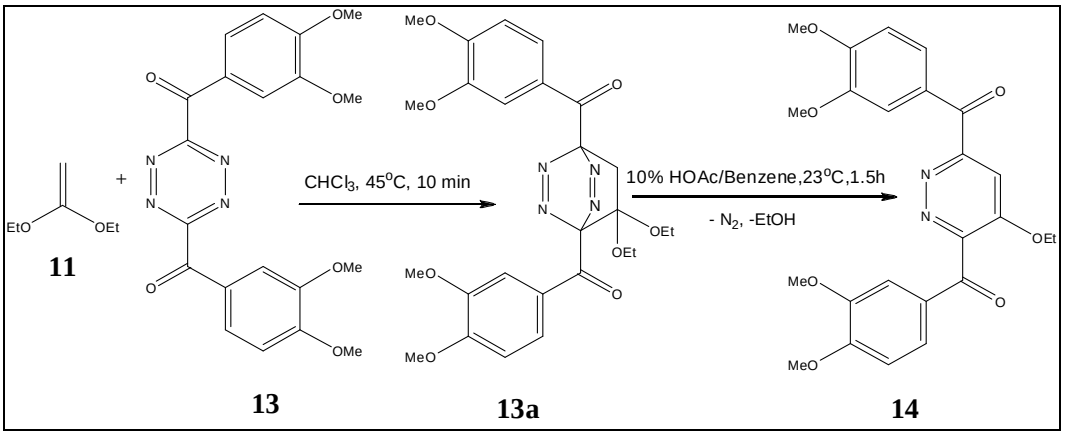
In 1936, McElvin and coworkers reported another route to ketene acetals.[6] They made 1,1-diethoxyethene (**11**) by the dehydrohalogenation of an iodoacetal (**12**) with potassium *t*-butoxide in *t*-butyl alcohol (Scheme 1.3).



Scheme 1.3 Synthesis of 1,1-Diethoxyethene (**11**) by the Dehydrohalogenation of the Iodoacetal (**12**)[6]

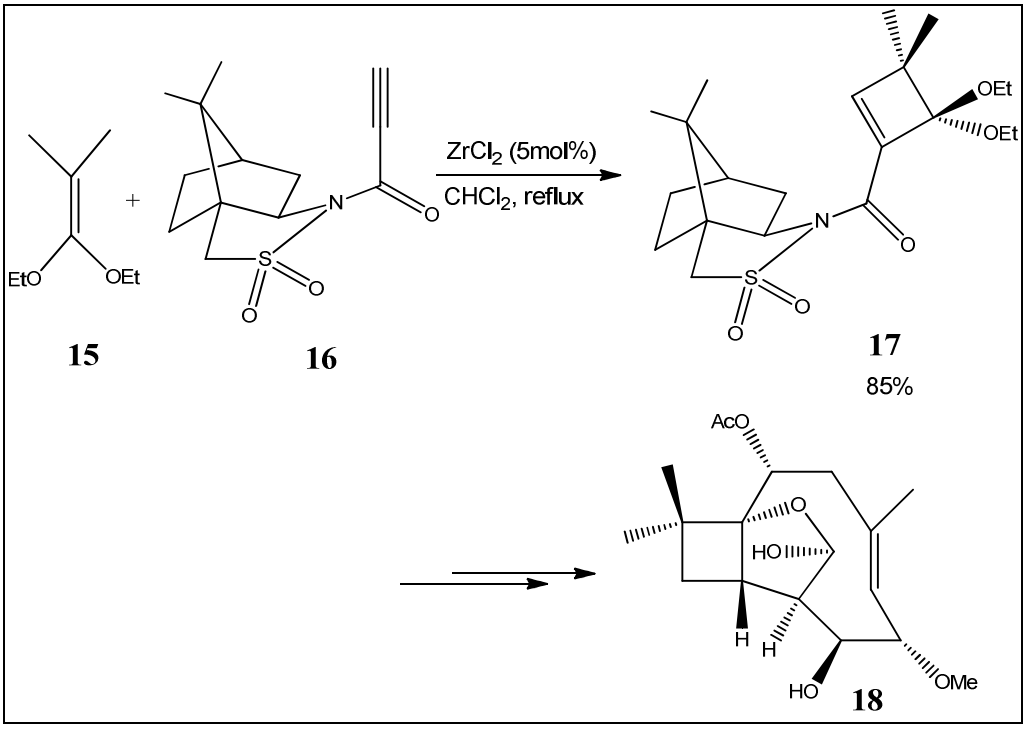
Adickers, Bergstrom, and others also reported the synthesis and uses of various ketene-*O*,*O*-acetals around that time.[7,8,9] Since then, ketene acetals have attracted a lot of research interest as reactants in a variety of cycloaddition reactions.[10-14]

In one recent example, Soenen et al. used electron rich 1,1-diethoxyethene (**11**) to obtain a 1,2-diazine (**14**) (Scheme 1.4).[10] The 1,2-diazine (**14**) was formed by a [4+2] inverse electron demand Diels-Alder reaction of **11** and 3,6-bis-(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine (**13**) followed by release of nitrogen and ethanol.



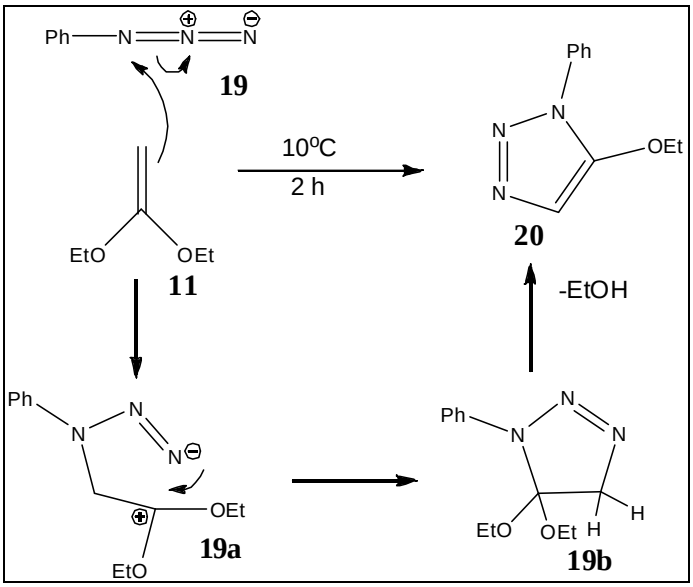
Scheme 1.4 Use of the 1,1-Diethoxyethene (**11**) in an Inverse Electron Demand Diels-Alder Reaction[10]

Ketene acetals have also been successfully used in normal Diels-Alder reactions.[11,12,13] Recently, Takao and coworkers used a substituted diethyl-*O*,*O*-ketene acetal, 1,1-diethoxy-2-methylprop-1-ene (**15**), in a [2+2] cycloaddition reaction to develop a synthesis of (-)-Pestalotiopsin A (**18**) (Scheme 1.5).[12] The Lewis acid catalyzed [2+2] cycloaddition is a dipolar reaction of 1,1-diethoxy-2-methyl-prop-1-ene (**15**) and **16** which generates the adduct **17** with 85% yield.



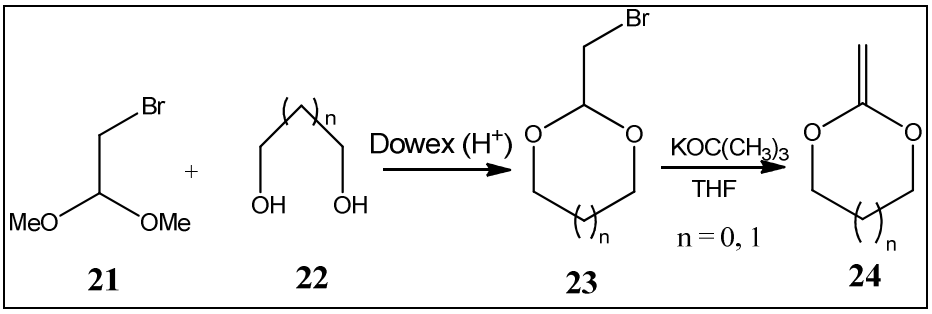
Scheme 1.5 Synthesis of (-)-Pestalotiopsin A (**18**) using 1,1-Diethoxy-2-methyl-prop-1-ene (**15**)[12]

Ketene-*O*,*O*-acetals undergo cycloaddition reactions with 1,3 dipolar reagents such as phenyl azide (**19**), where the spontaneous elimination of ethanol from **19b** generates the triazole (**20**) (Scheme 1.6).[14]



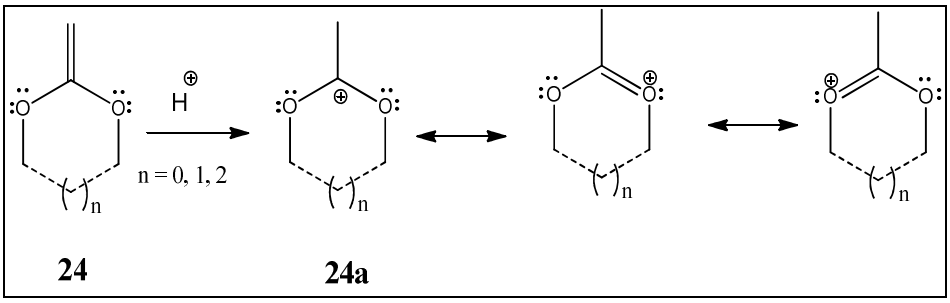
Scheme 1.6 Cycloaddition Reaction using Phenyl Azide (**19**)

Ketene-*O*,*O*-acetals were also used in other reactions such as addition to a Fisher carbene complex.[15] All these examples portrayed the usefulness of ketene-*O*,*O*-acetals in synthesis of variety of small or big molecules. The discovery and usefulness of keten-*O*,*O*-acetals led to the discovery of cyclic ketene-*O*,*O*-acetals. However, it took almost 40 years (after the first synthesis of a ketene-*O*,*O*-acetal) to synthesize the first cyclic ketene-*O*,*O*-acetal. In 1948, the first cyclic ketene-*O*,*O*-acetal was made by McElvain and coworkers.[16] They synthesized 2-methylene-1,3-dioxolane and 2-methylene-1,3-dioxane by the dehydrohalogenation of the corresponding halogenated cyclic acetals. Subsequently, new techniques were used to synthesize cyclic ketene-*O*,*O*-acetals. In one case, a Dowex resin acid catalyst was used to catalyze the formation of the cyclic ketal (**23**), which was then dehydrobrominated by potassium-*t*-butoxide, giving the cyclic ketene-*O*,*O*-acetal (**24**) (Scheme 1.7).[17]

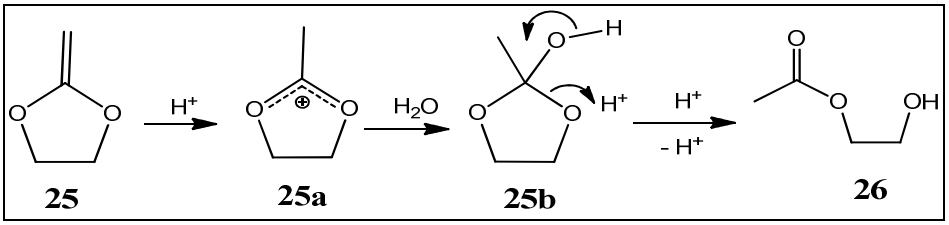


Scheme 1.7 Synthesis of Cyclic Ketene-*O*,*O*-Acetals[17]

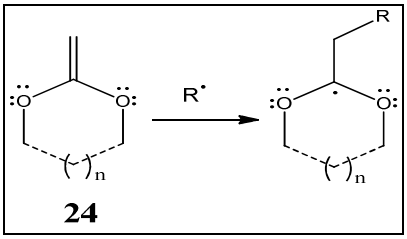
Cyclic ketene-*O*,*O*-acetals, just like their acyclic analogs, were also used in a wide range of cycloadditon reactions.[18] In addition, ring-opening reactions of cyclic ketene-*O*,*O*-acetals introduced a new approach to synthesize diversified products. Protonations of cyclic ketene-*O*,*O*-acetals generate stable dioxonium ions (**24a**) (Scheme 1.8) which can react with nucleophiles and facilitate ring opening.[19] For example, protonation of 2-methylene-1,3-dioxalone (**25**) followed by water attack leads to the ring opening and formation of the monoester (**26**) (Scheme 1.9). Cyclic ketene-*O*,*O*-acetals undergo similar types of reactions with radicals (Scheme 1.10). However, the resulting radicals, such as **24b**, are less stable than dioxonium ions. The generation of a small amount of dioxonium cation or the corresponding radical in the presence of a large excess of cyclic ketene acetals can trigger a polymerization. These properties of cyclic ketene-*O*,*O*-acetals have led to their use in polymer synthesis.[20]



Scheme 1.8 Resonance Structures of a Dioxonium Ion (**24a**)[19]

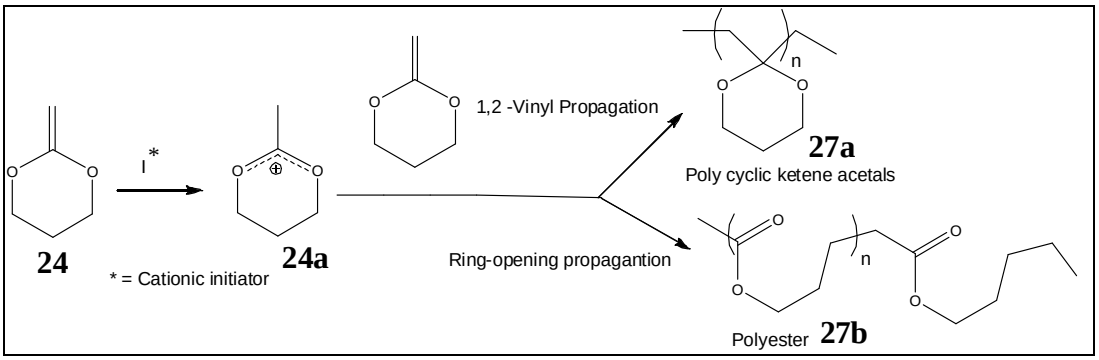


Scheme 1.9 Acid Catalyzed Ring Opening of 2-Methylene-1,3-dioxalone (**25**)[19]



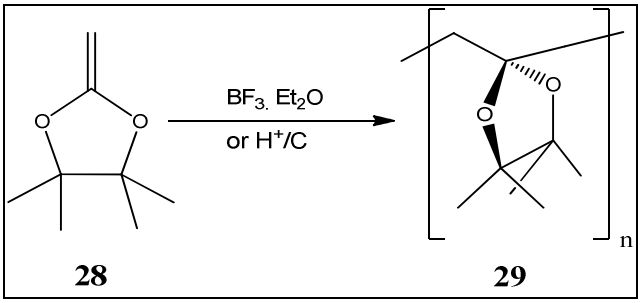
Scheme 1.10 Reaction of a Cyclic ketene-*O,O*-Acetal with a Radical[20]

Cyclic ketene-*O,O*-acetals have been used in both ring-opening and ring-retained (or 1,2-vinyl) polymerizations via cationic or radical initiations (Scheme 1.11).[20]



Scheme 1.11 Polymerization Schemes of a Cyclic Ketene-*O*,*O*-Acetal[20]

Zhu et al. reported a few examples where cyclic ketene-*O*,*O*-acetals were polymerized via a 1,2-vinyl propagation using a protic or Lewis acid (Scheme 1.12).[20]

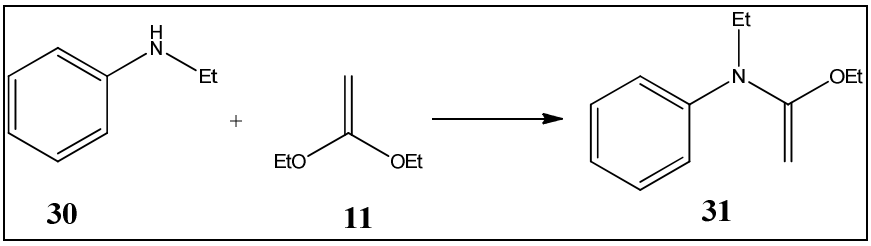


Scheme 1.12 1,2-Vinylic Polymerization of 4,4,5,5,-Tetramethyl-2-methylene-1,3-dioxalone (**28**) in Presence of a Lewis Acid[20]

This multiple reactivity pattern led cyclic ketene-*O*,*O*-acetals to be used to selectively synthesize different types of molecules and polymers.[19,21,22]

The synthesis of the first ketene-*N*,*O*-acetal (**31**) was achieved by McElvin in 1940 using *N*-ethylaniline (**30**) and 1,1-diethoxyethene (**11**) through an

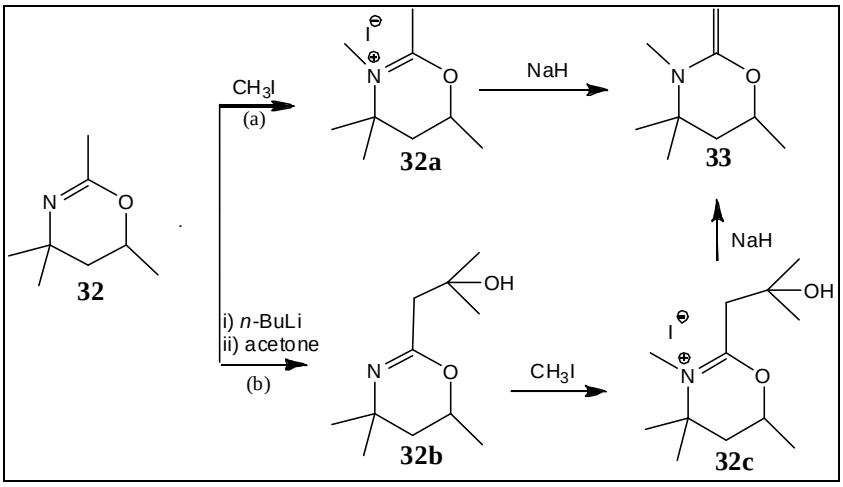
addition/elimination reaction (Scheme 1.13).[23] Then, other researchers also introduced new techniques to synthesize ketene-*N*,*O*-acetals.[24]



Scheme 1.13 First Synthesis of a Ketene-*N*,*O*-Acetal (**31**)[23]

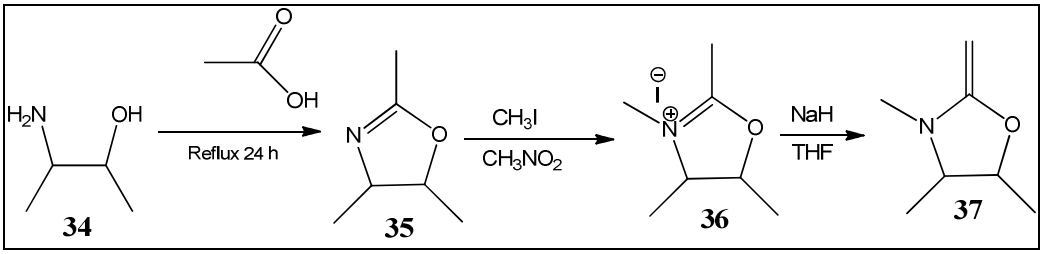
In 1972, Myers introduced two new approaches to synthesize the cyclic ketene-*N*,*O*–acetal, 3,4,4,6-tetramethyl-2-methylene-1,3-oxazane (**33**).[25] In the first method (**a**), the *N*-methyl cyclic ketene-*N*,*O*-acetal (**33**) was prepared by the treatment of 2,4,4,6-tetramethyl-1,3-oxazine (**32**) with methyl iodide followed by deprotonation with sodium hydride. In the second method (**b**), **32** was reacted with acetone in presence of *n*-BuLi to form an adduct (**32b**) which subsequently reacted with methyl iodide and then with sodium hydride to form 3,4,4,6-tetramethyl-2-methylene-1,3-oxazane (**33**).[26]

Pittman's group optimized method (**a**) and synthesized several cyclic ketene-*N*,*O*-acetals from amino alcohols.[27] The amino alcohol (**34**) was treated with acetic acid to form the oxazoline (**35**). The oxazoline was converted to its iodide salt (**36**) which was then deprotonated to make 3,4,5-trimethyl-2-methyleneoxazolidine (**37**) (Scheme 1.15).



Scheme 1.14 Two Approaches for the Synthesis of 3,4,4,6-Tetramethyl-2-methylene-1,3-oxazane (**33**)[25,26]

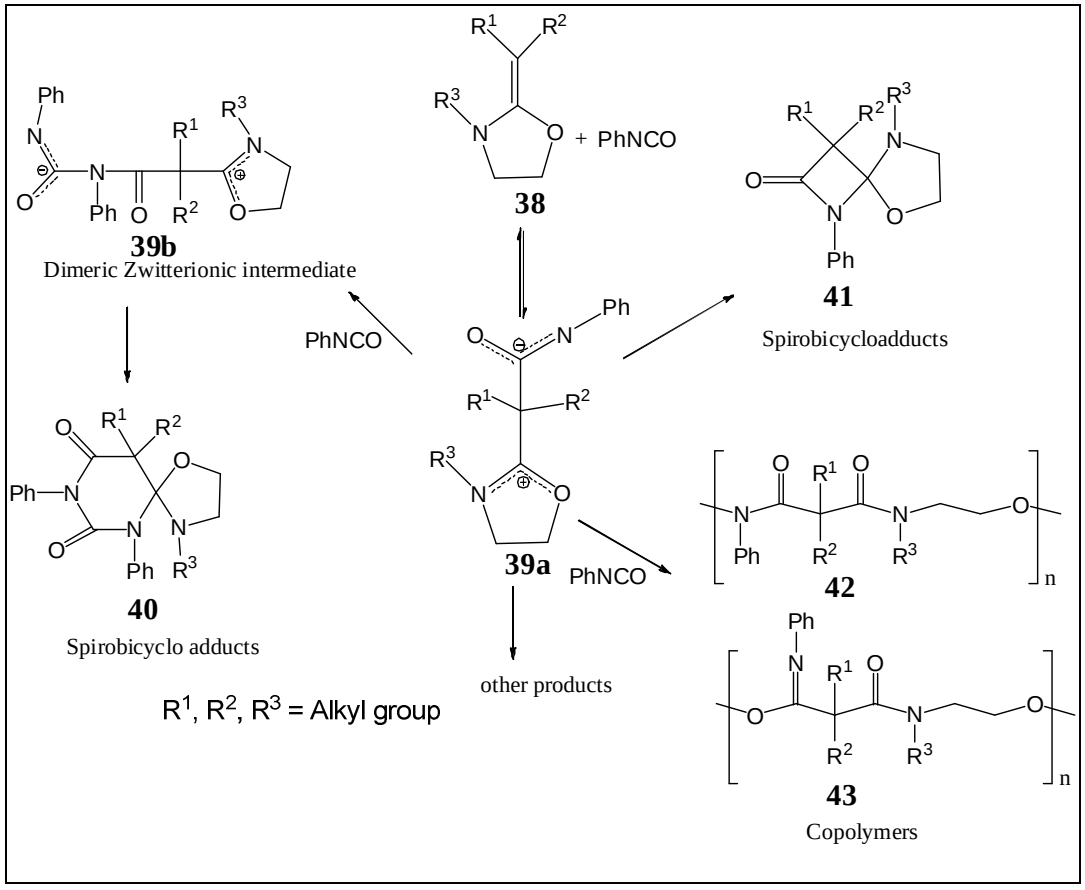
Ketene-*N*,*O*-acetals have also been used in a wide range of reactions to make various carbocycles and heterocycles.[28,29,30,31,32] Both nitrogen and oxygen lone electron pairs of a cyclic ketene-*N*,O-acetal are conjugated with the double bond. Nitrogen is a better electron donor than oxygen, so the *β*-carbon nucleophilicity is higher in a cyclic ketene-*N*,*O*-acetal than in a cyclic ketene-*O*,*O*-acetal. Thus, unlike cyclic ketene-*O*,*O*-acetals, cyclic ketene-*N*,*O*-acetals can react with weak electrophiles. However, since these acetals are extremely electron rich; they are very reactive and difficult to handle.



Scheme 1.15 Synthesis of 3,4,5-Trimethyl-2-methyleneoxazolidine (**37**)[27]

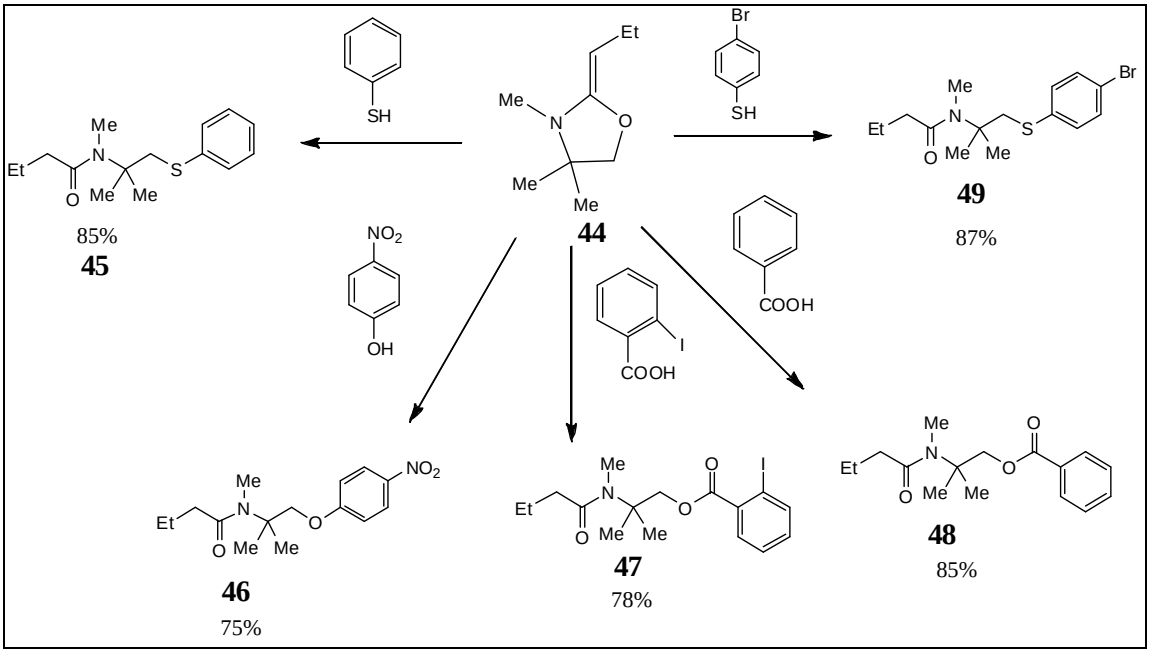
A potentially major application of ketene-*N*,*O*-acetals is in polymer synthesis. Reactions of ketene *N*,*O*-acetals with phenyl isocyanate can generate various products such as copolymers[29] (**42**, **43**), spirobicyclo adducts (**40**, **41**), etc (Scheme 1.16). [30,31,32] These reactions go through a zwitterionic intermediate, **39a**.

Zhou and Pittman performed several ring-opening reactions of *N*-methyl cyclic ketene-*N*,*O*-acetals using carboxylic acids, 4-nitrophenol and aryl thiols. These reactions resulted in the formations of amidoesters (**47**, **48**), amidoaryl ether (**46**) and amido thioethers (**45, 49**) (Scheme 1.17).[33]

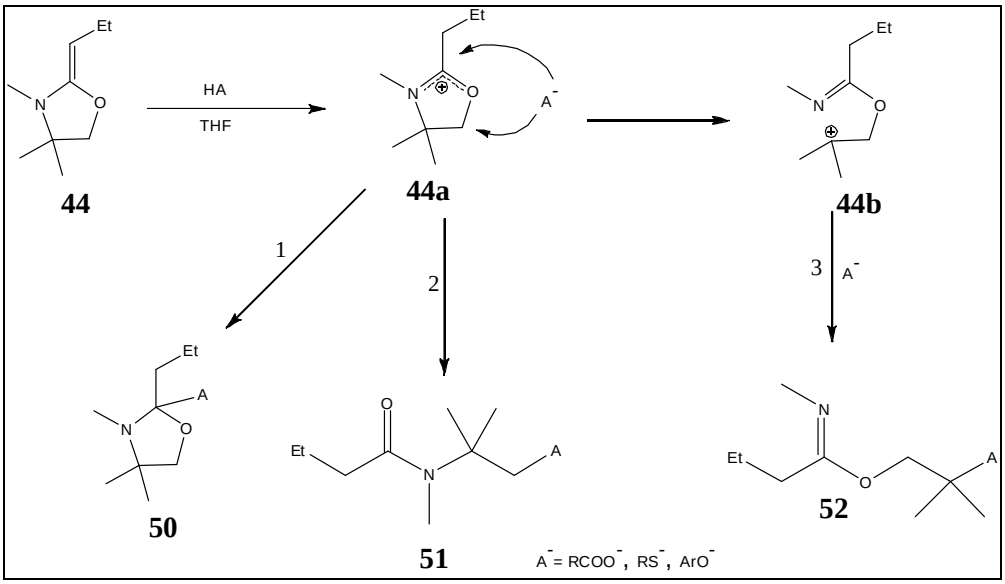


Scheme 1.16 Products (**40**-**43**) Generated by Reactions of *N*-Alkyl Cyclic Ketene-*N*,*O*-Acetals (**38**) and Excess Phenyl Isocyanate.[29,30,31,32]

These ring-opening reactions can be explained by the mechanism in Scheme 1.18. The protonation of **44** followed by attack of the nucleophile at different carbons of the ring-retained **44a** and the ring-opened product **44b** generates different products **50**, **51,** **52**. These reactions show that cyclic ketene-*N*,*O*-acetals could be useful reagents in combinatorial synthesis.

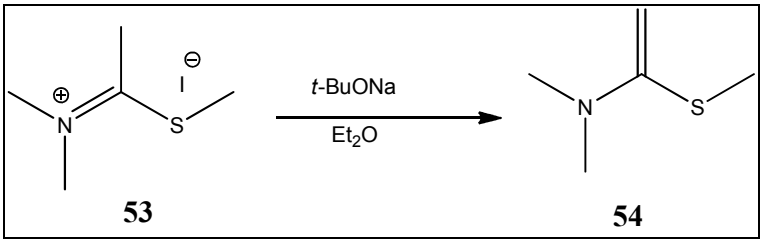


Scheme 1.17 Reactions of 3,4,4-Trimethyl-2-propylideneoxazolidine (**44**) with Carboxylic Acids, 4-Nitrophenol and Aryl Thiols[33]



Scheme 1.18 Mechanisms for the Reactions of 3,4,4- Trimethyl-2-propylidene oxazolidine with a Carboxylic Acid, 4-Nitrophenol and an Aryl Thiol[33]

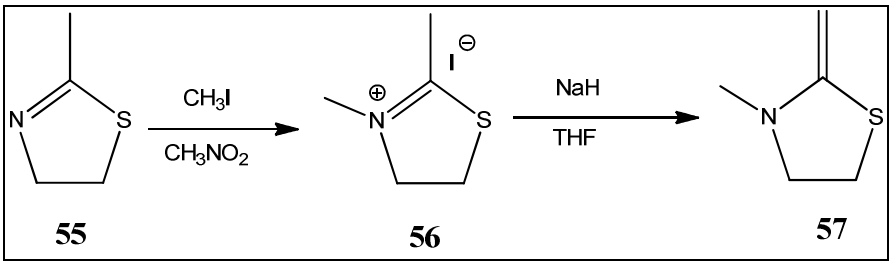
Synthesis of the first ketene-*N*,*S*-acetal, *N*,*N*-dimethyl-1-(methylthio)ethenamine (**54**) was reported in 1964. *N*,*N*-Dimethyl-1-(methylthio)ethenamine (**54**) was prepared by the deprotonation of the salt, **53** using sodium-*t*-butoxide (Scheme 1.19).[34]



Scheme 1.19 First Synthesis of a Ketene-*N*,*S*-Acetal (**54**)[34]

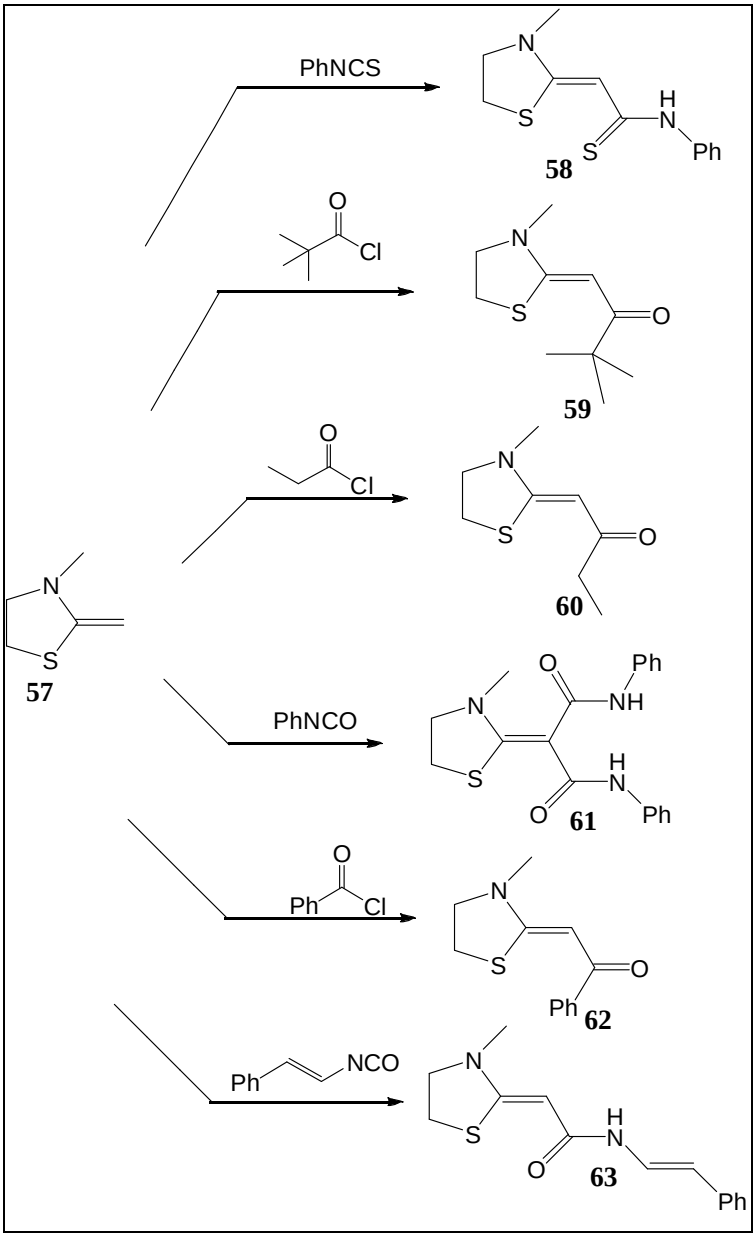
Pittman and coworkers made the first cyclic ketene-*N*,*S*-acetal, **57** by the methylation of 2-methylthiazoline (**55**) followed by deprotonation with sodium hydride

(Scheme 1.20).[35] This group used *N*-methyl cyclic ketene-*N*,*S*-acetals in various reactions with different electrophiles. They synthesized various cyclic *N*-methyl-*β*-keto (acyl, amido and thiamido)-ketene-*N*,*S*-acetals by treating 3-methyl-2-methylenethiazolidene (**57**) with acid chlorides, isocyanates and isothiocyanates respectively, under different conditions (Scheme 1.21).[36] In most of the cases, only one equivalent of the electrophile was consumed. The higher activity of the phenyl isocyanate caused the double addition of the electrophile to give **61**.



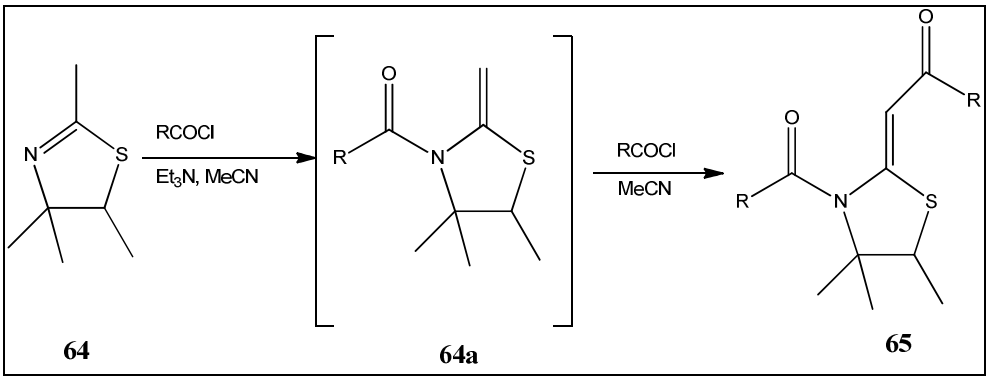
Scheme 1.20 First Synthesis of the Cyclic Ketene-*N*,*S*-Acetal (**57**)[35]

The synthesis of cyclic ketene-*N*,*X*-acetals (X = O, S) requires care as these acetals are highly reactive and readily react with moisture.[37,38] Pittman's group reported a convenient way to generate and use *N*-acyl-*β*-keto cyclic ketene-*N*,*X*-acetals (X = O, S) (**65**).[37] Alkyl oxazolines, alkyl thiazolines, alkyl oxazines or alkyl thiazines were reacted with acid chlorides in presence of a base to make these acetals as is shown in Scheme 1.22 for alkyl thiazolines. The reaction goes through *in situ* generated *N*-acyl cyclic ketene-*N*,*X*-acetals (X = O, S) (**64a**), which further react with the excess acid chloride.

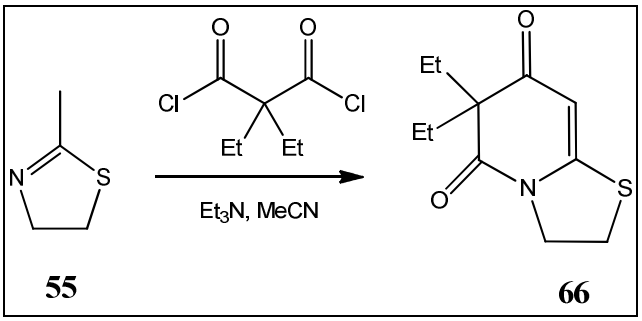


Scheme 1.21 Reactions of the 3-Methyl-2-methylenethiazolidine (**57**) with Different Electrophiles[36]

Pittman's group obtained several bicyclic-ketene-*N*,*S*-acetals such as **66** using diacid chlorides (in place of monoacid chlorides) and 2-methylthiazoline (Scheme 1.23)[39]

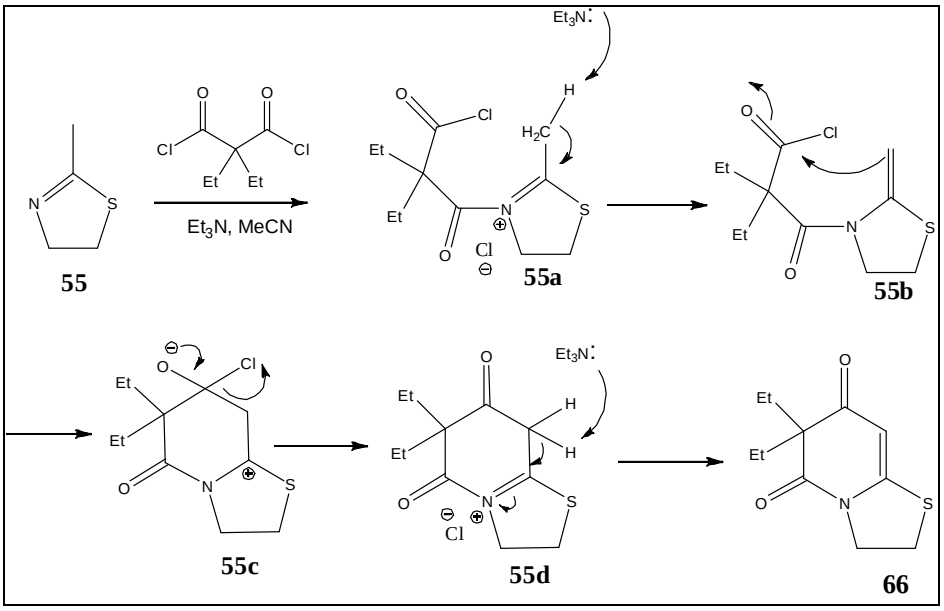


Scheme 1.22 Synthesis of the *N*-Acyl-*β*-Acyl Cyclic Ketene-*N*,*S*-Acetal (**65**)[38]



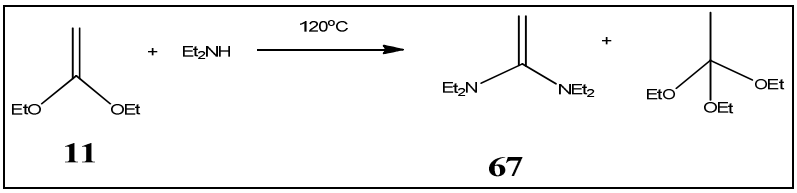
Scheme 1.23 Cyclization Reaction of 2-Methylthiazoline (**55**) with Diethylmalonyl Chloride[39]

The reaction initiates by attack of the sp^2 nitrogen on one of the carbonyl carbons of the diacid chloride (Scheme 1.24). The *N*-acyl cyclic ketene-*N*,*X*-acetal (X = O, S) (**55b**) is formed by deprotonation from the *β* carbon of **55a**. Next, **55b** undergoes an intramolecular cyclization, by nucleophilic *β* carbon attack on the remaining carbonyl carbon of the diacid chloride. The release of the chloride from **55c** generates **55d** which is deprotonared forming 6,6-diethyl-2H-thiazolo[3,2-*a*] pyridine-5,7(3H,6H)-dione (**66**).[39]



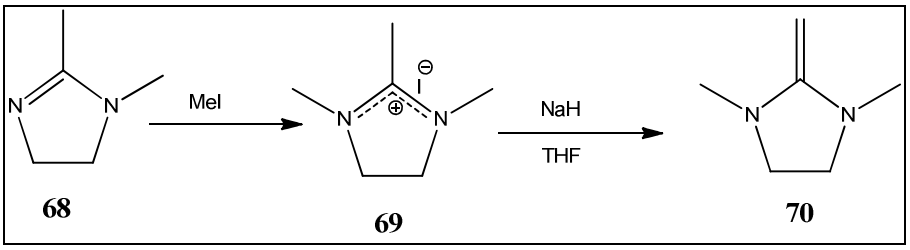
Scheme 1.24 Mechanism Proposed for the Reaction of 2-Methylthiazoline with a Diacid Chloride[39]

The first synthesis of a ketene-*N*,*N'*-acetal (**67**) was reported by McElvin in 1945. The ketene-*N*,*N'*-acetal (**67**) was made by the reaction of diethyl ketene-*O*,*O*-acetal (**11**) with an amine (Scheme 1.25).[40] Ketene-*N*,*N'*-acetals are more nucleophilic than ketene-*N*,*X*-acetals (X = O, S). Ketene-*N*,*N*'-acetals have been also used in nucleophilic and cycloaddition reactions.[41-48]

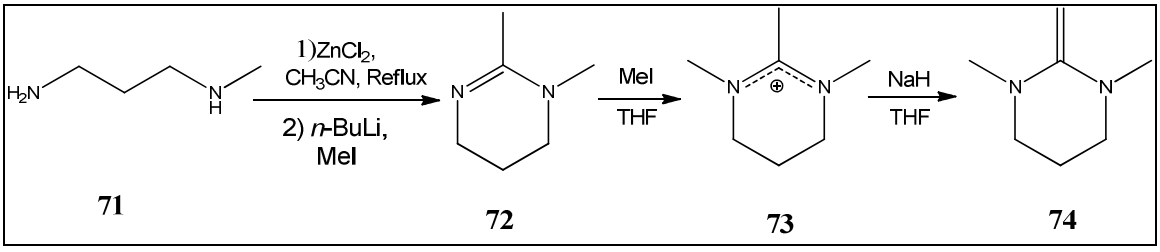


Scheme 1.25 First Reported Synthesis of a Ketene-*N*,*N'*-Acetal (**67**)[40]

The first cyclic ketene-*N*,*N*′-acetal was synthesized by Gruseck and Heuschmann in 1987. They made the cyclic ketene-*N*,*N*′-acetal (**70**) by reacting 1,2-dimethylimidazoline (**68**) with methyl iodide followed by the addition of sodium hydride (Scheme 1.26).[49] Recently, Pittman's group applied Gruseck and Heuschmann's process for the synthesis of several five and six-membered cyclic ketene-*N*,*N*′-acetals.[50] This group prepared cyclic ketene-*N*,*N*′-acetals directly from substituted imidazolines by sequential methylation and deprotonation. They reported another technique where the six-membered cyclic ketene-*N*,*N*′-acetal (**74**) was synthesized directly from readily available starting materials such as *N*-methylpropanediamine (**71**) and various nitriles in the presence of $ZnCl_2$ (Scheme 1.27).[50]



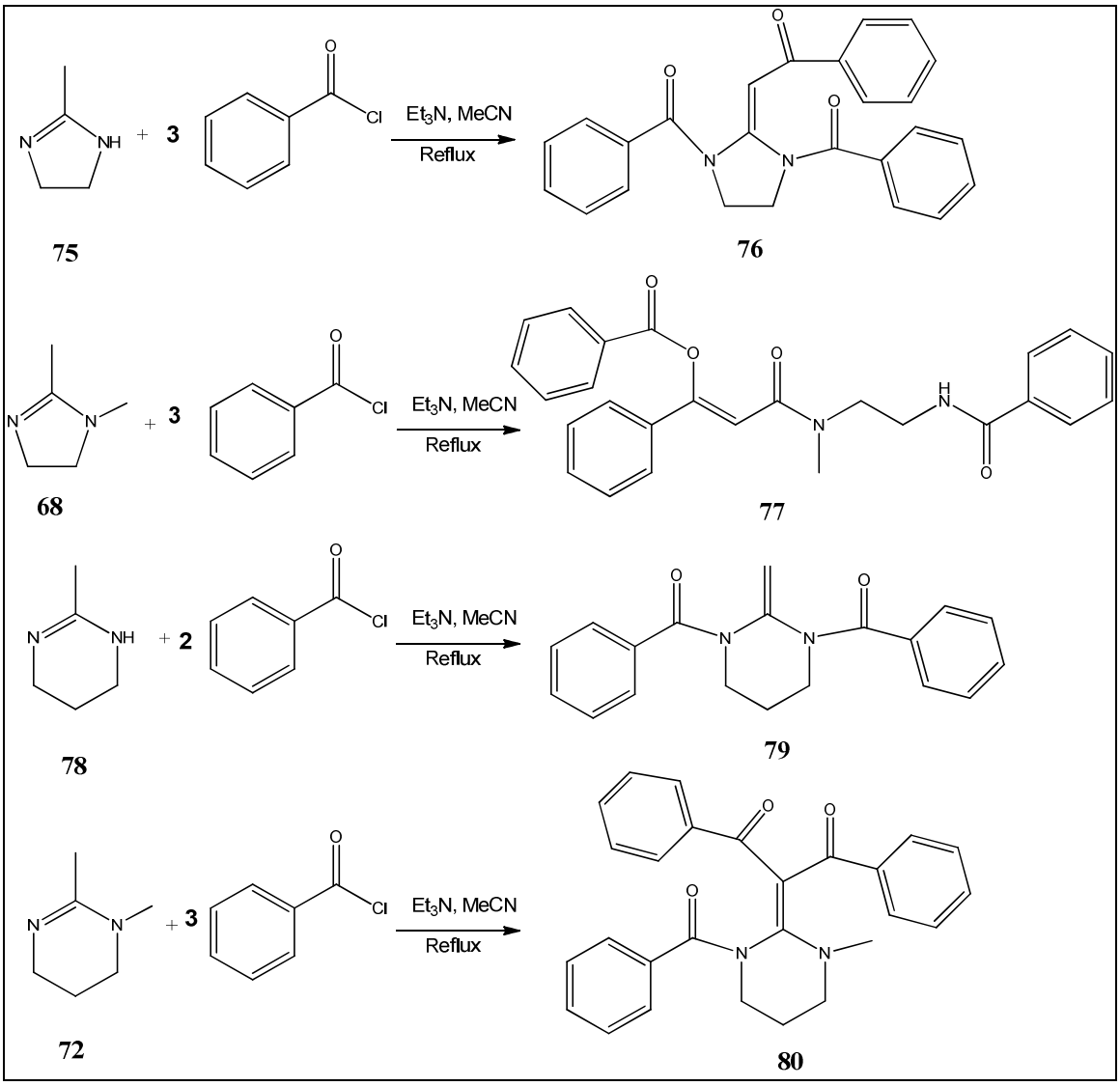
Scheme 1.26 First Reported Synthesis of a Cyclic Ketene-*N*,*N*′-Acetal (**70**)[47]



Scheme 1.27 Synthesis of the Six-Membered Cyclic Ketene-*N*,*N*′-Acetal[50]

Pittman's group also explored various other ways to synthesize substituted cyclic ketene-*N*,*N'*-acetals (Scheme 1.28). [51,52] In one case, when 2-methylimidazoline (**75**) was reacted with excess benzoyl chloride in the presence of triethylamine, a *N*,*N'*-diacyl-*β*-acyl-cyclic ketene-*N*,*N'*-acetal,2-(2-oxo-2-phenylethylidene-imidazolidine-1,3-diyl)-bis-(phenylmethanone), (**76**) was formed. Surprisingly, under similar conditions 1,2-dimethylimidazoline (**68**) gave a ring opened product, **77**. When 2-methyl-1,4,5,6-tetrahydropyrimidine (**78**) was reacted with excess acid chloride, only *N*,*N'*-diacyl-cyclic ketene-*N*,*N'*-acetal, 2-methylenedihydropyrimidine-1,3(2H,4H)-diyl)-bis-(phenylmethanone) (**79**) was obtained without any acylation on the exocyclic carbon. In contrast, when 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (**72**) was treated with excess acid chloride, it resulted in a *N*-acyl, *N*-methyl cyclic ketene-*N*,*N'*-acetal, 2-(1-benzoyl-3-methyltetrahydropyrimidin-2(1H)-ylidene)-1,3-diphenylpropane-1,3-dione (**80**), with double acylation on the exocyclic carbon. All these results show that by creating small changes in structures of substrates or corresponding ketene acetals different products can be obtained.

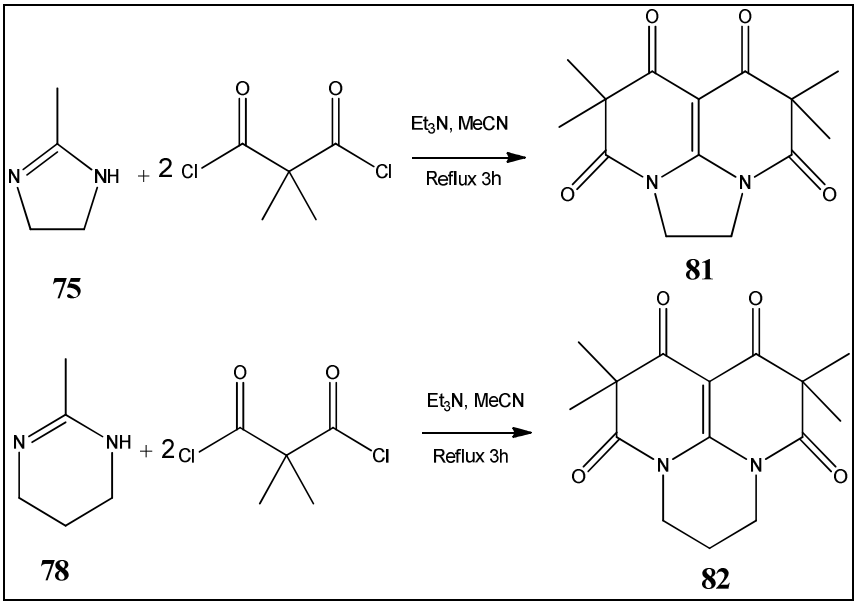
Ye et al. reported the synthesis of polycyclic ketene-*N*,*N'*-acetals by reacting 2-methylimidazoline or 2-methyl-1,4,5,6-tetrahydropyrimidine with diacid chlorides. The reaction generated highly functionalized, potentially bioactive 1,8-napthyridinetetraones (**81**, **82**) (Scheme 1.29).[53] These reactions follow a tandem reaction pathway.



Scheme 1.28 Reactions of 2-Methylimidazoline (**75**), 1,2-Dimethylimidazoline (**68**), 2-Methyl-1,4,5,6-tetrahydropyrimidine (**78**) and 1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine (**72**) with Benzoyl Chloride[51,52]

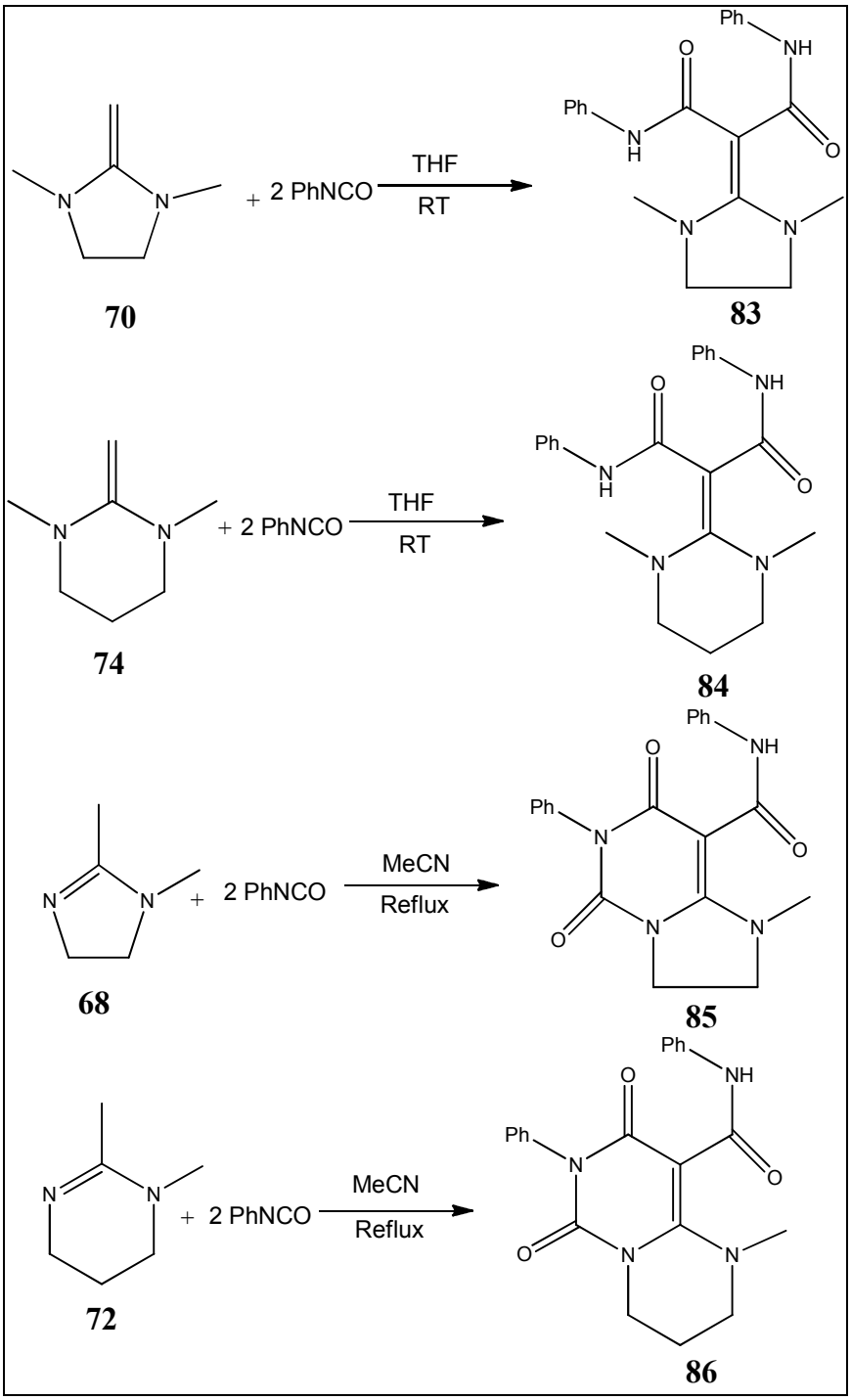
Reactions of five and six membered cyclic ketene-*N*,*N'*-acetals with isocyanates generated new push-pull alkenes (Scheme 1.30). In contrast, bicyclic ketene-*N*,*N'*-acetals were obtained when 1,2-dimethylimidazoline and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine were reacted with excess isocyanates (Scheme 1.30).[54]

All the above examples clearly demonstrate that by selecting proper substitutents and reactions conditions, cyclic ketene-*N*,*X*-acetals (X = O, N, S) can be used to make a large pool of interesting molecules.[52-56] However, the high reactivity of these acetals make the handling of these reagents difficult. Thus, reactions using *in situ* generated cyclic ketene-*N*,*X*-acetals (X = O, N, S) may be a better option.



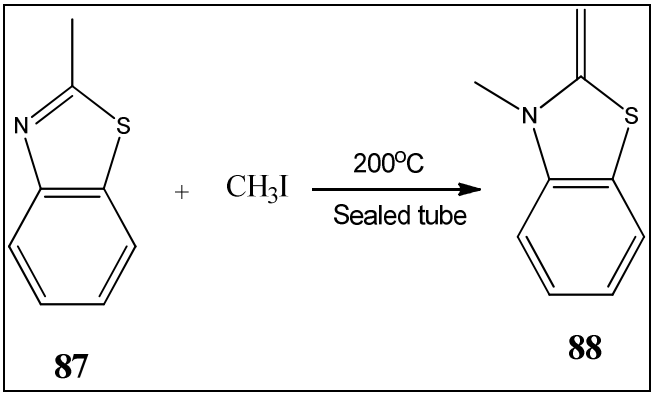
75 **81** **78** **82**

Scheme 1.29 Reactions of 2-Methylimidazoline (**75**) and 2-Methyl-1,4,5,6-tetrahydropyrimidine (**78**) with Dimethyl Malonyl Chloride[53]



Scheme 1.30 Reactions of 1,3-Dimethyl-2-methyleneimidazolidine (**70**), 1,3-Dimethyl-2-methylenehexahydropyrimidine (**74**), 1,2-Dimethylimidazoline (**68**) and 1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine (**72**) with Phenyl Isocyanate[54]

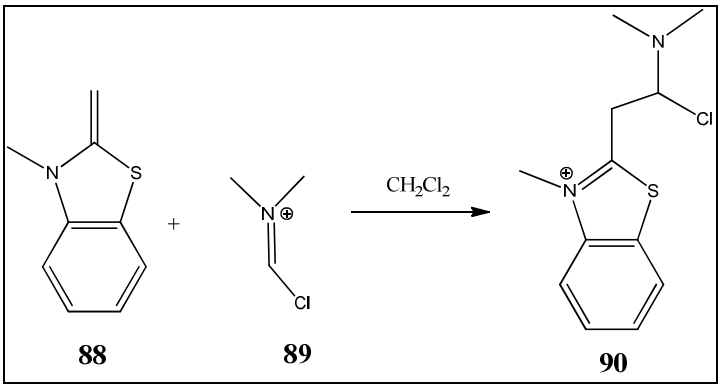
Other sets of cyclic ketene-*N*,*X*-acetals (X = O, N, S), can be derived from aromatic heterocycles such as benzoxazoles, benzothiazoles, etc. Konig et al. reported the first synthesis of a benzothiazole based cyclic ketene acetal in 1925 (Scheme 1.31).[57] They heated methyl iodide and 2-methylbenzothiazole at 200°C in a sealed tube forming the ketene acetal, 3-methyl-2-methylene-2,3-dihydrobenzothiazole (**88**).



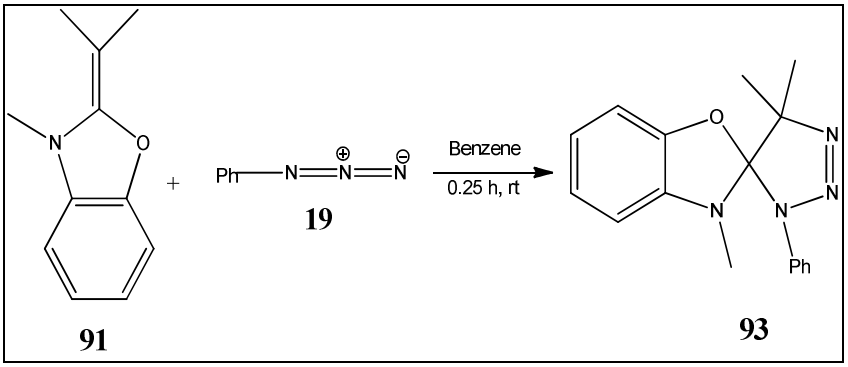
Scheme 1.31 First Reported Synthesis of Benzothiazole Based Cyclic Ketene-*N*,*S*-acetal, 3-Methyl-2-methylene-2,3-dihydrobenzothiazole (**88**)[57]

Zollinger et al.[58] and Schoeni et al.[59] explored a few reactions of **88**. In one case, Zollinger group used 3-methyl-2-methylene-2,3- dihydrobenzothiazole (**88**) with 2-chloro-*N*,*N*-dimethyl-ethenamine (**89**) (Scheme 1.32).[58]

The chemistry of the benzoxazole-based cyclic ketene acetals is underexplored. In 1992, Quast et al. reported a few 1,3-dipolar cycloaddition reactions of benzoxazole based cyclic ketene acetals.[60,61] In one case, the spirocyclic cycloadduct, **93** was made by the reactions of phenyl azide (**19**) and 3-methyl-2-(propan-2-ylidene)-2,3-dihydrobenzooxazole (**91**) (Scheme 1.33).[61]



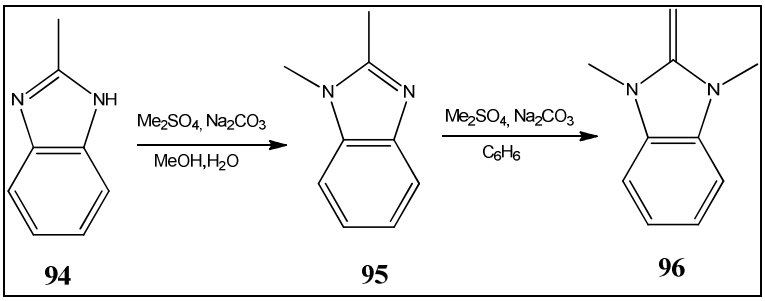
Scheme 1.32 Reaction of 3-Methyl-2-methylene-2,3-dihydrobenzothiazole (**88**) with *N*-(chloromethylene)-*N*-methylmethanaminium (**89**)[58]



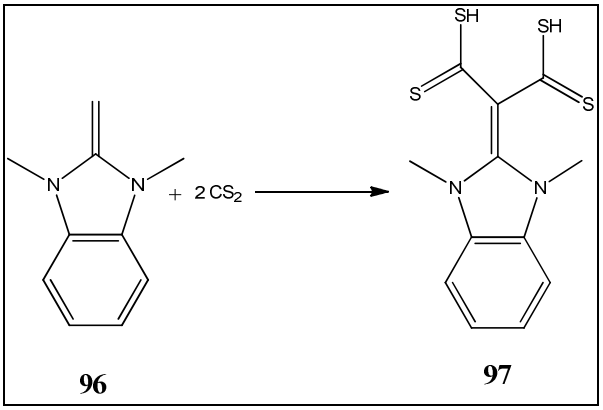
Scheme 1.33 Cycloaddition Reaction of 3-Methyl-2-(propan-2-ylidene)-2,3-dihydrobenzooxazole (**91**) with Phenyl Azide (**19**)[61]

The synthesis of benzoimidazole based cyclic ketene-*N*,*N'*-acetal (**96**) was first reported by Bris et al. in 1959 (Scheme 1.34).[62] They synthesized 1,2-dimethylbenzimidazole (**96**) from 2-methylbenzimidazole (**94**). Me_2SO_4 and Na_2CO_3 are used as the methylating agent and base respectively. The methylation of 1,2-dimethylbenzimidazole (**95**) with Me_2SO_4 in benzene resulted in a benzoimidazole-based yclic ketene-*N*,*N'*-acetal, 1,3-dimethyl-2-methylene-2,3-dihydro-1H-benzoimidazole (**96**).

Just like benzothiazole and benzoxazole, benzimidazole-based cyclic ketene acetal chemistry is also less explored.[63-66] Bourson, et al. studied a few reactions of 1,3-dimethyl-2-methylene-2,3-dihydro-1H-benzoimidazole (**96**).[64-66] In one case, the reaction of 1,3-dimethyl-2-methylene-2,3-dihydro-1H-benzoimidazole (**96**) with carbon disulfide gave the dithioic acid derivative (**97**) (Scheme 1.35).[64,65] He also reported the acylation and alkylation reactions of this cyclic ketene acetal.[66]



Scheme 1.34 First Reported Synthesis of a Imidazole Based Cyclic Ketene Acetal (**96**)[62]



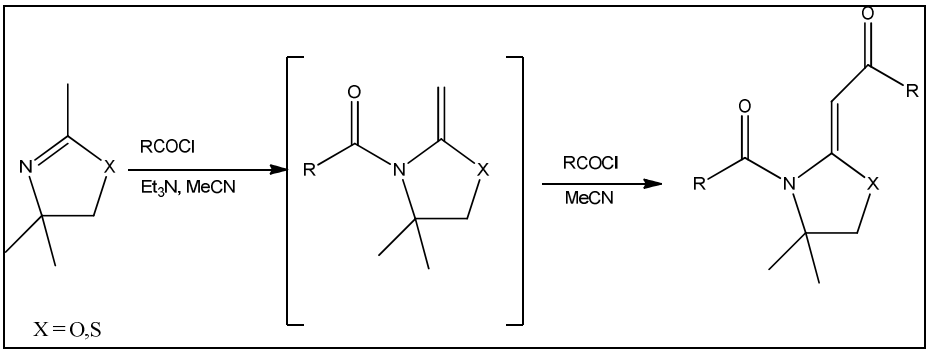
Scheme 1.35 Synthesis of 2-(1,3-Dimethyl-1H-benzoimidazol-2-(3H)-ylidene) propanebis (dithioic) acid (**97**) using 1,3-Dimethyl-2-methylene-2,3 dihydro-1H-benzoimidazole (**96**)[64,65]

In summary, many reports about the chemistry of ketene -*O*,*O*-, -*N*,*O*-, -*N*,*S*-, -*N*,*N'*- acetals and cyclic ketene-*O*,*O*-, -*N*,*O*-, -*N*,*S*-, -*N*,*N'*- acetals are present. There are also a few reports on the benzothiazole-based cyclic ketene acetals, but only few electrophiles are used in those reactions. On the other hand, benzoxazole and benzimidazole-based cyclic ketene acetal chemistry remains largely unexplored. Also, thiazole, oxazole and imidazole-based cyclic ketene acetals have not been well studied.

Research Goals

The goal of this dissertation research is to study reactions of *in situ* generated cyclic ketene acetals with electrophiles.

Pittman and coworkers reported several reactions where cyclic ketene acetals were generated *in situ* and reacted with eletrophiles.[35-39, 50-54] For example, the reaction described in the Scheme 1.22 (Page 19) is a classic example where this protocol generated heterocycle such as (*Z*)-2-(3-benzoylthiazolidin-2-ylidene)-1-phenylethanone. A general reaction is given below (Scheme1.36).



Scheme 1.36 Reaction of an *in situ* Generated Cyclic Ketene Acetal

In all of these cases, heterocycles such as 2-substituted oxazolines, thiazolines or imidazolines are used as starting materials to generate cyclic ketene acetals *in situ*. In this dissertation, attempts to generate cyclic ketene acetals from differently substituted heterocycles such as alkyl imidazoles, alkyl thiazoles, alkyl oxazoles or their corresponding benzo analogs will be described. These heterocycles have an extra double bond within their ring. Therefore, they and their corresponding cyclic ketene acetals are structurally different from previously used precursors (oxazolines, thiazolines or imidazolines) as illustrated in Figure 1.3 and 1.4. In addition, imidazoles, oxazoles and thiazoles are aromatic (Figure 1.5).

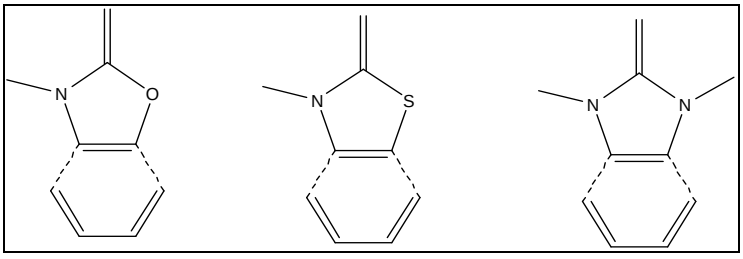


Figure 1.3 Cyclic Ketene Acetals Based on Aromatic Heterocycles

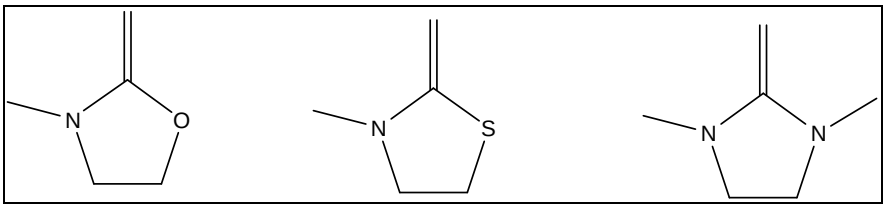


Figure 1.4 Cyclic Ketene Acetals Based on Nonaromatic Heterocycles

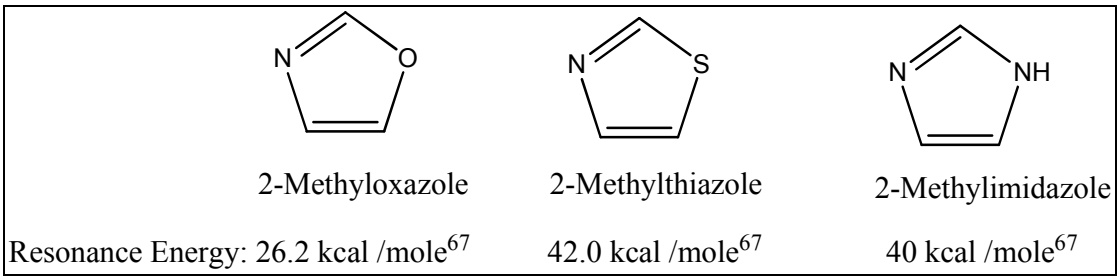


Figure 1.5 Aromatic Heterocycles

Resonance energies are based on difference between ΔH_f and the summation of standard bond energies. Resonance energy of benzene is in this range : 45.8 kcal/mole[67]

Nitrogen heterocycles containing π-electrons have always been considered important substrates for studying various aspects of aromaticity.[67-69] Thus, the goal of the first part of the dissertation is to synthesize cyclic ketene acetals from aromatic nitrogen heterocyclic precursors and study their reactions. In all cases, a one pot reaction was chosen, where an *in situ* generated cyclic ketene acetal was made. Once generated, these cyclic ketene acetals could react with electrophiles present in the system. More specifically, 1,3-diacid chlorides were reacted with *in situ* generated cyclic ketene acetals from substituted imidazoles to determine if useful syntheses could be observed. This was the first goal of this dissertation.

Also, reactions of cyclic ketene acetals from substituted oxazoles and thiazoles with acid chlorides in the presence of different bases and different solvents were explored. This was the second goal of this dissertation. These reactions represented examples of carbon-carbon bond formation through *in situ* generated cyclic ketene acetal

A third goal was to explore the reactions of 2-methylbenzoxazole with acid chlorides. This resulted in the formation of ortho amido esters.

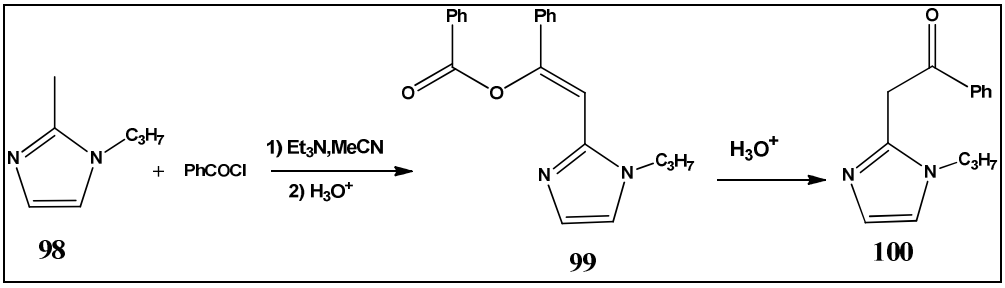
Reactions to contribute to future upgrading of bio-oil represent a separate study in this dissertation. The background and research goals of the upgrading of bio-oil are described in the chapter V of this dissertation.

CHAPTER II

REACTIONS OF 2-ALKYLIMIDAZOLES AND 2-METHYL BENZIMIDAZOLE WITH DIACID CHLORIDES

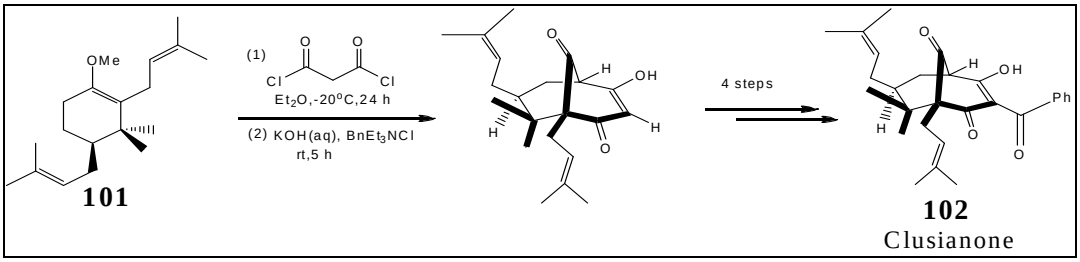
Introduction and Objective

The reactions of imidazoles and *N*-substituted imidazoles with acid chlorides have been well documented.[70-82] Macco et al. showed that imidazoles react with acid chlorides in different ways. Imidazoles without an *N*-substituent gave *N*-substituted derivatives when treated with acid chlorides in an inert solvent. On the other hand, *N*-substituted imidazoles upon treatment with benzoyl chlorides and triethylamine in refluxing acetonitrile gave enol esters, which on hydrolysis generated a variety of 2-(2-imidazolyl) acetophenones (Scheme 2.1).[82]



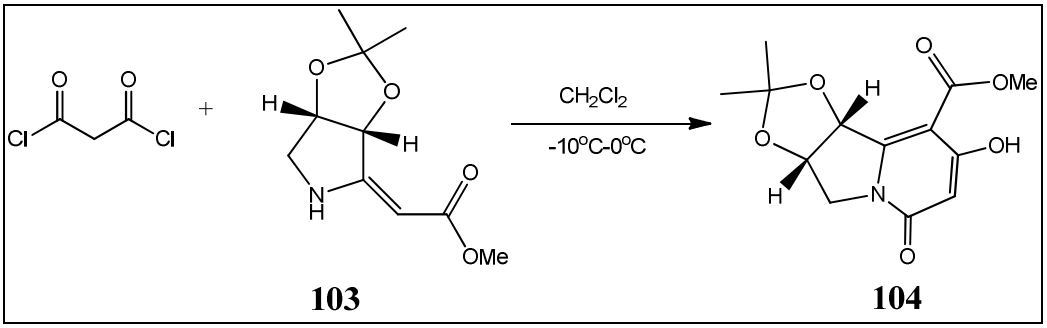
Scheme 2.1 Synthesis of Imidazoylacetophenones[82]

Surprisingly, the reactions of imidazoles with diacid chlorides are not well established. Diacid chlorides are bis-electrophiles. They undergo cyclization reactions to give carbocycles and heterocycles.[39,83-85] Recently, malonyl dichloride was used to make the core structure of Clusianone (**102**), an anti-HIV molecule (Scheme 2.2).[85]



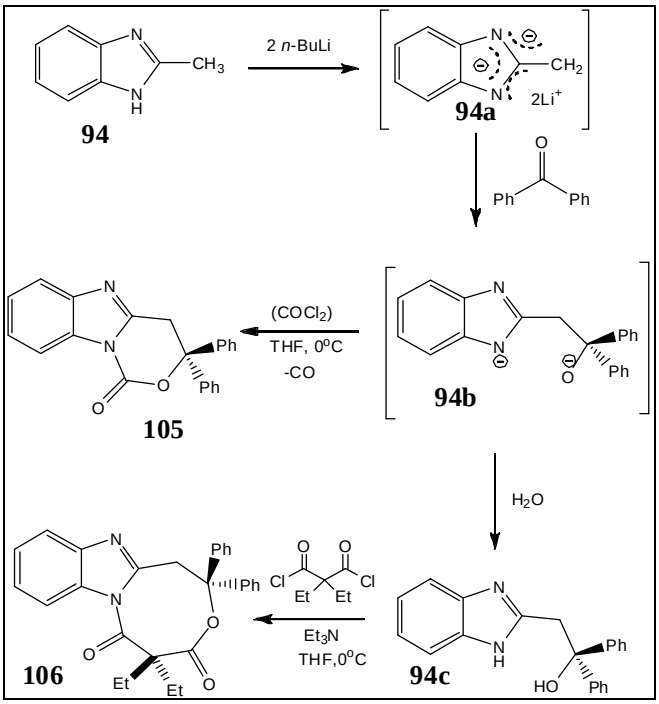
Scheme 2.2 Total Synthesis of Clusianone (**102**)[85]

Cyclizations of secondary enamines (like **103**) with diacid chlorides were used to make nitrogen-containing heterocycles such as indolinzinone carboxylate (**104**) (Scheme 2.3).[83]



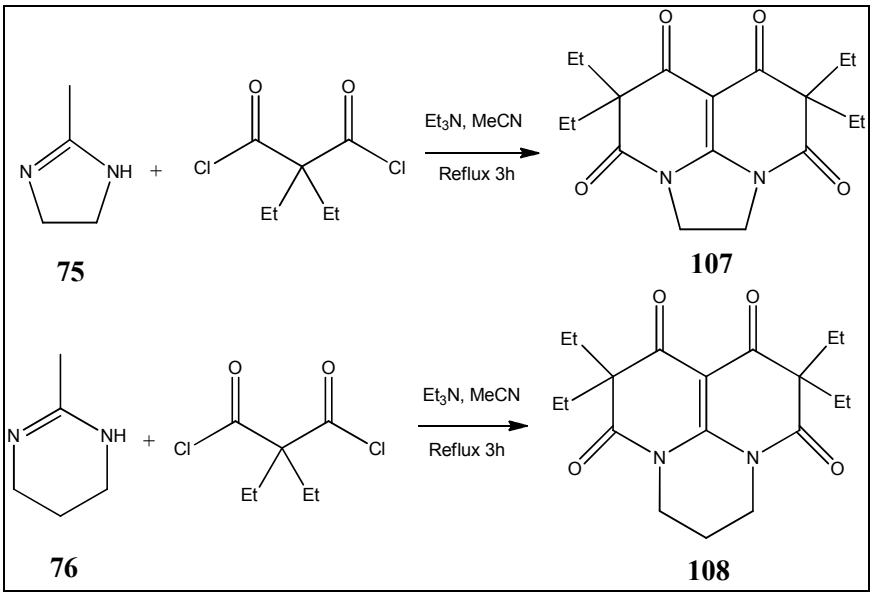
Scheme 2.3 Reaction of a Cyclic Secondary Enamine and Malonyl Dichloride to form Indolinzinone Carboxylate (**104**)[82]

There are a few reports where different medium ring-sized lactones have been synthesized by reactions of the dianion of 2-methylbenzimidazole with benzophenone followed by treatment with diacid chlorides like diethylmalonyl chloride, oxalyl chloride and 1,2-benzenedicarbonyl dichloride (Scheme 2.4).[86-87]



Scheme 2.4 Synthesis of Medium-sized Lactones using 2-Methylbenzimidazole, Benzophenone and Diacid Chlorides[86,87]

Recently, Ye et al. reported a series of 1,3-diacid chloride reactions with both 2-methylimidazoline (**75**) (the non-aromatic analogue of 2-methylimidazole (**111**)) and 2-methyl-1,4,5,6-tetrahydropyrimidine (**78**).[53] In these reactions, *N*,*N*'-diacyl cyclic ketene acetals were generated *in situ* and further reacted in a tandem pathway to give 1,8-napthyridinetetraones like (**107**) and (**108**), respectively (Scheme 2.5).



Scheme 2.5 Reactions of 2-Methylimidazoline and 2-Methyl-1,4,5,6-tetrahydro-pyrimidine with 1,3-Diacid Chloride[53]

These results raised a question of whether these cyclizations with diacid chlorides could be extended to the corresponding aromatic systems such as 2-alkylimidazoles and 2-methylbenzimidazole. 2-Alkylimidazoles, like 2-alkylimidazolines can be envisioned to give four consecutive attacks on electrophiles through two nitrogens and the exocyclic β carbon of their corresponding cyclic ketene-*N*,*N*'-acetal intermediates. This ultimately might provide a route to generate highly functionalized heterocyclic ring systems. However, aromaticities of these heterocycles are sensitive towards structural changes. A few reports showed changes in aromaticity when internal double bond is converted to two exocyclic double bonds to attached substituent carbons. Krygowski et al. compared the aromaticities of pyrazole (**109**) and an analog **109a**, with exocyclic double bonds at C3 and C4 (Figure 2.1).[68] He found **109a** was less aromatic. Similarly, pyrrole rings in

porphyrins were found to loose most of their aromaticity when exocyclic bonds at the 2 or 5 positions gain more double bond character (Figure 2.1).[69]

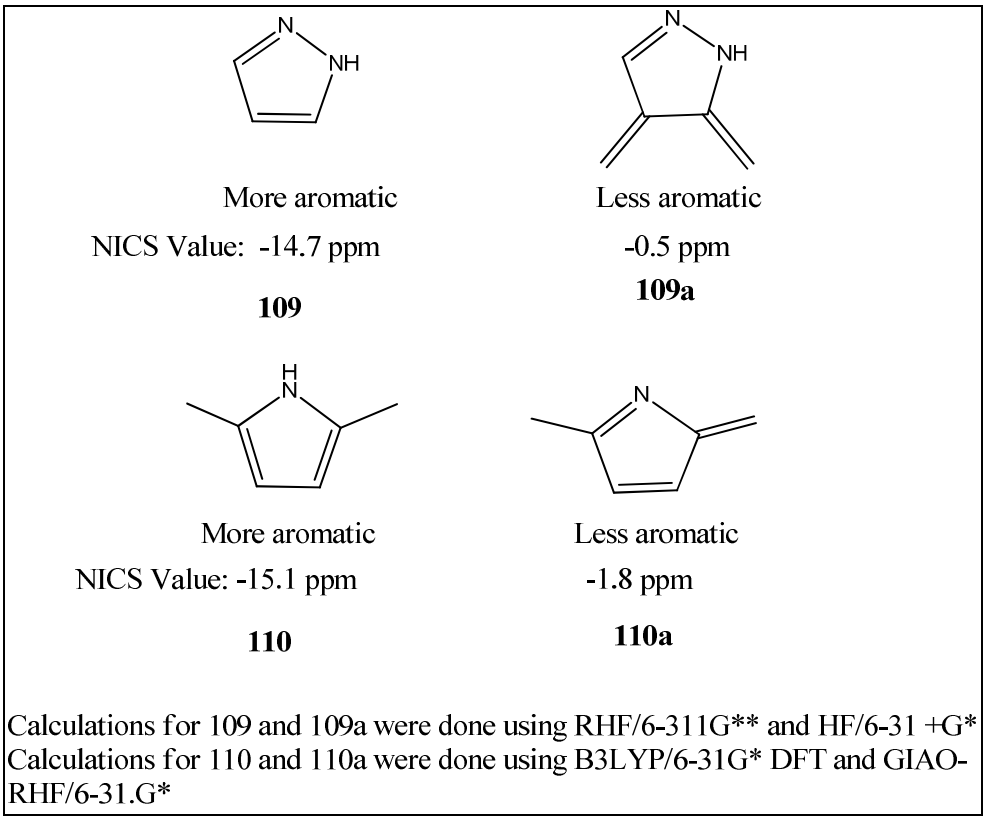


Figure 2.1 Comparison of Aromaticity [68,69]

A NICS (Nucleous Indepenent Chemical Shift) calculation on imidazole and corresponding cyclic ketene acetal also support this assumption. The NICS(0) value of a 5-membered ring ketene-*N*,*N*'-acetal intermediate (-3.65 ppm) was found to be less negative than corresponding value of imidazole (-32.41 ppm) in the same scale (NICS(0) value of benzene -36.00 ppm) , which clearly indicated a loss of aromaticity (Figure 2.2).[88a]

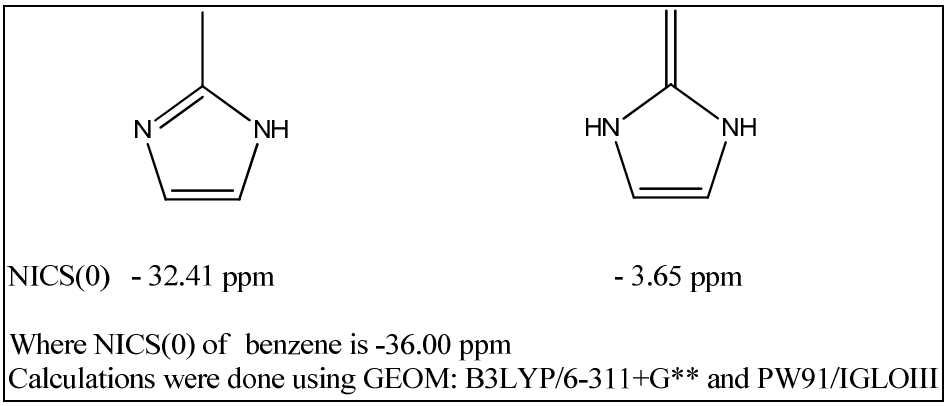
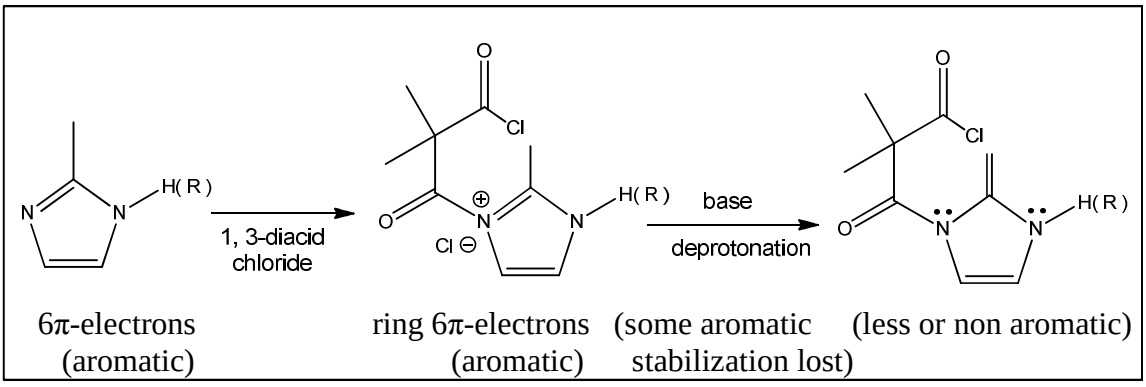
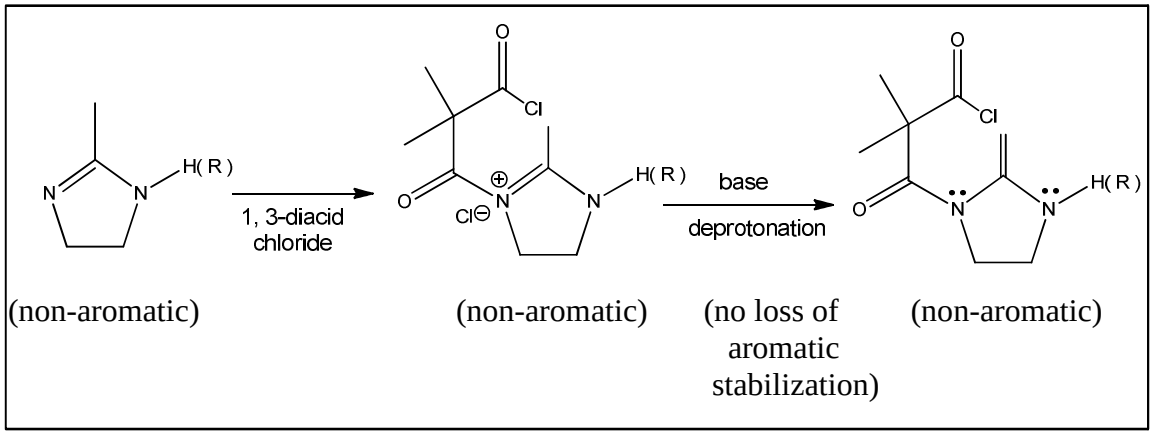


Figure 2.2 Comparison of Aromaticity [88a]

Thus, the formation of a 5-membered ring ketene-*N*,*N*'-acetal intermediate from 2-methylimidazole could involve some loss of aromaticity present in the imidazole (Scheme 2.6 and Scheme 2.7). This loss of aromaticity is postulated to influence the formation of cyclic ketene acetals from the aromatic precursors as compared to non-aromatic precursors such as imidazolines. This may decrease yields or change the product distributions versus reactions using ketene acetals generated from nonaromatic heterocycles.



Scheme 2.6 Generation of a Cyclic Ketene-*N*,*N*'-Acetal from-2-Methylimidazole



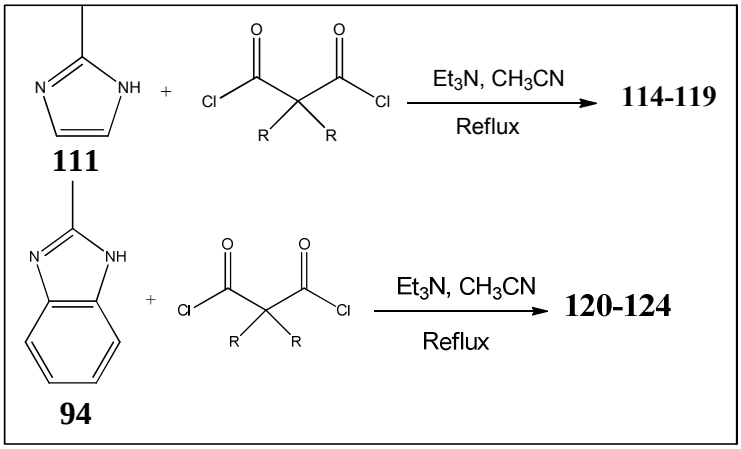
Scheme 2.7 Generation of a Cyclic Ketene-*N*,*N*'-Acetal from-2-Methylimidazoline

Thus, a series of reactions of 2-alkylimidazoles (R= methyl, ethyl, isopropyl) (**111, 112, 113**) and 2-methylbenzimidazole (**94**) were conducted with various 1,3-diacid chlorides in acetonitrile and triethylamine.

Results and Discussions

A series of reactions of 2-alkylimidazoles (R= methyl, ethyl, isopropyl) (**111, 112, 113**) and 2-methylbenzimidazole (**94**) with various 1,3-diacid chlorides in acetonitrile and triethylamine generated products **114-129**. The structures of these products depend on the 1,3-diacid chloride's structure as illustrated in Tables 2.1-2.4.

Table 2.1 Reactions of 2-Methylimidazole and 2,2-Disubstituted-1,3-Diacid Chlorides and Et_3N in Acetonitrile



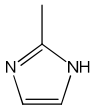
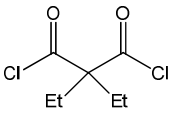
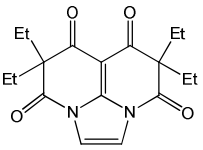
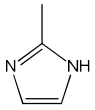
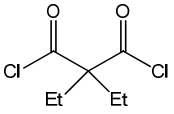
Entry	Substrate	Diacid Chloride	Reflux time (h)	Product Isolated	Yield (%)
1[a]			3	 **114**	50
2[b]			3	**114**	59

Table 2.1 (Continued)

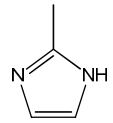
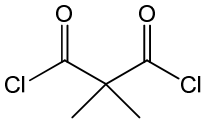
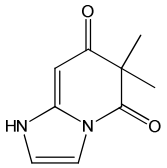
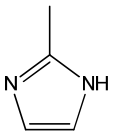
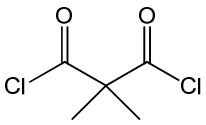
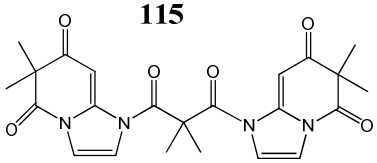
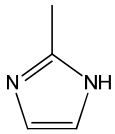
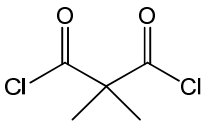
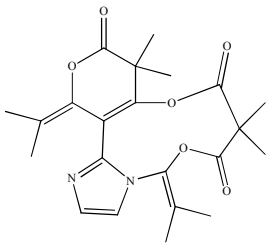
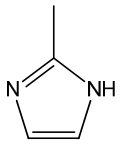
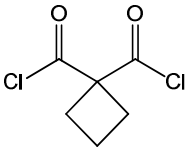
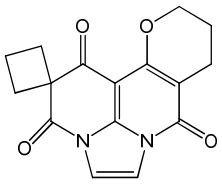
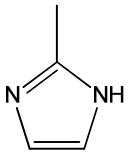
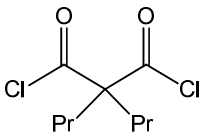
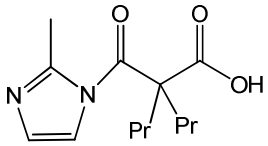
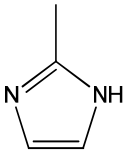
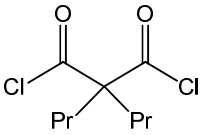
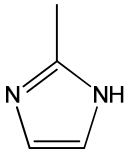
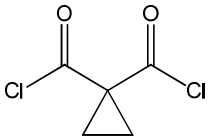
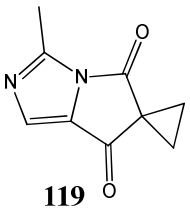
Entry	Substrate	Diacid Chloride	Reflux time (h)	Product Isolated	Yield (%)
3[b]			3	 **115**	39
4[c]			5	 **116**	51
				115	12
5[d]			3	**116**	34
				115	45
				 **116a**	13

Table 2.1 (Continued)

Entry	Substrate	Diacid Chloride	Reflux time (h)	Product Isolated	Yield (%)
6			3	 **117**	54
7			3	 **118**	57
8			6	**118**	70
9			3	 **119**	71

(Mole ratio of 2-methylimidazole, diacid chloride and base is 1/2.4/6 mole ratio, 2.4 mmol (0.20 g) of 2-methylimidazole was used unless otherwise mentioned)

.

[a] Only **114** was found in the product mixture.

[b] Reaction was performed with 0.25 g of 2-methylimidazole. Only **114** was found in the product mixture.

[c] Compound **115** was isolated as the major spot.

[d] Both **115** and **116** were isolated.

[e] Reaction was performed with 0.25 g of 2-methylimidazole. Compunds **115**, **116** and **116a** were isolated. Several batches of reactions were performed to isolate pure **116a.** An amount of 0.08 g of column residue was obtained after eluting the column with 1:1 ethyl acetate and hexane. A crystal structure of **116a** was obtained.

The structures were established by ^{1}H and ^{13}C NMR and FT-IR. In the case of **116a**, a X-ray crystal structure was obtained by Dr. W. P. Henry of Mississippi State University.

Seven different product types were isolated upon reacting 2-methylimidazole with various 2,2-disubstituted-1,3-diacid chlorides under identical conditions (Table 2.1).

Tandem dicyclization gave **114** when the 2-alkyl substituents of the diacid chloride were ethyl groups. Monocyclized product **115** and a linearly dimerized product **116** were isolated with methyl substituents. These reactions were run couple of times to confirm the above results. The reactions of 2-methylimidazole with diethyldiacid chloride in presence of triethylamine generated tricyclic products in all cases. On the other hand, besides generating **115** and **116**, reactions of 2-methylimidazole with dimethyldiacid chloride was also found to generate a highly functionalized product **116a**. It has a 10-membered ring fused to an imidazole and also to a six-membered ester ring. It has a cyclic ketene-*N*,*O*-acetal function and 3 ethers that are all part of rings. It has a diene unit cross conjugated with the imidazole ring. This compound was unstable in air. A small amount of residue from the column was recovered. However, no tricyclic product similar to **114** was found in any case.

Tandem dicyclization also occurred when employing cyclobutane-1,1-dicarbonyl dichloride and this was followed by a ring expansion of only one of the two four-membered rings to produce **117**. When the dipropylmalonyl dichloride was used, no cyclized product was isolated and only monoamide (**118)** formation was detected.

Cyclopropane-1,1-dicarbonyl dichloride was investigated in the anticipation of observing tandem dicyclization analogous to **114**, with the possibility of one or two further ring expansions, analogous to the formation of the fused dihydropyran ring in **118**. Unexpectedly, cyclization occurred instead onto the imidazole ring producing 3'-methylspirocyclopropane-1,6'-pyrrolo[1,2-*c*]imidazole-5',7'-dione (**119)** (Table 2.1, last entry). The diacid chloride mono- and dicyclizations observed upon forming **114-117** and **119** all are consistent with reactions proceed through formation of intermediate cyclic ketene-*N*,*N'*-acetals (Schemes 2.8 and 2.9). When the same types of reactions were explored with 2-methylbenzimidazole, monocyclized product **121** was isolated only with dimethylmalonyl dichloride (Table 2.2). No other cyclized products could be isolated with other diacid chlorides. Only the monoamides (**120**, **122, 123**) were isolated when the R substituent on the diacid chloride was ethyl, cyclobutyl or propyl, respectively.

The cyclization pathway onto the imidazole ring to give **119**, exhibited by cyclopropane-1,1-dicarbonyl dichloride, becomes the predominant route taken by other 1,3-diacid chlorides when the 2-alkyl group on imidazoles is changed to either ethyl or isopropyl (Table 2.3 & 2.4). The 2-ethyl (Table 2.3) and 2-isopropyl (Table 2.4) imidazoles readily cyclize onto the imidazole ring, generating derivatives **124**, **126-129** with two fused 5-membered rings.

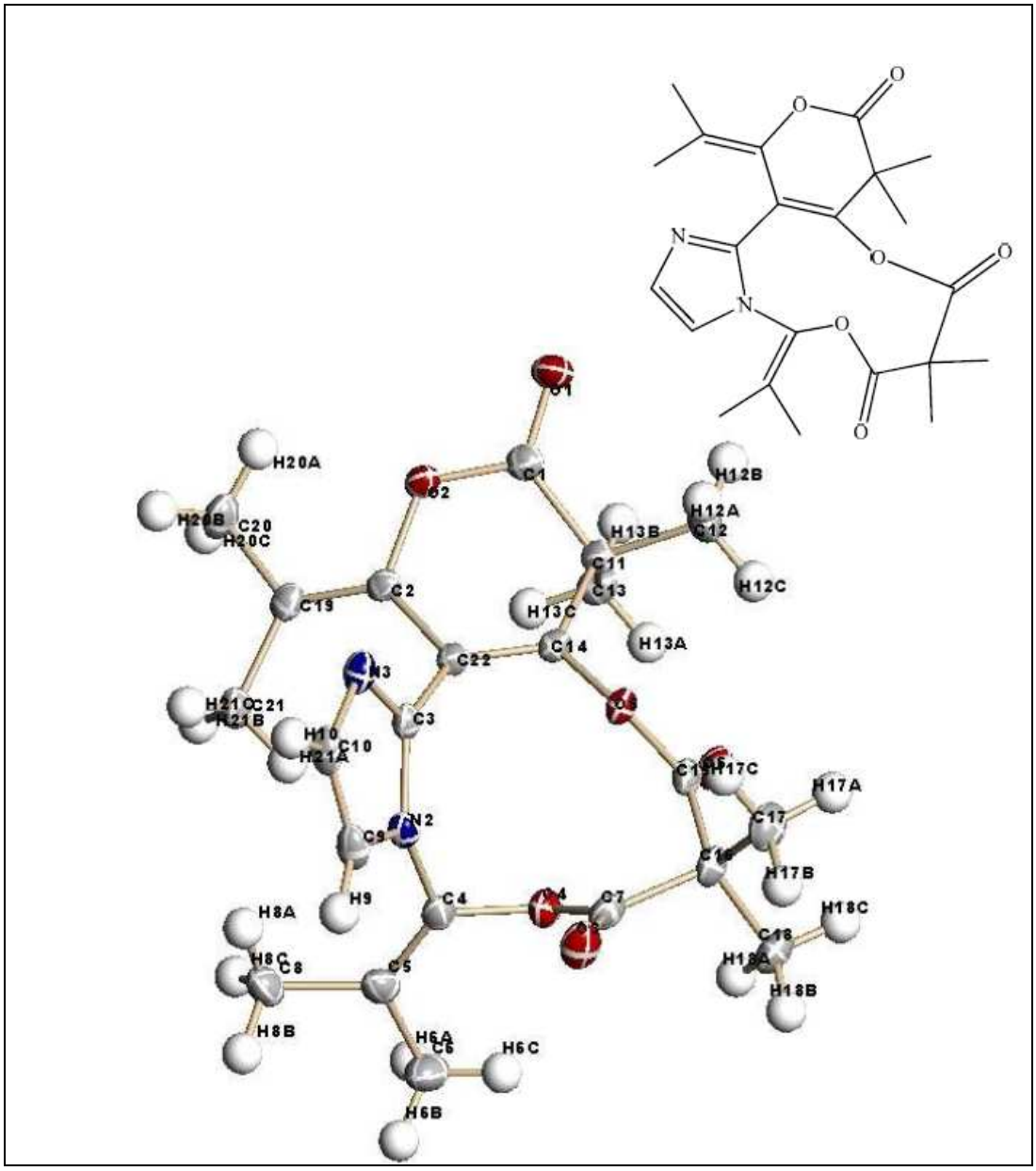
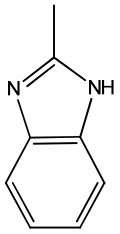
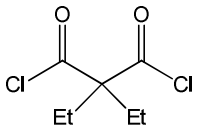
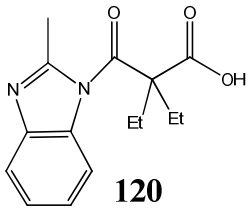
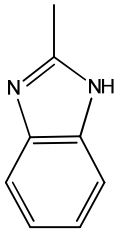
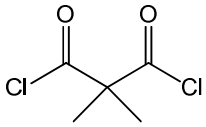
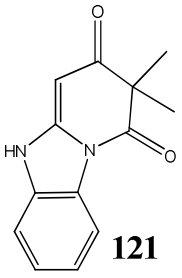
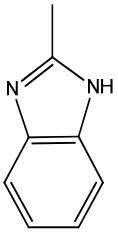
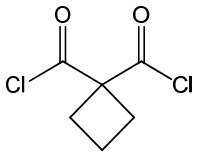
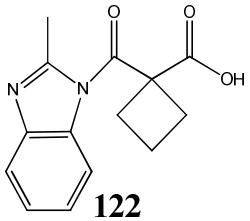
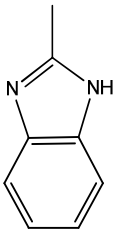
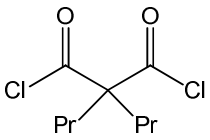
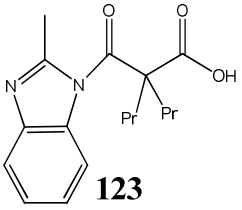


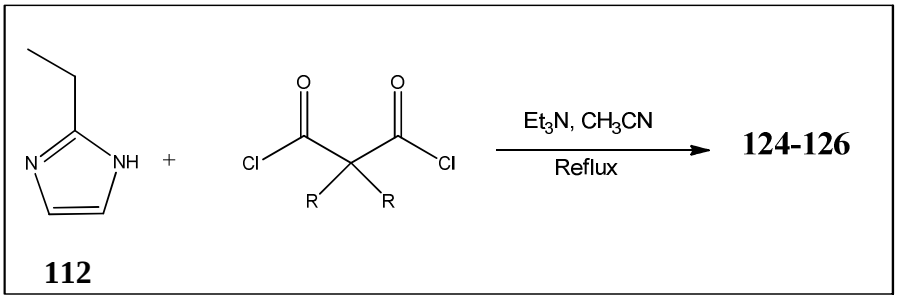
Figure 2.3 The Crystal Structure of 8,8,11,11-tetramethyl-5,14-di(propan-2-ylidene)-5H-imidazo[1,2-*c*]pyrano[3,4-*e*][1,7,3]dioxazecine-7,9,12(8H,11H,14H)-trione (**116a**)[88b]

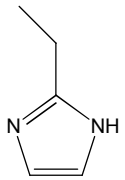
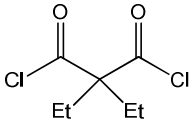
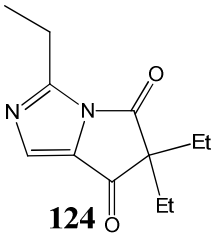
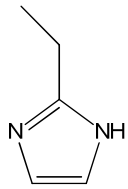
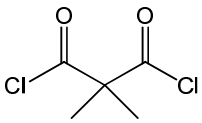
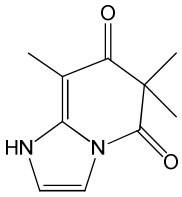
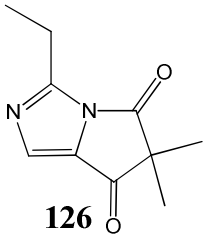
Table 2.2 Reactions of 2-Methylbenzimidazole with 1,3-Diacid Chlorides[a] and Et_3N in Acetonitrile[a]

Entry	Substrate	Diacid Chloride	Reflux time (h)	Product Isolated	Yield (%)
1			3	 **120**	67
2			3	 **121**	59
3			3	 **122**	68
4			3	 **123**	73

[a] Mole ratio of 2-methylbenzimidazole, diacid chloride and base is 1/2.4/6

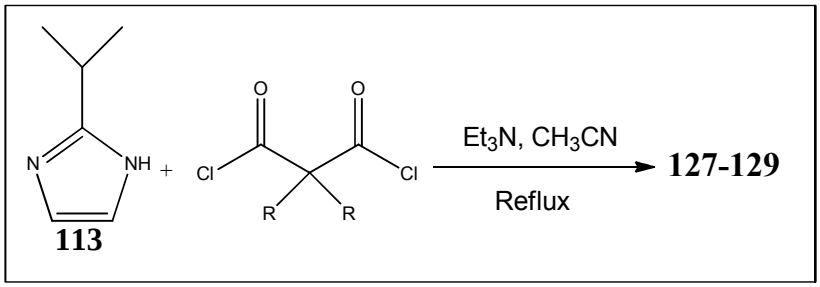
Table 2.3 Reactions of 2-Ethylimidazole with 2,2-Disubstituted-1,3-Diacid Chlorides and Et_3N in Acetonitrile[a]

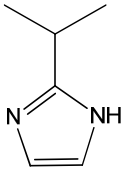
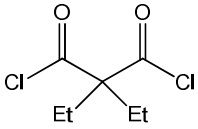
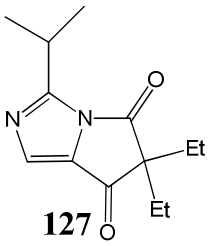
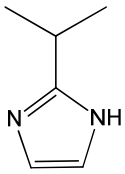
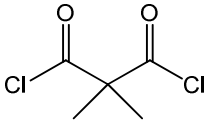
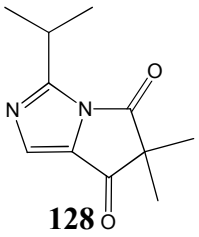
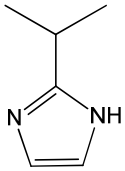
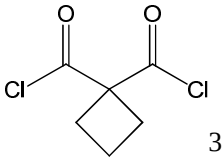
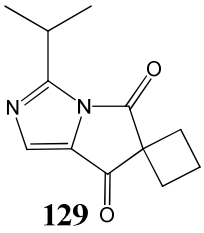


Entry	Substrate	Diacid Chloride	Reflux time (h)	Product Isolated	Yield (%)
1			3	 **124**	71
2			3	 **125**	28
				 **126**	58

[a] Mole ratio of 2-ethylimidazole, diacid chloride and base is 1/2.4/6

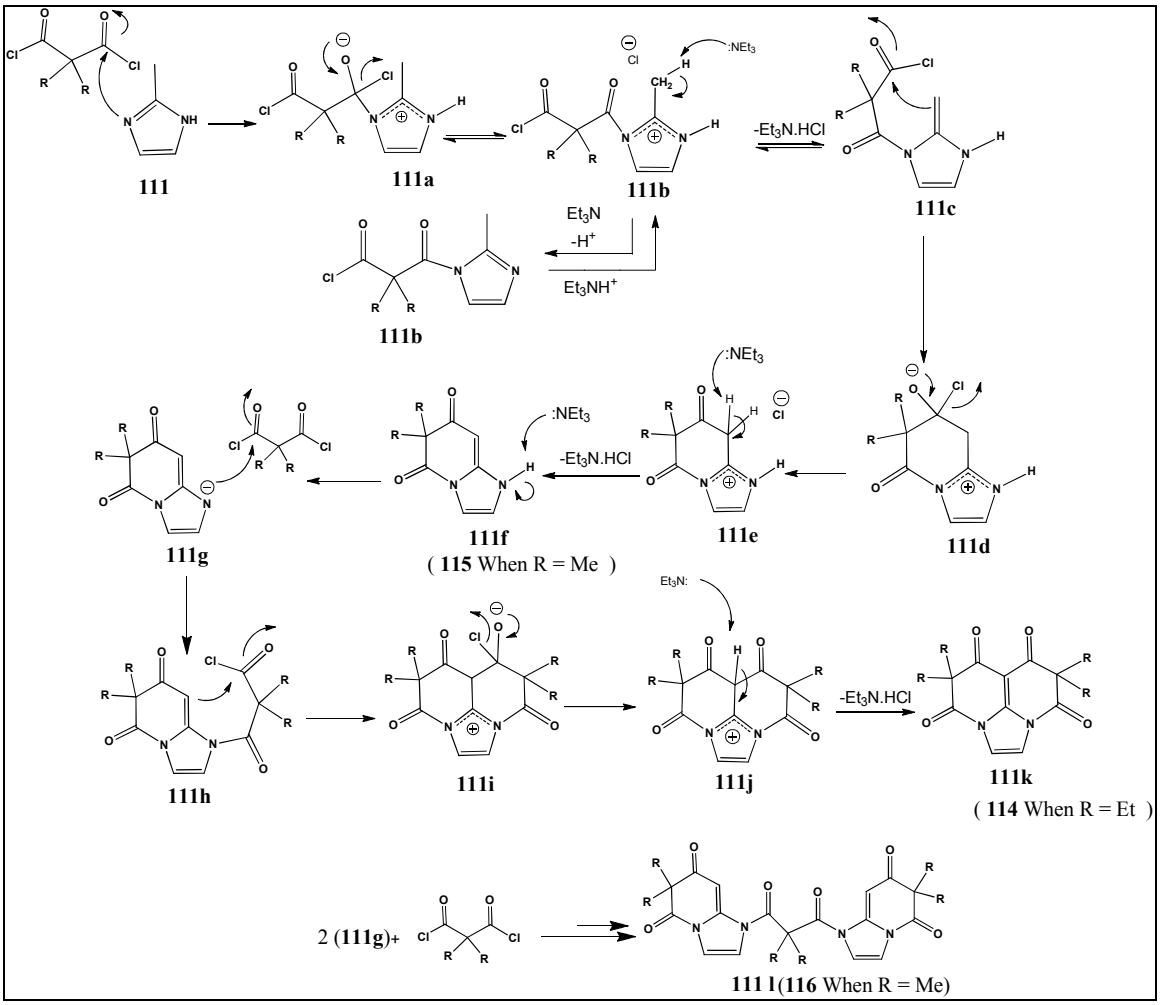
Table 2.4 Reactions of 2-Isopropylimidazole with 2,2-Disubstituted-1,3-Diacid Chlorides and Et_3N in Acetonitrile[a]



Entry	Substrate	Diacid Chloride	Reflux time (h)	Product Isolated	Yield (%)
1			3	 **127**	76
2			3	 **128**	71
3			3	 **129**	70

[a] Mole ratio of 2-isopropylylimidazole, diacid chloride and base is 1/2.4/6

A suggested mechanism for the formation of products **114-116** (Table 2.1) is shown in the Scheme 2.8. The same path shown in Scheme 2.8 leading to **115**, can account for the formation of **121** when the starting reagent was 2-methylbenzimidazole.



Scheme 2.8 Plausible Mechanism for the Formation of **114-116**

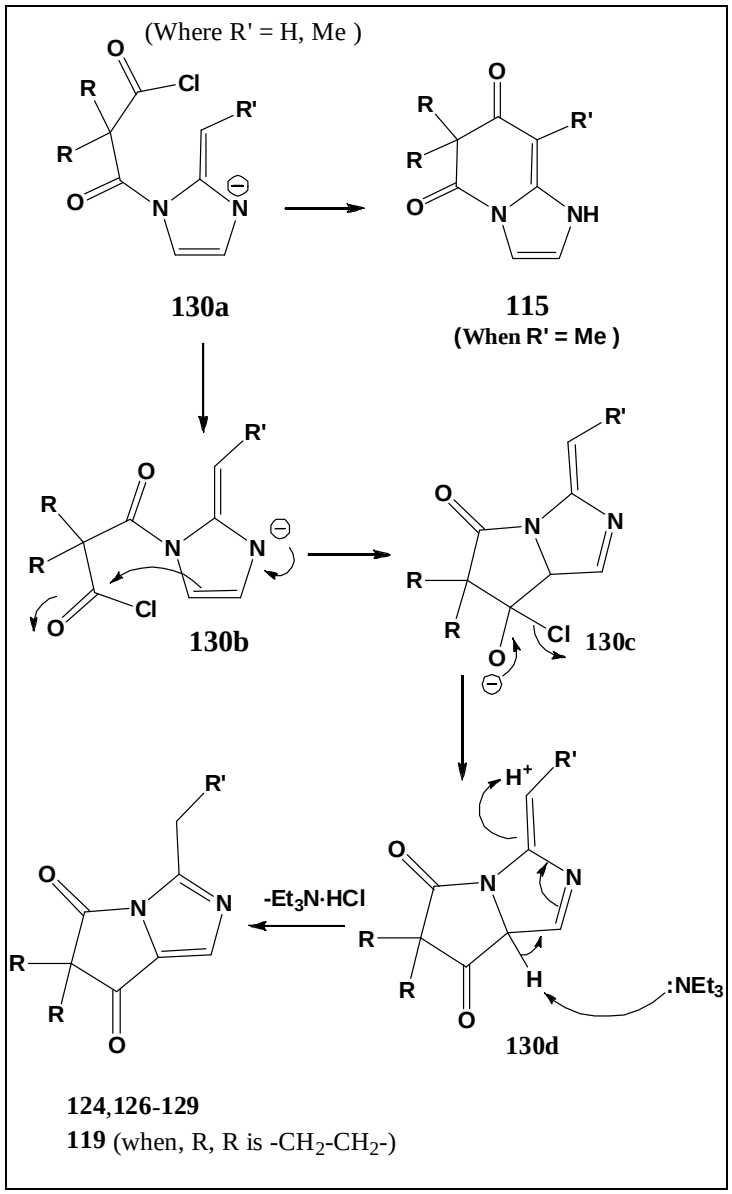
Initial nucleophilic acyl attack by nitrogen of 2-methylimidazole (**111**) on a diacid chloride carbonyl carbon generates zwitterionic intermediate (**111a**). Ion pair (**111b**) is

formed by the loss of chloride. Reversible proton removal from either the methyl group or nitrogen could occur to give **111c** or its tautomer, respectively. In the case of *N*-acyl cyclic ketene-*N*,*N*'-acetal (**111c**) where an intramolecular acyl nucleophilic attack of the exocyclic *β*-carbon results in another zwitterionic intermediate (**111d**). Loss of chloride and subsequent proton removal by Et_3N from **111e** gives the monocyclic product (**111f** or **115,** where R = CH_3). Proton removal by Et_3N generates anion **111g** which then reacts with an acid chloride to form **111h**. It cyclizes by nucleophilic attack of the exocyclic ketene-*N*,*N*'-acetal's carbon. Loss of chloride from **111i** and deprotonation of **111j** finally forms the highly functionalized tricylic product (**111k**) (**114**, where R = Et). When two molecules of **111g** react with one diacid chloride, **111l** (**116**, where R = Me) is formed.

The cyclizations onto the imidazole ring to form imidazopyrollodiones are illustrated in Scheme 2.9. The generation of two fused five-membered rings may be activated by the generation of anion **130a** (Scheme 2.9). Placement of one or two methyl groups on the exocyclic methylene carbon of the ketene-*N*,*N*'-acetal intermediate (**130a**) favors cyclization onto the imidazole ring.

The variability of these 2-alkylimidazole and 2-methylbenzimidazole reactions with diacid chlorides, which form highly functionalized imidazonapthyridinetetraone (**114**), imidazopyridinediones (**115, 121, 125**) and imidazopyrrolodiones (**119, 124, 126-129**) and imidazodioxazecinetrione (**116a**) under identical conditions, is interesting.

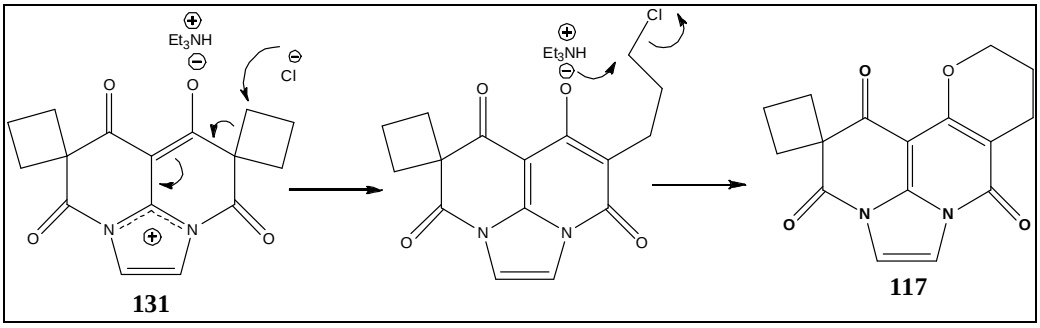
Tandem dicyclizations or single cyclizations at the exocyclic methylene and cyclization onto the imidazole ring are all observed. Each reaction can be rationalized as proceeding through an *in situ* generated cyclic ketene-*N*,*N*'-acetal intermediate.



Scheme 2.9 Proposed Mechanism for Cyclization on the Five-membered Ring

In some reactions, involving 2-methylimidazole and 2-methylbenzimidazole, no cyclic product was isolated. In most of these cases TLC analyses revealed a complex stich which could not be analyzed by several solvent mixtures.

The formation of these different products probably arises through small differences in the activation barriers among these routes. Thus, subtle steric and electronic factors and solvation differences favor alternative pathways. For example, reactions conducted, where enhanced steric crowding was introduced at the 2-position, favored cyclization at the imidazole ring in all cases (Tables 2.3 and 2.4). Steric effects reduced the nucleophilicity of the *β*-carbon, enhancing cyclization onto the imidazole ring (via Scheme 2.9 relative to Scheme 2.8). Opening of one of the two four-membered rings during the formation of **117** is likely the result of chloride nucleophilic attack on the four-membered ring's carbon of **131** mediated by positive charge on the imidazole ring's C2. Significant charge separation in (**131**) is the result of its push-pull structure.



Scheme 2.10 Plausible Mechanism for the Formation of **117**

In related ketene-*N*,*N'*-acetals with two carbonyl functions bound to the *β*-carbon, long bond lengths and lower bond orders were found between the ring carbon and *β*-

carbon.[21] This is indicative of a strong contribution from a zwitterion-like dipolar structure. Opening of the four membered ring is followed by nucleophilic displacement of chloride by oxygen to give a six-membered ring in (**117**). This ring expansion of **131** to form **117** decreases the dipolar character. This reduces the propensity of the second four-membered ring to open. Other four-membered ring expansions to carbonyl oxygens have been reported.[89-90] However, all of the mechanisms suggested here are strictly postulated and no further mechanistic studies have been performed.

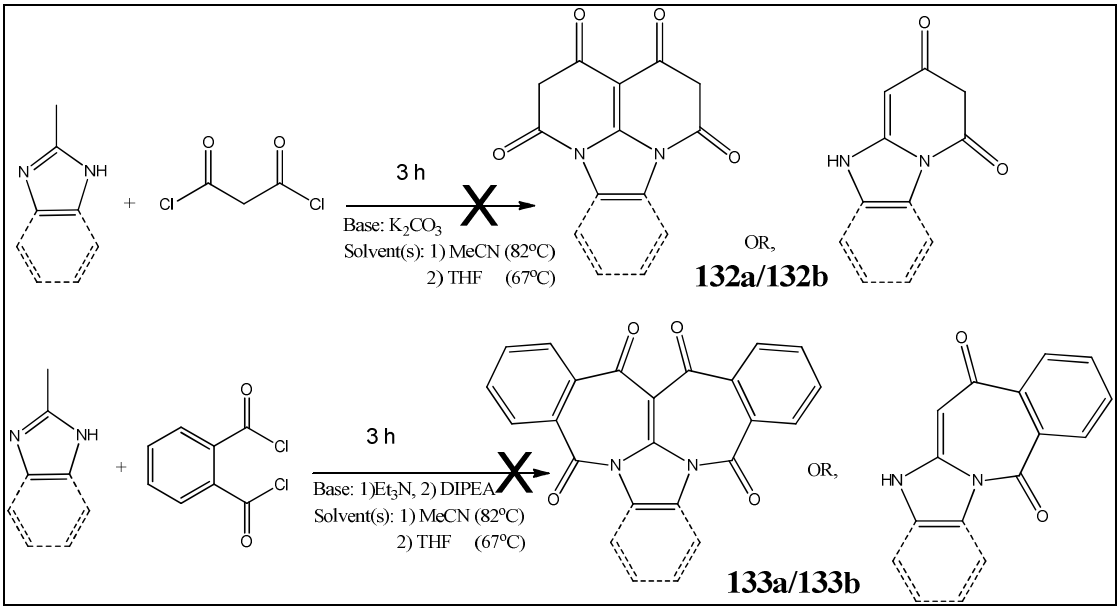
In the anticipation of forming other interesting heterocyclic products, a group of other bis-electrophiles were used. Malonyl dichloride, phthaloyl dichloride, *N*-Chlorocarbonyl isocyanate and *N*-Chlorosulfonyl isocyanate were each reacted with both 2-methylimidazole and 2-methylbenzimidazole.

Malonyl chloride is a bis-electrophile without any substitutent at the α position. The reaction of 2-methylimidazole or 2-methylbenzimidazole with malonyl chloride in the presence of a suitable base could potentially lead to bicyclic or tricyclic ring systems (**132a**/**132b**) (Scheme 2.10). However, malonyl chloride contains two acidic hydrogens so that use of a base like Et_3N could also result in dehydrohalogenation to a ketene.

Both 2-methylimidazole and 2-methylbenzimidazole were reacted with malonyl chloride. K_2CO_3 was used as the base. Reactions were run in both refluxing acetonitrile (82°C) and refluxing THF (66°C) (Scheme 2.10). The resulting crude product mixtures from these reactions did not show any spots above the baseline on TLC analysis when eluted with several solvent mixtures of different polarity. The single spot on the baseline did not move with any solvent systems tried (e.g. 100% ethyl acetate, 100% hexane,

EA/hexane = 1:1, 1:2, acetone etc). Therefore, no further analyses or attampts at separation were made.

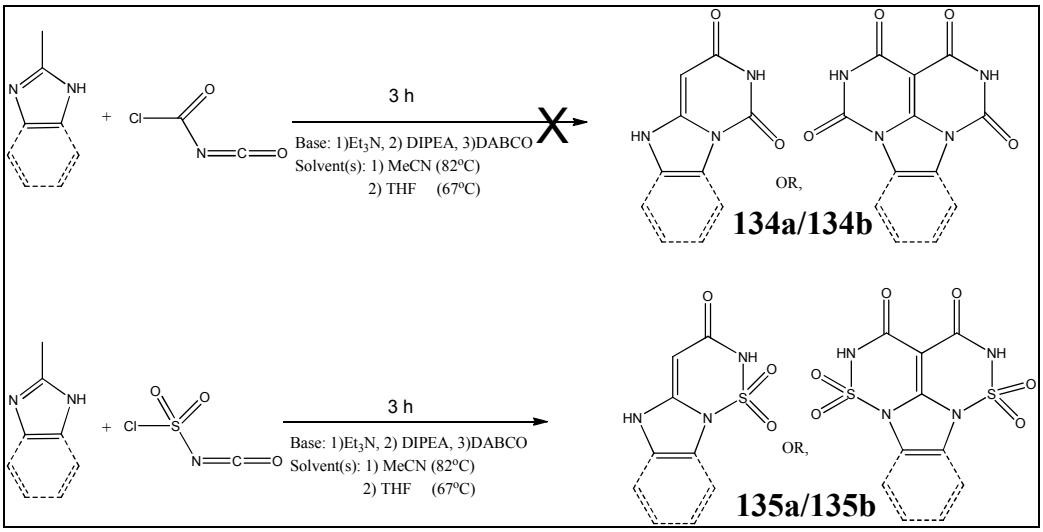
It was hoped that reactions of phthaloyl chloride with 2-methylimidazole or 2-methylbenzimidazole could result in a polycyclic molecule with one or two seven-membered rings (**133a**/**133b**, Scheme 2.10). Thus, phthaloyl chloride was reacted with 2-methylimidazole and 2-methylbenzimidazole in both refluxing acetonitrile and THF (Scheme 2.10). Two bases, Et_3N and DIPEA (diisopropylethyl amine) were used.



Scheme 2.11 Unsuccessful Reactions of 2-Methylimidazole or 2-Methylbenzimidazole with Malonyl Chloride and Phthaloyl Chlorides (expected products that were not obtained are shown on the right. Imidazole-based products are labeled with '**a**' and benzimidazole-based products are labeled with '**b**'. The mole ratio of substrate/ bis-electrophile/ base was 1/2.4/6 in these reactions).

In all eight cases crude product mixtures showed spots for unreacted starting materials (ethyl acetate/ hexane 1:1). No new spot was observed. No further attempts were made.

N-Chlorocarbonyl isocyanate and *N*-Chlorosulfonyl isocyante were used as other biselectrophiles in reactions with 2-methylimidazole and 2-methylbenzimidazole under similar conditions. Three bases Et_3N, DIPEA (diisopropylethyl amine),and DABCO-(1,4-diazabicyclo[2.2.2]octane**)** were used.



Scheme 2.12 Unsuccessful Reactions of 2-Methylimidazole or 2-Methylbenzimidazole with Bis-Electrophiles (expected products that were not obtained are shown on the right. Imidazole-based products are labeled with '**a**' and benzimidazole-based products are labeled with '**b**'. The mole ratio of substituted imidazole/ biselectrophile/ base was 1/2.4/6 in these reactions)

Thus, each of these bis-electrophiles was tried with three bases in two solvents for a trial of six attempted reactions (twelve reactions altogether). Complex product mixtures were indicated by TLC analysis (solvent systems: 100% EA, 100% hexane, EA/hexane = 1:1, 1:2, acetone: hexane: 1:1, 100% acetone, etc). Only in the case, where *N*-Chlorosulfonyl isocyante was reacted with

2-methylimidazole in refluxing acetonitrile in the presence of triethylamine, TLC analysis (with 100 % acetone) of the crude product mixture give a promising spot. The ^{1}H NMR of the isolated product corresponding to this spot was very complex and could not be interpreted. No further analysis was performed. However, no analogous TLC spot was observed in case of 2-methylbenzimidazole. TLC analysis exhibited only one spot at the baseline which was not be eluted by any solvent mixture tried (100% ethyl acetate), 100% hexane, EA/hexane = 1:1,1:2, acetone: hexane: 1:1, 100% acetone, etc).

Conclusions

Reactions of 2-methylimidazole and 2-methylbenzimidazole with various 1,3 diacid chlorides in presence of a base generated a variety of products. Formation of most of these products can be explained by postulating an *in situ* generated ketene-*N,N´*-acetal intermediate. Thus, it can be said that the reactions of 2-methylimidazoline and 2-methyl-1,4,5,6-tetrahydro-pyrimidine with 1,3-diacid chlorides can be extended to aromatic 2-susbstituted imidazoles or 2-methylbenzimidazoles. However, as described in the chapter I, generation of these cyclic ketene-*N,N´*-intermediate resulted in a decrese in aromaticity of the starting 2-methyl imidazolium or the 2-methylbenzimidazolium cation

intermediates formed in these reactions. This factor apparently affected the product distributions relative to those observed with reactions of 2-methylimidazoline and 2-methyl-1,4,5,6-tetrahydro-pyrimidine. In some cases, the extra double bond in the five-membered ring also facilitated alternate route, which ultimately generated a different array of products. These products were not observed with 2-substituted imidazolines.

There were a few reactions of imidazoles and benzimidazoles in this chapter, where no cyclic product was obtained. All of these reactions were performed several times and the results were reproduced. However, in all those cases, different products were found that did not occur with imidazolines. In addition, product mixtures from these reactions showed complex streaks or baseline spots in TLC that could not be separated. Different results obtained in these reactions included competing reactions (e.g. dimer formations or an intermediates to the dimers). In some cases, oligomerization/ polymerizatuon might occur during these reactions which would be faster than tandem cyclizations to the desired tricyclic products. Also, the *gem*-dialkyl substitutents on C-2 of malonyl chloride might play an inportant role in all these reactions. It is a well established fact that some of cyclizations were not successful without the presence of any dialkyl group.[91] This might happen in reactions of malonyl chloride with 2-methylimidazole or 2-methylbenzimidazole also. In general, cyclizations are facilitated with the presence of a dialkyl group in near proximity. This effect is called *gem*-dialkyl effect or Thorpe-Ingold effect. It was found that the steric interactions of two alkyl groups increase the angle between them, which simultaneously decrease the angle on the opposite side. Thus, two reacting termini can come close to form a cyclic system.[91]

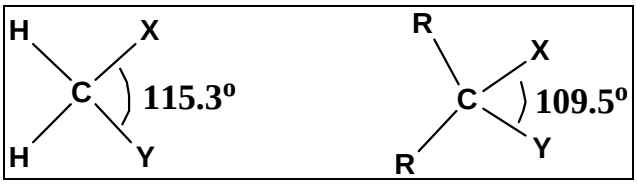


Figure 2.4 Thorpe-Ingold Effect[91]

However, this dialkyl effect depends on the steric environment. In one case, Smith et al. showed that the equilibrium constant for acetalization of the cyclohexanone portion of the dione of 5α-androstane-3,17-dione increased by changing the dialkyl group from dimethyl to diethyl.[92] Whereas, in the case of the γ-lactone formation reaction of benzenesulfonyl bromide and allyl acrylates, changing the dialkyl group from dimethyl to diisopropyl decreased the yield of the lactone.[93] In another case, Jung et al. found that in an intramolecular Diels-Alder reaction of 2-furfuryl methyl fumarates, dialkyl groups like dimethyl, diethyl, etc. gave similar results.[94] These types of steric factors might also play a role in the reactions of 2-methylimidazole with different 1,3-diacid chlorides. Thus, in future, the sensitivity of the products formed with substituents on C-2 of malonyl chloride needs to be further studied. Also, investigations should be conducted to understand how to specifically control and optimize each pathway.

A series of ^{1}H and ^{13}C NMR spectra are shown in page 59-68. All experimental data is given in pages 58-67 in this dissertation.

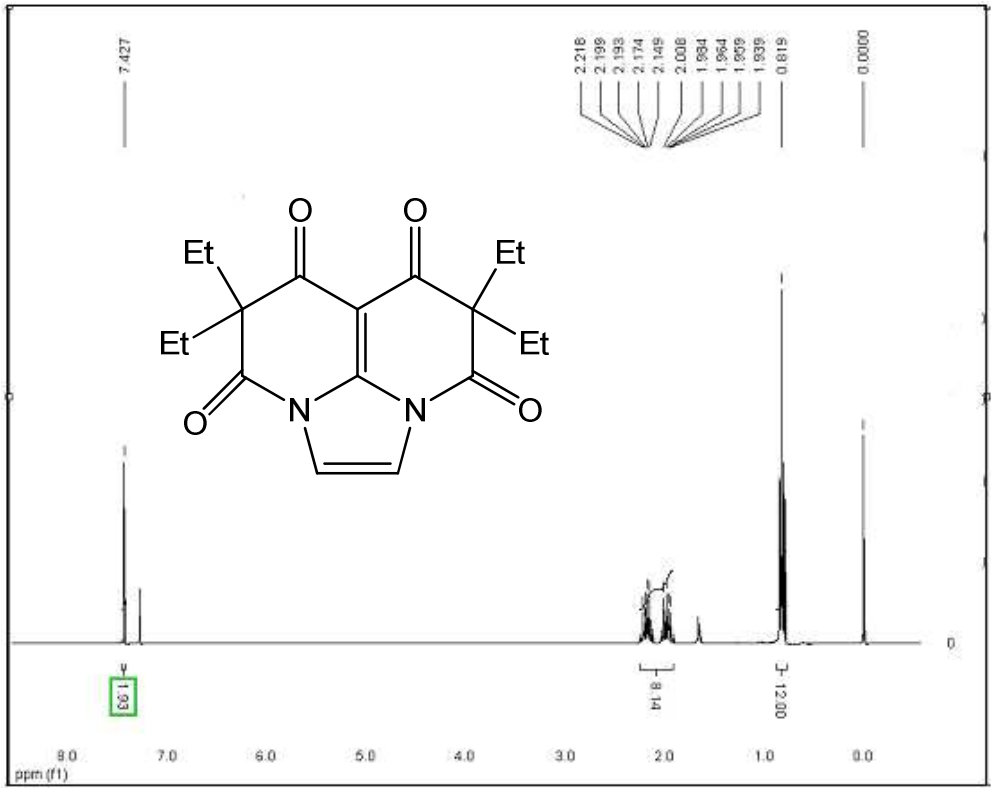


Figure 2.5 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 5,5,8,8-Tetraethyl-imidazo[1,2,3-*i*,*j*][1,8]napthyridine-4,6,7,9-tetraone (**114**)

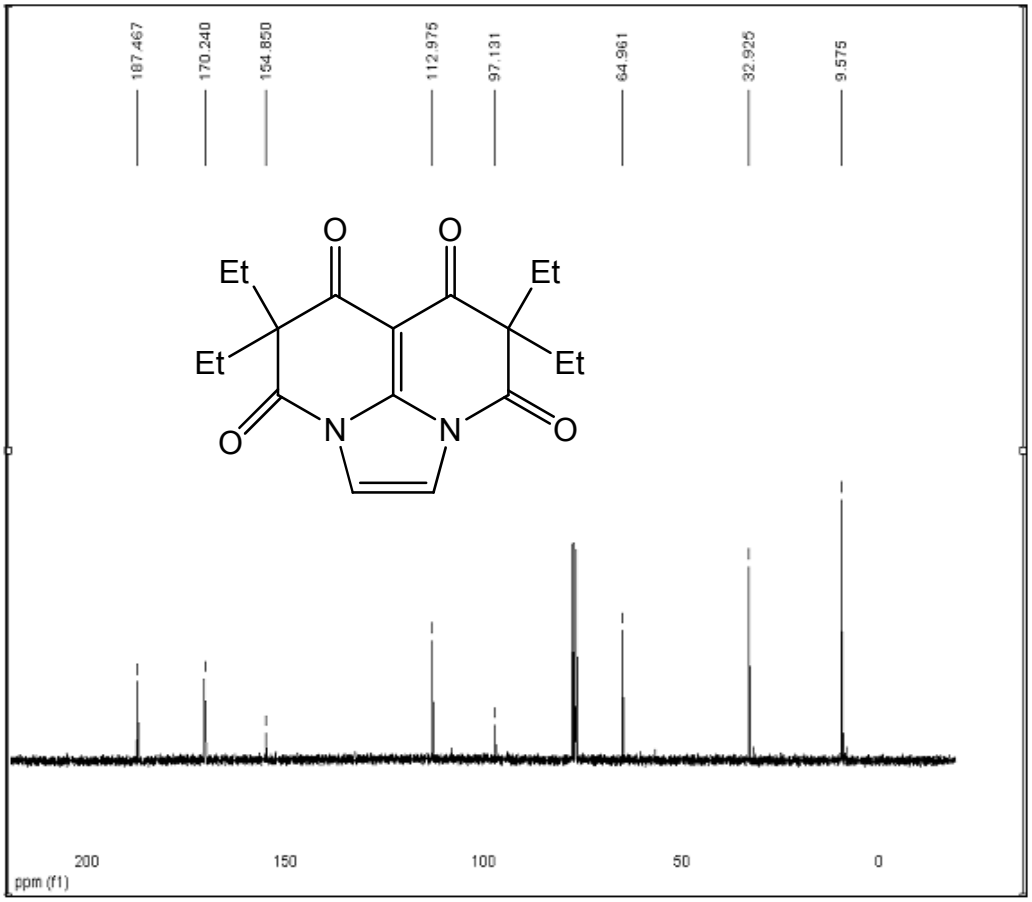


Figure 2.6 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 5,5,8,8-Tetraethyl-imidazo[1,2,3-*i,j*][1,8]napthyridine-4,6,7,9-tetraone (**114**)

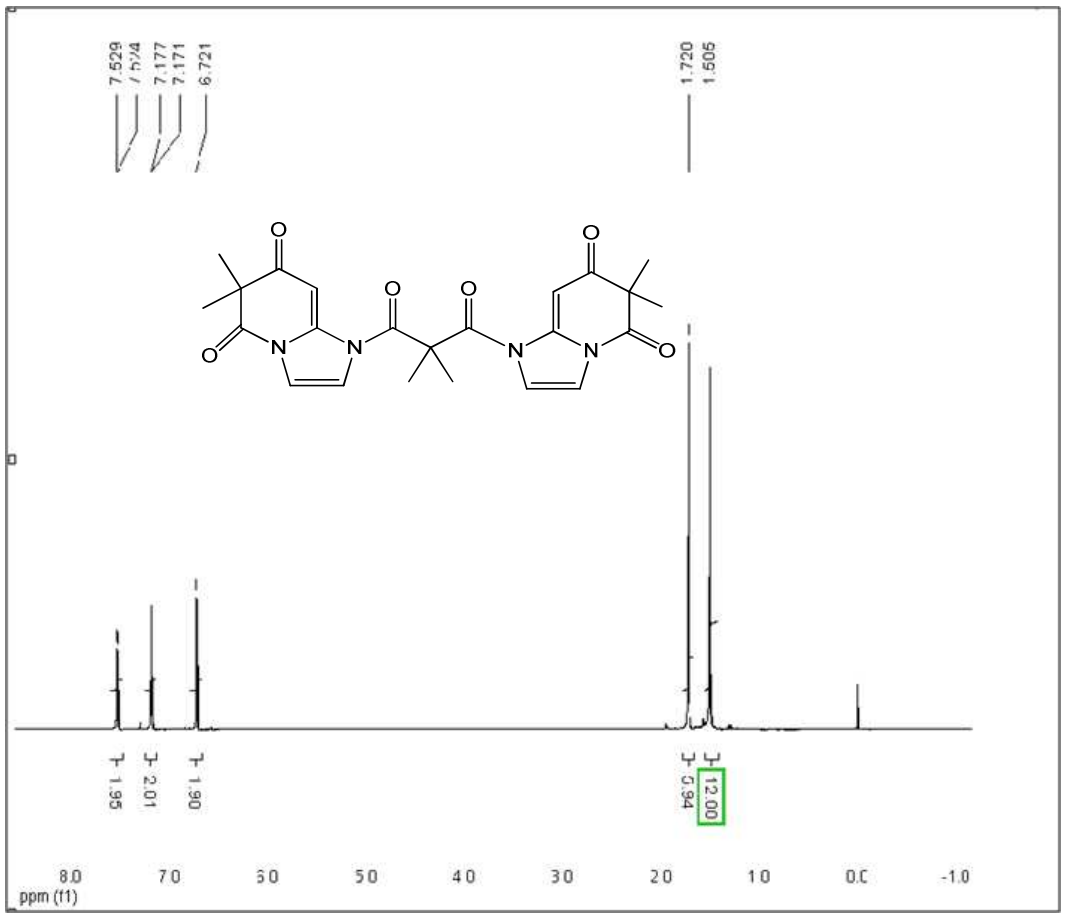


Figure 2.7 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-[2,2-Dimethyl-3-(6,6-dimethyl-5,7-dioxo-6,7-dihydro-5H-imidazo[1,2-*a*]pyridine-1-yl)-3-oxo-propionyl]-6,6-dimethyl-1H-imidazo(1,2-*a*]pyridine-5,7-dione (**116**)

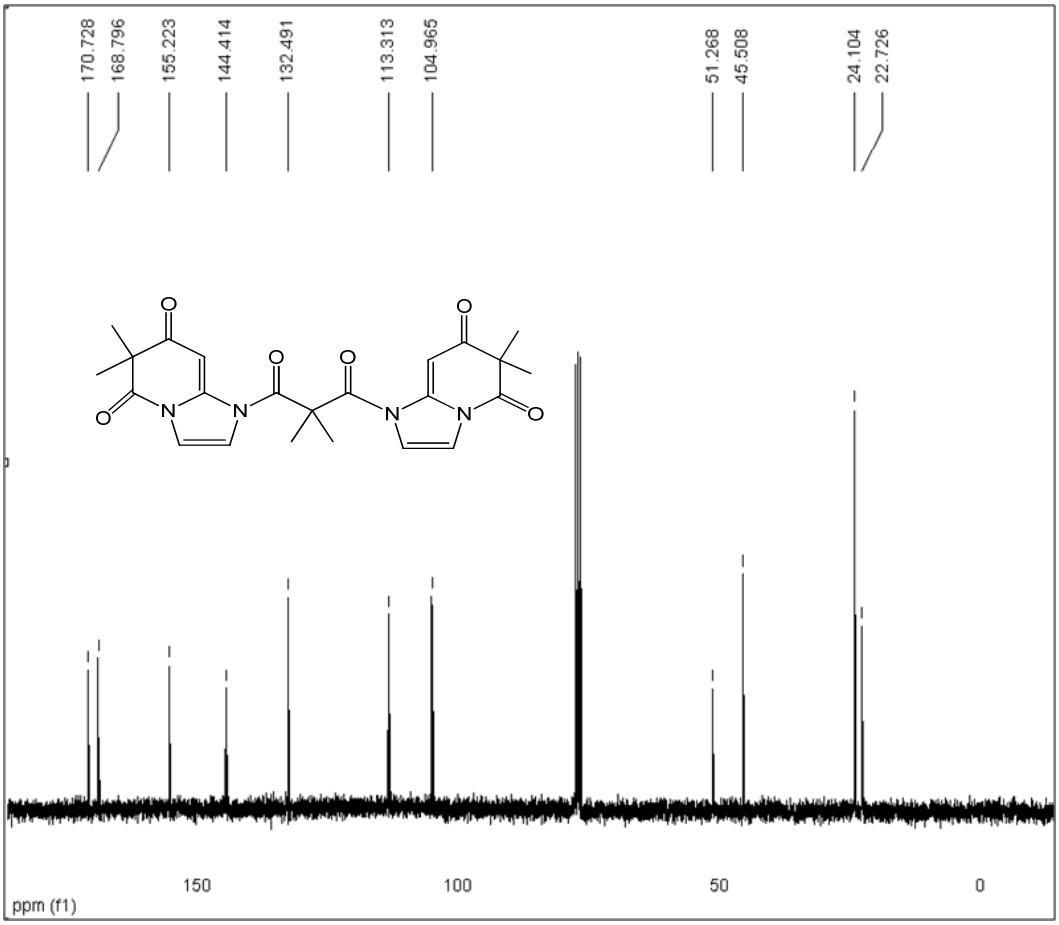


Figure 2.8 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1-[2,2-Dimethyl-3-(6,6-dimethyl-5,7-dioxo-6,7-dihydro-5H-imidazo[1,2-*a*]pyridine-1-yl)-3-oxo-propionyl]-6,6-dimethyl-1H-imidazo(1,2-*a*]pyridine-5,7-dione (**116**)

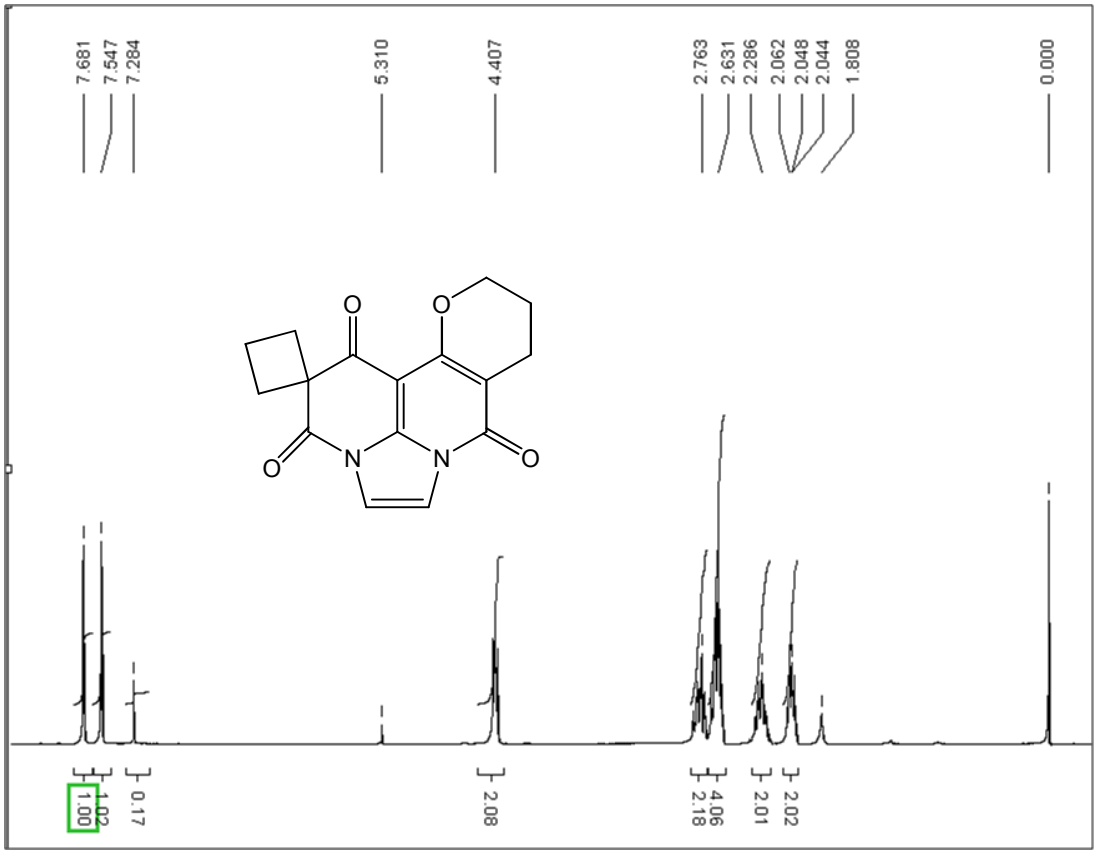


Figure 2.9 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 8,9-Dihydro-7H-10-oxa-3a,5a-diaza-acephenanthrylene-1,3,6-trione (**117**)

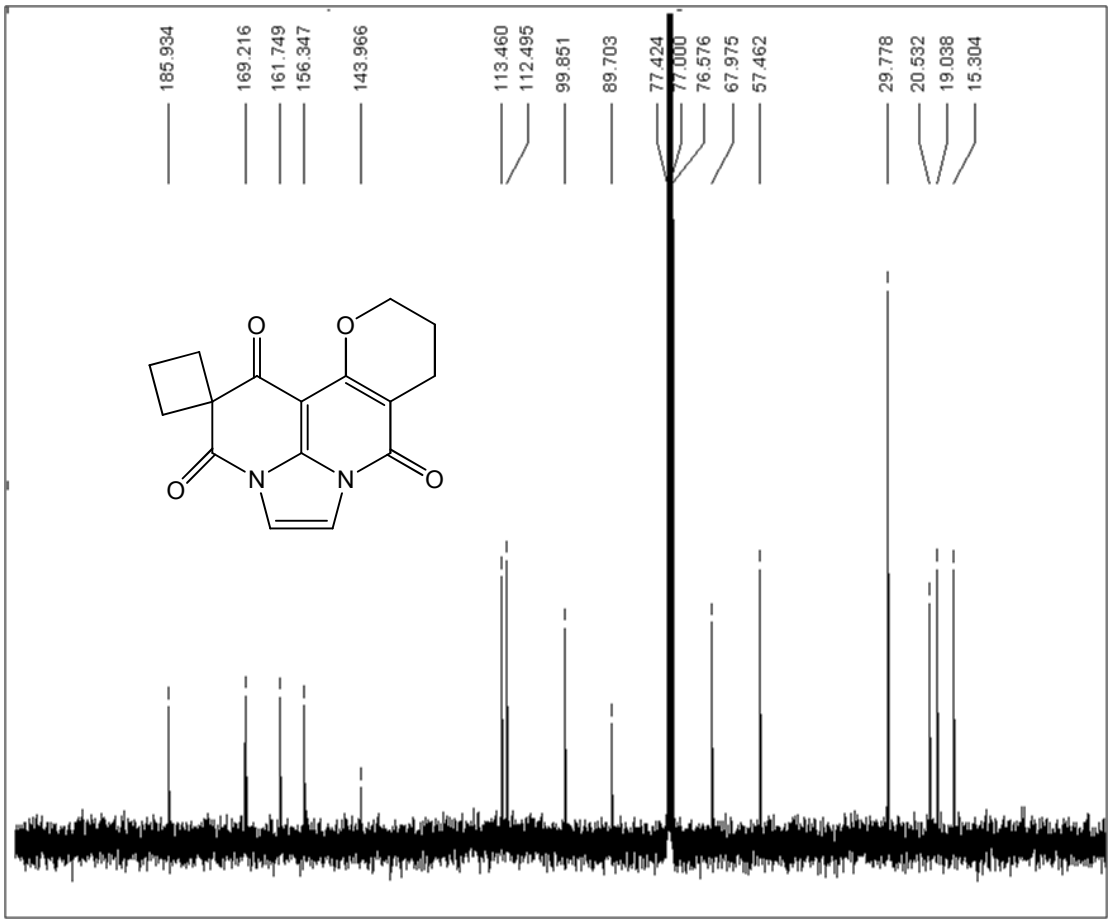


Figure 2.10 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 8, 9-Dihydro-7H-10-oxa-3a,5a-diaza-acephenanthrylene-1,3,6-trione (**117**)

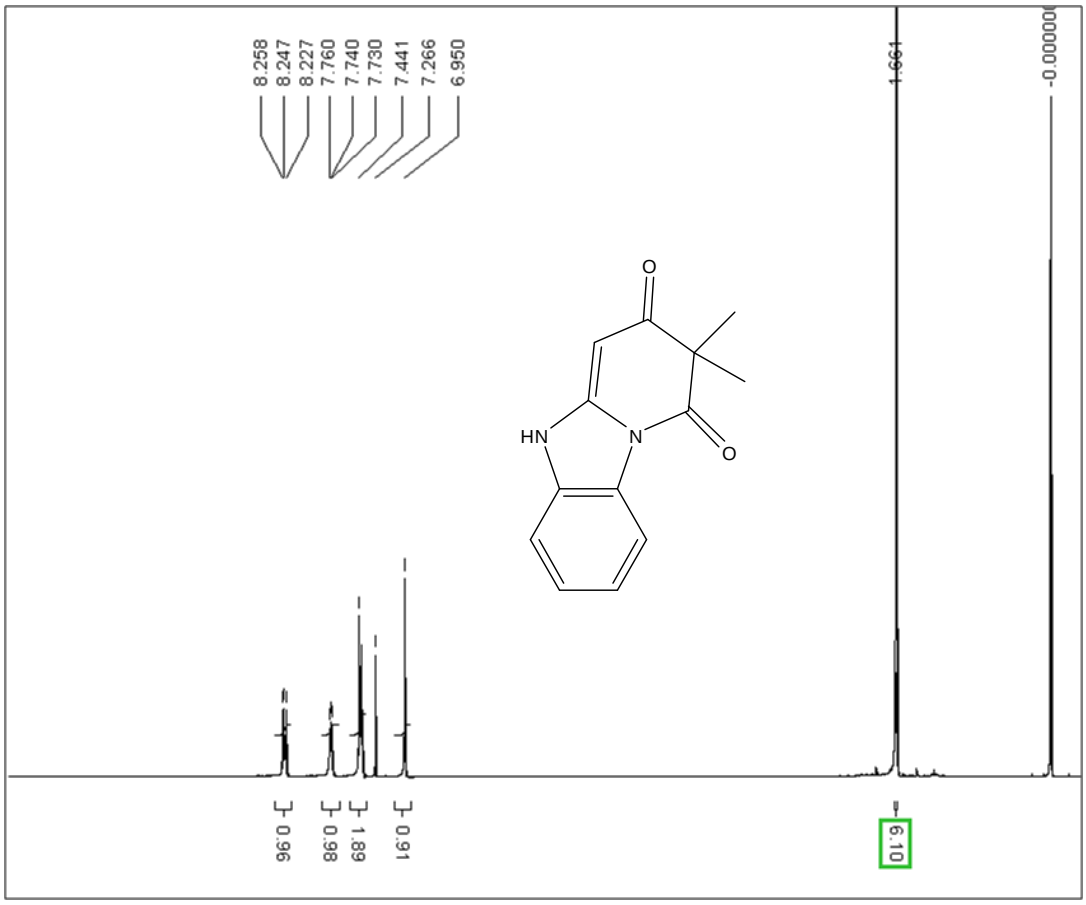


Figure 2.11 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2,2-Dimethyl-5H-benzo[4, 5]imidazo[1, 2-*a*]pyridine-1,3-dione (**121**)

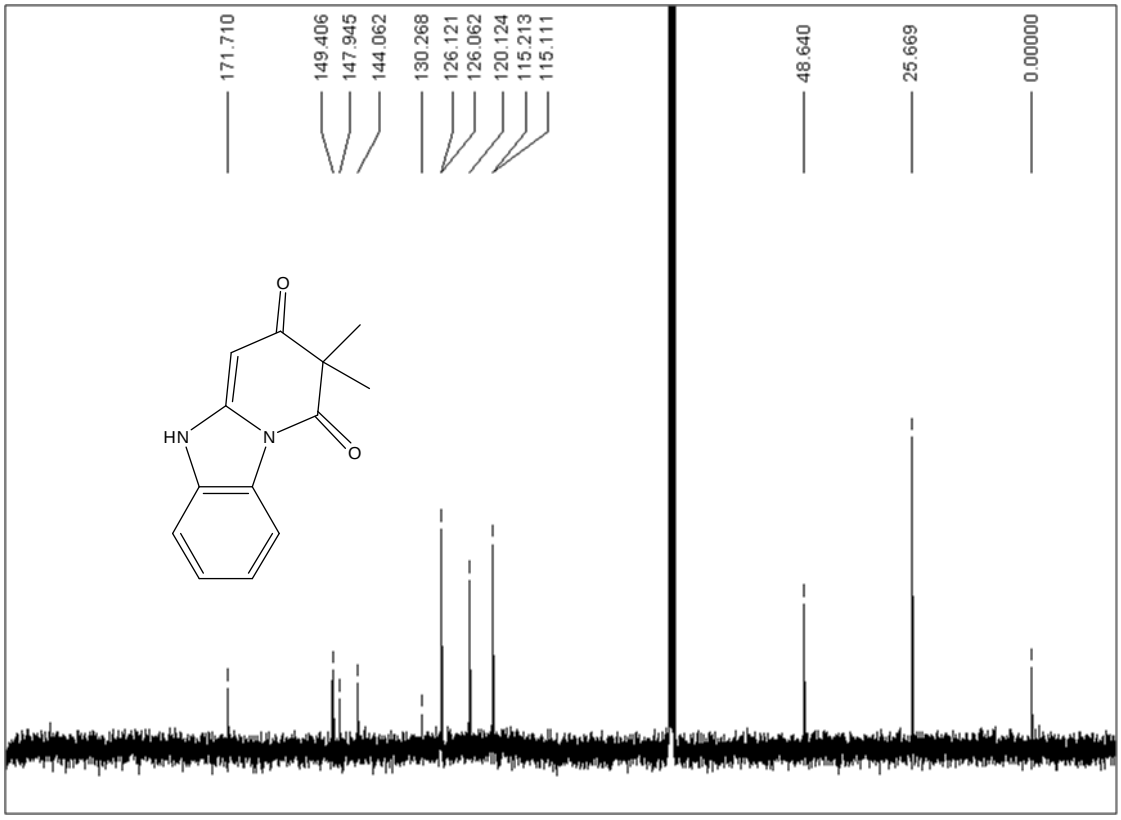


Figure 2.12 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2,2-Dimethyl-5H-benzo[4, 5]imidazo[1, 2-*a*]pyridine-1,3-dione (**121**)

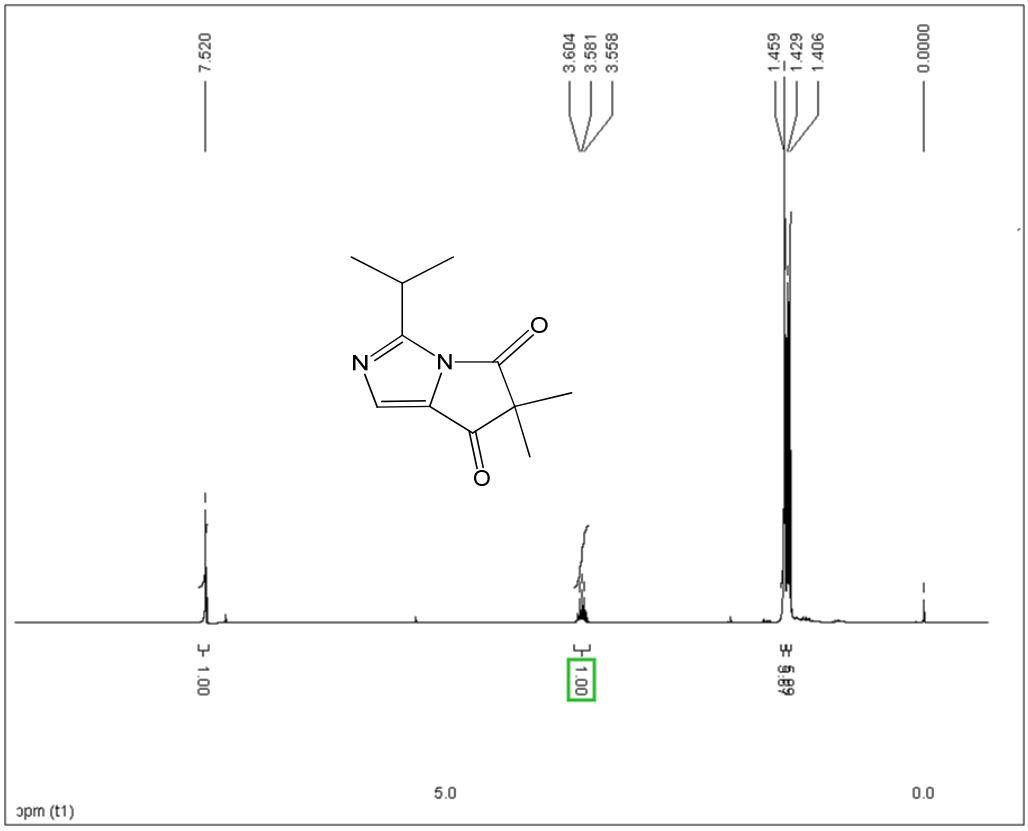


Figure 2.13 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-Isopropyl-6,6-dimethyl-pyrrolo[1,2-*c*]imidazole-5,7-dione (**128**)

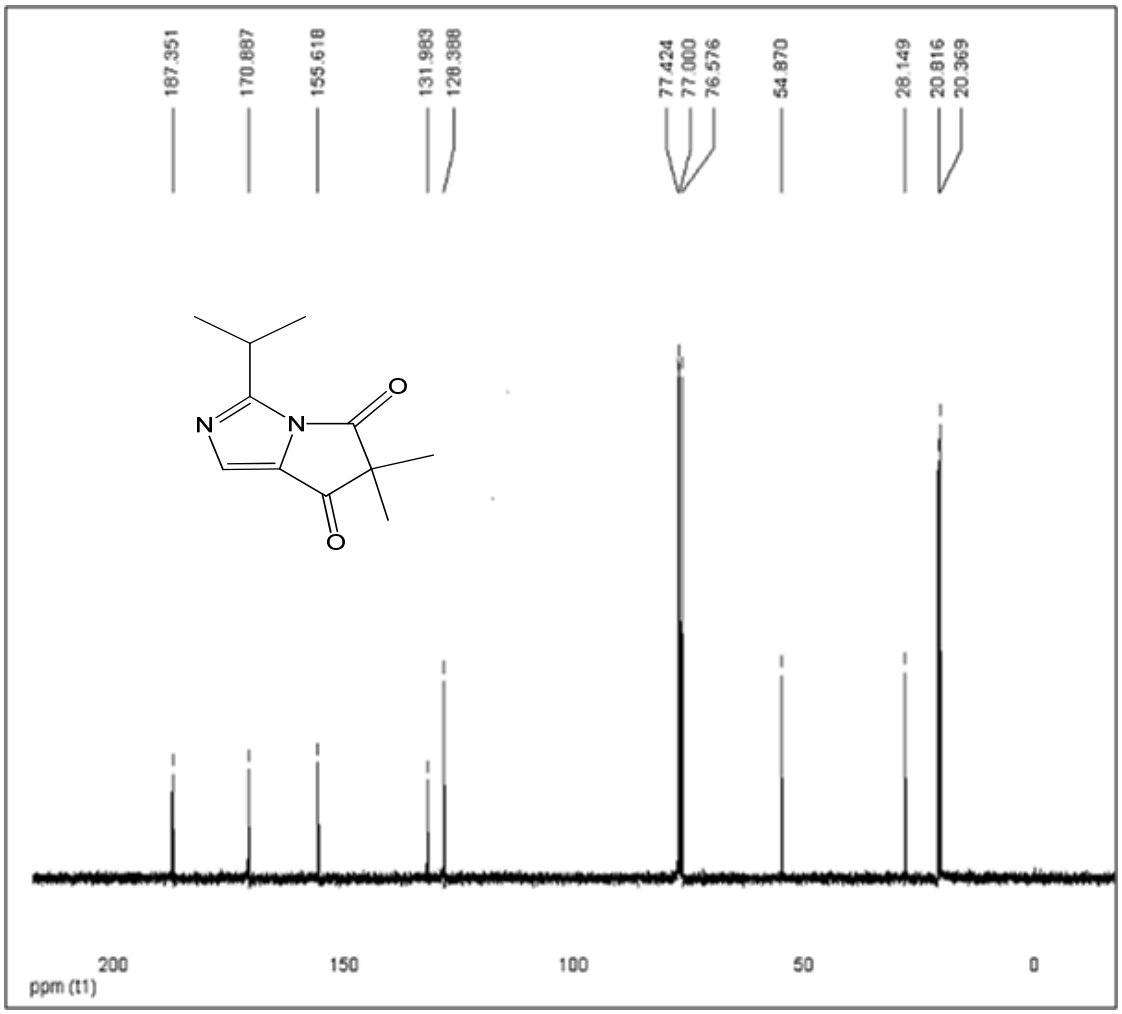


Figure 2.14 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 3-Isopropyl-6,6-dimethyl-pyrrolo[1,2-*c*]imidazole-5,7-dione (**128**)

Experimental

Materials and Instruments

The ^{1}H and ^{13}C NMR spectra were collected using a 300 MHz spectrometer (Bruker AVANCE III) operating at 300 MHz for proton and 75 MHz for carbon. Chemical shifts were reported in ppm downfield from TMS in $CDCl_3$ solvent for all NMR samples. The FT-IR spectra were collected as films as neat or using salt plates. Splitting patterns are designated as 's, d, t, q and m', for ' singlet, doublet, triplet, quartet and multiplet'. All reactions were performed under nitrogen. Acetonitrile and triethylamine were dried by distillation over calcium hydride under nitrogen. Dichloromethane was pre-dried with calcium chloride and then distilled from calcium hydride under nitrogen. Dipropylmalonyl dichloride, 1,1-cyclobutane-dicarbonyl diacid chloride were made by a literature procedure.[95] All other chemicals were obtained commercially and used as received.

Synthesis using 2-Methylimidazole as the Starting Material

5,5,8,8-Tetraethyl-imidazo[1,2,3-*i*,*j*][1,8]napthyridine-4,6,7,9-tetraone (**114**)

2-Methylimidazole (**111**) (0.20 g, 2.4 mmol) was dissolved in acetonitrile (15 mL). Triethylamine (1.5 g, 14 mmol) was then added dropwise. A solution of diethylmalonyl dichloride (1.15 g, 5.7 mmol) in acetonitrile (15 mL) was added dropwise into this solution under nitrogen at room temperature. The reaction mixture was refluxed

for 3 h and the solvent was removed by rotary evaporation. Acetone (3 x 20 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and the solid obtained was thoroughly washed with acetone (3 x 15 mL).The combined filtrates were concentrated *in vacuo* and residue was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give (**114)** (396 mg, 50%), R_f = 0.7, white solid; mp. 258-260°C. The reaction was also carried out with 0.25 g of 2-methylimidazole, where the ratio of 2-methylimidazole/diacid chloride/triethylamine was 1/2.4/6. Similar result obtained with a yield of 0.57 mg (59 %).

IR ($cm^{-1)}$: 3039, 2974, 2950 1713, 1710, 1635, 1536, 1481.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.42 (s, -N-C<u>H</u>=C<u>H</u>-N-, 2H), 2.07 (m, C-C<u>H_2</u>-CH_3, 8 H), 0.81 (t, *J* = 7.4 Hz, C-CH_2-C<u>H_3</u>, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C =187.46 (C-<u>C</u>O-C), 170.24 (N-<u>C</u>O-C), 154.85 (><u>C</u>=C-$(CO)_2$), 112.97 (N-<u>C</u>=C-N), 97.13 (>C=<u>C</u>-$(CO)_2$), 64.96 ($(CO)_2$-<u>C</u>-CH_2-CH_3), 32.92 (-C-<u>C</u>H_2-CH_3), 9.57 (-C-CH_2-<u>C</u>H_3).

<u>6,6-Dimethyl-1H-imidazo[1,2-*a*]pyridine-5,7-dione (**115**)</u>

Compound **115** was isolated with some inseparable spots in the first run (this reaction was performed several times) using 2-methylimidazole (**111**) (0.20 g, 2.4 mmol) and dimethylmalonyl dichloride (0.99 g, 5.7 mmol) by the general procedure (165 mg, 39%). When the reaction was run for 5 h, the obtained yield was 51 mg (12%) where **116** was found as the major product. Recently the reaction was repeated (0.25 g of 2-methylimidazole was used, where the ratio of 2-methylimidazole/diacid

chloride/triethylamine was 1/2.4/6) where the yield was 231 mg (45%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.70; dark brown liquid.

IR (cm^{-1}): 3153, 2977, 2934, 1733, 1636, 1542, 1458, 1385, 1282.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.51 (d, *J* =1.3 Hz, -CON-C<u>H</u>=CH-NH, 1H), 7.16 (d, *J* = 1.4 Hz, CON-CH=C<u>H</u>-NH, 1H), 6.84 (s, >C=C<u>H</u>-CO, 1H), 1.58 (s, -C-C<u>H_3</u>, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta_{C=}$ 171.49 (=CH-<u>C</u>O-C$(CH_3)_2$), 145.26 (N-<u>C</u>O-C$(CH_3)_2$), 132.31 (><u>C</u>=CH-CO), 114.62 (CO-N-<u>C</u>H=CH-NH), 113.18 (CO-N-CH=<u>C</u>H-NH), 47.96 (>C=<u>C</u>H-CO), 45.73 (><u>C</u>$(CH_3)_2$), 25.42 (-C-<u>C</u>H_3).

<u>1-[2, 2-Dimethyl-3-(6,6-dimethyl-5,7-dioxo-6,7-dihydro-5H-imidazo[1, 2-*a*]pyridine-1-yl)-3-oxo-propionyl]-6,6-dimethyl-1H-imidazo[1, 2-*a*]pyridine-5,7-dione (**116**)</u>

Compound **116** could not be isolated in the first few runs. It was first isolated when the reaction was run for a longer time (5 h) (281 mg, 51%), where **115** was also found as the minor product. However, recently, when this reaction was run several times (with 0.25 g of 2-methylimidazole), **116** was found even after 3 h of reaction time (225 mg, 34 %). R_f = 0.45; dark brown liquid.

IR (cm^{-1}): 3070, 2970, 2932, 1756, 1700, 1622, 1538, 1455, 1386, 1264.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.53 (d, *J* = 1.3 Hz, CON-C<u>H</u>=CH-NH, 2H), 7.18 (d, *J* = 1.7 Hz, CON-CH=C<u>H</u>-NH, 2H), 6.73 (s, >C=C<u>H</u>-O, 2H), 1.73 (s, CO-C-C<u>H_3</u>, 6H), 1.51 (s, CO-C-C<u>H_3</u>(ring), 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ170.81 (=CH-<u>C</u>O-C$(CH_3)_2$), 168.87 (N-<u>C</u>O-C$(CH_3)_2$ (ring)), 155.30 (N-<u>C</u>O-C$(CH_3)_2$), 144.49 (><u>C</u>=C-CO), 132.57(CO-N-<u>C</u>H=CH-NH),

113.39 (CO-N-CH=CH-NH), 105.04 (>C=CH-CO), 51.33 (>C(CH_3)$_2$ (ring)), 45.57 (>C(CH_3)$_2$), 24.17 (-C-CH_3), 22.79 (-C-CH_3 (ring)).

8,8,11,11-tetramethyl-5,14-di(propan-2-ylidene)-5H-imidazo[1,2-*c*]pyrano[3,4-e][1,7,3]dioxazecine-7,9,12(8H,11H,14H)-trione (**116a**)

Compound **116a** could not be isolated in the first few runs. It was first isolated when the reaction was recently performed with 0.25 g of 2-methylimidazole (mole ratio of 2-methylimidazole/1,3-diacid chloride/base were 1/2.4/6). The experimental procedure as same as the synthesis of **115**. The reaction was run for 3 h. The obtained yield was 169 mg (13%). R_f = 0.60; yellow crystal. mp. 179-180°C. A crystal structure is also obtained (Page 46).

IR (cm^{-1}): 3158, 3122, 2989, 1789, 1759, 1725, 1658, 15546, 1403.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.10 (d, *J* = 1.5 Hz, -C=N-CH=CH-N-C(=C<)-O-, 1H), 7.05 (d, *J* = 1.5 Hz, -C=N-CH=CH-N-C(=C<)-O-, 1H), 1.87 (s, CH_3-C(CH_3)=C(N)-O, 3H), 1.83 (s, CH_3-C(CH_3)=C(N)-O, 3H), 1.66 (s, CH_3-C(CH_3)=C(N)-O, 3H), 1.65 (s, CH_3-C(CH_3)=C(N)-O, 3H), 1.55 (s, -C(=O)-C(CH_3)$_2$-C(-O)-, 3H), 1.47 (s, -C(=O)-C(CH_3)$_2$-C(-O)-, 3H), 1.40 (s, -C(=O)-C(CH_3)$_2$-C(=O)-, 3H), 1.20 (s, -C(=O)-C(CH_3)$_2$-C(=O)-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 171.45 (-O-C(=O)-C(CH_3)$_2$-), 170.26 (-O-C(=O)-C(CH_3)$_2$-C(=O)-O-), 169.55 (-O-C(=O)-C(CH_3)$_2$-C(=O)-O-), 154.12 (-O-C=CH-C=N-), 140.86 (-N=C(-C=C-)-N-), 138.37 (-C=C-C-C(=C(CH_3)$_2$)-O-), 131.08(-N-C(=C(CH_3)$_2$-O-), 128.05 (-C=N-C(H)=C(H)-N-), 124.68 (-C=C-C-C(=C(CH_3)$_2$)-O-), 121.11 (-C=N-

C(H)=C(H)-N-), 120.16 (-N=C(-C=C-)-N-), 50.47 (-N-C(=C(CH$_3$)$_2$-O-), 45.88(-O-C(=O)-C(CH$_3$)$_2$-C(=O)-O-), 22.95 (-O-C(=O)-C(CH$_3$)$_2$-), 21.29 ((-O-C(=O)-C(CH$_3$)$_2$-C(=O)-O-), 2C), 19.66 (-C=C-C-C(=C(CH$_3$)$_2$)-O-), 19.49 (-C=C-C-C(=C(CH$_3$)$_2$)-O-),, 18.56 (-O-C(=O)-C(CH$_3$)$_2$-), 18.33 (-N-C(=C(CH$_3$)$_2$-O-), 17.83 (-N-C(=C(CH$_3$)$_2$-O-).

8, 9-Dihydro-7H-10-oxa-3a,5a-diaza-acephenanthrylene-1, 3, 6-trione (**117**)

Compound **117** was prepared using 2-methylimidazole **(111)** (0.20 g, 2.4 mmol) and cyclobutane-1,1-dicarbonyl dichloride (1.03 g, 5.7 mmol) by the general procedure (388 mg, 54%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.45; dark brown liquid.

IR (cm^{-1}): 3010, 2920, 1738, 1683, 1538, 1241, 1125, 1110, 1088, 1061.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.68 (d, *J* = 2.7 Hz, -CON-CH=CH-N, 1H), 7.54 (d, *J* = 2.7 Hz, CON-CH=CH-N, 1H), 4.40 (t, *J* = 5.2 Hz, C-O-CH$_2$-CH$_2$-CH$_2$-, 2H), 2.76 (m, C-O-CH$_2$-CH$_2$-CH$_2$-, 2H), 2.63 (m, -CH$_2$-CH$_2$-C-, 4H), 2.28 (m, -CH$_2$-CH$_2$-C-, 2H), 2.04 (m, C-O-CH$_2$-CH$_2$-CH$_2$-, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 186.00 (=C-CO-C-), 169.29 (-N-CO-C-), 161.82 (-N-CO-C=C-), 156.42 (=C-O-CH$_2$-), 144.04 (>C=C-CO-), 113.53 (-N-C=C-N), 112.56 (-N-C=C-N), 99.92 (>C=C-CO-), 89.77 (-CO-C=C-O), 68.04 (-O-CH$_2$-CH$_2$-CH$_2$-), 57.53 (-(CH$_2$)$_2$-C-(CO)$_2$), 29.85(-CH$_2$-CH$_2$-C-(CO)$_2$), 20.60 (C-O-CH$_2$-CH$_2$-CH$_2$-C=C-), 19.11 (C-O-CH$_2$-CH$_2$-CH$_2$-C=C-), 15.37 (CH$_2$-(CH$_2$)$_2$-).

2-(2-Methyl-imidazole-1-carbonyl)-2-propyl-pentaoic acid (**118**)

Compound **118** was prepared using 2-methylimidazole **(111)** (0.20 g, 1.4 mmol) and dipropylmalonyl dichloride (1.3 g, 5.7 mmol) by the general procedure (346 mg, 57%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.70; dark yellow liquid.

IR (cm^{-1}): 3140, 2957, 2933, 1712, 1633, 1555, 1465, 1408, 1309.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.28 (d, *J* = 1.7 Hz, CON-C<u>H</u>=CH-N=C-, 1H), 6.91(d, *J* = 1.8 Hz, CON-CH=C<u>H</u>-N=C-, 1H), 2.99 (s, -OH, 1H), 2.67 (s, >C-C<u>H</u>$_3$, 3H), 1.64 (m, -C-C<u>H</u>$_2$-CH$_2$-CH$_3$, 4H), 1.31 (m, -C-CH$_2$-C<u>H</u>$_2$-CH$_3$, 4H), 0.91 (t, *J* = 7.2 Hz, -C-C<u>H</u>$_2$-CH$_2$-CH$_3$, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ174.67 (N-<u>C</u>O-C-), 163.34(-C-<u>C</u>O-OH), 148.36 (><u>C</u>-CH$_3$), 128.17 (-N-<u>C</u>H=CH-N-), 116.85 (-N-<u>C</u>H=CH-N-), 45.57 (-CO-<u>C</u>(CH$_2$-CH$_2$-CH$_3$)$_2$-CO-), 34.56 (-C-<u>C</u>H$_2$-CH$_2$-CH$_3$), 20.49 (-C-CH$_2$-<u>C</u>H$_2$-CH$_3$), 17.43 (-C-CH$_2$-CH$_2$-<u>C</u>H$_3$), 13.76 (>C-<u>C</u>H$_3$).

3'-Methylspiro[cyclopropane-1,6'-pyrrolo][1, 2-*c*]imidazole-5',7'-dione (**119**)

Compound **119** was prepared using 2-methylimidazole **(111)** (0.20 g, 2.4 mmol) and cyclopropane-1,1-dicarbonyl dichloride (0.95 g, 5.7 mmol) by the general procedure (301 mg, 71%). Flash column chromatography (silica gel, ethyl acetate); R_f = 0.55; white solid, mp. 110-112°C.

IR (cm^{-1}): 3140, 2973, 2935, 1710, 1650, 1538, 1466, 1410, 1384, 1226, 1139, 1083.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.45 (s, N-C<u>H</u>=C-CO-, 1H), 2.74 (s, -N=C-C<u>H</u>$_3$, 3H), 1.85 (m, -C-C<u>H</u>$_2$-C<u>H</u>$_2$-, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 182.73 (-N-<u>C</u>O-C-), 167.80 (C=C-<u>C</u>O-C-), 146.73 (-N=<u>C</u>-CH_3), 133.77 (-CO-N-<u>C</u>H=CH-NH-), 127.69 (-CO-N-CH=<u>C</u>H-NH-), 36.46 (-CO-<u>C</u>-CO-), 20.55 (-C-<u>C</u>H$_2$-<u>C</u>H$_2$-), 14.48 (N=C-<u>C</u>H$_3$).

Synthesis using 2-Methylbenzimidazole as the Starting Material

<u>2-Ethyl-2-(2-methyl-benzoimidazole-1-carbonyl)-butyric acid (**120**)</u>

2-Methylbenzimidazole (**94**) (0.20 g, 1.4 mmol) was dissolved in 15 mL of acetonitrile. Triethylamine (0.849 g, 8.4 mmol) was then added dropwise. A solution of diethylmalonyl dichloride (0.662 g, 3.3 mmol) in acetonitrile (10 mL) was added dropwise into this solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and the solvent was removed by rotary evaporation. Acetone (3 x 20 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and the solid obtained was thoroughly washed with acetone (3 x 15 mL). Then the combined filtrates were concentrated in *vacuo* and residue was purified by flash column chromatography (silica gel, 5:1 hexane/ethyl acetate) to give **120** (278 mg, 67%), R_f = 0.45, yellow liquid.

IR (cm^{-1}): 2965, 2929, 2850, 1813, 1722, 1623, 1574, 1455, 1385, 1289.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.70 (m, 1H (benzylic)), 7.35 (m, 3H (benzylic)), 2.78 (s, >C-C<u>H</u>$_3$, 3H), 2.34 (m, 4H), 0.91 (t, *J* = 7.5 Hz, -C-CH$_2$-C<u>H</u>$_3$, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 173.13 (N-CO-C-), 169.96 (-C-CO-OH), 153.17 (>C-CH_3), 142.37 (-N-CH=CH-N-CO-), 131.189 (-N-CH=CH-N-CO-), 124.45 (benzylic), 124.23 (benzylic), 120.11 (benzylic), 112.71 (benzylic), 70.77 (-CO-C-CO-), 25.58 (-C-CH_2-CH_3), 18.68 ((>C-CH_3), 8.11 ((-C-CH_2-CH_3).

2, 2-Dimethyl-5H-benzo[4,5]imidazo[1,2-*a*]pyridine-1,3-dione (**121**)

Compound **121** was prepared using 2-methylbenzimidazole (**94**) (0.20 g, 1.4 mmol) and dimethylmalonyl dichloride (0.567 g, 3.3 mmol) by the general procedure (199 mg, 59%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.9, yellow liquid.

IR (cm^{-1}): 3085, 2980, 2934, 1715, 1637, 1593, 1379, 1355, 1283, 1235, 1219, 1157.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.24 (m, 1H (benzylic)), 7.75 (m, 1H (benzylic)), 7.42 (m, 2H (benzylic)), 6.95 (s, >C=CH-CO-, 1H), 1.66 (s, -C-CH_3, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 171.73 (>C=CH-CO-), 149.43 (N-CO-C-), 147.97 (>C=CH-), 144.09 (-N-CH=CH-N-CO-), 130.29 (-N-CH=CH-N-CO-), 126.14 (benzylic), 126.08 (benzylic), 120.15 (benzylic), 115.24 (benzylic), 115.13 ((>C=CH-CO-), 48.66 (-CO-C-$(CH_3)_2$), 25.69 (CO-C-CH_3).

1-(2-Methyl-benzoimidazole-1-carbonyl)-cyclobutanecarboxylic Acid (**122**)

Compound **122** was prepared using 2-methylbenzimidazole (**94**) (0.20 g, 1.4 mmol) and cyclobutane-1,1-dicarbonyl dichloride (0.6 g, 3.3 mmol) by the general

procedure (245 mg, 68%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.8, yellow liquid.

IR (cm^{-1}): 3085, 2980, 2933, 1696, 1650, 1416, 1264, 1217, 1167.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.66 (m, 2H(benzylic)), 7.30 (m, 2H(benzylic)), 2.85 (s, >C-C$\underline{H}_3$, 3H), 2.5 (m, -C-(C$\underline{H}_2$)$_2$-CH_2, 4H), 2.12 (m, -C-$(CH_2)_2$-C$\underline{H}_2$, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ174.35 (N-$\underline{C}$O-C-), 153.46 (-C-$\underline{C}$O-OH), 142.57 (>$\underline{C}$-CH_3), 132.27 (-N-CH=$\underline{C}$H-N-CO-), 124.32 (-N-$\underline{C}$H=CH-N-CO-), 123.41 (benzylic), 119.72 (benzylic), 114.26 (benzylic), 113.54 (benzylic), 40.9 (-CO-$\underline{C}$-CO-OH), 25.04 (-C-($\underline{C}H_2$)$_2$-CH_2), 18.97 (-C-$(CH_2)_2$-$\underline{C}H_2$), 17.96 (>C-$\underline{C}H_3$).

2-(2-Methyl-benzoimidazole-1-carbonyl)-2-propyl-pentanoic Acid (**123**)

Compound **123** was prepared using 2-methylbenzimidazole (**94**) (0.20 g, 1.4 mmol) and dipropylmalonyl dichloride (0.8 g, 3.3 mmol) by the general procedure (309 mg, 73%). Flash column chromatography (silica gel, 5:1 hexane/ethyl acetate); R_f = 0.65, dark brown liquid.

IR (cm^{-1}): 2970, 2925, 2683, 1699,1610, 1593, 1435, 1264, 1153, 1114.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.69 (m, 2H (benzylic)), 7.34 (m, 2H (benzylic)), 2.83 (s, >C-C$\underline{H}_3$, 3H), 1.86 (m, -C-C$\underline{H}_2$-CH_2-CH_3, 4H), 1.40 (m, J = 7.3 Hz, C-CH_2-C$\underline{H}_2$-CH_3, 4H), 0.91 (t, J = 7.2 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 176.82 (N-$\underline{C}$O-C-), 153.16 (-C-$\underline{C}$O-OH), 142.72 (>$\underline{C}$-CH_3), 132.49 (-N-CH=$\underline{C}$H-N-CO-), 124.24 (-N-$\underline{C}$H=CH-N-CO-), 119.89 (benzylic),

113.48 (benzylic), 46.21 (-CO-C-CO-OH), 34.27(-C-CH_2-CH_2-CH_3), 20.47 (-C-CH_2-CH_2-CH_3), 18.96 (-C-CH_2-CH_2-CH_3), 14.22 (>C-CH_3).

Synthesis using 2-Ethylimidazole as the Starting Material

3-Ethyl-6,6-dimethyl-pyrrolo[1,2-*c*]-imidazole-5,7-dione (**124**)

2-Ethylimidazole (**112**) (0.20 g, 2.0 mmol) was dissolved in acetonitrile (15 mL). Triethylamine (1.2 g, 12 mmol) was then added dropwise. A solution of diethylmalonyl dichloride (0.96 g, 4.8 mmol) in acetonitrile (10 mL) was added dropwise into this solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and the solvent was removed by rotary evaporation. Acetone (3 x 20 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and the solid obtained was thoroughly washed with acetone (3 x 15 mL). Then the combined filtrates were concentrated *in vacuo* and residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **124** (325 mg, 71%), R_f = 0.8, yellow liquid.

IR (cm^{-1}): 3128, 2970, 2938, 1774, 1723, 1549, 1495, 1460, 1376, 1272, 1121, 1090.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.49 (s, -N-CH=C-, 1H), 3.13 (q, *J* = 7.5 Hz, -N=C-CH_2-CH_3, 2H), 1.91 (m, >C-CH_2-CH_3, 4H), 1.41 (t, *J* = 7.5 Hz,-N=C-CH_2-CH_3, 3H), 0.83 (t, *J* = 7.5 Hz, >C-CH_2-CH_3, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 187.93 (N-CO-C-), 170.65 (=C-CO-C-), 151.45 (N=C-CH_2-CH_3), 134.01 (=C-CO-C-), 127.56 (-N-CH=C-CO-), 65.31 (-$(CO)_2$-C-CH_2-CH_3),

28.35 (-$(CO)_2$-C-$\underline{C}H_2$-CH_3), 22.02 (-N=C-$\underline{C}H_2$-CH_3), 11.33 ((-N=C-CH_2-$\underline{C}H_3$), 9.17 (-$(CO)_2$-C-CH_2-$\underline{C}H_3$).

6,6,8-Trimethyl-1 H-imidazo[1,2-*a*]pyridine-5, 7-dione (**125**)

Compound **125** was prepared using 2-ethylimidazole (**112**) (0.20 g, 2.0 mmol) and dimethylmalonyl dichloride (0.81 g, 4.8 mmol) by the general procedure (107 mg, 28%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.9, yellow liquid.

IR (cm^{-1}): 3156, 2983, 2936, 2876, 1725, 1631, 1537, 1489, 1376, 1290, 1204.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.53 (d, *J* = 1.6 Hz, -N-CH=C$\underline{H}$-N-CO-, 1H), 7.17 (d, *J* = 1.7 Hz, -N-C$\underline{H}$=CH-N-CO-, 1H), 2.30 (s, >C=CH-C$\underline{H}_3$, 3H), 1.58 (s, -C-C$\underline{H}_3$, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 171.80 (>C=C-$\underline{C}$O-C-), 146.85 (-N-$\underline{C}$O-C-), 140.66 (-N-$\underline{C}$=C-CO-), 132.12 (-N-CH=$\underline{C}$H-N-CO-), 120.82 (-N-$\underline{C}$H=CH-N-CO-), 113.57 (>C=$\underline{C}$-CO-C-), 48.29 (-CO-$\underline{C}$-CH_3), 26.01 (-CO-C-$\underline{C}H_3$), 13.91 (-N-C=C-CH_3).

3-Ethyl-6,6-dimethyl-pyrrolo[1,2-*c*]-imidazole-5,7-dione (**126**)

Compound **126** was formed as the major product in the reaction described for the synthesis of **125** (222 mg, 58%). Flash column chromatography (silica gel, 1:1 hexane/ethyl acetate); R_f = 0.8, white solid, mp. 92-95°C.

IR (cm^{-1}): 3128, 2974, 2938, 1771, 1730, 1651, 1554, 1537, 1495, 1391, 1374, 1311,

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.51 (s, -N-C$\underline{H}$=C-N-CO-, 1H), 3.11 (q, *J* = 7.5 Hz,-N=C-C$\underline{H}_2$-CH_3, 2H), 1.45 (s, CO-C-C$\underline{H}_3$, 6H), 1.41 (t, *J* = 7.5 Hz, -N=C-CH_2-C$\underline{H}_3$, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 187.33 (-N-<u>C</u>O-C-), 177.04 (-C=C-CO-C-), 151.67 (-N=<u>C</u>-C-), 132.05 (-N-C=<u>C</u>-CO-C-), 128.65 (-N-<u>C</u>=C-CO-C-), 54.87 (-CO-<u>C</u>-CO-), 20.85 (-CO-C-<u>C</u>H_3), 19.47 (-N=C-<u>C</u>H_2-CH_3), 11.27 (-N=C-CH_2-<u>C</u>H_3).

Synthesis using 2-Isopropylimidazole as the Starting Material

<u>6,6-Diethyl-3-isopropyl-pyrrolo[1,2-*c*]-imidazole-5, 7-dione (**127**)</u>

2-Isopropylimidazole (**113**) (0.20 g, 1.7 mmol) was dissolved in acetonitrile (15 mL). Triethylamine (1.08 g, 10 mmol) was then added dropwise. A solution of diethylmalonyl dichloride (0.82 g, 4.1 mmol) in acetonitrile (10 mL) was added dropwise into this solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and the solvent was removed by rotary evaporation. Acetone (3 x 20 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and the solid obtained was thoroughly washed with acetone (3 x 15 mL). Then the combined filtrates were concentrated *in vacuo* and residue was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **127** (416 mg, 76%), R_f = 0.9, yellow liquid.

IR (cm^{-1}): 3100, 2970, 2934, 2878, 1771, 1723, 1687, 1551, 1493, 1385, 1353, 1324, 1299, 1264.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.51 (s, -N-C<u>H</u>=C-N-CO-, 1H), 3.62 (m, -N=C-C<u>H</u>-$(CH_3)_2$, 1H), 1.92 (m, -CO-C-C<u>H</u>$_2$-CH_3, 4H), 1.44 (d, J = 7.5 Hz, -N=C-CH-(C<u>H</u>$_3$)$_2$, 6H), 0.84 (t, J = 7.4 Hz, -CO-C-CH_2-C<u>H</u>$_3$, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 187.82 (-N-CO-C-), 170.37 (-C=C-CO-C-), 155.24 (-N=C-CH), 133.92 (-N-CH=CH-N-CO-), 127.16 (-N-CH=CH-N-CO-), 65.20 (-CO-C-CO-), 28.25 (-N=C-CH-$(CH_3)_2$), 26.01 (-N=C-CH-$(CH_3)_2$), 20.11 (-C-CH_2-CH_3), 9.02 (-C-CH_2-CH_3).

3-Isopropyl-6,6-dimethyl-pyrrolo[1,2-*c*]-imidazole-5,7-dione (**128**)

Compound **128** was prepared using 2-isopropylimidazole (**113**) (0.20 g, 1.7 mmol) and dimethylmalonyl dichloride (0.82 g, 4.1 mmol) by the general procedure (350 mg, 71%). Flash column chromatography (silica gel,1:1 hexane/ethyl acetate); R_f = 0.8, yellow liquid.

IR (cm^{-1}): 3130, 2975, 2938, 2873, 1770, 1720, 1554, 1490, 1475, 1382, 1283.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.50 (s, -N-CH=C-N-CO-, 1H), 3.58 (m, -N=C-CH-$(CH_3)_2$, 1H), 1.45 (m, -CO-C-CH_3, 6H), 1.41 (d, *J* = 7.5 Hz, -N=C-CH-$(CH_3)_2$, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 187.35 (-N-CO-C-), 170.88 (-C=C-CO-C-), 155.61 (-N=C-CH), 131.98 (-N-CH=CH-N-CO-), 128.38 (-N-CH=CH-N-CO-), 54.87 (-CO-C-CO-), 28.14 (-N=C-CH-$(CH_3)_2$), 20.81 (-N=C-CH-$(CH_3)_2$), 20.39 (-C-CH_3).

3'-Isopropylspiro[cyclobutane-1,6'-pyrrolo[1,2-c]imidazole]-5',7'-dione (**129**)

Compound **129** was prepared using 2-isopropylimidazole (**113**) (0.20 g, 1.7 mmol) and cyclobutane-1,1-dicarbonyl dichloride (0.76 g, 4.1 mmol) by the general procedure (271 mg, 70%). Flash column chromatography (silica gel,1:1 hexane/ethyl acetate); R_f = 0.85, dark brown liquid.

IR (cm^{-1}): 2972, 1777, 1730, 1652, 1551, 1493, 1456, 1364, 1283, 1124.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.48 (s, -N-C<u>H</u>=C-N-CO-, 1H), 3.58 (m, -N=C-C<u>H</u>-$(CH_3)_2$, 1H), 2.58 (t, *J* = 8.1 Hz, -CH_2-C<u>H</u>$_2$-C-, 4H), 2.30 (q, *J* = 7.6 Hz, -C<u>H</u>$_2$-CH_2-C-, 2H), 1.41 (m, -N=C-CH-(C<u>H</u>$_3$)$_2$, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.72 (-C=C-<u>C</u>O-C-), 158.89 (-N-<u>C</u>O-C-), 146.02 (-N=<u>C</u>-CH),, 134.90 (-N-CH=<u>C</u>H-N-CO-), 130.67 (-N-<u>C</u>H=CH-N-CO-), 41.79 (CH_2-$(CH_2)_2$-<u>C</u>-$(CO)_2$), 28.47 ((CH_2-(<u>C</u>H_2)$_2$-C-$(CO)_2$), 2C), 25.12 (-N=C-<u>C</u>H-$(CH_3)_2$), 21.21 ((-N=C-CH-(<u>C</u>H_3)$_2$), 2C), 18.20 ((CH_2-(<u>C</u>H_2)$_2$-C-$(CO)_2$), 2C).

Unsuccessful Reactions

<u>Reaction of 2-Methylimidazole with Malonyl Dichloride (**132a**)</u>

2-Methylimidazole **(111)** (0.20 g, 2.4 mmol) was dissolved in 15 mL of acetonitrile, and potassium carbonate (2.0 g, 14.5 mmol) was added. The mixture was stirred for 10 min by a magnetic stirring system. A solution of malonyl dichloride (0.80 g, 5.7 mmol) in 10 mL of acetonitrile added dropwise into the above mixture under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. After cooling the reaction mixture to room temperature, the reaction mixture was analyzed using TLC plate. No spot was eluted from the baseline spot when eluting solvents of different polarity (hexane/ethyl acetate: 1:1, 1:2, 2:1, 100% hexane, 100% ethyl acetate) were used. No further purification was tried. The reaction was repeated using THF under the similar conditions. Same result was obtained.

Reaction of 2-Methylimidazole with Phthaloyl Chloride (**133a**)

2-Methylimidazole **(111)** (0.20 g, 2.4 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (1.4 g, 14.5 mmol) was added dropwise. A solution of phthaloyl chloride (1.16 g, 5.7 mmol) in 10 ml of acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and the solvent was removed by rotary evaporation. Acetone (3 x 20 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and thoroughly washed with acetone and residue was purified by flash chromatography (silica gel, 1:1 hexane/ethyl acetate), starting material was isolated. The reaction was repeated by 1) using a different base, DIPEA and 2) using a different reaction solvent, THF. The same result was obtained.

Reaction of 2-Methylimidazole with *N*-Chlorocarbonyl Isocyanate (**134a**)

2-Methylimidazole **(111)** (0.20 g, 2.4 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (1.4 g, 14 mmol) was added dropwise. A solution of *N*-Chlorocarbonyl isocyanate (0.60 g, 5.7 mmol) in 10 mL acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and the solvent was removed by rotary evaporation. The white residue was found to be insoluble in, ethylacetate, hexane, acetone, tetrahydrofuran, dimethylformammide, methanol, water and dichloromethane. No further purification was tried. Use of another reaction solvent (THF) and other bases (DIPEA, DABCO) did not change the result.

Reaction of 2-Methylimidazole with *N*-Chlorosulfonyl Isocyanate (**135a**)

2-Methylimidazole **(111)** (0.20 g, 2.4 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (1.4 g, 14 mmol) was added dropwise. A solution of *N*-Chlorosulfonyl isocyanate (0.80 g, 5.7 mmol) in 10 mL acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and the solvent was removed by rotary evaporation. Dichloromethane (3 x 20 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and thoroughly washed with dichloromethane and residue was purified by flash chromatography (silica gel, acetone). R_f : 0.85; the product was found to be soluble in DMSO-d6, the proton NMR was found to be complicated (might be mixture), no further isolation was done. Use of other reaction solvent (THF) and other bases (DIPEA, DABCO) did not change the result.

Reaction of 2-Methylbenzimidazole with Malonyl Dichloride (**132b**)

2-Methylbenzimidazole **(94)** (0.20 g, 1.4 mmol) was dissolved in 15 mL of acetonitrile, and potassium carbonate (1.15 g, 8.4 mmol) was added dropwise. A solution of malonyl dichloride (0.465 g, 3.3 mmol) in 10 mL acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. After cooling the reaction mixture to room temperature, the reaction mixture was analyzed using TLC plate. No spot was eluted from the baseline spot when eluting solvents of different polarity (hexane/ethyl acetate: 1:1, 1:2, 2:1, hexane, ethyl

acetate) were used. No further purification was tried. Use of THF as the reaction solvent did not change the result.

Reaction of 2-Methylbenzimidazole with Phthaloyl Chloride (**133b**)

2-Methylbenzimidazole **(94)** (0.20 g, 1.4 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (0.849 g, 8.4 mmol) was added dropwise. A solution of phthaloyl chloride (0.67 g, 3.3 mmol) in 10 mL acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. After cooling the reaction mixture to room temperature, the reaction mixture was analyzed using TLC. Only one spot was eluted (R_f : 0.75, 1:1 hexane/ethyl acetate was used as solvent) which was found to be hydrolyzed product of phthaloyl chloride. Use of THF as the reaction solvent and DIPEA as the base did not change the result.

Reaction of 2-Methylbenzimidazole with *N*-chlorocarbolnyl Isocyanate (**134b**)

2-Methylbenzimidazole **(94)** (0.20 g, 1.4 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (0.84 g, 8.4 mmol) was added dropwise. A solution of *N*-Chlorocarbonyl isocyanate (0.35 g, 3.3 mmol) in 10 mL acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 hours and the solvent was removed by rotary evaporation. The crude mixture was analyzed using TLC. No spot eluted. No further purification was tried. Use of other reaction solvent (THF) and other bases (DIPEA, DABCO) did not change the result.

Reaction of 2-Methylbenzimidazole with *N*-Chlorosulfonyl Isocyanate (**135b**)

2-Methylbenzimidazole **(94)** (0.20 g, 1.4 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (0.84 g, 8.4 mmol) was added dropwise. A solution of *N*-Chlorosulfonyl isocyanate (0.46 g, 3.3 mmol) in 10 mL acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 hours. After cooling the reaction mixture to room temperature, the reaction mixture was analyzed using TLC plate. No spot was eluted from the baseline spot when eluting solvents of different polarity (hexane/ ethyl acetate: 1:1, 1:2, 2:1, hexane, ethyl acetate) were used. No further purification was tried. Use of THF as the reaction solvent and use of bases such as DIPEA, DABCO did not change the result.

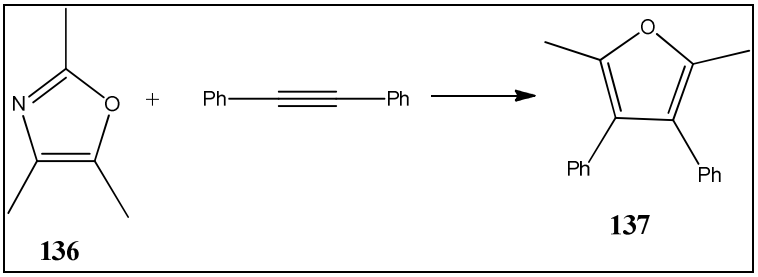
CHAPTER III

REACTIONS OF SUBSTITUTED OXAZOLES AND THIAZOLES WITH ACID CHLORIDES: FORMATION OF CARBON-CARBON BONDS THROUGH CYCLIC KETENE ACETALS

Introduction and Objective

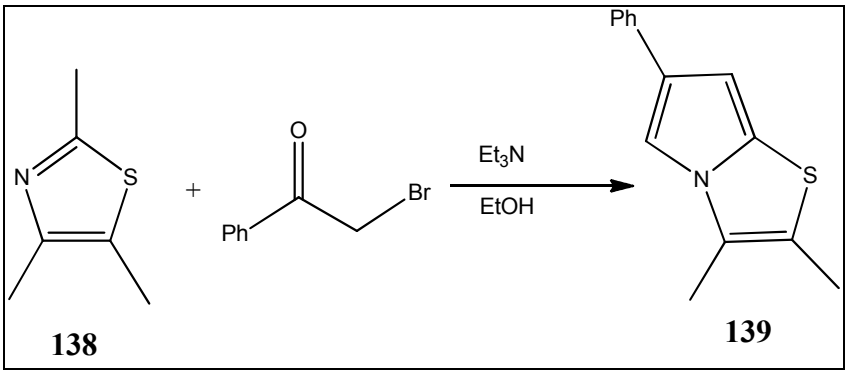
Oxazoles and thiazoles have been prepared and used in organic synthesis for a long time. Horst and coworkers used 2,4,5-trimethyloxazole (**136**) and diphenyl acetylene in a cyclocondensation reaction to make a substituted furan (**137**).[96] Galera et al. used 2,4,5-trimethlthialzole (**138**) with 2-bromo-1-phenylethanone in a condensation reaction to make 2,3-dimethyl-7-phenylpyrrolo[2,1-b]thiazole (**139**).[97]

The biological activities of differently substituted oxazoles and thiazoles are well known. Oxazoles and thiazoles have a sextet of electrons. On the other hand, they have some structural similarities with oxazolines and thiazolines, respectively.



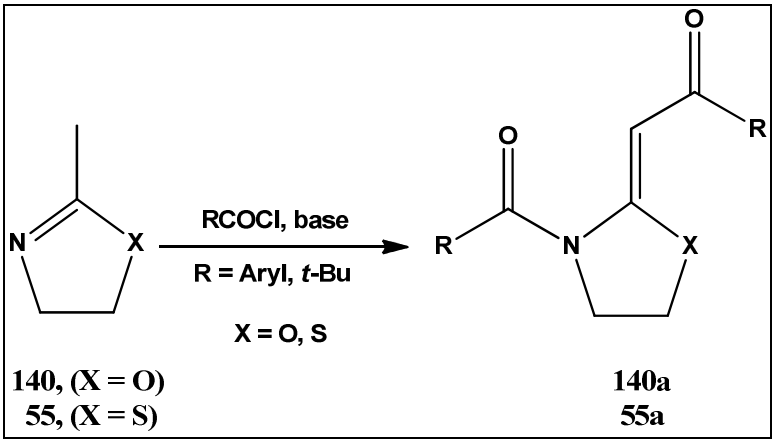
136 **137**

Scheme 3.1 Cycloaddition Reaction of 2,4,5-Trimethyloxazole[96]



Scheme 3.2 Condensation Reaction of 2,4,5-Trimethylthiazole[97]

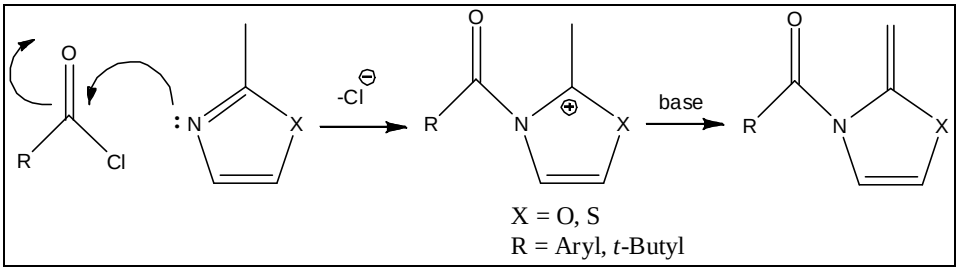
2-Methyloxazolines (**140**) and 2-methylthiazolines (**55**) were reported to generate various *N*-acyl-*β*-keto cyclic ketene-*N*,*X*-acetals (X = O, S) with excess aroyl or 2,2-dimethyl propanoyl chloride in the presence of a base (Scheme 3.3).[35-39]



Scheme 3.3 Products Obtained by Reactions of 2-Methyloxazoline (**140**) or 2-Methylthiazoline (**55**) with Excess of Acid Chlorides in Presence Base[35-39]

These products were reported to form through the *in situ* formation of *N*-acyl cyclic ketene acetals (Scheme 3.4) which further reacted via nucleophilic attack by the

exocyclic β-carbon on excess acid chloride. Cyclic ketene acetals are readily protonated and then react rapidly with water. [20,37,98,99] Thus, they are often difficult to isolate and use. Therefore, instead of isolating them before use, *in situ* generation followed by reacting with electrophiles is advantageous.



Scheme 3.4 Generation of *N*-Acyl Cyclic Ketene Acetals

Pittman's group recently reported that 2-methylimidazoline, 2-methyl-1,4,5,6-tetrahydropyrimidine and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine gave various cyclic and acyclic products via cyclic ketene-*N*,*N'*-acetals when treated with aroyl chlorides in the presence of base.[51,52] Also, 2-methylimidazoline, 2-methylimidazole and 2-methylbenzimidazole formed both polycyclic and acyclic products with diacid chlorides through cyclic ketene acetal intermediates in presence of a base.[53,101] Thus, analogous aromatic oxazoles and thiazoles with a 2-methyl group might undergo similar reactions with acid chlorides to those in Scheme 3.3. When an oxazole or thiazole is converted to its *N*,*O*-ketene acetal, one would expect the aromaticity would also decrease (Figure 1.7). There would be similar structural changes expected during formations of cyclic ketene acetals from imidazoles (chapter 1). This structural change could lead to a decrease of

aromaticity in these cases. Dr. Steven Gwaltney of Mississippi State University also found that the difference in the Gibbs free energy between 2-methyloxazoline and 2-methyleneoxazolidine is 16 kcal /mole (Figure 3.1). In contrast, 2-methyloxazole is 24 kcal/mole lower in energy than to its exocyclic double bond containing tautomer, 2-methylene-2,3-dihydrooxazole. Thus, it appears the apparent aromaticity loss in the case of 2-methyloxazole is 8 kcal/mole larger than in the case of 2-methyloxazoline where aromaticity is never involved. Generation of cyclic ketene acetals from these aromatic heterocycles might be more difficult since aromatic stabilization may be lost during formation of the exocyclic double bond in the cyclic ketene acetals.

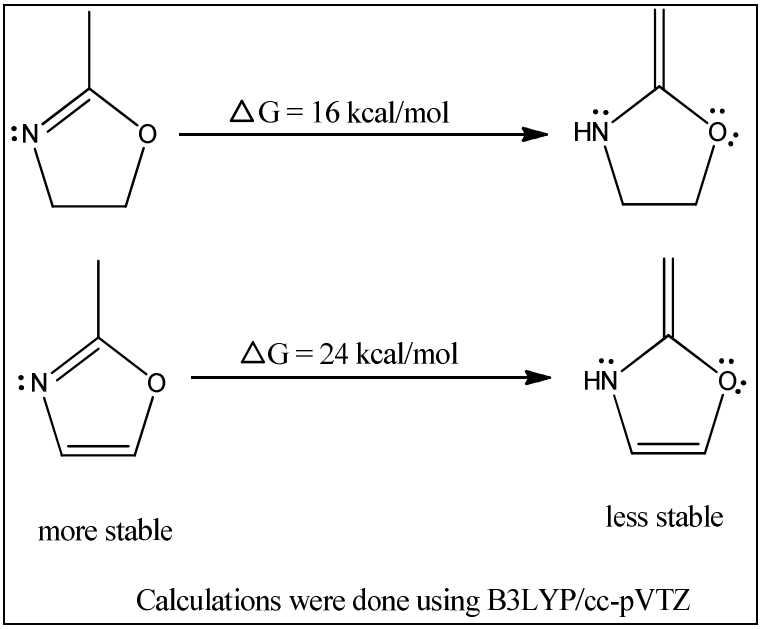


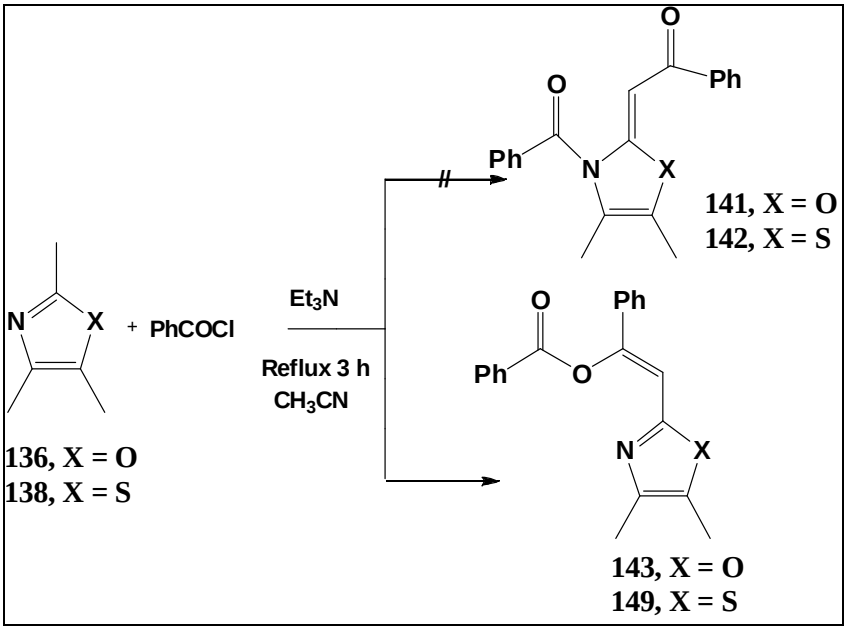
Figure 3.1 Differences in Gibbs Free Energy[99a]

2-Methylbenzoxazole and 2-methylbenzothiazole were reported to give 2-(*β*-aryl-*β*-aryloxy) vinyl-benzoxazoles and 2-(*β*-aryl-*β*-aryloxy) vinyl-benzothiazoles, respec-

tively, upon reactions with aroyl chlorides in the presence of a base.[102] However, only a few examples were given and no mechanistic path was proposed. The analogous oxazole and thiazole reactions (Scheme 3.5) have never been reported. Thus, oxazole and thiazole reactions are of interest versus the behavior of 2-methyl derivatives of benzoxazoles, benzothiazoles and benzimidazoles. Our intent was to react 2,4,5-trimethyloxazole (**136**) and 2,4,5-trimethylthiazole (**138**) with an excess of various aroyl chlorides and base to generate the corresponding *N*-acyl-*β*-keto cyclic ketene-*N*,*X*-acetals (X = O, S) **(141, 142)** (Scheme 3.5).

Results and Discussions

Reactions of 2,4,5-trimethyloxazole (**136**) and 2,4,5-trimethylthiazole (**138**) with excess benzoyl chlorides and 3.66 equivalents of base (Entries 1-14 in Table 3.1) were performed in acetonitrile However, the expected derivatives, **141, 142** were not formed, in sharp contrast to what had been previously observed with 2-methyl oxazolines and thiazolines[35-37] (Scheme 3.3). Instead, the 2-(oxazol-2-yl)-1-phenyl-vinyl ester, **(143)**, from 2,4,5-trimethyloxazole and the corresponding 2-(thiazol-2-yl)-1-phenyl-vinyl ester, **(149)**, from 2,4,5-trimethylthiazole were readily generated (Scheme 3.5). Reactions of 2,4,5-trimethyloxazole with other aroyl chlorides with 3.66 equivalents of base (Table 3.1) were only performed in acetonitrile.



Scheme 3.5 Reactions of 2,4,5-Trimethyloxazole with Benzoyl Chloride

Table 3.1 Reactions of 2,4,5-Trimethyloxazole (**136**) with Acid Chlorides and Base in Refluxing MeCN, THF, DMF or DMAc[a]

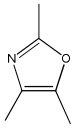
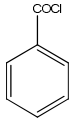
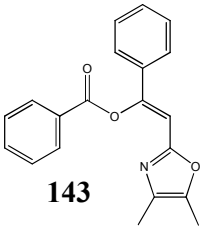
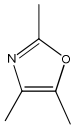
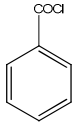
Entry	Substrate	Acid Chloride	Solvent	Product Isolated	Yield[b] (%)
1[c,d]			MeCN	 **143**	54
2[c,d]			THF	**143**	33

Table 3.1 (Continued)

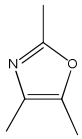
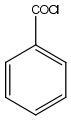
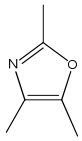
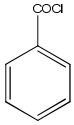
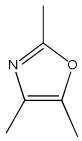
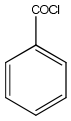
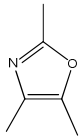
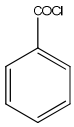
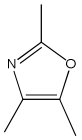
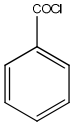
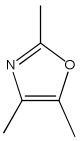
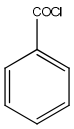
Entry	Substrate	Acid Chloride	Solvent	Product Isolated	Yield[b] (%)
3[c,e]			MeCN	**143**	68
4[c,f]			MeCN	**143**	21
5[d,g]			MeCN	**143**	64
6[c,d]			DMF	-	none
7[d,g]			DMF	-	none
8[c,d]			DMAc	-	none

Table 3.1 (Continued)

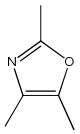
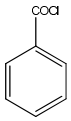
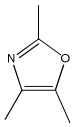
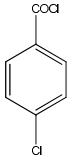
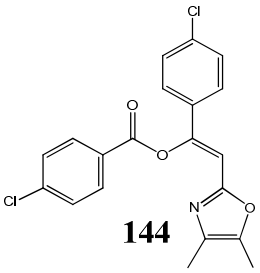
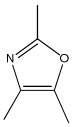
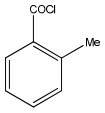
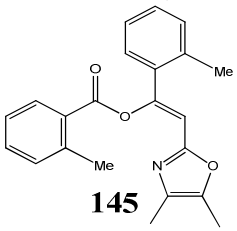
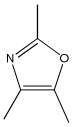
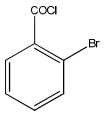
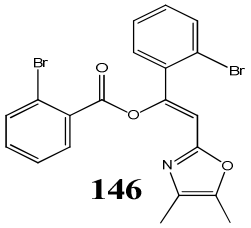
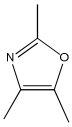
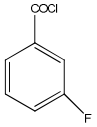
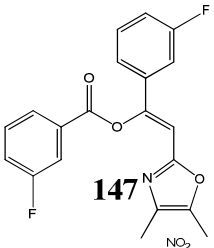
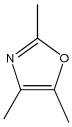
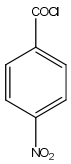
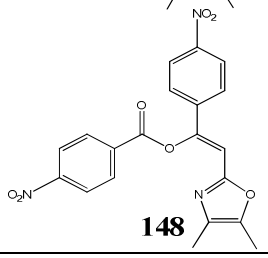
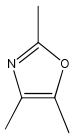
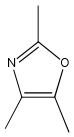
Entry	Substrate	Acid Chloride	Solvent	Product Isolated	Yield[b] (%)
9[d,g]			DMAc	-	none
10[c,d]			MeCN	 **144**	49
11[c,d]			MeCN	 **145**	47
12[c,d,h]			MeCN	 **146**	51
13[c,d]			MeCN	 **147**	54
14[c,d]			MeCN	 **148**	47

Table 3.1 (Continued)

Entry	Substrate	Acid Chloride	Solvent	Product Isolated	Yield[b] (%)
15[c,d]		CH_3CCOCl	MeCN	-	none
16[d,i]		CH_3COCl	MeCN	-	none

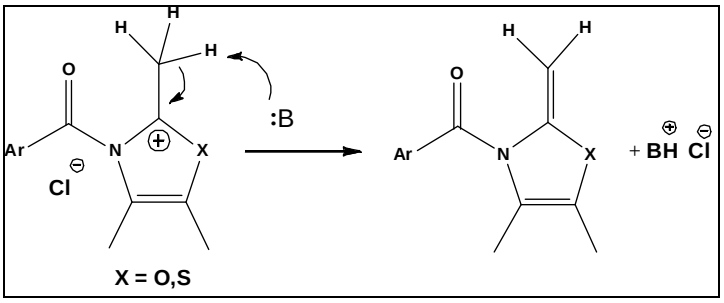
[a] The mole ratio of **136**/base = 1:3.66
[b] Isolated yields after column chromatography over silica gel
[c] Triethylamine was used as the base
[d] Oxazole to acid chloride mole ratio was 1:3
[e] Oxazole to acid chloride mole ratio was 1:6
[f] Oxazole to acid chloride mole ratio was 1:1
[g] DIPEA was used as the base and the oil bath temperature was 125°C
[h] A crystal structure was obtained on the product
[i] K_2CO_3 was used as base; the ratio of **136**/ K_2CO_3 = 1:3.66

Reactions with benzoyl chloride were performed in acetonitrile, THF (tetrahydrofuran), DMF (dimethylformamide) and DMAc (dimethylacetamide) at various temperatures under nitrogen. Reactions in refluxing acetonitrile generated 2-(oxazol-2-yl)-1-aryl-vinylesters of aryl carboxylic acids (**143-148**) in every case with moderate yields. An X-ray crystal structure confirmed the structure of **146 (**Figure 3.1). Only the (*Z*)-isomers of **143-148** were formed in all cases. Aliphatic acid chlorides did not react with substituted oxazoles under these conditions (Entries 15-16) and the substituted

oxazoles were recovered. The yield of **143** in THF was lower than that in acetonitrile as illustrated by Entry 1 versus Entry 2 in Table 3.1. The higher polarity and higher reflux temperature of acetonitrile presumbly facilitated the reaction. Reactions were also attempted in the highly polar, high boiling solvents, DMF or DMAc where both diisopropylethyl amine (DIPEA) and triethylamine were used as bases (Entries 6-9, Table 3.1). None of the reactions in DMA and DMAc gave the aryl vinyl ester (**143**). Complex mixtures of products were obtained. DMF was reported to react with benzoyl chloride, [103,104] and this might have happened here, complicating the reaction. Using a large excess of benzoyl chloride increased the yield of **143** (e.g. Table 3.1, Entry 3). Substituents on the aroyl chloride did not appear to effect the reaction and similar yields were obtained in all reactions (Entries 10-14).

The reactions of these aromatic oxazole (or thiazole) derivatives possibly proceed through 5-membered cyclic ketene-*N*,*X*-acetal (X = O, S) intermediates formed after *N*-aroylation by deprotonation of the aromatic (6π-electron) *N*-aroyl-2-methyloxazolium (or, thiazolium) chloride salts (Scheme 3.6).

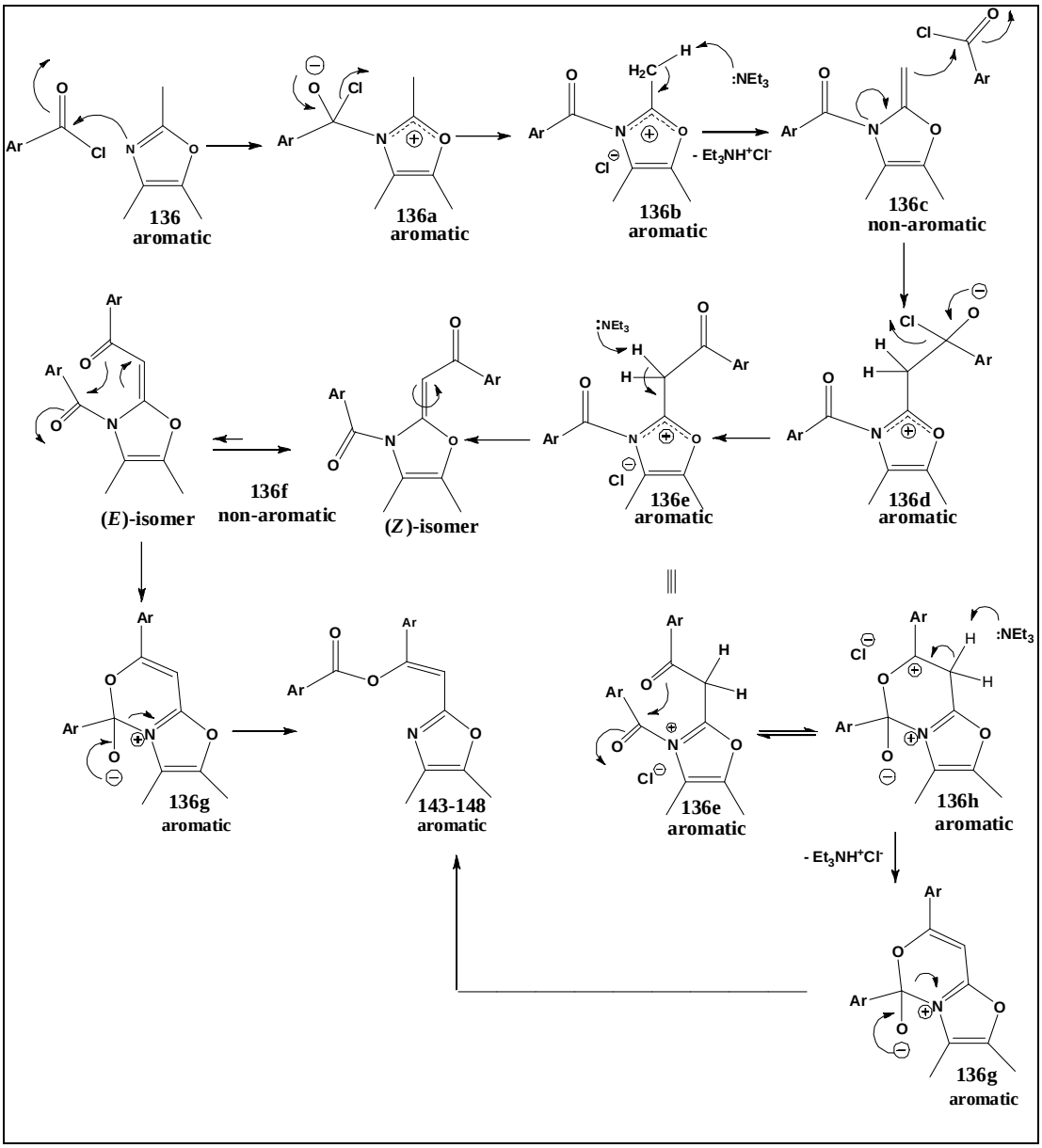
These cyclic ketene-*N*,*X*-acetals are less aromatic compared to starting materials. Thus, the 6π-electron ring cations will loose a portion of their aromaticity upon proton loss (see Chater I, Pages 30-34 and also see Schemes 2.6 and 2.7 of this dissertation). The next question is: how do **143** and **149** form from these cyclic ketene-*N*,*X* (X = O, S)-acetals?



Scheme 3.6 Generation of Non-Aromatic Cyclic Ketene Acetals

Two suggested mechanisms for this reaction are shown in Scheme 3.7. This route is analogous to that described previously for the conversion of 2-methyloxazolines (and thiazolines)[35-37] into *N*-acyl-*β*-keto cyclic ketene-*N*,*X*-acetals (Scheme 3.3), up to the intermediate **136e** in Scheme 3.7. If the base deprotonates **136e** to the nonaromatic **136f**, then **136f** could be further converted to **136g**. An interesting feature of this mechanism is the loss of aromaticity upon deprotonation of the two 6π-electron oxazolium intermediates **136b** and **136e** to cyclic ketene-*N*,*O*-acetal, intermediates **136c** and **136f**, respectively. This feature is not present when either 2-methyloxazolines or 2-methylthiazolines react with aroyl chlorides via cyclic ketene-*N*,*X*-acetals (X = O, S) intermediates (Scheme 3.3).

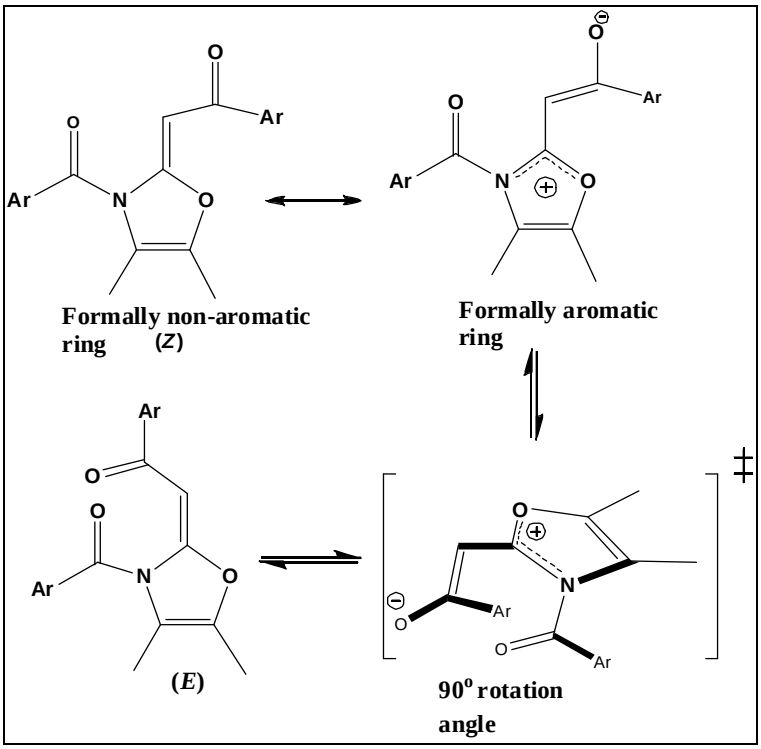
Initial nucleophilic acyl attack by the nitrogen of 2,4,5-trimethyloxazole on an acid chloride's carbonyl carbon generates the zwitterionic intermediate **136a** (Scheme 3.7). Ion pair **136b** is formed by the loss of chloride. Proton removal from **136b** by Et_3N generates $Et_3NH^+Cl^-$ and *N*-acyl cyclic ketene-*N*,*O*-acetal **136c**. Conversion of **136c** to intermediate **136d** by a second acylation at the *β*-carbon regenerates aromaticity.



Scheme 3.7 Proposed Mechanism for the Formation of **143-148**

Both nitrogen and oxygen in **136c** activate the exocyclic double bond of **136c** to promote nucleophilic attack on a second acid chloride. The high nucleophilicity of the exocyclic *β*-carbon promotes the second rapid aroylation, explaining why **136c** is not observed, even when a 1:1 substrate to acid chloride is used (Table 3.1, Entry 4). Loss of

chloride from **136d** forms **136e** which might be deprotonated by triethylamine generating **136f**. The further conversion of **136f** to **136g**, and ultimately the (*Z*)-isomers **143-148**, requires the (*E*)-isomer of **136f** to be available. The (*Z*)-isomer is formed with oxazolines and thiazolines (Scheme 3.3), so it also would likely be preferentially formed upon deprotonation of **136e** here. A low rotational barrier is postulated between the (*Z*) and (*E*) isomers of **136f**, made possible by the push-pull electronic structure which reduces[52,54,105] the exocyclic double bond's order (Scheme 3.8).



Scheme 3.8 Rotation Through a Push-Pull Electronic Structure

Intramolecular nucleophilic attack of the *C*-acyl carbonyl oxygen on the *N*-acyl carbonyl carbon, only possible in the (*E*)-isomer, generates zwitterionic aromatic **136g**.

Further, opening of the six membered ring in **136g** results in the products **143-148**. This is in contrast to 2-methyloxazoline or thiazoline reactions where N to O aroyl transfer does not occur.[33-3] It can be also postulated that deprotonation of **136e** to **136f** will be slow (see Scheme 3.7) with oxazoles and thiazoles due to loss of aromaticity in this process. Thus, **136e** might react, generating **136h** by nucleophilic attack of the carbonyl on the, now activated, amide carbonyl carbon of **136e**. Intermediate **136h** would now rapidly deprotonate to give **136g**. This route establishes the new double bond with only the (*Z*) geometry. Ring-opening of **136h** between carbon and nitrogen must not occur prior to deprotonation. If this happened, both the (*E*) and (*Z*) isomers could form. This route offers an explanation for why **143-148** form with oxazoles and thiazoles but the same route is not followed by oxazolines or thiazolines. These latter two classes of compounds might deprotonate rapidly from their **143e** analogs, because no aromaticity is lost in those cases. These reactions (Scheme 3.5) generate *N*-aroyl-*β*–keto cyclic ketene acetals where the rotation about the exo-double bond might also have a low barrier.

Reactions of 2,4,5-trimethylthiazole with aroyl chlorides under similar conditions produced the corresponding thiazole-based vinyl esters (**149 - 154**). For example, benzoyl chloride and **138** gave benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-vinylester (**149**). The X-ray crystal structure of the 3-bromobenzoyl analog, **152**, is shown in Figure 3.3 (page 117), confirming the (*Z*)-isomer was formed. All yields in this series were moderate.

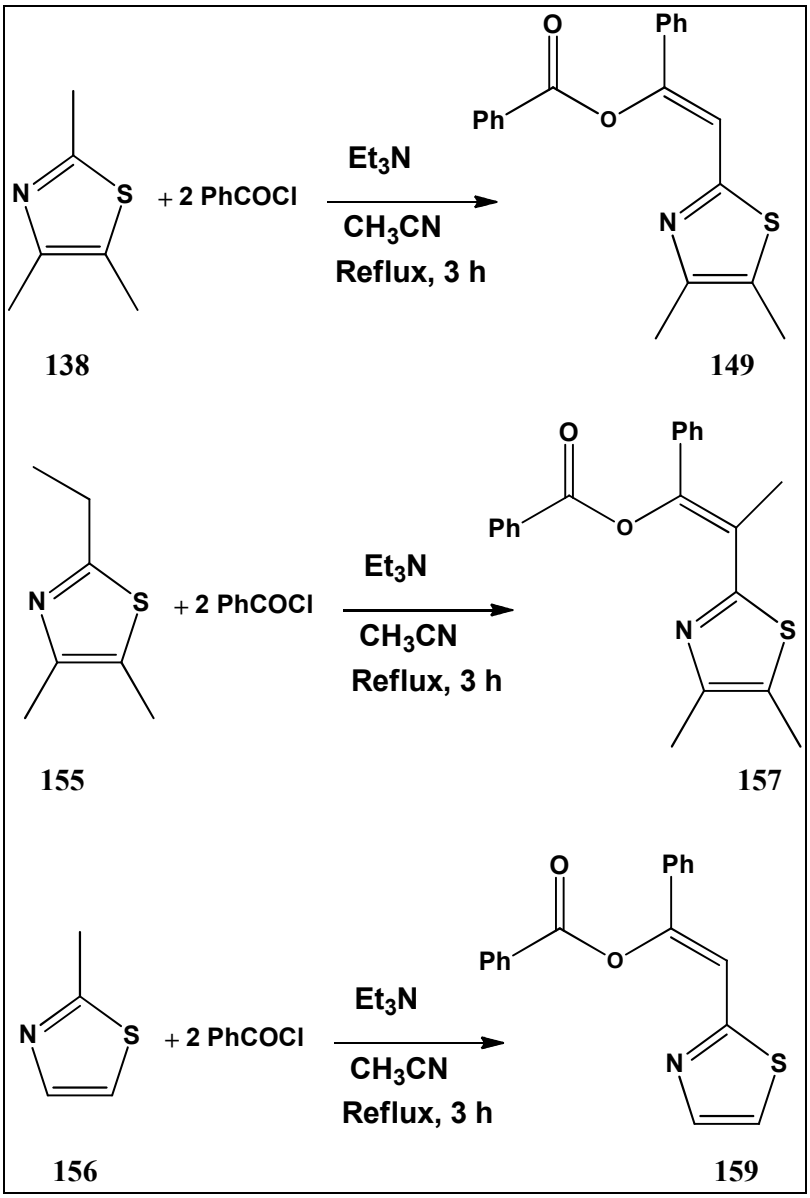
2-Ethyl-4,5-dimethylthiazole (**155**) produced the same type of product (**157**) upon reaction with benzoyl chloride and with 4-chlorobenzoyl chloride (**158**) (Table 3.2,

Entries 7-8) was formed. The X-ray crystal structure of **157** is shown in Figure 3.5 (page 120). Thus, an ethyl substituent at the 2-position does not effect the mechanistic pathway. Again, the (*Z*)-isomer is exclusively formed for **149-154**, and for both **157** and **158** (See Scheme 3.9). Reactions of 2-methylthiazole (**156**) with benzoyl chlorides or *o*-methylbenzoyl chloride in presence of a base also generated the corresponding vinyl esters **159** and **160**, respectively. The yields were higher than the corresponding products from 2,4,5-trimethylthiazole.

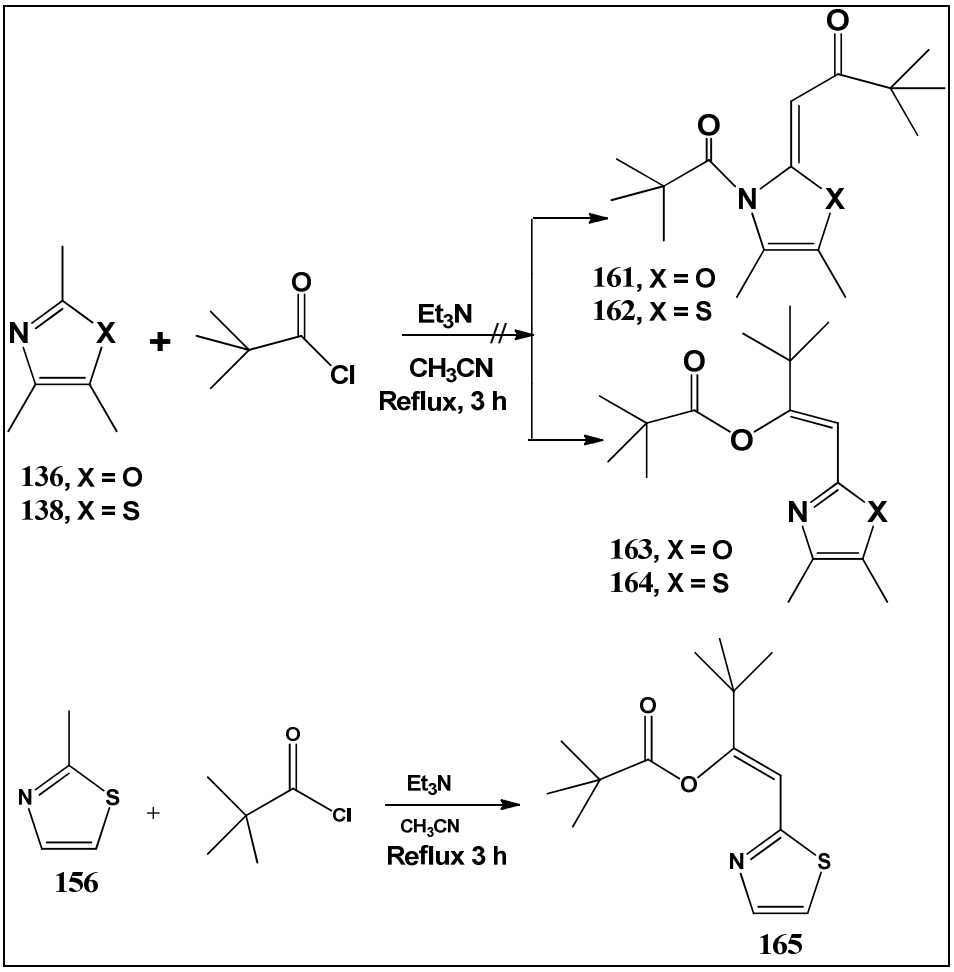
Just like the case of 2,4,5-trimethyloxazole, reactions of 2,4,5-trimethylthiazole or 2-ethyl-4,5-dimethylthiazole with alkyl acid chlorides resulted only in recovery of the reactants (Scheme 3.10). This was found using both 2,2-dimethylpropanoyl chloride (Scheme 3.10) and acetyl chloride (Table 3.2, Entries 12-14). In contrast, 2-methyl-thiazole (**156**) reacted with 2,2-dimethyl-propanoyl chloride in presence of base to form (2,2-dimethylpropionic acid-2,2-dimethyl-1-thiazol-2-ylmethylene-propyl ester (**165**) (Scheme 3.10) (Table 3.2, Entry 11). This result suggests that, in the reaction of 2,4,5-trimethyloxazole or 2,4,5-trimethylthiazole, the two methyl groups at the the 4,5 positions are creating steric hinderence.

In all of these reactions, tri-aroylated products were never obtained. In anticipation of obtaining a tri-aroylated product, a stronger base was used. When 2,4,5-trimethylthiazole was quantitatively converted to its anion by treatment with *n*-BuLi in THF and then reacted with aroyl chlorides, tri-aroylated products were obtained. Treating 2,4,5-trimethylthiazole with *n*-BuLi followed by benzoyl chloride generated benzoic acid 2-(4,5-dimethylthiazol-2-yl)-3-oxo-1,3-diphenylpropenyl ester (**166**) (Table 3.3, Entry 1).

4-Chlorobenzoyl chloride gave **167** when reacted with 2,4,5-trimethylthiazole under identical conditions.



Scheme 3.9 Reactions of 2,4,5-Trimethylthiazole (**138**), 2-Ethyl-4,5-dimethylthiazole (**155**) and 2-Methylthiazole (**156**) with Benzoyl Chlorides and Triethylamine.



Scheme 3.10 Reactions with 2,2-Dimethylpropanoyl Chloride

The mole ratio of aroyl chloride to thiazole did not change the product obtained. Tribenzoylated products were obtained in lower yields at aroyl chloride /thiazole ratios of 2:1 without the isolation of mono- or diaroylated products (Table 3.3, Entry 2).

Table 3.2 Reactions of 2,4,5-Trimethylthiazole (**138**), 2-Ethyl-4,5-dimethylthiazole (**155**) and 2-Methylthiazole (**156**) with Acid Chlorides and Base in Refluxing CH_3CN[a]

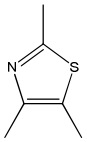
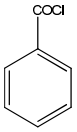
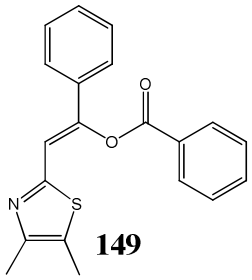
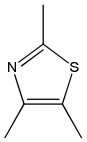
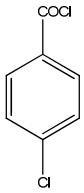
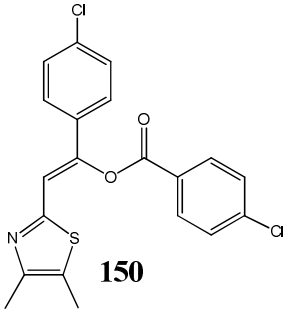
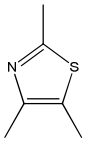
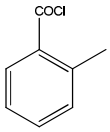
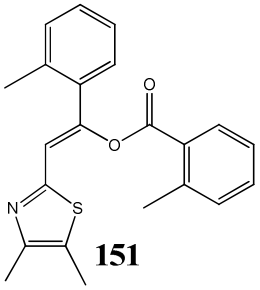
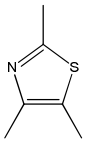
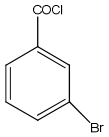
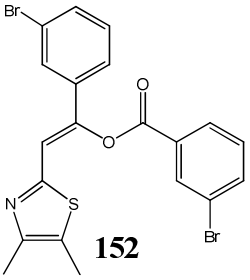
Entry	Substrate	Acid Chloride	Reflux time (h)	Product Isolated	Yield[b] (%)
1			3	 **149**	44
2			3	 **150**	48
3			3	 **151**	44
4[c]			3	 **152**	43

Table 3.2 (Continued)

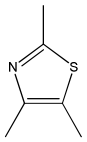
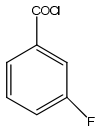
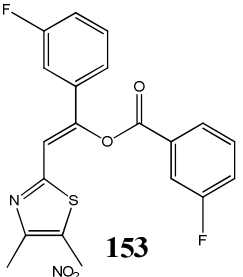
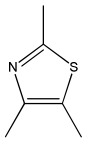
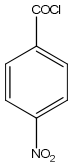
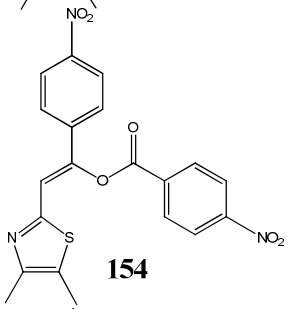
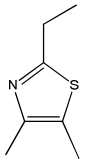
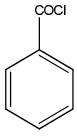
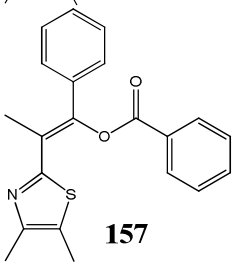
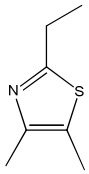
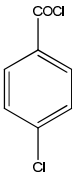
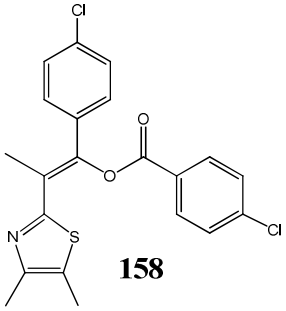
Entry	Substrate	Acid Chloride	Reflux time (h)	Product Isolated	Yield[b] (%)
5			3	 **153**	47
6			3	 **154**	46
7[c]			3	 **157**	52
8			3	 **158**	46

Table 3.2 (Continued)

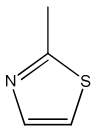
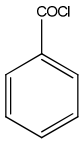
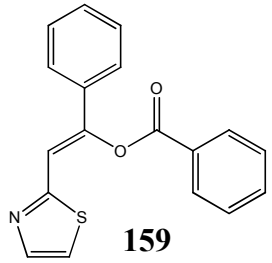
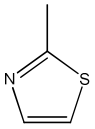
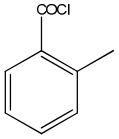
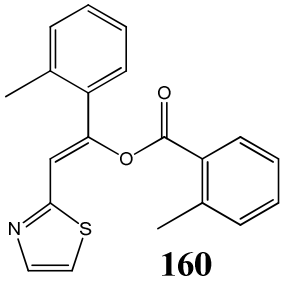
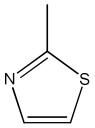
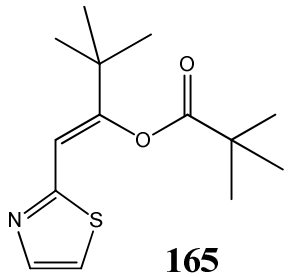
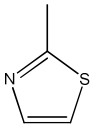
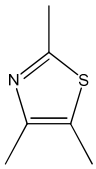
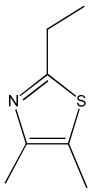
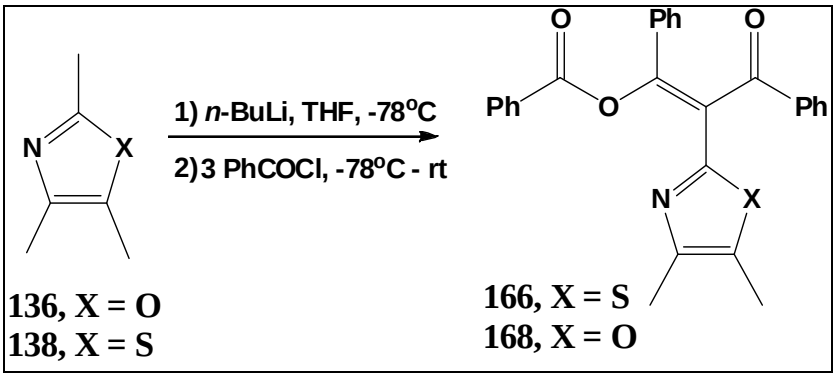
Entry A	Substrate	Acid Chloride	Reflux time (h)	Product Isolated	Yield[b] (%)
9			3	 **159**	76
10			3	 **160**	62
11		$(CH_3)_3CCOCl$	3	 **165**	59
12		$(CH_3)_3CCOCl$	3	-	none

Table 3.2 (Continued)

Entry	Substrate	Acid Chloride	Reflux time (h)	Product Isolated	Yield[b] (%)
13[d]		CH_3COCl	3	-	none
14[d]		CH_3COCl	3	-	none

[a] The ratio of substrate /Et_3N = 1:3.66 ; The ratio of substrate /acid chloride = 1:3, acetonitrile was used as solvent in all cases.
[b] Isolated yields after column chromatography over silica-gel
[c] A crystal structure was obtained on the product
[d] K_2CO_3 was used as base, the ratio of substrate / K_2CO_3 = 1:3.66

This observation implies that each succeeding aroylation is faster than the preceeding aroylation step. Finally, tri-aroylation also occurred using the oxazole analog, 2,4,5-trimethyloxazole, with *n*-BuLi followed by adding benzoyl chloride under these conditions (Table 3.3, Entry 4). Thus **168** was isolated.



Scheme 3.11 Reactions of 2,4,5-Trimethylthiazole and 2,4,5-Trimethyloxazole with Benzoyl Chloride using *n*-BuLi in THF

In sharp contrast to aroyl chlorides, reacting 2,4,5-trimethylthiazole with *n*-BuLi followed by 2,2-dimethylpropanoyl chloride generated 1,1-bis-(4,5-dimethyl-thiazol-2-yl)-2,2-dimethyl-propan-1-ol, (**169**) (Entry 5 in Table 3.3). Thus, nucleophilic attack of the 2,4,5-trimethylthiazole anion on the acid chloride first generated the C-alkylated ketone, with which a second mole of anion reacted to give the Li^+ salt of the alcohol (Scheme 3.12). Reactions of 2-methylthiazole and *n*-BuLi generated the thiazolium anion. 2,2-dimethyl-1-(2-methylthiazol-5-yl)propan-1-one (**170**), which was formed via attack by the anion on the 2,2-dimethylpropanoyl chloride. (*Z*)-3,3-dimethyl-1-(thiazol-2-yl)but-1-en-2-yl pivalate (**165**) was also generated in the same reaction. However, **170** was the major product. The vinyl ester **165** was obtained as the only product when 2-methylthaizole was reacted with 2,2-dimethylpropanoyl chloride and

Et_3N in refluxing acetonitrile.

Table 3.3 Reactions of 2,4,5-Trimethylthiazole with Aryl and Alkyl Acid Chloride Using *n*-BuLi and THF[a]

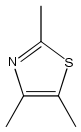
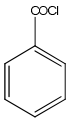
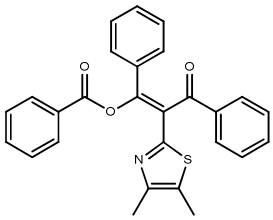
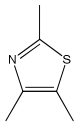
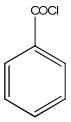
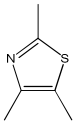
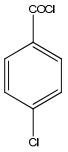
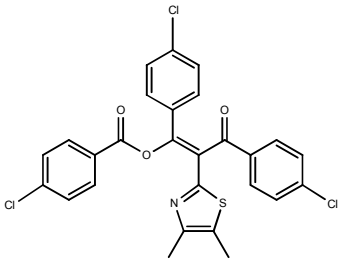
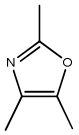
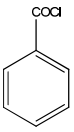
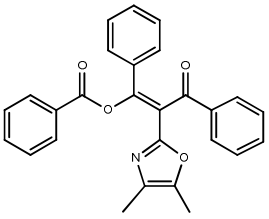
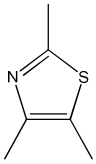
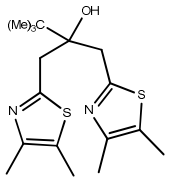
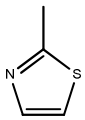
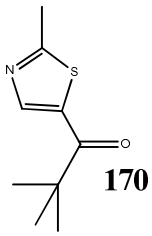
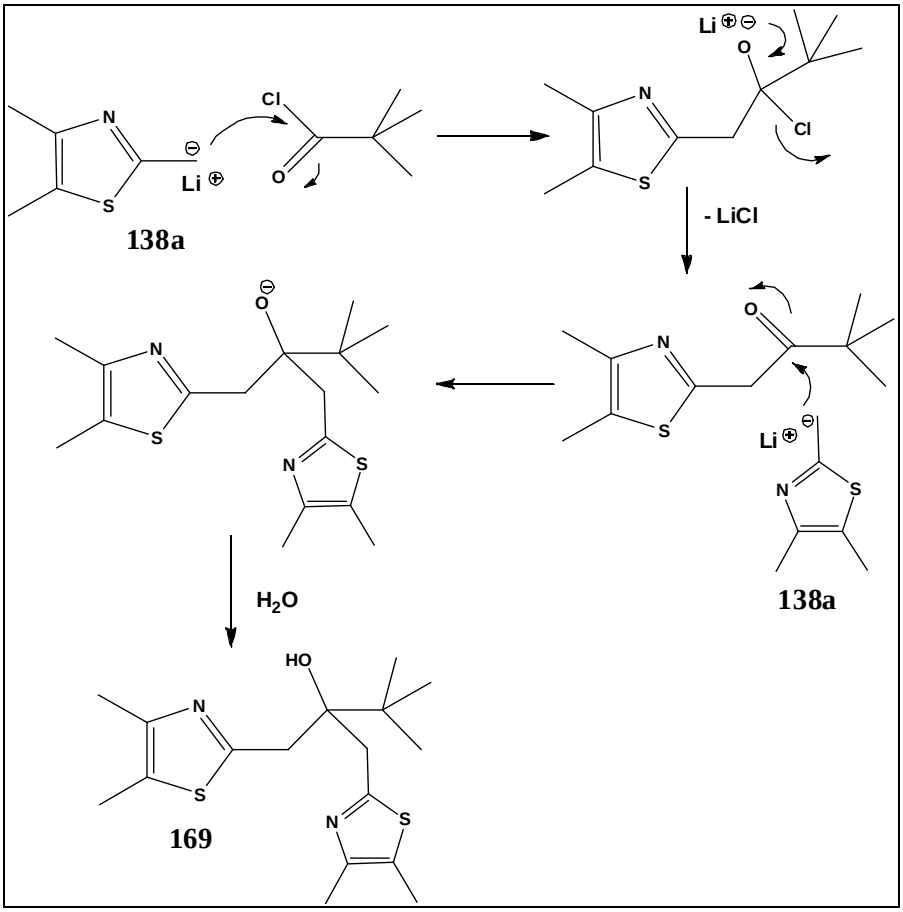
Entry	Substrate	Acid Chloride	Product Isolated	Yield (%)
1			 **166**	28
2[b]			**166**	22
3			 **167**	32
4[c]			 **168**	35

Table 3.3 (Continued)

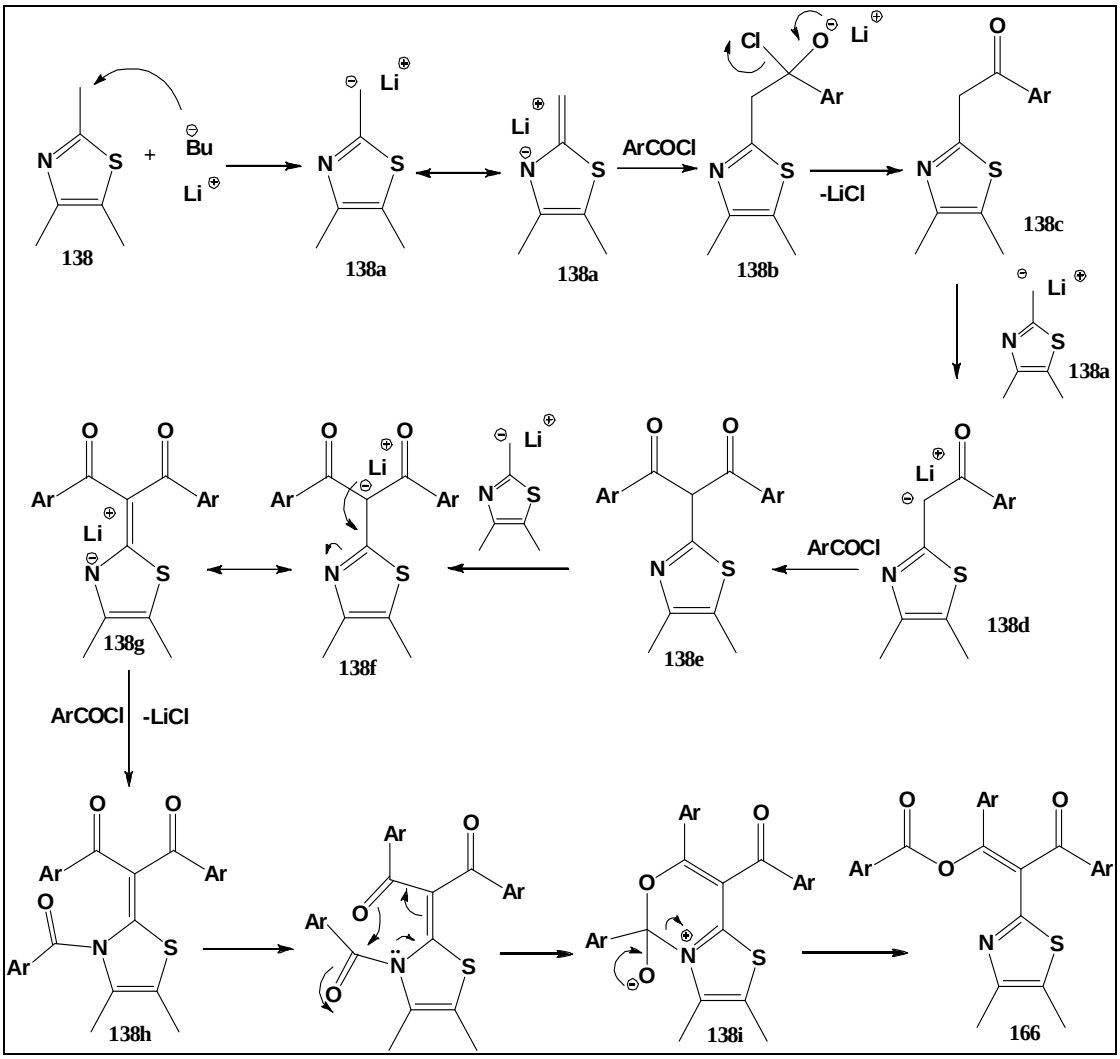
Entry A	Substrate	Acid Chloride	Product Isolated	Yield (%)
5		$(CH_3)_3CCOCl$	 **169**	44
6		$(CH_3)_3CCOCl$	 **170**	22
			165	10

[a] The ratio of substrate /acid chloride = 1:3, The ratio of substrate/*n*-BuLi = 1/1.2 ; THF was used as solvent in all cases.
[b] The ratio of substrate /acid chloride = 1:2, The ratio of substrate/*n*-BuLi = 1/1.4

Thus, triaroylation of both 2,4,5-trimethylthiazoles and 2,4,5-trimethyloxazoles was demonstrated by formation of **166-168** in Table 3.3. A possible mechanism for these reactions using 2,4,5-trimethylthaizole is shown in the Scheme 3.13.



Scheme 3.12 Proposed Mechanism for the Formation of **169**



Scheme 3.13 Proposed Mechanism for the Formation of **166-168**

Deprotonation of 2,4,5-trimethylthiazole with *n*-BuLi, gives anion **138a** shown as two resonance hybrids. This anion reacts with acid chloride and forms the 2-(4,5-dimethylthiazol-2-yl)-1-phenylethanone (**138c**). Compound **138c** reacts with thaizolium anion and forms **138d**, which further reacts with another mole of acid chloride and forms **138e**. After reacting with another thiazolium anion, the compound **138e** forms **138f**. The anion **138f**, react with another acid chloride, but, in this case the reaction occurs through

nitrogen due to the steric reason. Compound **138h** undergoes rearrangement and form **166 (**when Ar = Ph).

Single crystals of **146, 152** and **157** were obtained by slow evaporization of **146, 152** and **157** using acetone and hexane respectively**.** These structures are shown in Figure 3.1, 3.3 and 3.5 respectively. The crystal structures were deposited in the Cambridge Crystallography Data Base with CCDC numbers 765577 (for **146**), 765578 (for **152**) and 765826 (for **157**).

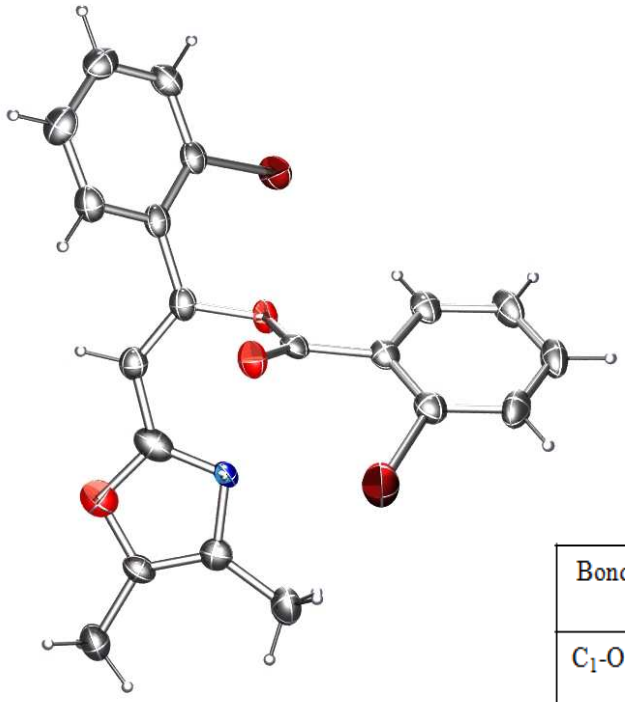
Conclusions

Reactions of various substituted oxazoles and thiazoles with excess acid chlorides in the presence of bases generated highly functionalized aryl-vinyl esters of benzoic acid and substituted benzoic acids and their thiazole analogues. Similar compounds have been reported to show insecticidal activities.[106] These aryl vinyl esters can also be used as starting materials to make different types of complex heterocycles.[107]

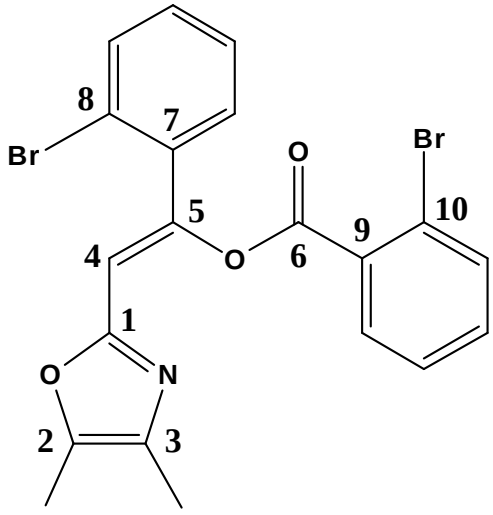
These results were in accordance with the results obtained with substituted oxazoline and thiazoline (non-aromatic). However, intramolecular rearrangements in analogous reactions involving aromatic heterocycles, oxazoles and thiazoles, resulted in formations of different products. In most of the aromatic substrates, only diaroylation occurred. Use of different bases (such as DIPEA, DABCO, etc) and different solvents (DMF, DMAc) did not give any different result. However, when a stronger base such as *n*-BuLi was used, triaroylated products were obtained. Most probably these triaroylation

products were formed by generating an anionic intermediate which then reacted with acid chlorides. All these triaroylated compounds were new and never reported anywhere.

All diaroylation reactions probably preceded through *in situ* generated cyclic ketene acetal intermediates.



Bond	Angle (°)
O-C_5-C_4	120.6
C_5-C_4-C_1	126.7
C_4-C_1-O	121.2
C_6-O-C_5	115.7
C_8-C_7-C_5	124.5
C_7-C_5-C_4	124.1



Bond	Length (Å)
C_1-O	1.327
C_1-N	1.325
C_2-C_3	1.344
O-C_2	1.387
N-C_3	1.389
C_1-C_4	1.434
C_4-C_5	1.336
C_5-C_7	1.478
C_5-O	1.403

Bond	Length (Å)
O-C_6	1.369
C_6-O	1.193
C_6-C_9	1.490
C_9-C_{10}	1.397
C_{10}-Br	1.897
C_7-C_8	1.398
C_8-Br	1.897

Figure 3.2 Crystal Structure of 2-Bromobenzoic acid-1-(2-bromophenyl)-2-(4,5-dimethyloxazol-2-yl)-vinyl ester (**146**). CCDC Number: 765577

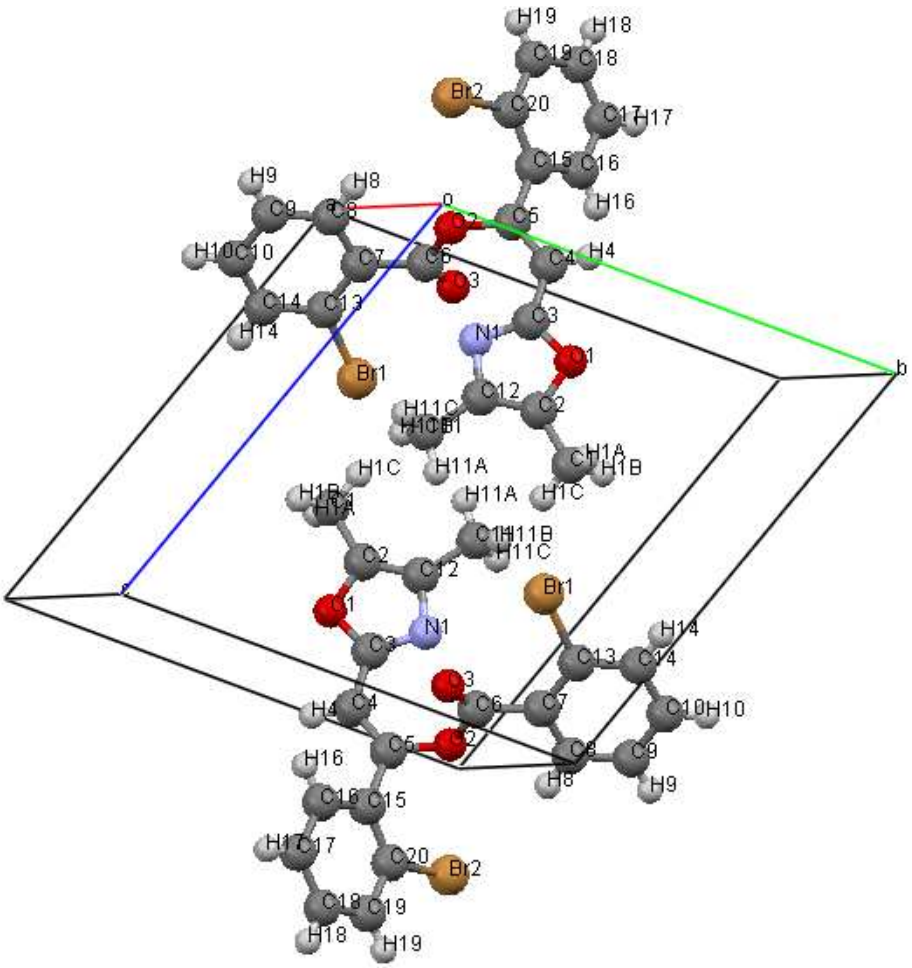
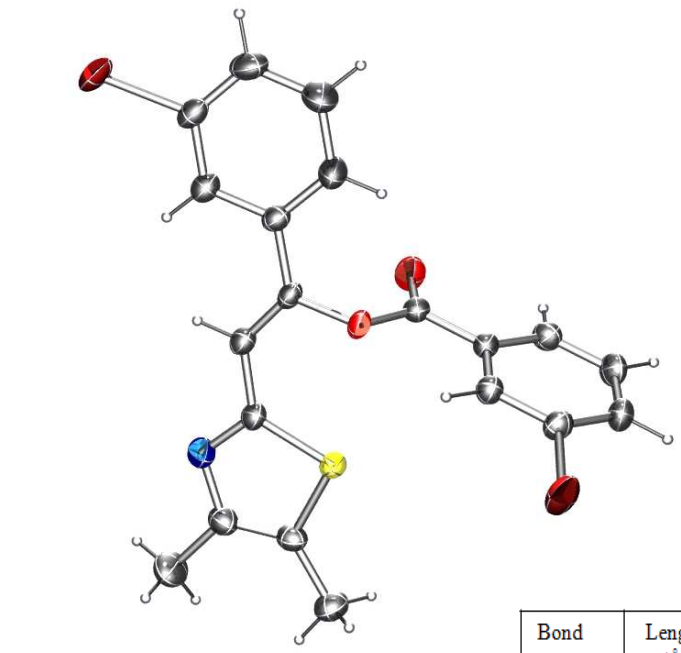
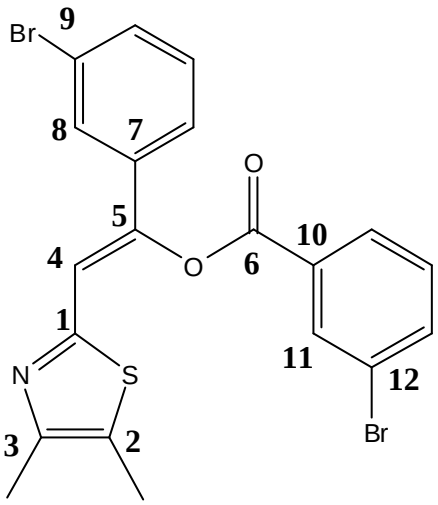


Figure 3.3 Crystal Packing [1 1 1] of 2-Bromobenzoic acid-1-(2-bromophenyl)-2-(4,5-dimethyloxazol-2-yl)-vinyl ester (**146**). CCDC Number: 765577

Table 3.4 Sample and Crystal Data of 2-Bromobenzoic acid-1-(2-bromophenyl)-2-(4,5-dimethyloxazol-2-yl)-vinyl ester (**146**). CCDC Number: 765577

Chemical formula	$C_{20}H_{16}Br_2NO_3$	
Formula weight	478.16	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.0284(5) Å	α = 108.134(4)°
	b = 10.9067(7) Å	β = 91.052(4)°
	c = 11.7129(7) Å	γ = 109.037(4)°
Volume	913.13(10) $Å^3$	
Z	2	
Density (calculated)	1.739 Mg/cm^3	
Absorption coefficient	4.459 mm^{-1}	
F(000)	474	





Bond	Angle (°)
O-C_5-C_4	117.69
C_5-C_4-C_1	127.84
C_4-C_1-S	125.78
C_6-O-C_5	116.79
C_8-C_7-C_5	120.13
C_7-C_5-C_4	126.68

Bond	Length (Å)
C_1-S	1.736
C_1-N	1.315
C_2-C_3	1.364
S-C_2	1.721
N-C_3	1.376
C_1-C_4	1.450
C_4-C_5	1.339
C_5-C_7	1.469
C_5-O	1.411

Bond	Length (Å)
O-C_6	1.368
C_6-O	1.201
C_6-C_{10}	1.487
C_{10}-C_{11}	1.393
C_{11}-C_{12}	1.387
C_{12}-Br	1.891
C_8-C_9	1.385
C_9-Br	1.900

Figure 3.4 Crystal Structure of 3-Bromobenzoic acid 1-(3-bromophenyl)-2-(4,5-dimethylthiazol-2-yl)-vinyl ester (**152**). CCDC Number: 765578

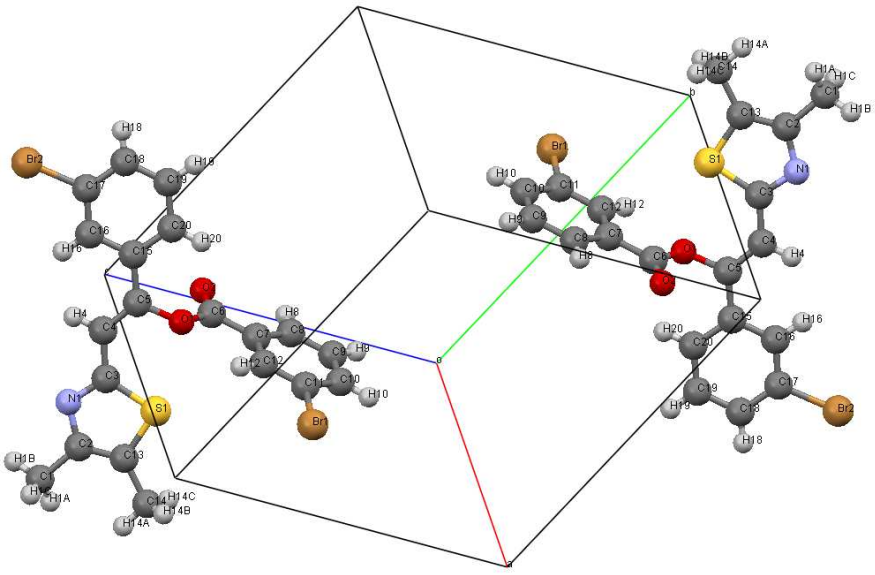
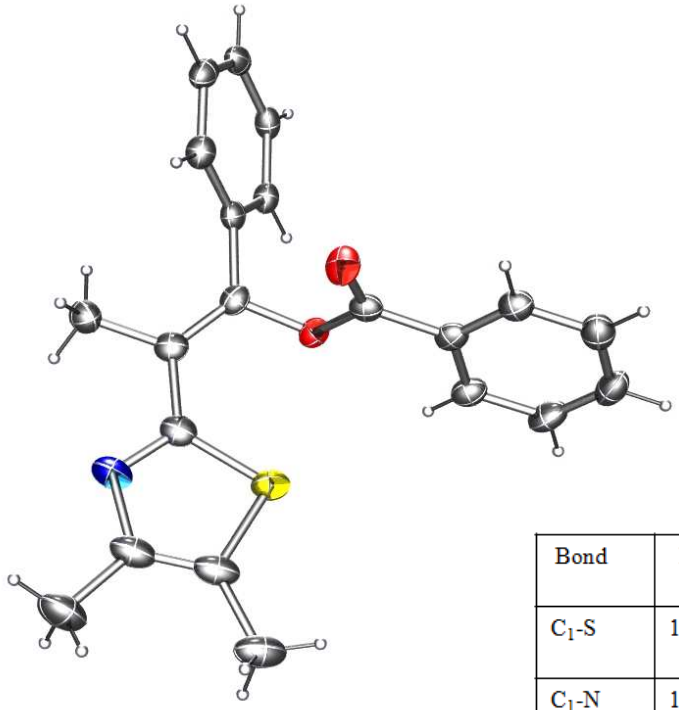


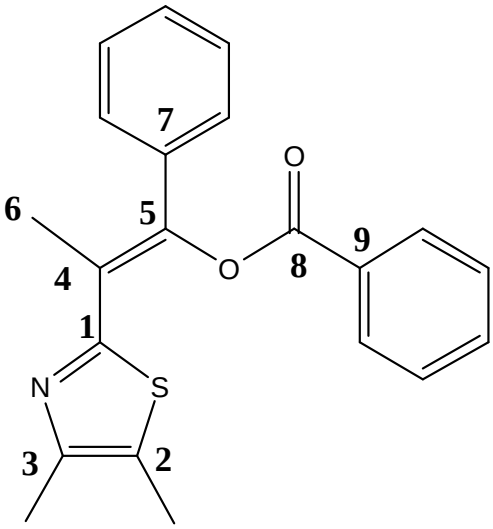
Figure 3.5 Crystal Packing [1 1 1] of 3-Bromo-benzoic acid 1-(3-bromophenyl)-2-(4,5-dimethylthiazol-2-yl)-vinyl ester (**152**). CCDC Number: 765578

Table 3.5 Sample and Crystal Data of of 3-Bromobenzoic acid 1-(3-bromophenyl)-2-(4,5-dimethylthiazol-2-yl)-vinyl ester (**152**). CCDC Number: 765578

Chemical formula	$C_{20}H_{15}Br_2NO_2S$	
Formula weight	493.21	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.30 x 0.30 x 0.30 mm	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.6468(7) Å	α = 111.363(3)°
	b = 10.8191(9) Å	β = 93.099(3)°
	c = 11.2267(9) Å	γ = 104.084(3)°
Volume	936.79(13) $Å^3$	
Z	2	
Density (calculated)	1.749 Mg/cm^3	
Absorption coefficient	4.453 mm^{-1}	
F(000)	488	



Bond	Angle (°)
O-C_5-C_4	119.48
C_5-C_4-C_1	124.11
C_4-C_1-S	125.77
C_8-O-C_5	115.72



Bond	Length (Å)
C_1-S	1.736
C_1-N	1.315
C_2-C_3	1.355
N-C_3	1.381
S-C_2	1.725
C_1-C_4	1.473
C_4-C_5	1.338
C_5-C_7	1.487
C_5-O	1.417

Bond	Length (Å)
O-C_8	1.373
C_8-O	1.201
C_8-C_9	1.482
C_4-C_6	1.506

Figure 3.6 Crystal Structure of 3-Bromobenzoic acid Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-propenyl ester (**157**). CCDC Number: 765826

Table 3.6 Sample and Crystal Data of 3-Bromobenzoic acid Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-propenyl ester (**157**). CCDC Number: 765826

Identification code	SBSN1	
Chemical formula	$C_{21}H_{19}NO_2S$	
Formula weight	349.43	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.2298(5) Å	α = 79.820(2)°
	b = 11.3133(5) Å	β =76.492(2)°
	c = 15.4529(5) Å	γ = 72.466(2)°
Volume	1808.21(13) $Å^3$	
Z	4	
Density (calculated)	1.284 Mg/cm^3	
Absorption coefficient	0.192 mm^{-1}	
F(000)	736	

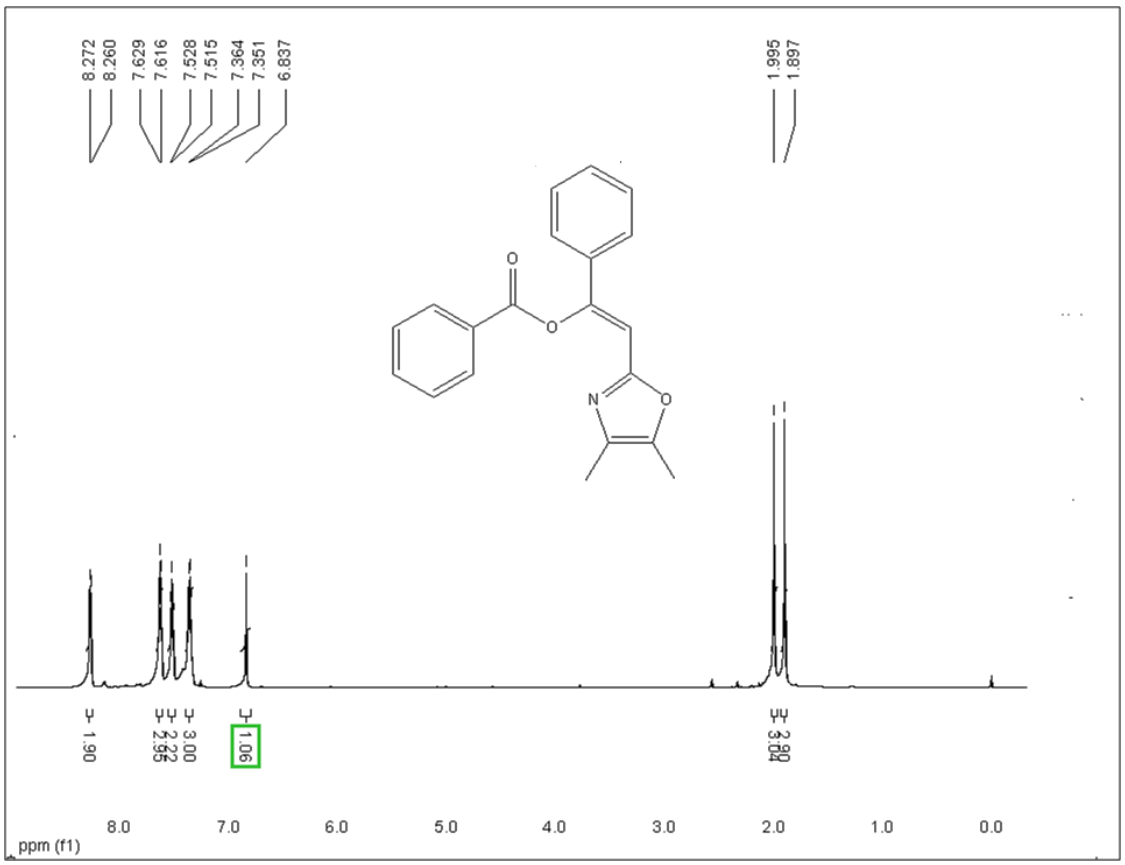


Figure 3.7 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Benzoic acid-2-(4,5-dimethyloxazol-2-yl)-1-phenyl-vinyl ester **(143)**

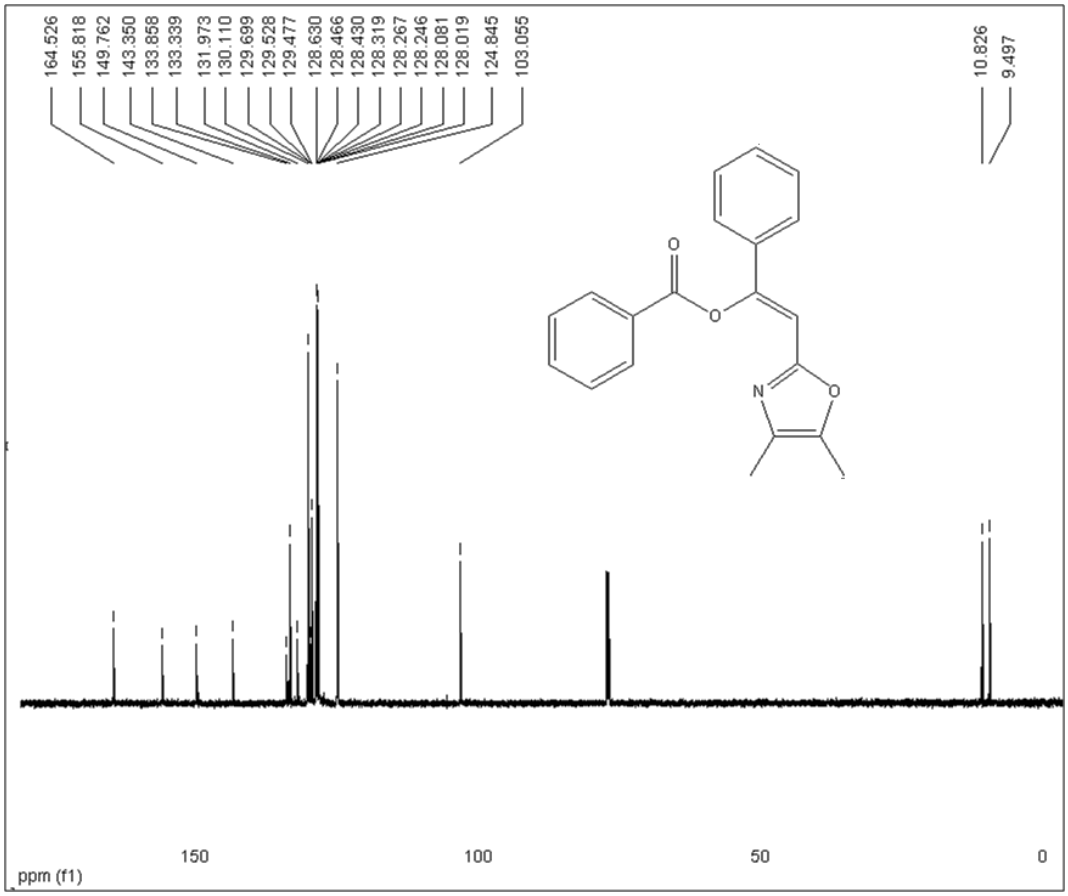


Figure 3.8 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Benzoic acid-2-(4,5-dimethyloxazol-2-yl)-1-phenyl-vinyl ester (**143**)

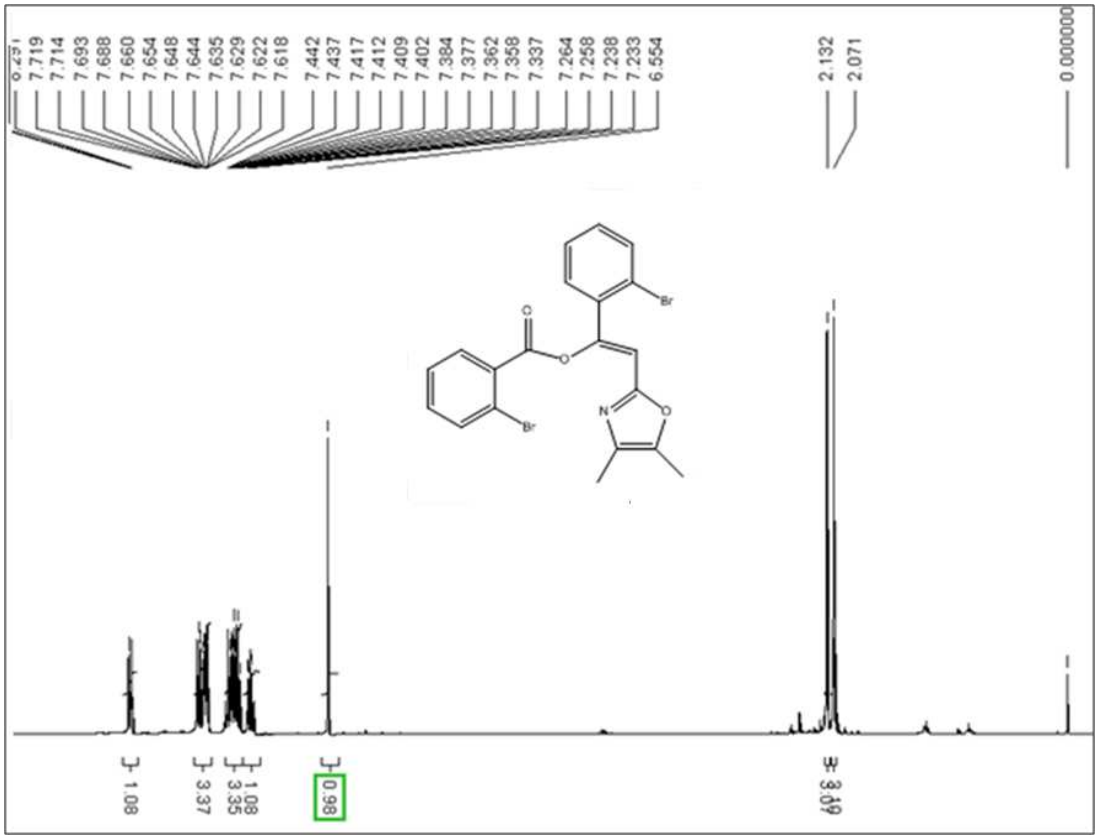


Figure 3.9 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Bromobenzoic acid-1-(2-bromophenyl)-2-(4,5-dimethyloxazol-2-yl)-vinyl ester (**146**)

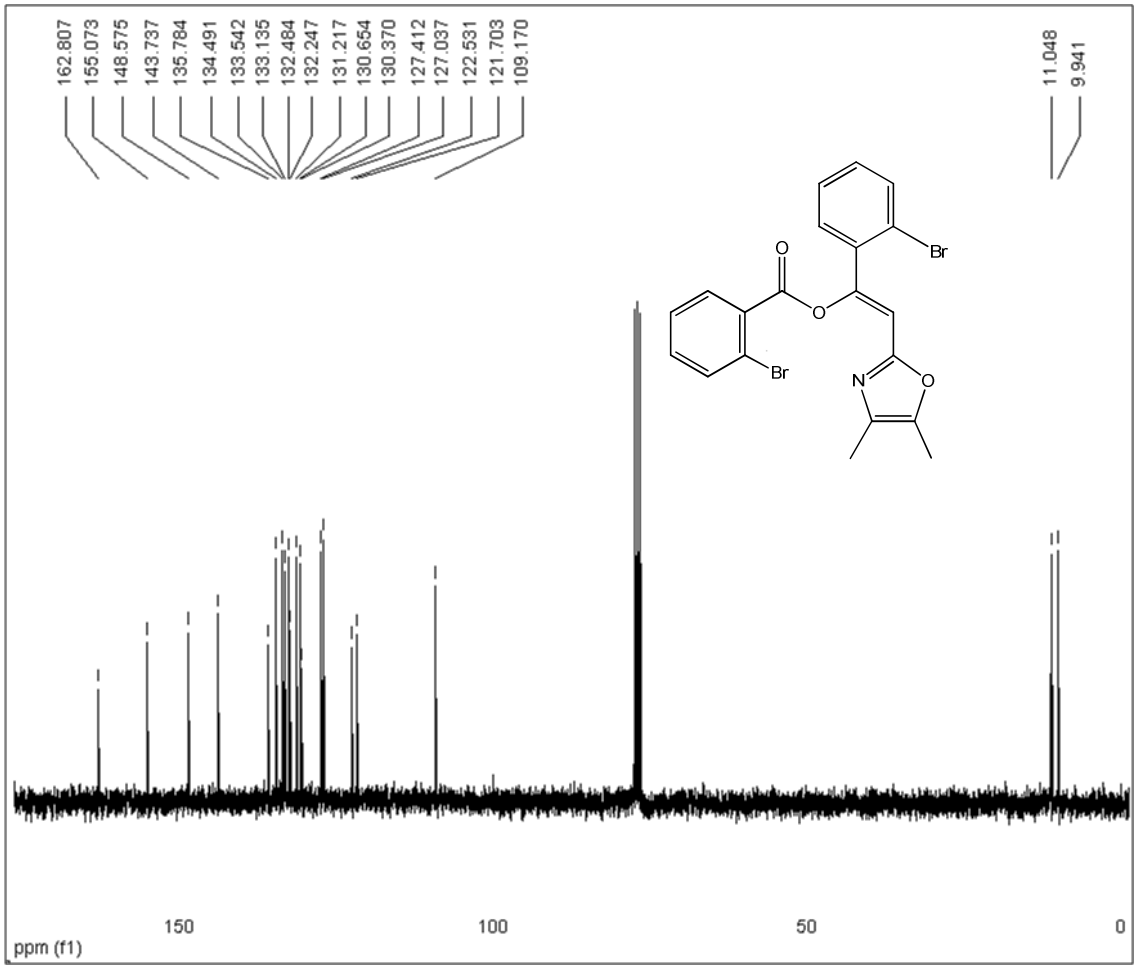


Figure 3.10 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Bromobenzoic acid-1-(2-bromo-phenyl)-2-(4,5-dimethyloxazol-2-yl)-vinyl ester (**146**)

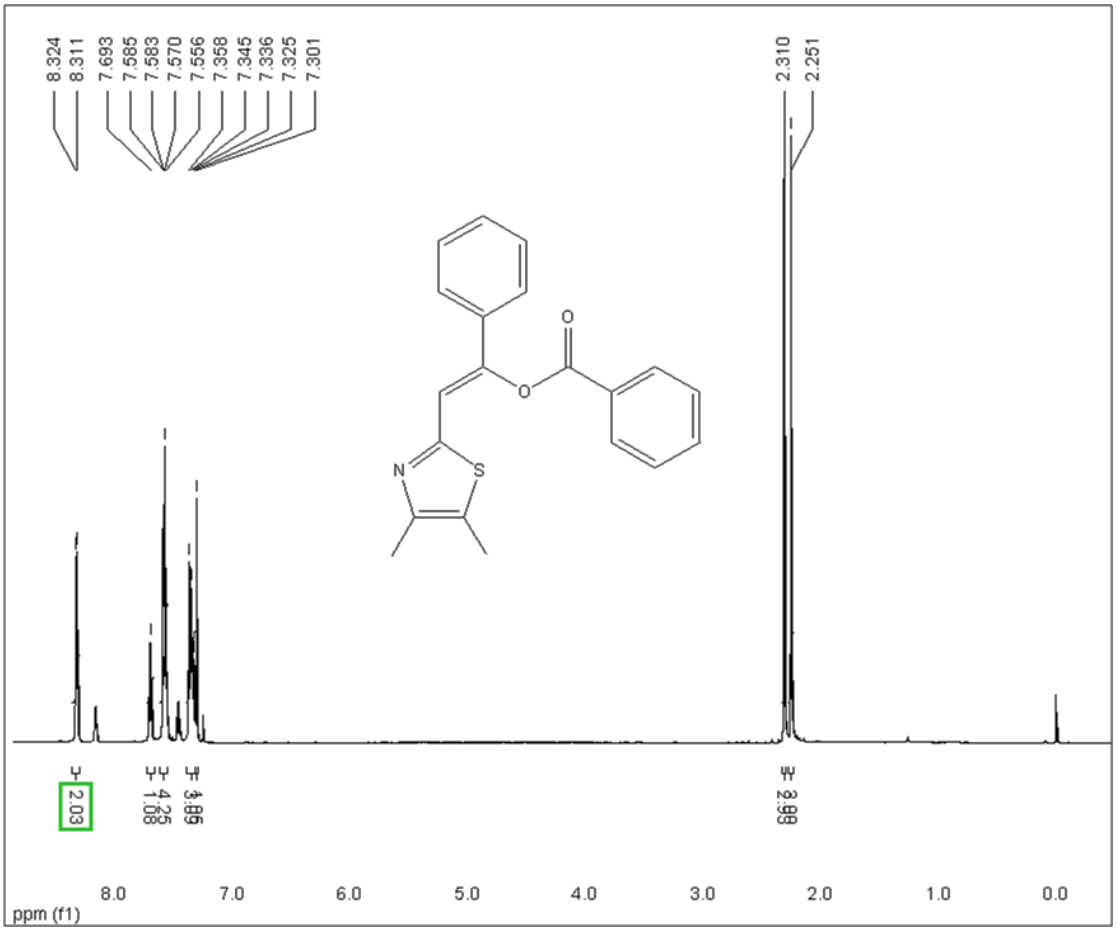


Figure 3.11 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-vinyl ester (**149**)

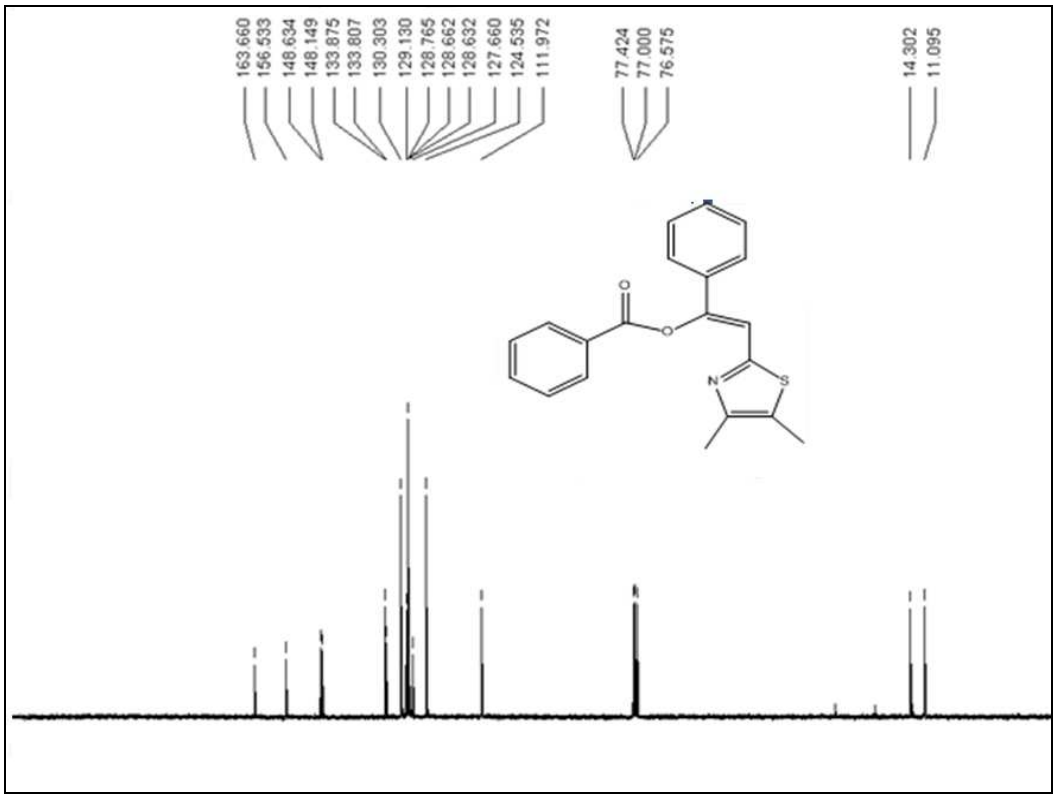


Figure 3.12 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-vinyl ester (**149**)

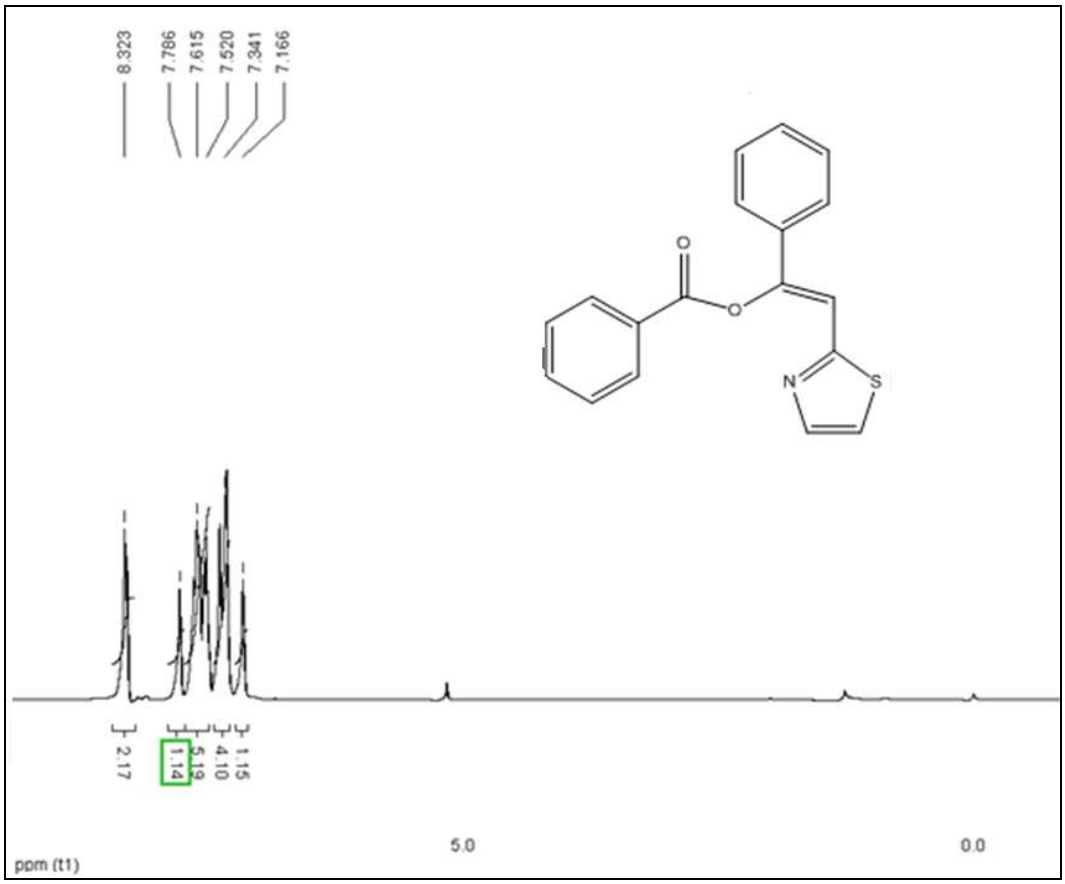


Figure 3.13 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Benzoic acid 1-phenyl-2-thiazol-2-yl-vinyl ester (**159**)

.

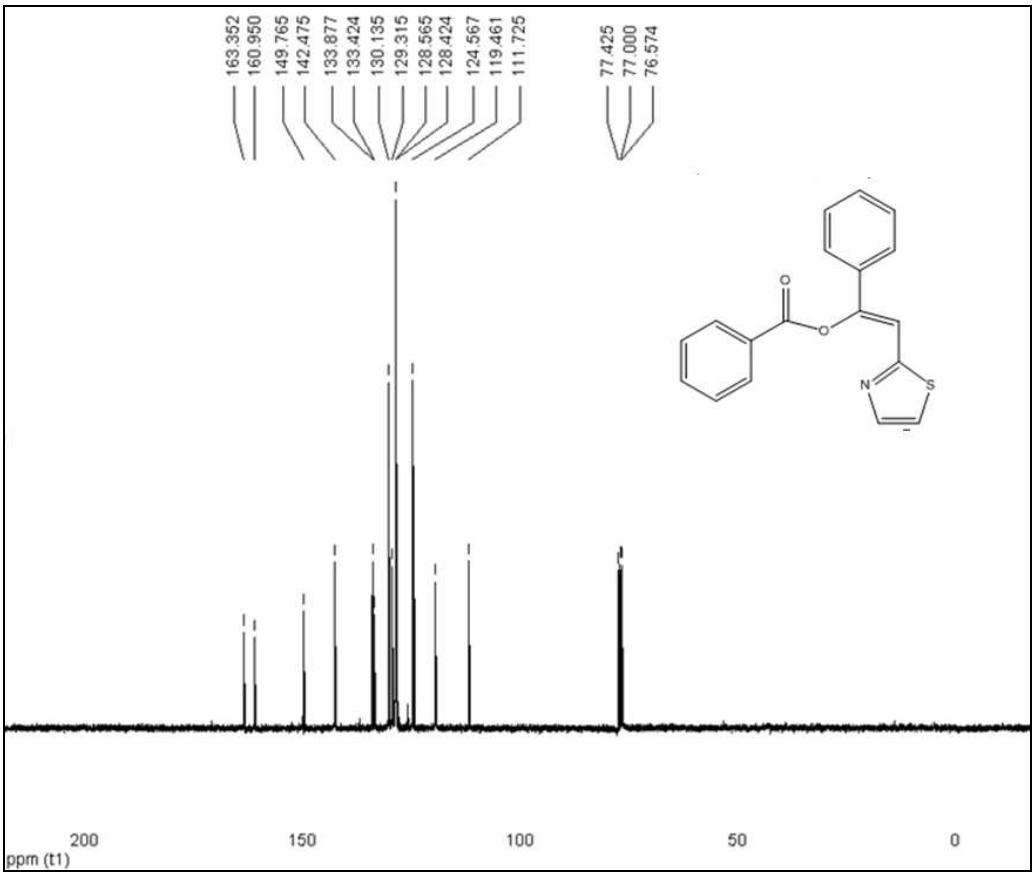


Figure 3.14 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Benzoic acid-1-phenyl-2-thiazol-2-yl-vinyl ester (**159**)

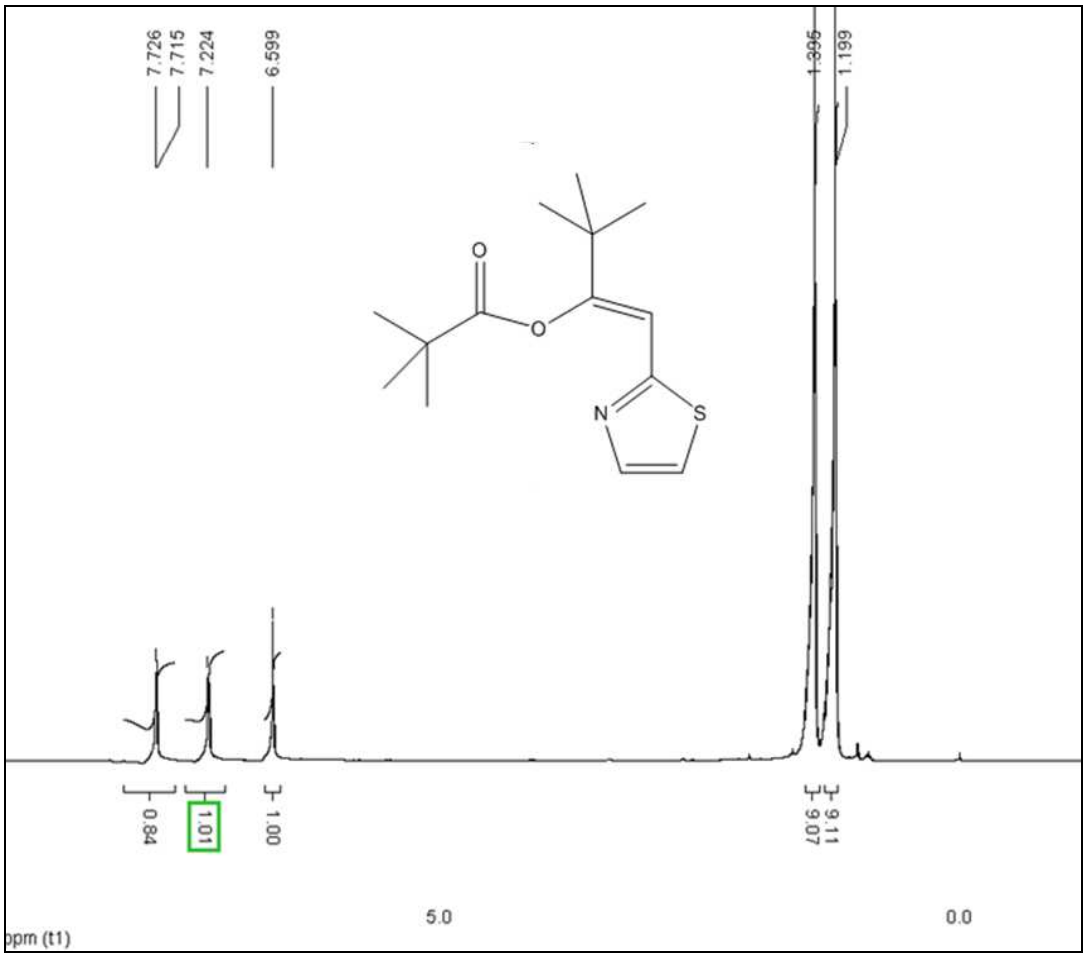


Figure 3.15 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2,2-Dimethyl-propionic acid-2,2-dimethyl-1-thiazol-2-yl-methylene-propyl ester (**165**)

.

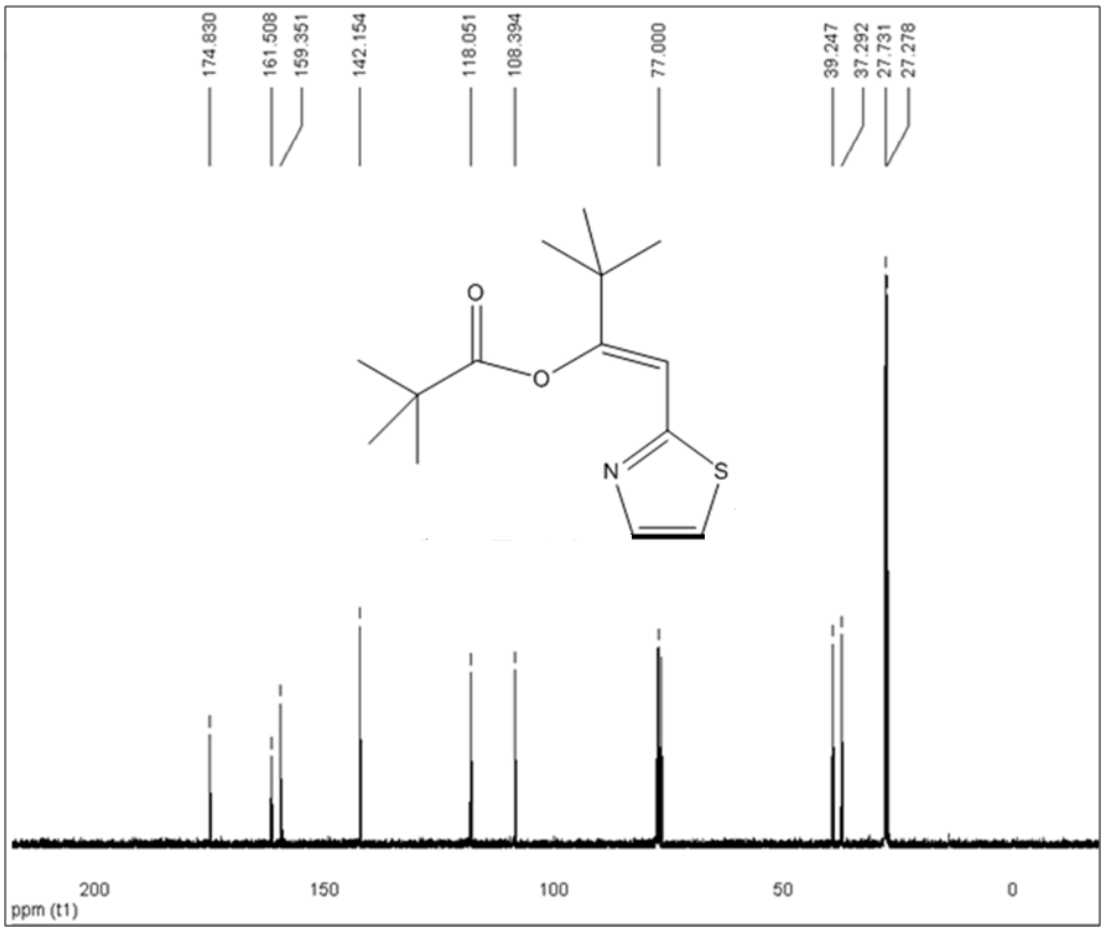


Figure 3.16 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2,2-Dimethyl-propionic acid-2,2-dimethyl-1-thiazol-2-yl-methylene-propyl ester (**165**)

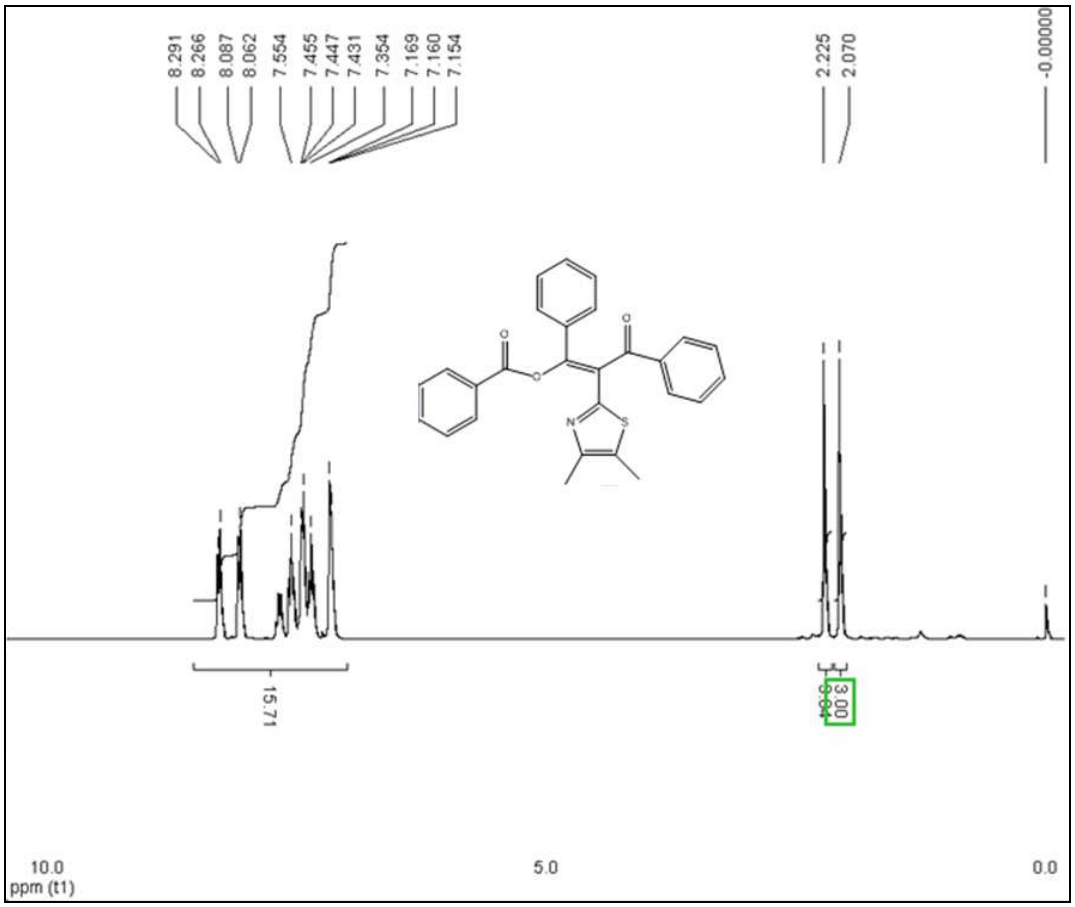


Figure 3.17 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-3-oxo-1,3-diphenyl-propenyl ester (**166**)

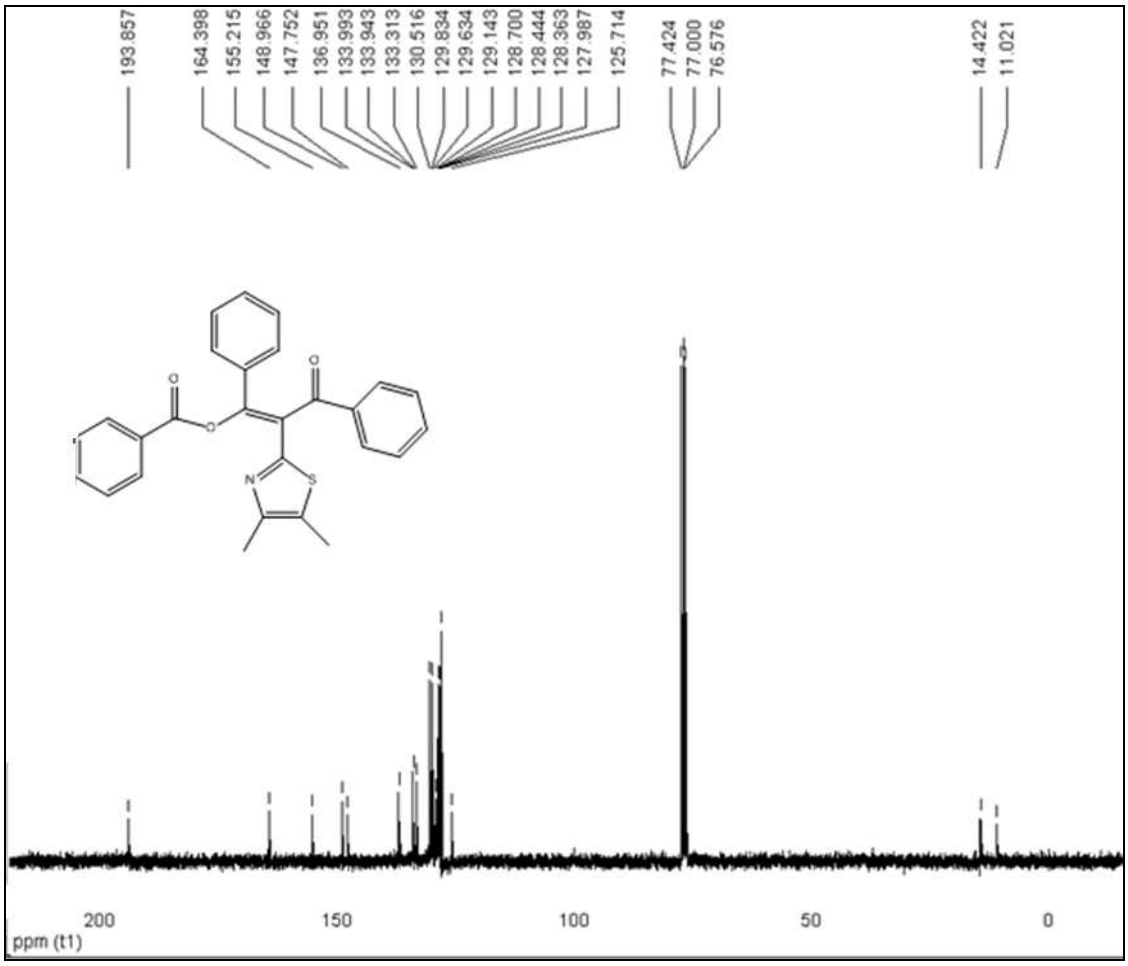


Figure 3.18 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Benzoic Acid-2-(4,5-dimethylthiazol-2-yl)-3-oxo-1,3-diphenyl-propenyl ester (**166**)

Experimental

Materials and Instruments

The ^{1}H and ^{13}C NMR spectra were collected using a Bruker AVANCE III spectrometer in the Department of Chemistry, Mississippi State University operating at

300 MHz for proton and 75 MHz for carbon. Chemical shifts were reported in ppm downfield from TMS (Tertamethylsilenae). $CDCl_3$ (Deutarated Chloroform) was used as the solvent for all NMR samples. Splitting patterns are designated as 's, d, t, q and m'; these symbolize 'singlet, doublet, triplet, quartet and multiplet'.

The FT-IR (Fourier Transformed Infrared) spectra were collected as films on salt plates or on a diamond window. All reactions were performed under nitrogen. Acetonitrile, tetrahydrofuran and triethylamine were dried by distillation over calcium hydride under nitrogen. In case of tetrahydrofuran benzoquuinone was used to confirm the absence of water.

Dichloromethane or methylene chloride was pre-dried with calcium chloride and then distilled from calcium hydride under nitrogen atmosphere. *N*,*N*-Dimethylformamide (DMF) was pre-dried with anhydrous magnesium sulfate and then distilled under reduced pressure under nitrogen atmosphere. Anhydrous *N*,*N*-dimethylacetamide (DMAc) was purchased commercially from Fisher Scientific USA. All other chemicals (such as 2,4,5-trimethyloxazole, 2,4,5-trimethylthiazole, 2-methylthiazole, 2-ethyl-4,5-dimethylthiazole, substituted and normal benzoyl chloride, normal Butyl Lithium, etc) were obtained commercially from Sigma Aldrich or Fisher Scientific and used as received.

A dry ice/ acetone external cooling bath (-78°C) was employed in several reactions. Melting points were obtained on a Mel-Temp instrument with a heating rate of 5°C/min and are uncorrected.

Synthesis using 2,4,5- Trimethyloxazole as the Starting Material

Benzoic acid-2-(4,5-dimethyloxazol-2-yl)-1-phenyl-vinyl ester (**143**)

2,4,5-Trimethyloxazole (**136)** (0.25 g, 2.1 mmol) was dissolved in 15 mL of acetonitrile, and triethylamine (0.784 g, 7.6 mmol) was added dropwise. A solution of benzoyl chloride (0.90 g, 6.3 mmol) in 15 mL of acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and then the solvent was removed by rotary evaporation. Dichloromethane (20 mL) was added to the residue. This mixture was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL). The dichloromethane solution was dried over $MgSO_4$, and then reconcentrated. The concentrate was purified by flash chromatography (silica gel, 5:1 hexane/ethyl acetate) to give **143.**

It should be noted that, intially, a few workups were done using a second approach, where acetone (3 x 20 mL) was added to the residue obtained after removal of solvent. The resulting solid/liquid mixture was filtered and the collected solid was thoroughly washed with acetone (3 x 15 mL). The filtrate was concentrated *in vacuo* and the residue was purified using flash chromatography. After the first method was found to be more efficient, it was followed in all subsequent cases. However, the difference between the yields in the two methods was negligible.

Sticky yellow liquid; yield: 366 mg (54%), R_f = 0.6 (silica gel, 5:1 hexane/ ethyl acetate).

IR (KBr, cm^{-1}): 3063, 2923, 1920, 1740, 1634, 1600, 1449, 1313, 1240.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.26 (d, *J* = 7.1 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.62 (m, -O-CO-$C_6\underline{H}_5$ (aromatic), 3H), 7.51 (t, *J* = 7.7 Hz, -C=C-$C_6\underline{H}_5$ (aromatic *ortho*), 2H); 7.35 (m, -C=C-$C_6\underline{H}_5$ (aromatic), 3H), 6.83 (s, -N=C-C$\underline{H}$=C-, 1H), 1.99 (s, -O-C(C$\underline{H}_3$)-C(CH_3)-N-, 3H), 1.89 (s, -O-C(CH_3)-C(C$\underline{H}_3$)-N-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 164.52 (-O-$\underline{C}$O-C_6H_5), 155.81(-N=$\underline{C}$-CH=C-), 149.76 (-CH=$\underline{C}$-C_6H_5), 143.35 (-O-$\underline{C}$(CH_3)-C(CH_3)-N-) , 133.85 (-CH=C-$\underline{C}_6H_5$), 133.33 (-O-CO-$\underline{C}_6H_5$ (aromatic *para*)), 131.97 (-O-CO-$\underline{C}_6H_5$), 130.11 (-O-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 129.47 (aromatic *meta* of both phenyl groups, 4C), 128.63 (-O-CO-$\underline{C}_6H_5$(aromatic *para*)), 128.31 (-O-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 124.84 (-O-C(CH_3)-$\underline{C}$(CH_3)-N-), 103.05 (-N=C-$\underline{C}$H=C-), 10.82 (-O-C($\underline{C}H_3$)-C(CH_3)-N-), 9.49 (-O-C(CH_3)-C($\underline{C}H_3$)-N-).

4-Chlorobenzoic acid-1-(4-chlorophenyl)-2-(4,5-dimethyloxazol-2-yl)-vinyl ester (**144**)

Compound **144** was prepared using 2,4,5-trimethyloxazole (**136**) (0.25 g, 2.1 mmol) and 4-chlorobenzoyl chloride (1.10 g, 6.3 mmol) by the general procedure.

White crystals; mp. 123-125°C; yield: 403 mg (49%) R_f = 0.6 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3055, 2923, 1738, 1652, 1632, 1592, 1530, 1487, 1400, 1249.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.12 (d, *J* = 7.6 Hz, -O-CO-$C_6\underline{H}_4$Cl (aromatic *ortho*), 2H), 7.46 (d, *J* = 7.5 Hz, -O-CO-$C_6\underline{H}_4$Cl (aromatic *meta*), 7.45 (-C=C-$C_6\underline{H}_4$Cl (aromatic *ortho*), 2H), 7.28 (d, -C=C-$C_6\underline{H}_4$Cl (aromatic *meta*), 2H); 6.68 (s, -N=C-C$\underline{H}$=C-, 1H), 1.93 (s, -O-C(C$\underline{H}_3$)-C(CH_3)-N-, 3H), 1.89 (s, -O-C(CH_3)-C(C$\underline{H}_3$)-N-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 163.84 (-O-CO-C_6H_4Cl), 155.59 (-N=C-CH=C-), 148.54 (-CH=C-C_6H_4Cl), 143.81 (O-CO-C_6H_4Cl (aromatic *para*; Cl-bearing)), 140.25 (-O-C(CH_3)-C(CH_3)-N-) , 135.71 (-CH=C-C_6H_4Cl (aromatic *para*, Cl bearing)), 132.39 (-CH=C-C_6H_4Cl), 131.70 (-O-CO-C_6H_4Cl (aromatic *ortho*) 2C), 129.16 (-O-CO-C_6H_4Cl, 3C), 128.96 (CH=C-C_6H_4Cl (aromatic *meta*) 2C), 127.93 (CH=C-C_6H_4Cl (aromatic *ortho*) 2C), 126.22 (-O-C(CH_3)-C (CH_3)-N-), 103.68 (-N=C-CH=C-), 11.05 (-O-C(CH_3)-C (CH_3)-N-), 9.89 (-O-C(CH_3)-C(CH_3)-N-).

2-Methylbenzoic acid-2-(4,5-dimethyloxazol-2-yl)-1-*o*-tolyl-vinyl ester (**145**)

Compound **145** was prepared using 2,4,5-trimethyloxazole (**136**) (0.25 g, 2.1 mmol) and 2-methylbenzoyl chloride (0.993 g, 6.3 mmol) by the general procedure.

Brown liquid; yield: 345 mg, (47%); R_f = 0.45 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3065, 2925, 2300, 1740, 1636, 1456.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.25 (m, -O-CO-$C_6H_4CH_3$ (aromatic *ortho*), 1H), 7.53 (m, -O-CO-$C_6H_4CH_3$ (aromatic *para*), 1H), 7.46 (m, -O-CO-$C_6H_4CH_3$ (aromatic *meta*), 1H); 7.62 (m, (aromatic *ortho* and *para* Hs of -C=C-$C_6H_4CH_3$ and aromatic *ortho* Hs of both phenyl rings), 5H), 6.34 (s, -N=C-CH=C-, 1H), 2.59 (s, -C=C-$C_6H_4CH_3$, 3H) , 2.53 (s, -O-CO-$C_6H_4CH_3$, 3H) , 2.05 (s, -O-C(CH_3)-C(CH_3)-N-, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 164.78 (-O-CO-$C_6H_4CH_3$), 155.83 (-N=C-CH=C-), 151.03 (-CH=C $C_6H_4CH_3$), 143.40 (O-CO-$C_6H_4CH_3$ (aromatic *ortho*, Me-bearing)), 141.17 (-O-C(CH_3)-C(CH_3)-N-) , 136.29 (-CH=C-$C_6H_4CH_3$), 135.17 (-CH=C-$C_6H_4CH_3$

(aromatic *ortho*, Me-bearing), 132.52 (-O-CO-$\underline{C}_6H_4CH_3$ (aromatic *para*)), 131.88 (-O-CO-$\underline{C}_6H_4CH_3$), 131.66 (-O-CO-$\underline{C}_6H_4CH_3$ (aromatic *ortho*)), 131.40 (CH=C-$\underline{C}_6H_4CH_3$ (aromatic *meta*), 131.02 (-O-CO-$\underline{C}_6H_4CH_3$ (aromatic *meta*)), 129.31 (CH=C-$\underline{C}_6H_4CH_3$ (aromatic *para*)), 128.92 (CH=C-$\underline{C}_6H_4CH_3$ (aromatic *ortho*)), 128.62 (CH=C-$\underline{C}_6H_4CH_3$ (aromatic *meta*)), 125.96 ((-O-CO-$\underline{C}_6H_4CH_3$ (aromatic *meta*)), 125.75 (-O-C(CH_3)-$\underline{C}$(CH_3)-N-), 107.80 (-N=C-$\underline{C}$H=C-), 21.72 (CH=C-$C_6H_4\underline{C}H_3$), 20.95 (-O-CO-$C_6H_4\underline{C}H_3$), 11.09 (-O-C($\underline{C}H_3$)-C(CH_3)-N-), 9.85 (-O-C(CH_3)-C($\underline{C}H_3$)-N-).

2-Bromobenzoic acid-1-(2-bromophenyl)-2-(4,5-dimethyloxazol-2-yl)- vinyl ester (**146**)

Compound **146** was prepared using 2,4,5-trimethyloxazole (**136**) (0.25 g, 2.1 mmol) and 2-bromobenzoyl chloride (1.41 g, 6.3 mmol) by the general procedure.

Yellow crystals; mp. 92-93°C; yield: 514 mg (51%); R_f = 0.65 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3067, 2920, 2855, 1910, 1748, 1661, 1632, 1586, 1364.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.30 (dd, *J* = 7.4 Hz, -O-CO-$C_6\underline{H}_4$Br (aromatic *ortho*), 1H), 7.70 (dd, *J* = 7.7 Hz, -O-CO-$C_6\underline{H}_4$Br (*meta*, next to Br), 1H), 7.64 (m, -O-CO-$C_6\underline{H}_4$Br (aromatic *ortho* and *para*), 2H), 7.40 (m, -C=C-$C_6\underline{H}_4$Br (aromatic *ortho*, *para* and *meta* (next to Br), 3H), 7.23 (m, -C=C-$C_6\underline{H}_4$Br (aromatic *meta*), 1H), 6.55 (s, -N=C-C$\underline{H}$=C-, 1H), 2.13 (s, -O-C($C\underline{H}_3$)-C(CH_3)-N-, 3H), 2.07 (s, -O-C(CH_3)-C($C\underline{H}_3$)-N-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 162.80 (-O-$\underline{C}$O-C_6H_4Br), 155.07 (-N=$\underline{C}$-CH=C-), 148.57 (-CH=$\underline{C}$-C_6H_4Br), 143.73 ((-CH=C-$\underline{C}_6H_4$Br), 135.78 (-O-$\underline{C}$(CH_3)-C(CH_3)-N-) ,

134.49 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *para*), 133.54 (-O-CO-$\underline{C}_6H_4Br$ (C1)), 133.13 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *ortho*)), 132.48 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *meta* next to Br)), 132.24 (CH=C-$\underline{C}_6H_4Br$ (aromatic *meta* next to Br)), 131.21(CH=C-$\underline{C}_6H_4Br$ (aromatic *para*)), 130.65 (CH=C-$\underline{C}_6H_4Br$ (aromatic *ortho*)), 130.37 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *meta*)), 127.41 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *meta*), 127.03 (-O-C(CH_3)-$\underline{C}$(CH_3)-N-), 122.53 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *ortho*, Br bearing)), 121.70 (CH=C-$\underline{C}_6H_4Br$ (aromatic *ortho*, Br bearing)), 109.17 (-N=C-$\underline{C}$H=C-), 11.04 (-O-C($\underline{C}H_3$)-C(CH_3)-N-), 9.94(-O-C(CH_3)-C($\underline{C}H_3$)-N-).

3-Fluorobenzoic acid-2-(4,5-dimethyloxazol-2-yl)-1-(3-fluorophenyl)-vinyl ester (**147**)

Compound **147** was prepared using 2,4,5-trimethyloxazole (**136**) (0.25 g, 2.1 mmol) and 3-fluorobenzoylbenzoyl chloride (1.019 g, 6.3 mmol) by the general procedure.

Brown liquid; yield: 399 mg (54%); R_f = 0.6 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3076, 2937, 1733, 1661, 1591, 1455, 1416, 1380, 1273, 1224.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.05(m, -O-CO-$C_6\underline{H}_4F$ (aromatic *ortho*), 1H), 7.96 (m,-O-CO-$C_6\underline{H}_4F$ (aromatic *ortho*), 1H), 7.51 (m, -O-CO-$C_6\underline{H}_4F$ (aromatic *meta*), 1H); 7.40 (m, (aromatic *ortho* and *meta* H s of -C=C-$C_6\underline{H}_4F$ and aromatic *para* of -O-CO-$C_6\underline{H}_4F$), 3H), 7.06 (m, -C=C-$C_6\underline{H}_4F$ (aromatic *para*, 1H), 6.88 (s, -N=C-C$\underline{H}$=C-, 1H), 2.02 (s, -O-C(C$\underline{H}_3$)-C(CH_3)-N-, 3H), 1.96 (s,-O-C(CH_3)-C(C$\underline{H}_3$)-N-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 164.55 (-O-CO-$C_6\underline{H}_4F$ (aromatic *meta*, F bearing)), 163.44 (-O-$\underline{C}$O-C_6H_4F), 160.81(-CH=C-$\underline{C}_6H_4F$ (aromatic *meta*, F bearing)),

155.40 (-N=C-CH=C-), 148.30 (-CH=C-C_6H_4F), 143.89 (-O-C(CH_3)-C(CH_3)-N-), 136.06 (-CH=C-C_6H_4F), 132.30 (O-CO-C_6H_4F), 131.50 (-CH=C-C_6H_4F (aromatic *meta*)), 131.40 (O-CO-C_6H_4F (aromatic *meta*)), 130.36 (O-CO-C_6H_4F (aromatic *ortho*)), 130.13(-O-C(CH_3)-C(CH_3)-N-), 126.00 (-CH=C-C_6H_4F (aromatic *ortho*)), 120.58 (-O-CO-C_6H_4F (aromatic *para*)), 117.22(-O-CO-C_6H_4F (aromatic *ortho*)), 116.68 (CH=C-C_6H_4F(aromatic *para*)), 111.76 (CH=C-C_6H_4F (aromatic *ortho*)), 104.09 (-N=C-CH=C-), 10.82 (-O-C(CH_3)-C(CH_3)-N-), 9.63(-O-C(CH_3)-C(CH_3)-N-).

4-Nitrobenzoic acid-2-(4,5-dimethyloxazol-2-yl)-1-(4-nitrophenyl)-vinyl ester (**148**)

Compound **148** was prepared using 2,4,5-trimethyloxazole (**136**) (0.25 g, 2.1 mmol) and 4-nitrobenzoyl chloride (1.19 g, 6.3 mmol) by the general procedure.

Yellow solid; mp. 207-209°C; yield: 403 mg (47%); R_f = 0.45 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3113, 2923, 1733, 1625, 1594, 1522, 1410, 1341, 1245, 1121.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.42 (m, -O-CO-$C_6H_4NO_2$ (aromatic Hs), 4H), 8.27 (m, -C=C-$C_6H_4NO_2$ (aromatic *meta*), 2H), 7.75 (m, -C=C-$C_6H_4NO_2$ (aromatic *ortho*), 2H), 6.95 (s, -N=C-CH=C-, 1H), 2.03 (s,-O-C(CH_3)-C(CH_3)-N-, 3H), 1.60 (s, -O-C(CH_3)-C(CH_3)-N-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 162.64 (-O-CO-$C_6H_4NO_2$), 154.76 (-O-CO-$C_6H_4NO_2$ (aromatic *para*)), 151.16 (-N=C-CH=C-), 148.07 (-CH=C-$C_6H_4NO_2$), 146.70 (-CH=C-$C_6H_4NO_2$ (aromatic *para*)), 144.47 (-CH=C-$C_6H_4NO_2$ (C1)), 139.67 (-O-C(CH_3)-C(CH_3)-N-), 134.88 (O-CO-$C_6H_4NO_2$), 133.50 (O-CO-$C_6H_4NO_2$ (aromatic *ortho*), 2C),

131.62 (-CH=C-$\underline{C}_6H_4NO_2$ (aromatic *ortho*), 2C), 125.79 (-O-C(CH_3)-$\underline{C}$(CH_3)-N-), 124.42 (O-CO-$\underline{C}_6H_4NO_2$ (aromatic *meta*)), 123.98 (-CH=C-$\underline{C}_6H_4NO_2$ (aromatic *meta*)), 106.60 (-N=C-$\underline{C}$H=C-), 11.14 (-O-C($\underline{C}H_3$)-C(CH_3)-N-), 9.76 (-O-C(CH_3)-C($\underline{C}H_3$)-N-).

Synthesis using 2,4,5-Trimethylthiazole, 2-Ethylthiazole and 2-Methylthiazole as Starting Materials

Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-vinyl ester (**149**)

2,4,5-Trimethylthiazole (**138)** (0.25 g, 1.9 mmol) was dissolved in 15 mL of acetonitrile, and then triethylamine (0.712 g, 6.9 mmol) was added dropwise. A solution of benzoyl chloride (0.817 g, 5.7 mmol) in 15 mL of acetonitrile was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and then the solvent was removed by rotary evaporation. Dichloromethane (20 mL) was added to the residue. This mixture was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL). The dichloromethane solution was dried over $MgSO_4$, and then reconcentrated. The concentrate was purified by flash chromatography (silica gel, 5:1 hexane/ethyl acetate) to give **149.**

Yellow liquid; yield: 287 mg (44%); R_f = 0.40 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3063, 3043, 2949, 2917, 2854, 1910, 1740, 1699, 1538, 1492, 1314, 1235.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.32 (d, *J* = 7.8 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.69 (m, (aromatic Hs), 1H), 7.57 (m, (aromatic Hs), 4H), 7.35 (m, (aromatic Hs),

3H), 7.30 (s, -N=C-C<u>H</u>=C-, 1H), 2.31 (s,-N-C(C<u>H</u>$_3$)-C(CH$_3$)-S-,3H), 1.60 (s, -N-C(CH$_3$)-C(C<u>H</u>$_3$)-S-, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ_C = 163.75 (-O-<u>C</u>O-C$_6$H$_5$), 156.84 (-N=<u>C</u>-CH=C-), 148.90 (-S-C(CH$_3$)-<u>C</u>(CH$_3$)-N-), 148.20 (-CH=<u>C</u>-C$_6$H$_5$), 133.94 (-CH=C-<u>C</u>$_6$H$_5$), 130.46 (-O-CO-<u>C</u>$_6$H$_5$(aromatic *para*)), 129.88 (-O-CO-<u>C</u>$_6$H$_5$), 129.25 (-O-CO-<u>C</u>$_6$H$_5$ (aromatic *ortho*)), 129.00 (-O-CO-<u>C</u>$_6$H$_5$ (aromatic *meta*)), 128.79 (-CH=C-<u>C</u>$_6$H$_5$ (aromatic *meta*)), 128.18 (-N-C(CH$_3$)-<u>C</u>(CH$_3$)-S-), 127.73 (-CH=C-<u>C</u>$_6$H$_5$ (aromatic *para*)), 124.74 (-CH=C-<u>C</u>$_6$H$_5$ (aromatic *ortho*)), 112.01 (-N=C-<u>C</u>H=C-), 14.33 (-S-C(CH$_3$)-C(<u>C</u>H$_3$)-N-), 11.23 (-S-C(<u>C</u>H$_3$)-C(CH$_3$)-N-).

<u>4-Chlorobenzoicacid-1-(4-chlorophenyl)-2-(4,5-dimethylthiazol-2-yl)-vinyl ester (**150**)</u>

Compound **150** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and 4-chlorobenzoyl chloride (0.997 g, 5.7 mmol) by the general procedure.

Yellow liquid; yield: 378 mg (48%); R_f = 0.45 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2921, 1737, 1680, 1590, 1538, 1489, 1426, 1398, 1239, 1223, 1168.

^{1}H NMR (300 MHz, CDCl$_3$): δ_H = 8.23 (d, *J* = 8.5 Hz, -O-CO-C$_6$<u>H</u>$_4$Cl (aromatic *ortho*), 2H), 7.56 (d, *J* =8.5 Hz, -O-CO-C$_6$<u>H</u>$_4$Cl (aromatic *meta*, 2H), 7.47 (d, *J* = 8.6 Hz, -C=C-C$_6$<u>H</u>$_4$Cl (aromatic *ortho*) , 2H), 7.34 (d, *J* = 8.6 Hz, -C=C-C$_6$<u>H</u>$_4$Cl (aromatic *meta*), 2H); 6.68 (s, -N=C-C<u>H</u>=C-,1H), 2.30 (s, -S-C(CH$_3$)-C(C<u>H</u>$_3$)-N-, 3H), 2.29 (s, -S-C(C<u>H</u>$_3$)-C(CH$_3$)-N-, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ_C = 156.17 (-O-<u>C</u>O-C$_6$H$_4$Cl), 148.66 (-N=<u>C</u>-CH=C-), 147.43 (-S-C(CH$_3$)-<u>C</u>(CH$_3$)-N-), 140.78 (-CH=<u>C</u>-C$_6$H$_4$Cl), 135.28 (O-CO-<u>C</u>$_6$H$_4$Cl

(aromatic *para*, Cl bearing)), 132.47 (-CH=C-$\underline{C}_6H_4Cl$ (aromatic *para*, Cl-bearing, 2C)), 129.24 (-O-CO-$\underline{C}_6H_4Cl$ (aromatic *ortho*) 2C), 129.13 (-O-CO-$\underline{C}_6H_4Cl$ (aromatic *meta*), 4C), 128.16 (-O-CO-$\underline{C}_6H_4Cl$), 127.22 (-S-$\underline{C}(CH_3)$-C(CH_3)-N-), 125.96 (CH=C-$\underline{C}_6H_4Cl$ (aromatic *ortho*, 2C), 112.52 (-N=C-$\underline{C}$H=C-), 14.47 (-S-C(CH_3)-C($\underline{C}H_3$)-N-), 11.34 (-S-C($\underline{C}H_3$)-C(CH_3)-N-).

2-Methylbenzoic acid-2-(4,5-dimethylthiazol-2-yl)-*o*-tolyl-vinyl ester (**151**)

Compound **151** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and 2-methylbenzoyl chloride (0.899 g, 5.7 mmol) by the general procedure.

Yellow liquid; yield: 297 mg (44%); R_f = 0.65 (silica gel, 3:1 hexane/ ethyl acetate).

IR (neat, cm^{-1}): 3001, 2923, 1737, 1651, 1601, 1574, 1543, 1488, 1456, 1380, 1283, 1219, 1164.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.38 (m, -O-CO-$C_6\underline{H}_4$Me (aromatic *ortho*), 1H), 7.50 (m ,-O-CO-$C_6\underline{H}_4$Me (aromatic *para* and *meta* Hs), 2H), 7.37 (m, -O-CO-$C_6\underline{H}_4$Me (aromatic *meta*), 1H), 7.23 (m, -CH=C-$C_6\underline{H}_4$Me (aromatic Hs), 4H), 6.75 (s, (-N=C-C$\underline{H}$=C-,1H), 2.58 (s, -N-C(C$\underline{H}_3$)-C(CH_3)-S-, 3H), 2.54 (s, -O-CO-$C_6H_4C\underline{H}_3$, 3H), 2.30 (s, -CH=C-$C_6H_4CH_3$, 3H), 2.29 (s, -N-C(CH_3)-C(C$\underline{H}_3$)-S-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 163.50 (-O-$\underline{C}$O-C_6H_4Me), 157.01 (-N=$\underline{C}$-CH=C-), 149.89 (-S-C(CH_3)-$\underline{C}$(CH_3)-N-), 147.88 (-CH=$\underline{C}$-C_6H_4Me), 142.29 (-O-CO-$\underline{C}_6H_4$Me (aromatic *ortho*, Me-bearing)), 140.70 (-CH=C-$\underline{C}_6H_4$Me (aromatic *ortho*, Me-bearing)), 136.09 (-CH=C-$\underline{C}_6H_4$Me), 135.08 (-O-CO-$\underline{C}_6H_4$Me (aromatic *para*)), 133.05 (-O-CO-$\underline{C}_6H_4$Me)), 132.15 (-O-CO-$\underline{C}_6H_4$Me (aromatic *ortho*)), 131.65 (-O-CO-$\underline{C}_6H_4$Me (aromatic

meta)), 130.89 (-CH=C-$\underline{C}_6H_4Me$ (aromatic *meta*)), 129.00 (-S-$\underline{C}(CH_3)$-$C(CH_3)$-N-), 128.54 (-CH=C-$\underline{C}_6H_4Me$ (aromatic *para*), 127.58 (-CH=C-$\underline{C}_6H_4Me$ (aromatic *ortho*)), 127.48 (-O-CO-$\underline{C}_6H_4Me$ (aromatic *meta*)), 126.02 (-CH=C-$\underline{C}_6H_4Me$ (aromatic *meta*), 115.63 (-N=C-$\underline{C}$H=C-), 22.11 (-O-CO-$C_6H_4\underline{C}H_3$), 20.87 (CH=C-$C_6H_4\underline{C}H_3$),14.38 (-S-$C(CH_3)$-$C(\underline{C}H_3)$-N-), 11.29 (-S-$C(\underline{C}H_3)$-$C(CH_3)$-N-).

3-Bromobenzoic acid-1-(3-bromophenyl)-2-(4,5-dimethylthiazole-2-yl)-vinyl ester (**152**)

Compound **152** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and 3-bromobenzoyl chloride (1.27 g, 5.7 mmol) by the general procedure.

Yellow crystals, M.P: 133-135°C; yield: 406 mg (43%) R_f = 0.60 (silica gel, 3:1 hexane/ ethyl acetate).

IR (neat, cm^{-1}): 3059, 2916, 1957, 1734, 1634, 1590, 1563, 1538, 1473, 1372, 1221, 1113.

^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.43 (s, -O-CO-$C_6\underline{H}_4Br$ (aromatic *ortho*, next to Br), 1H), 8.25 (s, -O-CO-$C_6\underline{H}_4Br$ (aromatic *ortho*), 1H), 7.83 (m, -O-CO-$C_6\underline{H}_4Br$ (aromatic *para*), 1H), 7.69 (m, -CH=$\underline{C}$-C_6H_4Br (aromatic *ortho*, next to Br), 1H), 7.48 (m, (aromatic Hs), 3H), 7.25 (m, aromatic and vinylic Hs, 2H), 2.30 (s, -N-$C(C\underline{H}_3)$-$C(C\underline{H}_3)$-S-, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 162.50 (-O-$\underline{C}$O-C_6H_4Br), 156.08 (-N=$\underline{C}$-CH=C-), 148.70 (-S-$C(CH_3)$-$\underline{C}(CH_3)$-N-), 146.95 (-CH=$\underline{C}$-C_6H_4Br), 137.12 (-CH=C-$\underline{C}_6H_4Br$), 136.01 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *para*)), 133.39 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *ortho*, next to Br)), 132.31 (-O-CO-$\underline{C}_6H_4Br$), 130.68 (-CH=C-$\underline{C}_6H_4Br$ (aromatic *para*)), 130.42 (-O-

CO-$\underline{C}_6H_4Br$ (aromatic *meta*)), 130.39 (-CH=C-$\underline{C}_6H_4Br$ (aromatic *meta*), 129.07 (-CH=C-$\underline{C}_6H_4Br$ (aromatic *ortho*, next to Br)), 128.49 (-O-CO-$\underline{C}_6H_4Br$ (aromatic *ortho*)), 127.76 (-S-$\underline{C}(CH_3)$-C(CH_3)-N-), 123.38 (-CH=C-$\underline{C}_6H_4Br$ (aromatic *ortho*)), 123.10 (-O-CO-$\underline{C}_6H_4Br$ (Br bearing)), 122.91(-CH=C-$\underline{C}_6H_4Br$ (Br bearing)), 112.99 (-N=C-$\underline{C}$H=C-), 14.36 (-S-C(CH_3)-C($\underline{C}H_3$)-N-), 11.37 (-S-C($\underline{C}H_3$)-C(CH_3)-N-).

3-Fluorobenzoicacid-2-(4,5-dimethylthiazol-2-yl)-1-(3-fluorophenyl)-vinyl ester (**153**)

Compound **153** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and 2-fluorobenzoyl chloride (0.903 g, 5.7 mmol) by the general procedure.

White crystals; mp. 102-103°C; yield: 337 mg (47%); R_f = 0.6 (silica gel, 5:1 hexane/ ethyl acetate).

IR (KBr, cm^{-1}): 2976, 1730, 1586, 1538, 1482, 1445, 1333, 1253, 1230.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.11 (m, -O-CO-$C_6\underline{H}_4F$ (aromatic *ortho*), 1H), 7.98 (m, -O-CO-$C_6\underline{H}_4F$ (aromatic *ortho*), 1H), 7.57 (m, -O-CO-$C_6\underline{H}_4F$ (aromatic *meta*)), 1H), 7.40 (m, (aromatic *ortho* and *meta* Hs of -C=C-$C_6\underline{H}_4F$ and aromatic *para* of -O-CO-$C_6\underline{H}_4CF$), 3H), 7.23 (m, -C=C-$C_6\underline{H}_4F$ (aromatic *para*, 1H), 7.05 (s, -N=C-C$\underline{H}$=C-, 1H), 2.30 (s, -S-C(C$\underline{H}_3$)-C(C$\underline{H}_3$)-N- , 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 164.59 (-O-$\underline{C}$O-C_6H_4F), 162.70 (-O-CO-$C_6\underline{H}_4F$ (aromatic *meta*, F bearing)), 161.32 (-CH=C-$\underline{C}_6H_4F$ (aromatic *meta*, F bearing)), 156.06 (-N=$\underline{C}$-CH=C-), 148.67 (-S-C(CH_3)-$\underline{C}$(CH_3)-N-), 147.17 (-CH=$\underline{C}$-C_6H_4F), 136.21(-CH=C-$\underline{C}_6H_4F$), 130.77 (O-CO-$\underline{C}_6H_4F$), 130.59 (O-CO-$\underline{C}_6H_4F$ (aromatic *meta*)), 128.42 (-CH=C-$\underline{C}_6H_4F$) (aromatic *meta*)), 126.27 (-S-$\underline{C}$(CH_3)-C(CH_3)-N-), 126.23 (-O-CO-$\underline{C}_6H_4F$

(aromatic *ortho*)), 121.43 (-CH=C-$\underline{C}_6H_4F$ (aromatic *ortho*)), 120..44 (-O-CO-$\underline{C}_6H_4F$ (aromatic *para*)), 117.45 (-O-CO-$\underline{C}_6H_4F$ (aromatic *ortho*)), 116.10 (CH=C-$\underline{C}_6H_4F$(aromatic *para*)), 112.97 (CH=C-$\underline{C}_6H_4F$ (aromatic *ortho*)), 111.88 (-N=C-$\underline{C}$H=C-), 14.35 (-S-C(CH_3)-C($\underline{C}H_3$)-N-), 11.29 (-S-C($\underline{C}H_3$)-C(CH_3)-N-).

4-Nitrobenzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-(4-nitrophenyl)-vinyl ester (**154**)

Compound **154** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and 2-nitrobenzoyl chloride (1.05 g, 5.7 mmol) by the general procedure.

Yellow solid; mp. 218-220°C; yield: 376 mg (46%); R_f = 0.7 (silica gel, 1:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3114, 2980, 1741, 1686, 1597, 1526, 1428, 1374, 1311, 1228, 1079.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.49 (m, -O-CO-$C_6\underline{H}_4NO_2$ (aromatic Hs), 4H), 8.28 (m, -C=C-$C_6\underline{H}_4NO_2$ (aromatic *meta*), 2H), 7.73 (m, -C=C-$C_6\underline{H}_4NO_2$ (aromatic *ortho*), 2H), 7.44 (s, -N=C-C$\underline{H}$=C-, 1H), 2.32 (s,-S-C(CH_3)-C(C$\underline{H}_3$)-N-, 3H), 1.60 (s, -S-C(C$\underline{H}_3$)-C(CH_3)-N-, 3H).

^{13}C NMR (75 MHz,$CDCl_3$): δ_C = 163.19 (-O-$\underline{C}$O-$C_6H_4NO_2$), 150.00 (-O-CO-$\underline{C}_6H_4NO_2$ (aromatic *para*)), 149.81 (-N=$\underline{C}$-CH=C-), 138.92 (-CH=$\underline{C}$-$C_6H_4NO_2$), 131.67 (-CH=C-$\underline{C}_6H_4NO_2$ (aromatic *para*)), 131.26 (-CH=C-$\underline{C}_6H_4NO_2$), 130.63 (-S-$\underline{C}$(CH_3)-C(CH_3)-N-), 125.41 (O-CO-$\underline{C}_6H_4NO_2$), 124.27 (O-CO-$\underline{C}_6H_4NO_2$ (aromatic *ortho*), 2C), 124.04 (-CH=C-$\underline{C}_6H_4NO_2$ (aromatic *ortho*), 2C), 123.75 (-S-C(CH_3)-$\underline{C}$(CH_3)-N-), 123.20 (O-CO-$\underline{C}_6H_4NO_2$ (aromatic *meta*)), 121.99 (-CH=C-$\underline{C}_6H_4NO_2$ (aromatic *meta*)), 104.55 (-N=C-$\underline{C}$H=C-), 11.82 (-O-C($\underline{C}H_3$)-C(CH_3)-N-), 10.78(-S-C(CH_3)-C($\underline{C}H_3$)-N-).

Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-1-phenyl-propenyl ester (**157**)

Compound **157** was prepared using 2-ethyl-4,5-dimethylthiazole (**155)** (0.25 g, 1.7 mmol) and benzoyl chloride (0.73 g, 5.2 mmol) by the general procedure.

White crystals; mp. 129-131°C; yield: 312 mg (52%), Rf= 0.65 (silica gel, 5:1 hexane/ ethyl acetate).

IR (neat, cm^{-1}): 3071, 2920, 1979, 1734, 1682, 1583, 1451, 1323, 1246.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.21 (m, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.63 (m, -O-CO-$C_6\underline{H}_5$ (aromatic *para*), 1H), 7.54 (m, aromatic Hs of two aryl groups, 4H), 7.37 (m, aromatic Hs of two aryl groups, 3H), 2.38 (d, *J* = 5.8 Hz, -S-C(CH_3)-C($C\underline{H}_3$)-N-, 3H), 2.30 (d, *J* = 5.5 Hz, -S-C($C\underline{H}_3$)-C(CH_3)-N-, 3H), 2.26 (d, *J* = 5.5 Hz, -N=C-C($C\underline{H}_3$)=C-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 164.34 (-O-$\underline{C}$O-C_6H_5), 159.03 (-N=$\underline{C}$-CH=C-), 147.53 (-S-C (CH_3)-$\underline{C}$(CH_3)-N-), 145.64 (-CH=$\underline{C}$-C_6H_5), 135.52 (-CH=C-$\underline{C}_6H_5$), 133.62 (-O-CO-$\underline{C}_6H_5$ (aromatic *para*)), 130.43 (-O-CO-$\underline{C}_6H_5$), 129.60 (-O-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C)), 128.97(-O-CO-$\underline{C}_6H_5$ (*meta* positions, 2C)), 128.66 (-CH=C-$\underline{C}_6H_5$ (aromatic *meta*) 2C), 128.56 (-S-$\underline{C}$(CH_3)-C(CH_3)-N-), 128.16 (-CH=C-$\underline{C}_6H_5$ (aromatic *para*)), 127.35 (-CH=C-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 120.39 (-N=C-$\underline{C}$(CH_3)=C-), 14.5(-N=C-C($\underline{C}H_3$)=C-), 14.68 (-S-C(CH_3)-C($\underline{C}H_3$)-N-), 11.16(-S-C($\underline{C}H_3$)-C(CH_3)-N-).

2-Chlorobenzoic acid- 1-(2-chlorophenyl)-2-(4,5-dimethylthiazol-2-yl)-propenyl ester (**158**)

Compound **158** was prepared using 2-ethyl-4,5-dimethylthiazole (**155)** (0.25 g, 1.7 mmol) and 2-chlorobenzoyl chloride (0.99 g, 5.2 mmol) by the general procedure. White crystals; mp. 139-140°C; yield: 331 mg (46%), R_f = 0.60 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2922, 1750, 1653, 1590, 1544, 1470, 1377, 1271.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.19 (d, *J* = 7.5 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 1H), 7.67 (m, -O-CO-$C_6\underline{H}_5$ (aromatic *para*), 1H), 7.40 (m, aromatic Hs of two aryl groups, 7H), 2.31 (s, -S-C(CH_3)-C($C\underline{H}_3$)-N-, 3H), 2.29 (s, -S-C($C\underline{H}_3$)-C(CH_3)-N-, 3H), 2.16 (s, N=C-C($C\underline{H}_3$)=C-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 152.28 (-O-$\underline{C}$O-C_6H_5), 147.81 (-N=$\underline{C}$-CH=C-), 142.60 (-S-C (CH_3)-$\underline{C}$(CH_3)-N-), 142.58 (-CH=$\underline{C}$-C_6H_5), 134.97 (O-CO-$\underline{C}_6H_4$Cl (aromatic *ortho*, Cl bearing)), 134.05 (-CH=C-$\underline{C}_6H_4$Cl (C1)), 133.68, (-O-CO-$\underline{C}_6H_4$Cl (aromatic *para*)), 133.41 (-CH=C-$\underline{C}_6H_4$Cl (aromatic *ortho*, Cl-bearing)), 132.92 (-O-CO-$\underline{C}_6H_4$Cl (aromatic *ortho*)), 132.82 (-O-CO-$\underline{C}_6H_5$), 131.45(-CH=C-$\underline{C}_6H_4$Cl (aromatic *para*)), 130.27 (-O-CO-$\underline{C}_6H_5$ (*meta* position, next to Cl)), 129.72 (-CH=C-$\underline{C}_6H_5$ (*meta* position, next to Cl)), 127.82 (-S-$\underline{C}$ (CH_3)-C (CH_3)-N-), 126.71 (-CH=C-$\underline{C}_6H_5$ (aromatic *ortho*)), 126.68 (-O-CO-$\underline{C}_6H_4$Cl (aromatic *meta*)), 126.53 (-CH=C-$\underline{C}_6H_5$ (aromatic *meta*)), 122.73 (-N=C-$\underline{C}$(CH_3)=C-), 16.81(-N=C-C($\underline{C}H_3$)=C-), 14.68 (-S-C(CH_3) -C($\underline{C}H_3$)-N-), 11.20 (-S-C($\underline{C}H_3$)-C(CH_3)-N-).

Benzoic acid 1-phenyl-2-thiazol-2-yl-vinyl ester (**159**)

Compound **159** was prepared using 2-methylthiazole (**156)** (0.25 g, 2.4 mmol) and benzoyl chloride (1.01 g, 7.2 mmol) by the general procedure.

Yellow-white crystals; mp. 82-83°C; yield: 579 mg (76%), R_f = 0.65 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3062, 1735, 1642, 1598, 1474, 1448, 1226.

^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.32 (d, *J* = 7.3 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.78 (s, -S-CH-C<u>H</u>-N-), 7.61 (aromatic Hs and thiazole H, 5H), 7.31 (aromatic Hs), 7.16 (s, -N=C-C<u>H</u>=C-, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 163.35 (-O-<u>C</u>O-C_6H_5), 160.95 (-N=<u>C</u>-CH=C-), 149.76 (-CH=<u>C</u>-C_6H_5), 142.47(-S-CH-<u>C</u>H-N-), 133.87(-CH=C-<u>C</u>$_6H_5$), 133.42 (-O-CO-<u>C</u>$_6H_5$ (aromatic *para*)), 130.13 (-O-CO-<u>C</u>$_6H_5$), 129.31(O-CO-<u>C</u>$_6H_5$ (aromatic *ortho*, 2C)), 128.56 (aromatic *meta* H s of both rings, 4C), 128.42 (-CH=C-<u>C</u>$_6H_5$ (aromatic *para*)), 124.56 (-CH=C-<u>C</u>$_6H_5$ (aromatic *ortho*, 2C), 119.46 (-S-<u>C</u>H-CH-N-), 111.72 (-N=C-<u>C</u>H=C-).

2-Methyl-benzoicacid-2-thiazol-2-yl-1-*o*-tolyl-vinyl ester (**160**)

Compound **160** was prepared using 2-methylthiazole (**156)** (0.25 g, 2.4 mmol) and 2-methylbenzoyl chloride (1.11 g, 7.2 mmol) by the general procedure.

Yellowish liquid; yield: 518 mg (62%), R_f = 0.60 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2927, 1738, 1653, 1574, 1488, 1381, 1218, 1033.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.39 (d, *J* = 7.7 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic ortho), 1H), 7.81(d, *J* = 3.2 Hz, -S-CH-C<u>H</u>-N-, 1H), 7.23 (m, aromatic H s and thiazole ring Hs, 8H), 6.91(s, -N=C-C<u>H</u>=C-, 1H), 2.65(s, $C\underline{H}_3$-C_6H_4-, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 163.23 (-O-<u>C</u>O-$C_6H_4CH_3$), 151.12 (-N=<u>C</u>-CH=C-), 142.33(-CH=<u>C</u>-$C_6H_4CH_3$), 142.21 (-S-CH-<u>C</u>H-N-), 135.97 (-O-CO-<u>C</u>$_6H_4CH_3$ (aromatic *ortho*, Me bearing)), 134.75(-CH=C-<u>C</u>$_6H_4CH_3$), 133.12(-CH=C-<u>C</u>$_6H_4CH_3$ (aromatic *ortho*, Me bearing)), 132.11 (-O-CO-<u>C</u>$_6H_4CH_3$ (aromatic *para*), 131.50 (-O-CO-<u>C</u>$_6H_4CH_3$), 130.83 (-O-CO-<u>C</u>$_6H_4CH_3$ (aromatic *ortho*), 129.16 (aromatic *meta* H s of both rings, 2C), 128.53 (-CH=C-<u>C</u>$_6H_4CH_3$ (aromatic *para*)), 127.27 (-CH=C-<u>C</u>$_6H_4CH_3$ (aromatic *ortho*)), 125.95 (-O-CO-<u>C</u>$_6H_4CH_3$ (aromatic *meta*), 125.90 (-CH=C-<u>C</u>$_6H_4CH_3$ (aromatic *meta*)), 119.51 (-S-<u>C</u>H-CH-N-), 115.44(-N=C-<u>C</u>H=C-), 22.00 (CH=C-$C_6H_4\underline{C}H_3$), 20.78 (-O-CO-$C_6H_4\underline{C}H_3$).

<u>2,2-Dimethyl-propionic acid-2,2-dimethyl-1-thiazol-2-yl-methylene-propyl ester (**165**)</u>

Compound **165** was prepared using 2-methylthiazole (**156)** (0.25 g, 2.4 mmol) and trimethyl acetyl chloride (0.86 g, 7.2 mmol) by the general procedure.

Yellowish liquid; yield: 389 mg (59%), R_f = 0.75 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2970, 1751, 1648, 1479, 1394, 1264, 1091.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.71 (s, -S-CH-C<u>H</u>-N-, 1H), 7.22 (s, -S-C<u>H</u>-CH-N-, 1H), 6.59 (s, -N=C-C<u>H</u>=C-, 1H), 1.39 (s, -O-CO-C ($C\underline{H}_3$)$_3$, 9H), 1.19 (s, -CH=C-C ($C\underline{H}_3$)$_3$, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 174.83 (-O-<u>C</u>O-C (CH_3)$_3$, 161.50 (-CH=<u>C</u>-C-(CH_3)$_3$),

159.35 (-N=C-CH=C-), 142.15 (-S-CH-CH-N-), 118.05 (-S-CH-CH-N-), 108.39 (-N=C-CH=C-), 39.24 (-O-CO-C-$(CH_3)_3$), 37.29 (-CH=C-C-$(CH_3)_3$), 27.73 (-O-CO-C-$(CH_3)_3$), , 27.27(-CH=C-C-$(CH_3)_3$).

Synthesis using 2,4,5-Trimethylthiazole, 2,4,5-Trimethyloxazole and 2-Methylthiazole where normal Butyl Lithium was used as the Base

Benzoic acid-2-(4,5-dimethylthiazol-2-yl)-3-oxo-1,3-diphenylpropenyl ester (**166**)

n-BuLi (1.1 mL, 2.7 mmol) of a 2.5 M solution in hexane was added using a syringe to a solution of 2,4,5-trimethylthiazole (**138**) (0.25 g, 1.9 mmol) in 20 mL THF at -78°C under nitrogen. The reaction mixture turned yellow. The mixture was stirred at -78°C for 1 h and then benzoyl chloride (0.817 g, 5.7 mmol) was added with a syringe. The reaction mixture was stirred for another 1 h at -78°C and then warmed gradually to room temperature. The reaction mixture was further stirred for another 3 h at room temperature and then the solvent was removed by rotary evaporation. Water was added to the residue followed by the extraction with dichloromethane (3 x 40 mL). The organic layer was washed with 10% aqueous sodium bicarbonate (2 x 20 mL) and water (2 x 20 mL), and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (silica gel, 5:1 hexane/ethyl acetate) to give **166**. In TLC analysis, the spots for 2,4,5-trimethylthiazole and that of the product appear very close to each other when eluting with 3:1 hexane/ ethyl acetate or 5:1 hexane/ ethyl acetate. Pure fractions were obtained by column

chromatography over SiO_2, eluting with 5:1 hexane/ ethyl acetate. It should be noted that if the yield of this fraction are combined with the yield of a mostly pure (with very small amount of other spot and starting material), that can increase the total percent yield.

Yellowish liquid; yield: 232 mg (28%), R_f = 0.45 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2922, 1739, 1678, 1596, 1492, 1322, 1220.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.27 (d, *J* = 7.5 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 8.07 (d, *J* = 7.4 Hz, -N=C-C-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.67 (m, -O-CO-$C_6\underline{H}_5$ (aromatic *para*), 1H), 7.55 (m, -O-CO-$C_6\underline{H}_5$ (aromatic *meta*), 2H), 7.43 (m, -N=C-C-CO-$C_6\underline{H}_5$ (aromatic *meta* and *para* H s , 3H), 7.35 (m, -CH=C-$C_6\underline{H}_5$ (aromatic *ortho*, 2H), 7.16 (-CH=C-$C_6\underline{H}_5$ (aromatic *ortho* and *para* H s, 3H) , 2.22 (s,-N-C($C\underline{H}_3$)-C(CH_3)-S-,3H), 2.07 (s, -N-C(CH_3)-C($C\underline{H}_3$)-S-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 193.85 (-N=C-C-$\underline{C}O$-C_6H_5), 164.39 (-O-$\underline{C}O$-C_6H_5), 155.21 (-CH=$\underline{C}$-C_6H_5), 148.96 (-N=$\underline{C}$-CH=C-), 147.75 (-S-C(CH_3)-$\underline{C}$(CH_3)-N-), 136.95 (-N=C-C-CO-$\underline{C}_6H_5$), 133.99 (-CH=C-$\underline{C}_6H_5$), 133.94 (-N=C-C-CO-$\underline{C}_6H_5$ (aromatic *para*)), 133.31 (-O-$\underline{C}O$-C_6H_5 (aromatic *para*)), 130.51 (-O-CO-$\underline{C}_6H_5$), 129.83 (-O-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 129.63 (-N=C-C-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 129.14 (-N=C-C-CO-$\underline{C}_6H_5$ (aromatic *meta*), 2C), 128.70 (-CH=C-$\underline{C}_6H_5$ (aromatic *meta*), 2C), 128.44(-S-$\underline{C}$(CH_3)-C(CH_3)-N-), 128.36 (-O-$\underline{C}O$-C_6H_5 (aromatic *meta*), 2C), 127.98 (-CH=C-$\underline{C}_6H_5$(aromatic *para*)), 127.71 (-CH=C-$\underline{C}_6H_5$(aromatic *ortho*), 2C), 125.71 (-N=C-$\underline{C}$H=C-), 14.42 (S-C(CH_3)-C($\underline{C}H_3$)-N-), 11.02 (-S-C($\underline{C}H_3$)-C(CH_3)-N-).

4-Chlorobenzoic acid-1,3-bis-(4-chlorophenyl)-2-(4,5-dimethylthiazol-2-yl)-3-oxo-propenyl ester (**167**)

Compound **167** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and 4-chlorobenzoyl chloride (0.997 g, 5.7 mmol) by the general procedure.

Yellow crystals; mp. 217-219°C; yield: 322 mg (32%).

R_f = 0.35 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2922, 1733, 1679, 1594, 1487, 1401, 1256.

^1H NMR (300 MHz, $CDCl_3$): δ_H = 8.20 (d, *J* = 8.58 Hz, -O-CO-$C_6\underline{H}_4Cl$ (aromatic *ortho*), 2H), 8.99 (d, *J* = 8.56 Hz, -N=C-C-CO-$C_6\underline{H}_4Cl$ (aromatic *ortho*), 2H), 7.54 (d, *J* = 8.58 Hz, -O-CO-$C_6\underline{H}_4Cl$ (aromatic *meta*), 2H), 7.35 (m, -N=C-C-CO-$C_6\underline{H}_4Cl$ (aromatic *meta*) and -CH=C-$\underline{C}_6H_4Cl$ (aromatic *meta*), 4H), 7.17 (d, *J* = 8.58 Hz, -CH=C-$\underline{C}_6H_4Cl$ (aromatic *ortho*), 2H), 2.26 (s,-N-C($C\underline{H}_3$)-C(CH_3)-S-,3H), 2.08 (s, -N-C(CH_3)-C($C\underline{H}_3$)-S-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.39 (-N=C-C-$\underline{C}$O-C_6H_4Cl), 163.61 (-O-$\underline{C}$O-C_6H_4Cl), 154.52 (-CH=$\underline{C}$-C_6H_4Cl), 149.36 (-N=$\underline{C}$-CH=C-), 146.29 (-S-C(CH_3)-$\underline{C}$(CH_3)-N-), 140.82 (-N=C-C-CO-$\underline{C}_6H_4Cl$ (aromatic *para*, Cl bearing)), 140.14 (-O-$\underline{C}$O-C_6H_4Cl (aromatic *para*, Cl bearing)), 136.01 (-N=C-C-CO-$\underline{C}_6H_4Cl$), 135.09 (-CH=C-$\underline{C}_6H_4Cl$ (aromatic *para*, Cl bearing)), 132.20 (-CH=C-$\underline{C}_6H_4Cl$), 131.89 (-O-CO-$\underline{C}_6H_4Cl$ (aromatic *ortho*), 2C), 131.18 (-N=C-C-CO-$\underline{C}_6H_4Cl$ (aromatic *ortho*), 2C), 129.31 (-N=C-C-CO-$\underline{C}_6H_4Cl$ (aromatic *meta*), 2C), 129.22 (-O-$\underline{C}$O-C_6H_4Cl (aromatic *meta*), 129.05 (-CH=C-$\underline{C}_6H_4Cl$ (aromatic *meta*), 2C), 128.90 (-O-CO-$\underline{C}_6H_4Cl$), 128.59 (-S-$\underline{C}$(CH_3)-C(CH_3)-N-),

127.32 (-CH=C-$\underline{C}_6H_4Cl$ (aromatic *ortho*), 2C), 125.39 (-N=C-$\underline{C}$H=C-), 14.46 (S-C(CH_3)-C($\underline{C}H_3$)-N-), 11.12 (-S-C($\underline{C}H_3$)-C(CH_3)-N-).

Benzoic acid-2-(4,5-dimethyloxazol-2-yl)-3-oxo-1,3-diphenylpropenyl ester (**168**)

Compound **168** was prepared using 2,4,5-trimethyloxazole (**136**) (0.25 g, 2.1 mmol) and benzoyl chloride (0.90 g, 6.3 mmol) by the general procedure.

Yellow liquid; yield: 211 mg (24 %), R_f = 0.40 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 2981, 1737, 1675, 1580, 1449, 1357, 1221.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.24 (d, *J* = 8.26 Hz, -O-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 8.12 (d, *J* = 8.21 Hz, -N=C-C-CO-$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.50 (m, aromatic H's, 8H), 7.15 (m, aromatic Hs, 3H), 1.87 (s,-N-C(C$\underline{H}_3$)-C(CH_3)-S-,3H), 1.83 (s, -N-C(CH_3)-C(C$\underline{H}_3$)-S-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 192.35 (-N=C-C-$\underline{C}$O-C_6H_5), 165.21 (-O-$\underline{C}$O-C_6H_5), 154.36 (-CH=$\underline{C}$-C_6H_5), 149.64 (-N=$\underline{C}$-CH=C-), 143.64 (-O-$\underline{C}$(CH_3)-C(CH_3)-N-), 136.30 (-N=C-C-CO-$\underline{C}_6H_5$), 133.70 (-CH=C-$\underline{C}_6H_5$), 133.58 (-N=C-C-CO-$\underline{C}_6H_5$ (aromatic *para*)), 133.53 (-O-CO-$\underline{C}_6H_5$ (aromatic *para*)), 132.31 (-O-CO-$\underline{C}_6H_5$), 130.15 (-O-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 129.93 (-N=C-C-CO-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 129.85 (-N=C-C-CO-$\underline{C}_6H_5$ (aromatic *meta*), 2C), 129.27 (-CH=C-$\underline{C}_6H_5$ (aromatic *meta*) and -O-$\underline{C}$O-C_6H_5 (aromatic *meta*), 4C), 128.41 (-CH=C-$\underline{C}_6H_5$(aromatic *para*)), 128.25 (-CH=C-$\underline{C}_6H_5$ (aromatic *ortho*), 2C), 128.06 (-O-C(CH_3)-$\underline{C}$(CH_3)-N-), 118.78 (-N=C-$\underline{C}$H=C-), 10.88 (-O-C($\underline{C}H_3$)-C(CH_3)-N-), 9.46 (-O-C(CH_3)-C($\underline{C}H_3$)-N-).

1,1-Bis(4,5-dimethylthiazol-2-yl)-2,2-dimethylpropan-1-ol (**169**)

Compound **169** was prepared using 2,4,5-trimethylthiazole (**138)** (0.25 g, 1.9 mmol) and trimethylacetyl chloride (0.68 g, 5.7 mmol) by the general procedure.

Yellowish white crystals; mp. 46-47°C; yield: 141 mg (44%), R_f = 0.60 (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3316, 2959, 2921, 1558, 1469, 1307, 1259, 1179, 908.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 6.43 (s, -O<u>H</u>, 1H), 3.15 (s, -C<u>H</u>$_2$-, 4H), 2.23 (s, -N-C(C<u>H</u>$_3$)-C(CH_3)-S-, 6H), 2.16 (s, -S-C(C<u>H</u>$_3$)-C(CH_3)-N-, 6H), 0.99 (s, -C-C<u>H</u>$_3$, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 163.72 (-N=<u>C</u>-CH_2-, 2C), 146.47 (-S-C(CH_3)-<u>C</u>(CH_3)-N-, 2C), 125.32 (-S-<u>C</u>(CH_3)-C(CH_3)-N-, 2C), 39.21 (-<u>C</u>-OH), 37.71 (-<u>C</u>-CH_3), 25.79 (-C-<u>C</u>H$_2$-, 2C), 14.27 (-C-CH_3, 3C), 10.93 (=C-<u>C</u>H$_3$, 4C).

2,2-Dimethyl-1-(2-methylthiazol-5-yl)propan-1-one (**170**)

Compound **170** was prepared using 2-methylthiazole (**138)** (0.25 g, 2.4 mmol) and trimethyl acetyl chloride (0.86 g, 7.2 mmol) by the general procedure. In this reaction compound **165** was obtained as the minor product.

Yellowish liquid; yield: 102 mg (22%), R_f = 0.50 (silica gel, 5:1 hexane/ ethyl acetate).

IR (neat, cm^{-1}): 2917, 1660, 1513, 1500,1396, 1278, 1101.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.25 (s, -S-C<u>H</u>-CH-N-, 1H), 2.73 (-N=C-C<u>H</u>$_3$), 1.37 (s, -O-CO-C (C<u>H</u>$_3$)$_3$, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 174.83 (-O-<u>C</u>O-C (CH_3)$_3$, 161.50 (-CH=<u>C</u>-C-(CH_3)$_3$), 159.35 (-N=<u>C</u>-CH=C-), 142.15 (-S-CH-<u>C</u>H-N-), 118.05 (-S-<u>C</u>H-CH-N-), 108.39 (-N=C-

CH=C-), 39.24 (-O-CO-C-$(CH_3)_3$), 37.29 (-CH=C-C-$(CH_3)_3$), 27.73 (-O-CO-C-($CH_3)_3$), , 27.27(-CH=C-C-($CH_3)_3$).

CIF files deposited with CCDC numbers 765577 (for **160**), 765578 (for **166**) and 765826 (for **171**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Unsuccessful Reactions

Reaction of 2,4,5-Trimethyloxazole with Acetyl Chloride

2,4,5-Trimethyloxazole **(136)** (0.25 g, 2.1 mmol) was dissolved in 15 mL of acetonitrile, and potassium carbonate (1.06 g, 7.6 mmol) was added. The mixture was stirred for 15 min using a magnetic stirrer. A solution of acetyl chloride (0.50 g, 6.3 mmol) in 10 mL acetonitrile was added dropwise into the above mixture under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was analyzed by TLC. No new spot observed. 2,4,5-Trimethyloxazole was found unreacted. No further purification was tried.

Reaction of 2,4,5-Trimethyloxazole with 2,2-Diethylpropenyl Chloride

2,4,5-Trimethyloxazole **(136)** (0.25 g, 2.1 mmol) was dissolved in 15 mL of acetonitrile. Then triethylamine (0.784 g, 7.6 mmol) was added into the above solution. A solution of 2,2-diethylpropenyl chloride (0.77 g, 6.3 mmol) in 10 mL acetonitrile was

added dropwise into the above mixture under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was analyzed by TLC. 2,4,5-Trimethyloxazole was found unreacted. No further purification was tried. Use of other reaction solvent (THF) and base DIPEA did not change the result.

CHAPTER IV

REACTIONS OF 2-METHYLBENZOXAZOLE WITH ACID CHLORIDES: FORMATIONS OF ORTHO-AMIDOESTERS

Introduction and Objective

The benzoxazole ring scaffold can be found in a number of bioactive natural products and medicinally important compounds such as Calcimycin (**171**), Boxazomycin A (**172**), pseudopteroxaxole, etc.[108]

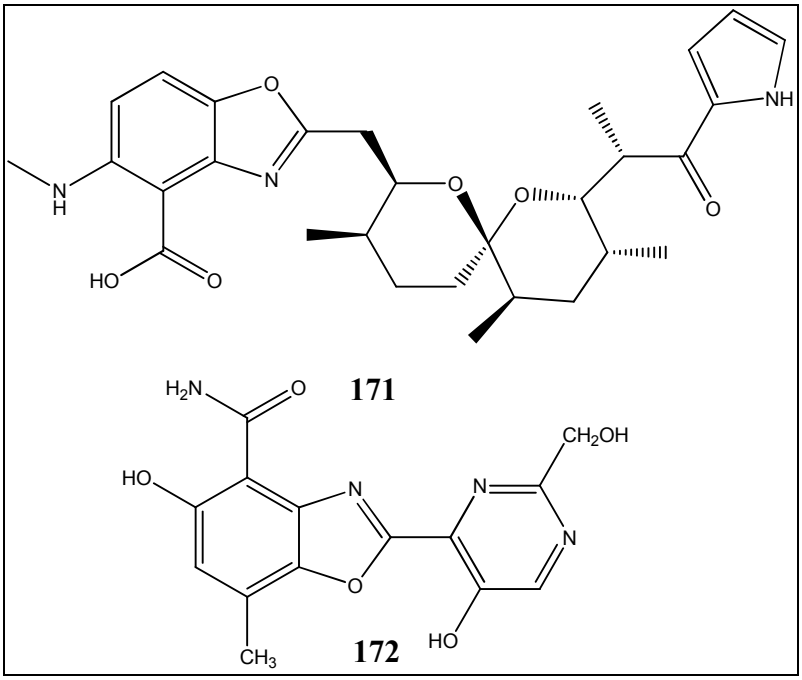
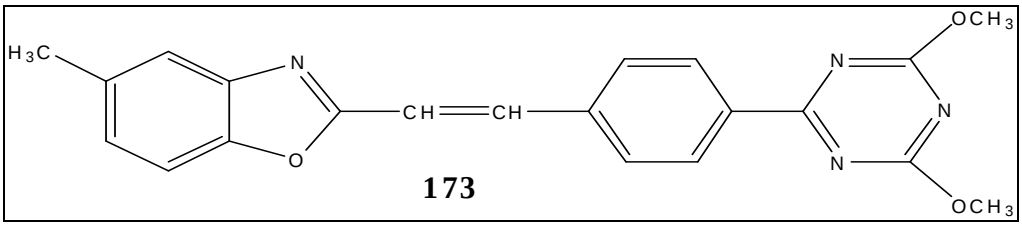


Figure 4.1 Structures of Calcimycin (**171**) and Boxazomycin (**172**)[108]

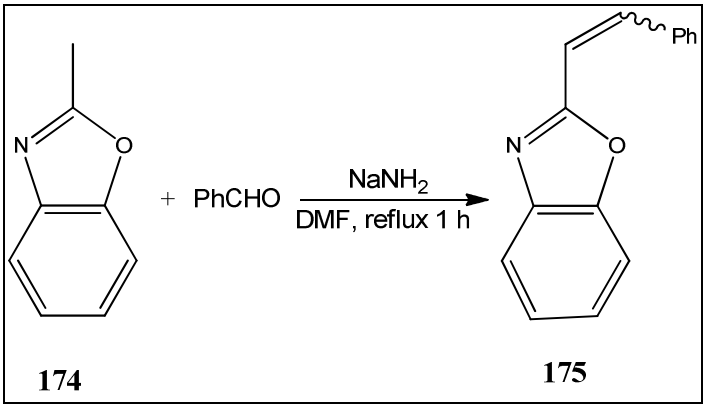
Benzoxazole is a common reagent used in dye and fluorophor synthesis because of its highly conjugated structure. There are several fluorescent dyes such as **173**, which contain the benzoxazole scaffold. [109]



173

Figure 4.2 The Structure of a Benzoxazole-based Fluroscent Dye[109]

The high nucleophilicity of the exocyclic β-carbon of the 2-methylbenzoxazole anion facilitates its acylation with carboxylic acid esters.[110-111] In presence of sodium amide, the reaction of 2-methylbenzoxazole (**174**) with benzaldehyde resulted in the formation of condensation product **175** (Scheme 4.1).[111]

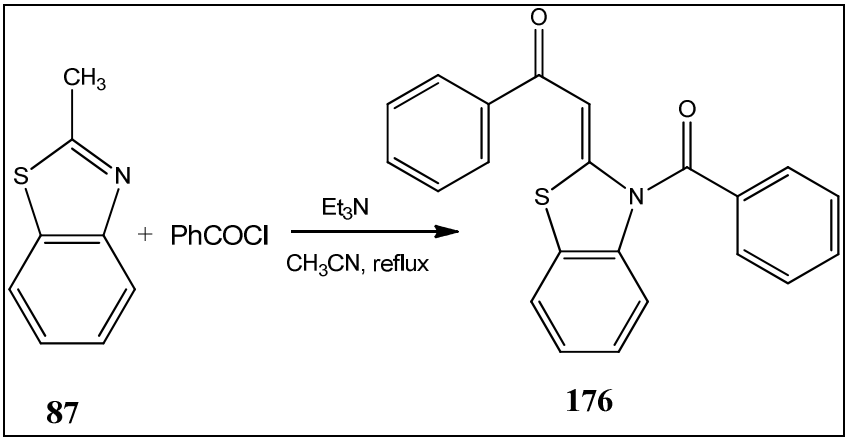


174 **175**

Scheme 4.1 Condensation Reaction of 2-Methylbenzoxazole (**174**) and Benzaldehyde[111]

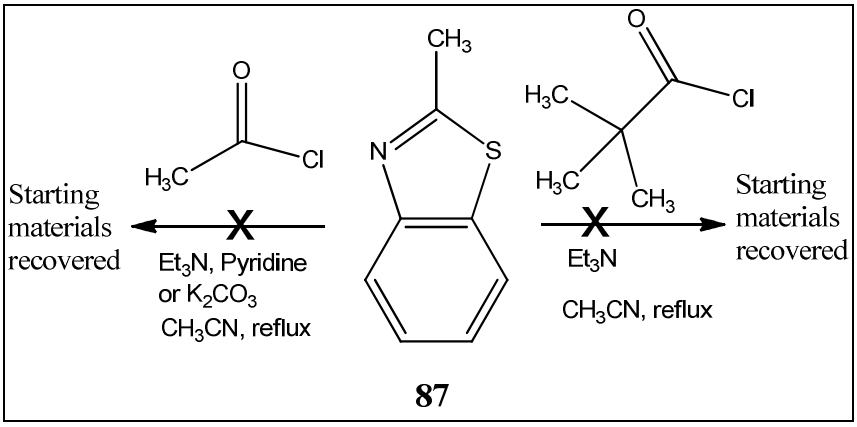
The structural similarities of 2-methylbenzoxazole with 2-methyloxazoline and 2,4,5-trimethyloxazole suggest that the reaction of 2-methylbenzoxazole with an acid chloride should go through an *in situ* generated *N*-acyl cyclic ketene-*N*,*O*-acetal intermediate. Ciurdaru et al. reported the reaction of 2-methylbenzoxazole with aromatic acid chlorides and triethylamine which gave benzoxazole based arylvinyl esters.[102] However, only very few examples were shown and no aliphatic acid chlorides were used. Also, no mechanistic pathway was proposed for these reactions.

Guo performed several aroylation reactions of 2-methylbenzothiazole with various acid chlorides (Scheme 4.2) in our laboratory.[112] Reactions with benzoyl chloride in refluxing acetonitrile in the presence of triethylamine resulted in the formation of (*Z*)-2-(3-benzoylbenzothiazol-2(3H)-ylidene)-1-phenylethanone (**176**). No reaction occurred when THF was used as the solvent. Guo was also unsuccessful with reactions of 2-methylbenzothiazole with aliphatic acid chlorides using the same conditions. Starting materials were recovered after the reaction (Scheme 4.3).

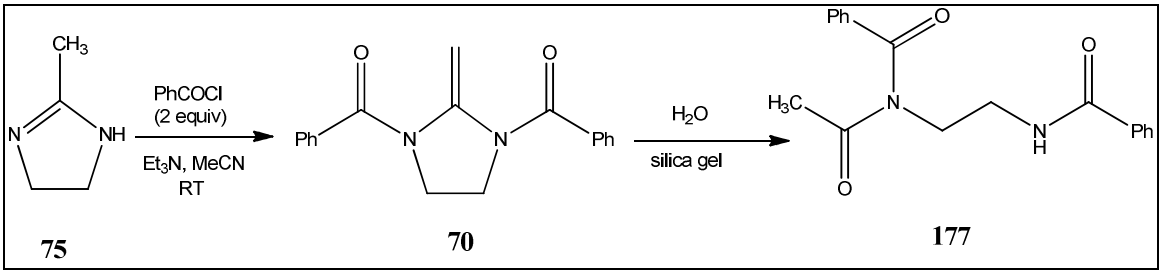


Scheme 4.2 Aroylation Reaction of 2-Methylbenzothiazole (**87**) using Benzoyl Chloride[112]

Ye et al.[51] recently reported the aroylation of 2-methylimidazoline at room temperature using triethylamine as the base. The dibenzoylated product, (2-methyleneimidazolidine-1,3-diyl)bis(phenylmethanone) (**70**) was obtained (Scheme 4.4). However, the isolation of **70** was not achieved because it underwent rapid ring opening during the column chromatography using silica gel and formed **177**.

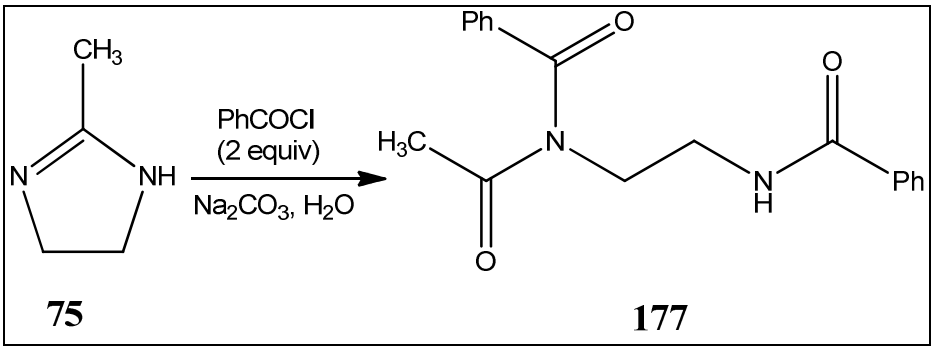


Scheme 4.3 Unsuccessful Reactions of 2-Methylbenzothiazole (**87**) with Aliphatic Acid Chlorides[112]



Scheme 4.4 Reaction of 2-Methylimidazoline (**75**) with Benzoyl Chloride at Room Temperature[51]

Aspinall et al. reported that the reaction of 2-methylimidazoline with benzoyl chloride in aqueous sodium carbonate solution formed a similar ring-opened product **177** (Scheme 4.5).[113]



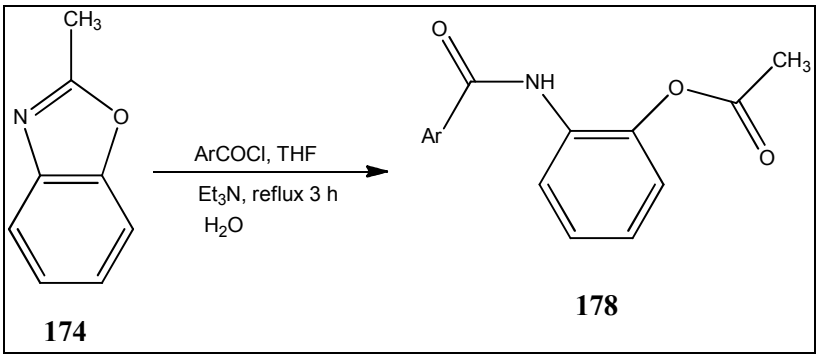
Scheme 4.5 Reaction of 2-Methylimidazoline (**75**) with Benzoyl Chloride in Aqueous Sodium Carbonate[113]

The use of benzoxazoles as a scaffold for synthesis through *in situ* generated cyclic ketene-*N*,*O*-acetal intermediates was the object of this investigation. 2-Methylbenzoxazole was treated with aromatic and aliphatic acid chlorides in refluxing THF where triethylamine or potassium carbonate was used as the base. Products and isolated yields of these reactions are shown in the Table 4.1.

Results and Discussions

All reactions resulted in the formation of ortho amido esters where the oxazole ring was opened (Scheme 4.6). Reactions of 2-methylbenzoxazole with aromatic acid chlorides formed monoacylated products **178-180**. The use of excess benzoyl chloride did not give a second benzoylation of the amide -N-H function to produce the corresponding

imide di-adduct. However, when acetyl chloride was used, the reaction generated the triacylated products **181**.



Scheme 4.6 Reaction of 2-Methylbenzoxazole (**174**) with Benzoyl Chloride in Refluxing THF

Table 4.1 Reactions of 2-Methylbenzoxazoles and 2-Methyl-5-phenylbenzoxazole with Acid Chlorides in Refluxing THF[a]

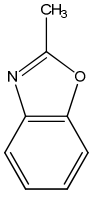
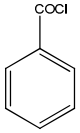
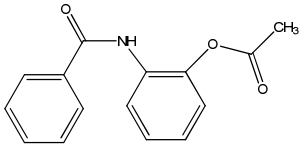
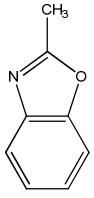
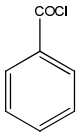
Entry	Substrate	Acid Chloride	Product Isolated	Yield (%)
1			 **178**	55
2[b]			**178**	58

Table 4.1(Continued)

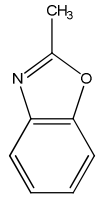
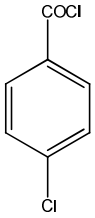
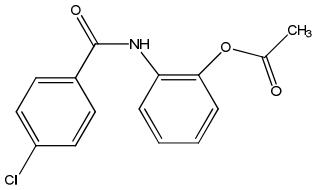
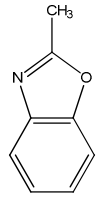
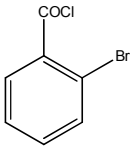
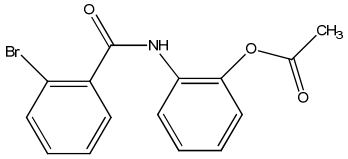
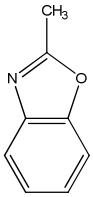
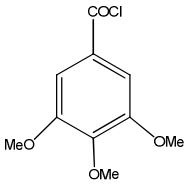
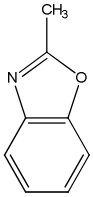
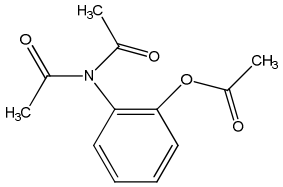
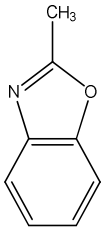
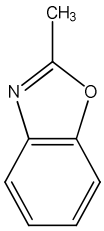
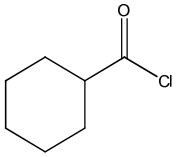
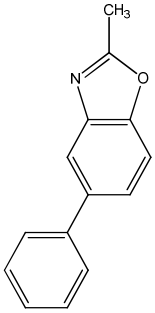
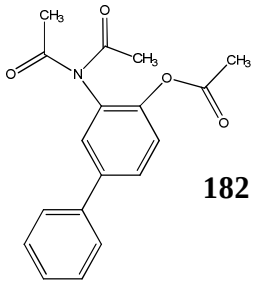
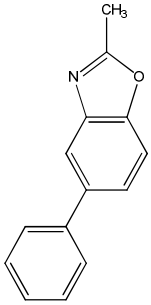
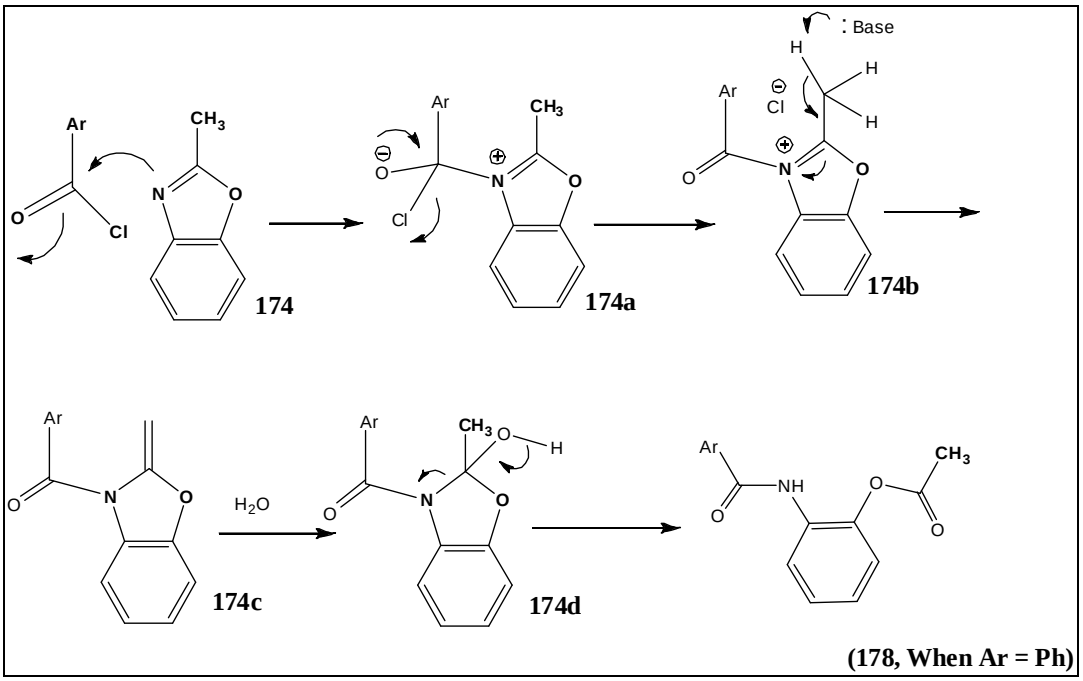
Entry	Substrate	Acid Chloride	Product Isolated	Yield (%)
3			 **179**	52
4			 **180**	54
5			-	none
6		CH_3COCl	 **181**	43

Table 4.1(Continued)

Entry	Substrate	Acid Chloride	Product Isolated	Yield (%)
7		CH_3CCOCl	-	none
8			-	none
9		CH_3COCl	 **182**	50
10		CH_3COCl	-	none

[a]2-Methylbenzoxazole, acid chloride and base were employed in a 1/2.4/6 mole ratio where 1.8 mmol of 2-methylbenzoxazole was used.
[b] 2-Methylbenzoxazole, acid chloride and base were employed in a 1/4/10 mole ratio, for entries, 6, 8 and 9, potassium carbonate was used as the base.

These reactions probably start with the attack of the nitrogen lone pair of the aromatic 2-methylbenzoxazole (**174**) on the carbonyl carbon of the acid chloride, generating a zwitterionic intermediate **174a** (Scheme 4.7). This intermediate looses the chloride and forms the corresponding salt **174b**, which upon deprotonation results in the formation of *N*-acyl cyclic ketene-*N*,*O*-acetal (**174c**).



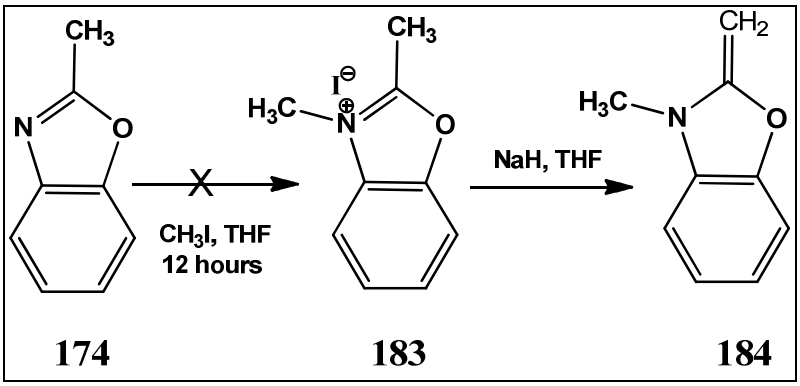
Scheme 4.7 Probable Mechanism for the Synthesis of Ortho Amido Esters

The heterocyclic ring of **174c** is no longer aromatic. However, the exocyclic methylene carbon does not make a nucleophilic attack on a second equivalent of aroyl chloride. The reason for this is unclear. This 2-methylbenzoxazole based *N*-acyl cyclic ketene-*N*,*O*-acetal (**174c**) undergoes ring opening hydrolysis to form the amido ester

178. Protonation of **174c** is extremely facile since the resulting oxazolium cation is very stable and also aromatic (6π-electrons). Rapid attack by water on this cation generates **174d**, which opens to the product **178**. The water might come from the solvent or bases used in these reactions.

The starting 2-methylbenzoxazole was recovered when 3,4,5-trimethoxy benzoyl chloride was used. The presence of three electron donating methoxy groups reduces the electrophilicity of its carbonyl carbon. Similarly, no new product was obtained and starting materials were recovered with trimethylacetyl chloride and cyclohexane carbonyl chloride were the acid chlorides used. The increased steric bulk of the *t*-butyl function in the former probably blocks this reaction. The cyclohexane may slow attack on cyclohexane carbonyl chloride. Moderate yields were obtained in all successful reactions.

In order to synthesize 2-methylbenzoxazole (**174**)-based *N*-methyl cyclic ketene-*N*,*O*-acetals, (**184**), a methylation reaction of 2-methylbenzoxazole was tried using a literature procedure for the methylation of 2-methyloxazoline (Scheme 4.8).[36] 2-Methylbenzoxazole was treated with methyl iodide at room temperature in THF. The reaction was stirred for 12 h but no benzoxazolium iodide salt **183** was formed. This demonstrates the lower reactivity of 2-methylbenzoxazole compared to its non-aromatic analogue, 2-methyloxazoline.



Scheme 4.8 Attempted Methylation of 2-Methylbenzoxazole (**174**) with Iodomethane

Conclusions

Reactions of 2-methylbenzoxazoles with excess acid chlorides in the presence of bases generated ortho amido esters. These results can be explained by postulating a water assisted ring opening of *in situ* generated 2-methylbenzoxazole based cyclic ketene acetal. The water might came from the solvent or the base used in any particular reaction. These results showed how a ketene acetal can be used to make a wide variety of compounds by slightly changing the reaction conditions.

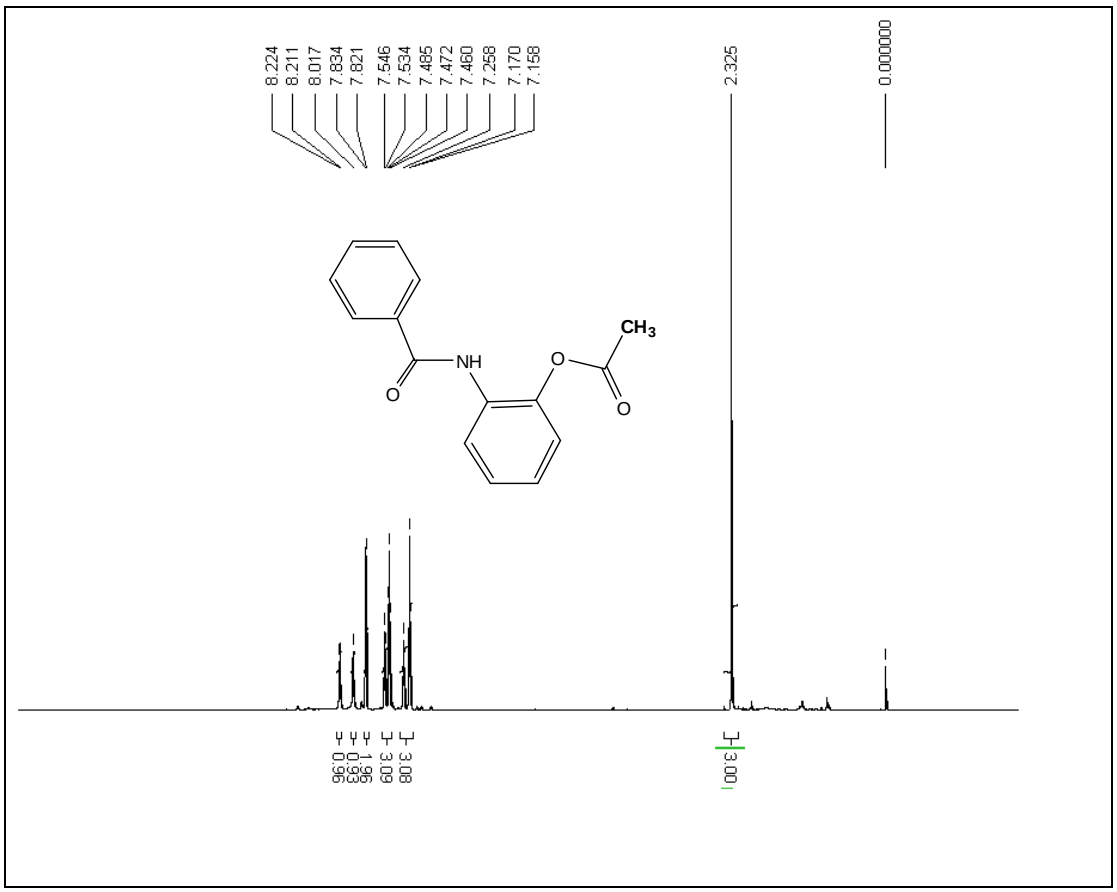


Figure 4.3 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Benzamidophenyl Acetate (**178**)

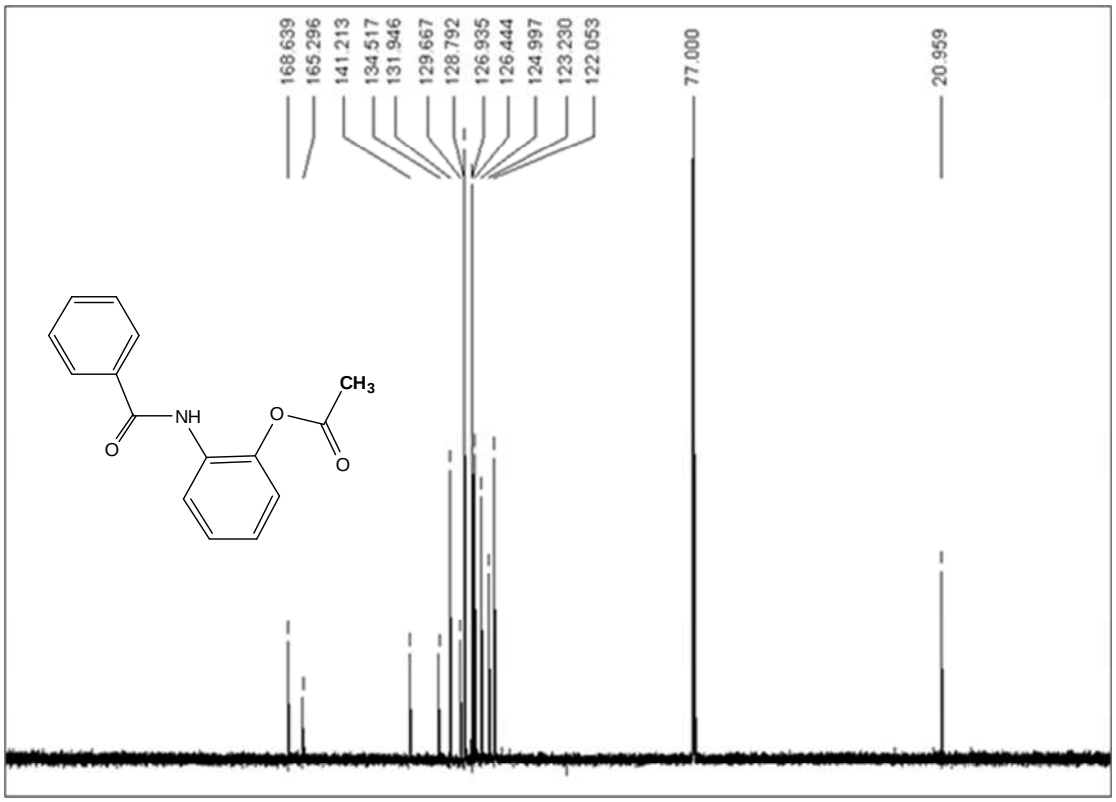


Figure 4.4 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Benzamidophenyl Acetate (**178**)

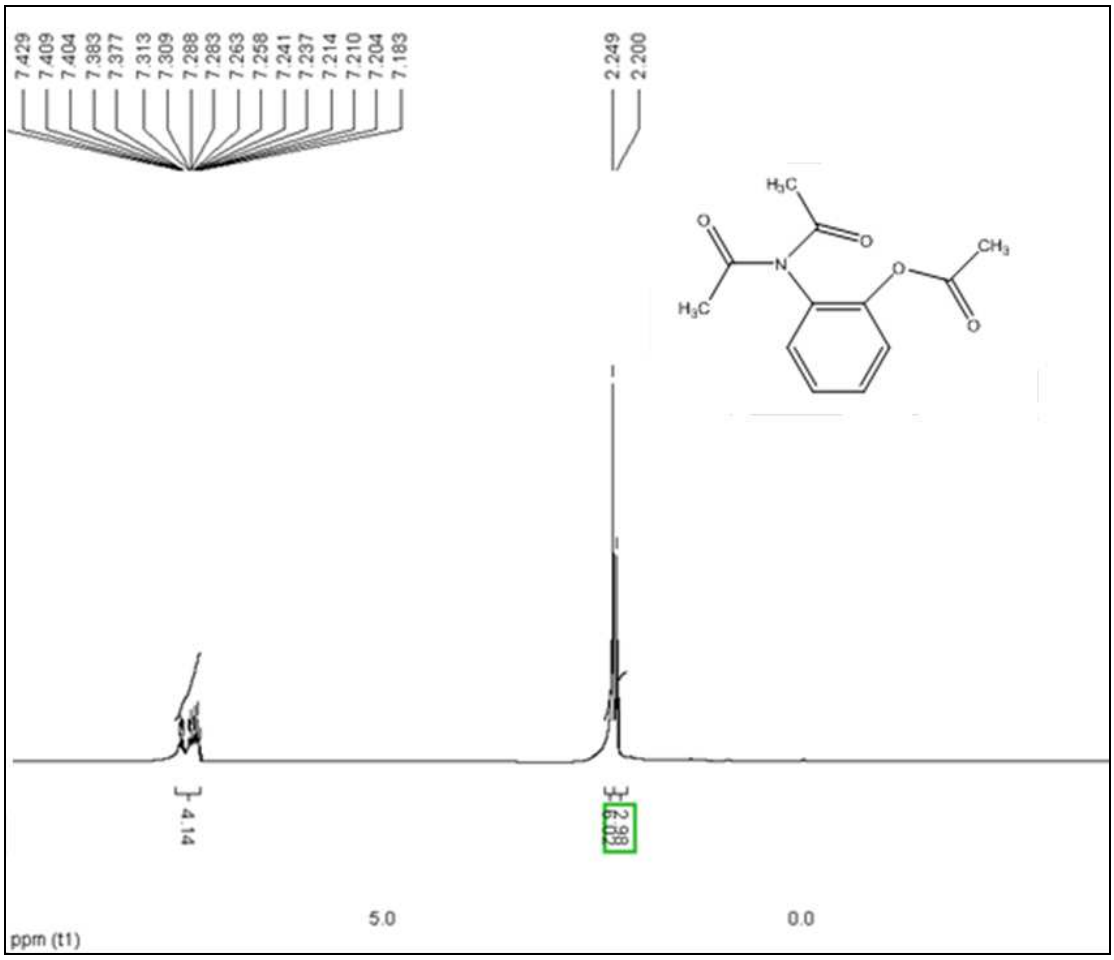


Figure 4.5 ^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-(*N*-Acetylacetamido)-phenyl Acetate (**181**)

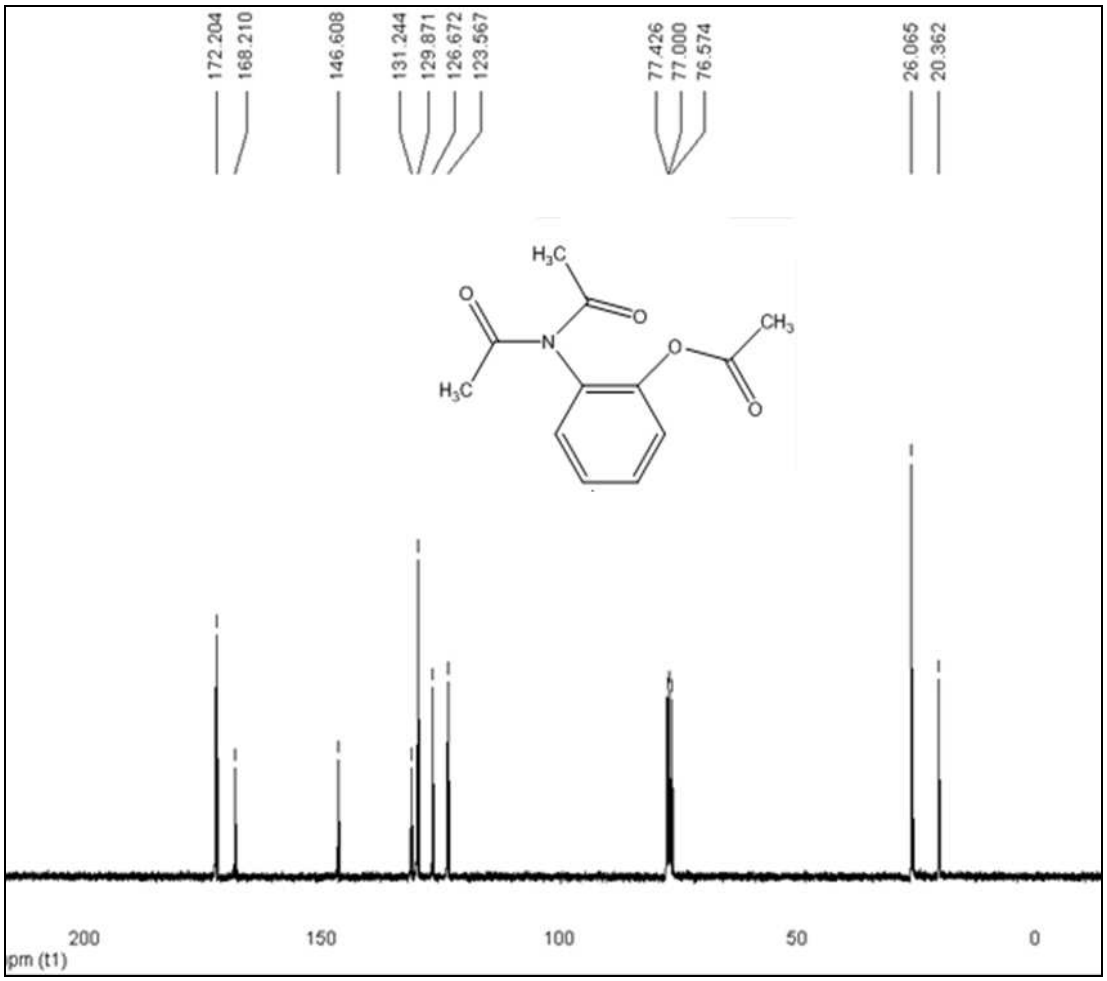


Figure 4.6 ^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-(*N*-Acetylacetamido)-phenyl Acetate (**181**)

Experimental

Materials and Instruments

The ^{1}H and ^{13}C NMR spectra were collected using a Bruker AVANCE III spectrometer in the Department of Chemistry, Mississippi State University operating at

300 MHz for proton and 75 MHz for carbon. Chemical shifts were reported in ppm downfield from TMS (Tetramethylsilane). $CDCl_3$ (Deuterated Chloroform) was used as the solvent for all NMR samples. Splitting patterns are designated as 's, d, t, q and m'; these symbolize 'singlet, doublet, triplet, quartet and multiplet'.

The FT-IR (Fourier Transformed Infrared) spectra were collected as films on KBr plates or on a diamond. Tetrahydrofuran and triethylamine were dried by distillation over calcium hydride under nitrogen. Dichloromethane was pre-dried with calcium chloride and then distilled from calcium hydride under nitrogen. All other chemicals (such as 2-methylbenzoxazole, 5-phenyl-2-methylbenzoxazole, methyl iodide, substituted and normal benzooyl chloride, acetyl chloride, trimethyl acetyl chloride, etc) were obtained commercially from Sigma Aldrich or Fisher Scientific and used as received. Melting points were obtained on a Mel-Temp instrument using a heating rate 5°C/ min and are uncorrected.

Synthesis

2-Benzamidophenyl Acetate (**178**)

2-Methylbenzoxazole (0.25 g, 1.8 mmol) was dissolved in 15 mL of THF. Then triethylamine (0.691 g, 6.7 mmol) was added and the mixture was stirred for 20 min. A solution of benzoyl chloride (0.796 g, 5.5 mmol) in 15 mL THF was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and then the solvent was removed by rotary evaporation.

Dichloromethane (20 mL) was added to dissolve the residue and this solution was then washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL). The dichloromethane solution was then dried over anhydrous sodium sulfate and subsequently concentrated. This residue was purified by column chromatography (silica gel, 5:1 hexane/ethyl acetate) to give **178.**

White solid, mp. 106-107°C, yield = 0.258 g (55%), R_f = 0.45, (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3229, 2980, 1751, 1654, 1637, 1542, 1524, 1508, 1497, 1183.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.21 (d, *J* = 7.7 Hz, -$C_6\underline{H}_4$- (next to the carbon bearing the acetyl group), 1H), 8.01(s, –N<u>H</u>-, 1H), 7.82 (d, *J* = 7.6 Hz, -$C_6\underline{H}_5$ (aromatic *ortho*), 2H), 7.54 (t, *J* = 7.4 Hz, -$C_6\underline{H}_4$-, 1H), 7.47 (t, *J* = 7.5 Hz, -$C_6\underline{H}_5$ (aromatic *meta*), 2H), 7.25 (m, -$C_6\underline{H}_4$-, 1H), 7.17 (m, -$C_6\underline{H}_4$- and -$C_6\underline{H}_5$ (aromatic *para*), 2H), 2.32 (s, -CO-$C\underline{H}_3$, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.63 (CH_3-<u>C</u>O-O-C_6H_4-), 165.29(C_6H_5-<u>C</u>O-NH-), 141.21 (CH_3-CO-O-<u>C</u>$_6H_4$-), 135.51(<u>C</u>$_6H_5$-CO-NH-), 121.94(<u>C</u>$_6H_5$-CO-NH-(aromatic *para*)), 129.66 (C_6H_5-CO-NH-<u>C</u>$_6H_4$-), 128.79(<u>C</u>$_6H_5$-CO-NH-C_6H_4- (aromatic *meta*), 2C), 126.93(<u>C</u>$_6H_5$-CO-NH-C_6H_4- (aromatic *ortho*), 2C), 126.44(C_6H_5-CO-NH-<u>C</u>$_6H_4$-), 124.99 (C_6H_5-CO-NH-<u>C</u>$_6H_4$-), 123.23 (C_6H_5-CO-NH-<u>C</u>$_6H_4$-), 122.05 (C_6H_5-CO-NH-<u>C</u>$_6H_4$-(next to the carbon bearing the -NH-)), 20.95 (<u>C</u>H_3-CO-O-C_6H_4-).

2-(4-Chlorobenzamido)-phenyl Acetate (**179**)

2-(4-Chlorobenzamido)phenyl acetate **(179)** was prepared by reacting 2-methylbenzoxazole (0.25 g, 1.8 mmol) and 4-chlorobenzoyl chloride (0.981 g, 5.5 mmol) using the process described for 2-benzamidophenyl acetate **(178).**

Yellowish solid, mp. 109-110° C, yield = 0.277 g (52 %), R_f = 0.5, (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3359, 2978, 1740, 1680, 1541, 1492, 1451, 1374, 1216, 1175.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.13 (d, *J* = 8.03 Hz, $C_6\underline{H}_4$ (next to the carbon bearing the acetyl group), 1H), 7.96 (s, –NH-, 1H), 7.75 (d, *J* = 8.5 Hz, -$C_6\underline{H}_4$Cl (aromatic *ortho*), 2H), 7.46 (d, *J* = 8.5 Hz, -$C_6\underline{H}_4$Cl (aromatic *meta*), 2H), 7.26 (m, -$C_6\underline{H}_4$-, 1H) , 7.16 (m, -$C_6\underline{H}_4$-, 2H), 2.33 (s, -CO-$C\underline{H}_3$, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.77 (CH_3-$\underline{C}$O-O-C_6H_4-), 164.35 (C_6H_4Cl-$\underline{C}$O-NH-), 141.36 (CH_3-CO-O-$\underline{C}_6H_4$-), 138.28 ($\underline{C}_6H_4$Cl-CO-NH-(Cl bearing carbon)), 132.82 ($\underline{C}_6H_4$Cl-CO-NH-), 129.38 (C_6H_4Cl-CO-NH-$\underline{C}_6H_4$-), 129.07 ($\underline{C}_6H_4$Cl-CO-NH-C_6H_4- (aromatic *ortho*), 2C), 128.42 ($\underline{C}_6H_4$Cl-CO-NH-C_6H_4- (aromatic *meta*), 2C), 126.54 (C_6H_4Cl-CO-NH-$\underline{C}_6H_4$-), 125.37 (C_6H_4Cl-CO-NH-$\underline{C}_6H_4$-), 123.49 (C_6H_4Cl-CO-NH-$\underline{C}_6H_4$-), 122.13 (C_6H_4Cl-CO-NH-$\underline{C}_6H_4$-), 21.03 ($\underline{C}H_3$-CO-O-C_6H_4-).

2-(2-Bromobenzamido)-phenyl Acetate (**180**)

2-(2-Bromobenzamido) phenyl acetate (**180)** was prepared by reacting 2-methylbenzoxazole (0.25 g, 1.8 mmol) and 2-bromobenzoyl chloride (1.24 g, 5.5 mmol) using the process described for 2-benzamidophenyl acetate (**178**).

Brown liquid, yield = 0.332 g (54%), R_f = 0.5, (silica gel, 5:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3293, 3064, 1768, 1667, 1528, 1452, 1316, 1180.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.37 (d, *J* = 8.07 Hz, $C_6\underline{H}_4$ (next to the carbon bearing the acetyl group), 7.96 (s, –N<u>H</u>-, 1H), 7.70 (m, Ar<u>H</u>, 2H), 7.63 (m, Ar<u>H</u>, 2H), 7.42 (m, Ar<u>H</u>, 1H), 7.30 (m, Ar<u>H</u>, 1H), 7.16 (m, Ar<u>H</u>, 1H), 2.34(s, -CO-C<u>H</u>$_3$, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.73 (CH_3-<u>C</u>O-O-C_6H_4-),165.14 (C_6H_4Br-<u>C</u>O-NH-), 140.68 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 137.35 (<u>C</u>$_6$H$_4$Br-CO-NH-), 133.66 (Ar-<u>C</u>), 131.99 (Ar-<u>C</u>), 130.56 (Ar-<u>C</u>), 129.41 (Ar-<u>C</u>), 127.96 (Ar-<u>C</u>), 126.61 (Ar-<u>C</u>), 125.14 (Ar-<u>C</u>), 122.60 (Ar-<u>C</u>), 122.29 (Ar-<u>C</u>-Br-bearing), 118.88 (Ar-<u>C</u>), 21.28 (<u>C</u>H$_3$-CO-O-C$_6$H$_4$-).

<u>2-(*N*-Acetylacetamido)-phenyl Acetate (**181**)</u>

2-Methylbenzoxazole (0.25 g, 1.8 mmol) was dissolved in 15 mL of THF then potassium carbonate (0.954 g, 6.7 mmol) was added. A solution of acetyl chloride (0.444 g, 5.5 mmol) in 15 mL THF was added dropwise into the above solution under nitrogen at room temperature. The reaction mixture was refluxed for 3 h and then the solvent was removed by rotary evaporation. Dichloromethane (20 mL) was added to the residue to make a solution which was then washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL). The dichloromethane solution was then dried over anhydrous sodium sulfate and subsequently concentrated. This residue was purified by the column chromatography (silica gel, 5:1 hexane/ethyl acetate) to give **181**.

White solid, mp. 110-111° C, yield = 0.187 g (43 %), R_f = 0.65, (silica gel, 1:1 hexane/ ethyl acetate).

IR (KBr, cm^{-1}): 2958, 1773, 1717, 1493, 1453, 1369, 1270, 1243, 1186.

^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.42 (m, -$C_6\underline{H}_4$- (next to the carbon bearing the acetyl group), 1H), 7.24(m, Ar-H, 4H), 2.28 (s, -N-(CO-C$\underline{H}_3)_2$, 6H), 2.23 (s, -CO-C$\underline{H}_3$, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 172.20 (-N-($\underline{C}$O-$CH_3)_2$, 2C), 168.21 (CH_3-$\underline{C}$O-O-C_6H_4-), 146.60 (CH_3-CO-O-$\underline{C}_6H_4$-), 131.24 (Ar-$\underline{C}$), 129.87 (Ar-$\underline{C}$), 126.67 (Ar-$\underline{C}$), 123.56 (Ar-$\underline{C}$), 26.06 (-N-(CO-$\underline{C}H_3)_2$, 2C), 20.36 ($\underline{C}H_3$-CO-O-C_6H_4-).

3-(*N*-Acetylacetamido)-biphenyl-4-yl Acetate (**182**)

2-Methyl-5-phenylbenzoxazole (0.25 g, 1.1 mmol) was dissolved in 15 mL of THF (tetrahydrofuran). Then potassium carbonate (0.603 g, 4.2 mmol) was added in the above solution. A solution of acetyl chloride (0.281 g, 3.5 mmol) in 15 mL THF (tetrahydrofuran) was added dropwise into the above mixture under nitrogen at room temperature.

The reaction mixture was refluxed for 3 h and then the product mixture was cooled to room temperature. Then the solvent was removed by rotary evaporation. Dichloromethane (20 mL) was added to the residue to make a solution which was then washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL). The dichloromethane solution was then dried over anhydrous sodium sulfate and subsequently concentrated. This residue was purified by the column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **182**.

White solid, mp. 118-120° C. yield = 0.182 g (50%), R_f = 0.5, (silica gel, 1:1 hexane/ ethyl acetate).

IR (cm^{-1}): 3441, 3154, 3035, 1759, 1688, 1601, 1576, 1492, 1469, 1370, 1316, 1252.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.31 (s, –N<u>H</u>-, 1H), 7.52 (m, Ar-<u>H</u>, 4H), 7.16 (m, Ar-<u>H</u>, 3H) , 2.32 (s, -N-CO-C<u>H</u>$_3$, 6H), 2.13 (m, C<u>H</u>$_3$-CO-O-, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 168.93 (CH_3-<u>C</u>O-O-C_6H_4-), 168.39 (-N-<u>C</u>O-CH_3, 2C), 140.07 (CH_3-CO-O-C_6H_4-<u>C</u>$_6$H$_5$), 139.89 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 139.48 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 129.78 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 128.64 (CH_3-CO-O-C_6H_4-<u>C</u>$_6$H$_5$), 127.39 (CH_3-CO-O-C_6H_4-<u>C</u>$_6$H$_5$), 127.07 (CH_3-CO-O-C_6H_4-<u>C</u>$_6$H$_5$), 123.37 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 122.24 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 121.88 (CH_3-CO-O-<u>C</u>$_6$H$_4$-), 24.34 (-N-CO-<u>C</u>H$_3$, 2C), 20.98 (<u>C</u>H$_3$-CO-O-).

Unsuccessful Reactions

<u>Reaction of 2-Methylbenzoxazole with 3,4,5-Trimethoxybenzoyl Chloride</u>

2-Methylbenzoxazole (0.25 g, 1.8 mmol) was treated with 3,4,5-trimethoxybenzoyl chloride (1.30 g, 5.5 mmol) using the process described for 2-benzamidophenyl acetate (**178**). Only starting materials spots were found in TLC (ethyl acettate/ hexane : 1:1, 1:5, 2:1). No further work-up procedures were performed.

<u>Reaction of 2-Methylbenzoxazole with 2,2-Dimethylpropanoyl Chloride</u>

2-Methylbenzoxazole (0.25 g, 1.8 mmol) was reacted with 2,2-dimethylpropanoyl chloride (0.678 g, 5.5 mmol) using the process described 2-(*N*-acetylacetamido)phenyl acetate (**181**). Unreacted 2-methylbenzoxazole spot was only found in TLC ((ethyl acettate/ hexane: 1:1, 1:5, 3:1). No further work-up procedures were performed.

Reaction of 2-Methylbenzoxazole with Cyclohexanecarbonyl Chloride

2-Methylbenzoxazole (0.25 g, 1.8 mmol) was reacted with cyclohexanecarbonyl chloride (0.830 g, 5.5 mmol) using the process described for 2-(*N*-acetylacetamido)phenyl acetate (**181**). Unreacted 2-methylbenzoxazole spot was only found in TLC ((ethyl acettate/ hexane: 1:1, 1:5, 3:1). No further work-up procedures were performed.

Reaction of 2-Methyl-5-phenylbenzoxazole with 2,2-Dimethylpropanoyl Chloride

2-Methyl-5-phenylbenzoxazole (0.25 g, 1.1 mmol) was reacted with 2,2-dimethylpropanoyl chloride (0.431 g, 3.5 mmol) using the process described for 3-(N-acetylacetamido)biphenyl-4-yl acetate (**182**). Unreacted 2-methyl-5-phenylbenzoxazole spot was only found in TLC ((ethyl acettate/ hexane: 1:1, 1:5). No further work-up procedures were performed.

(*Z*)-2-(3-Methylbenzo[d]oxazol-2(3H)-ylidene)-1-phenylethanone

2-Methylbenzoxazole (**174**) (0.25 g, 1.8 mmol) was treated with methyl iodide (0.56 g, 4.0 mmol) at room temperature in THF. The reaction was stirred for 12 h but no benzoxazolium iodide salt (**183**) was formed. This demonstrates the lower reactivity of 2-methylbenzoxazole compared to its non-aromatic analogue 2-methyloxazoline.

CHAPTER V

REACTIONS OF METHANOL, WATER, PHENOL, RAW AND MODIFIED BIO-OILS WITH OLEFINS: FIRST STEPS IN DEVELOPING A PROCESS FOR BIO-OIL UPGRADING

Introduction and Objective

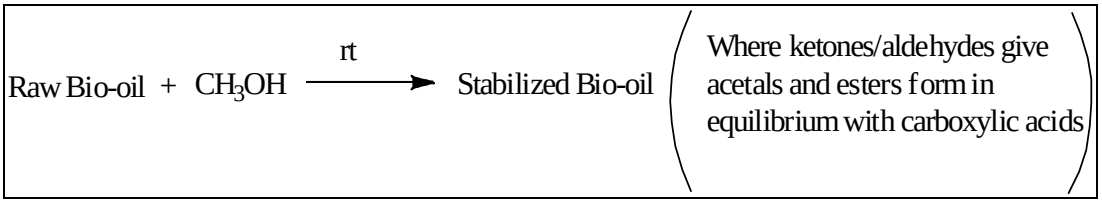
Biomass, especially lignocellulosic biomass, can be considered as a valuable renewable energy resource. This widely available biomass does not belong to the human food chain so it should not cause food price increases like corn-derived ethanol has done. Fast pyrolysis of lignocellulosic biomass results in an energy rich liquid, commonly known as bio-oil.[114] Bio-oil is considered to be an alternative to fossil fuel because of its easy handling and ecofriendly properties compared to fossil fuels.

Bio-oil is a complex mixture of low pH carboxylic acids (butyric, acetic, formic, propionoic, etc), methoxylated and alkylated phenols and catechols, hydroxyaldehydes, hydroxyketones, anhydro-monosacharides, furan derivatives, oligomeric compounds from cellulosic and lignin materials, other carboxyl compounds, etc.[115,116] All these reactive chemicals make bio-oil highly acidic (pH 2.5-3.1) and both thermally and chemically unstable. Raw bio-oil contains about (30-50%) oxygen and substantial amounts of water (15-40%).[117] This high water and oxygen content lowers the heat content and facilitates phase separations in bio-oil which ultimately restricts its fuel use.

The high oxygen content and hydrophilicity also make bio-oil immiscible with petroleum oil. Thus, bio-oil upgrading is required to make it less acidic, more stable, more hydrophobic and more suitable for use in current motors, boilers, generators, etc.

One of the most common techniques to remove oxygen content from bio-oil is hydrodeoxygentaion (HDO), but it has serious limitations. This process requires high temperatures (250-500°C) for which catalyst coking and polymerization occur frequently.[117,118] There are some other upgrading techniques such as catalytic reforming over acidic zeolites, steam reforming, etc. However, they require substantial development and new capital investments. Catalyst fouling is also a major problem.

Alternative approaches are available where partial bio-oil upgrading is performed. These processes keep a substantial amount of oxygen in bio-oil while converting it into a less hydrophilic, less acidic, higher heating value liquid. One such technique is the addition of methanol or ethanol. This generates esters and acetals from bio-oil's carboxylic acids and aldehydes/ ketones (Scheme 5.1).

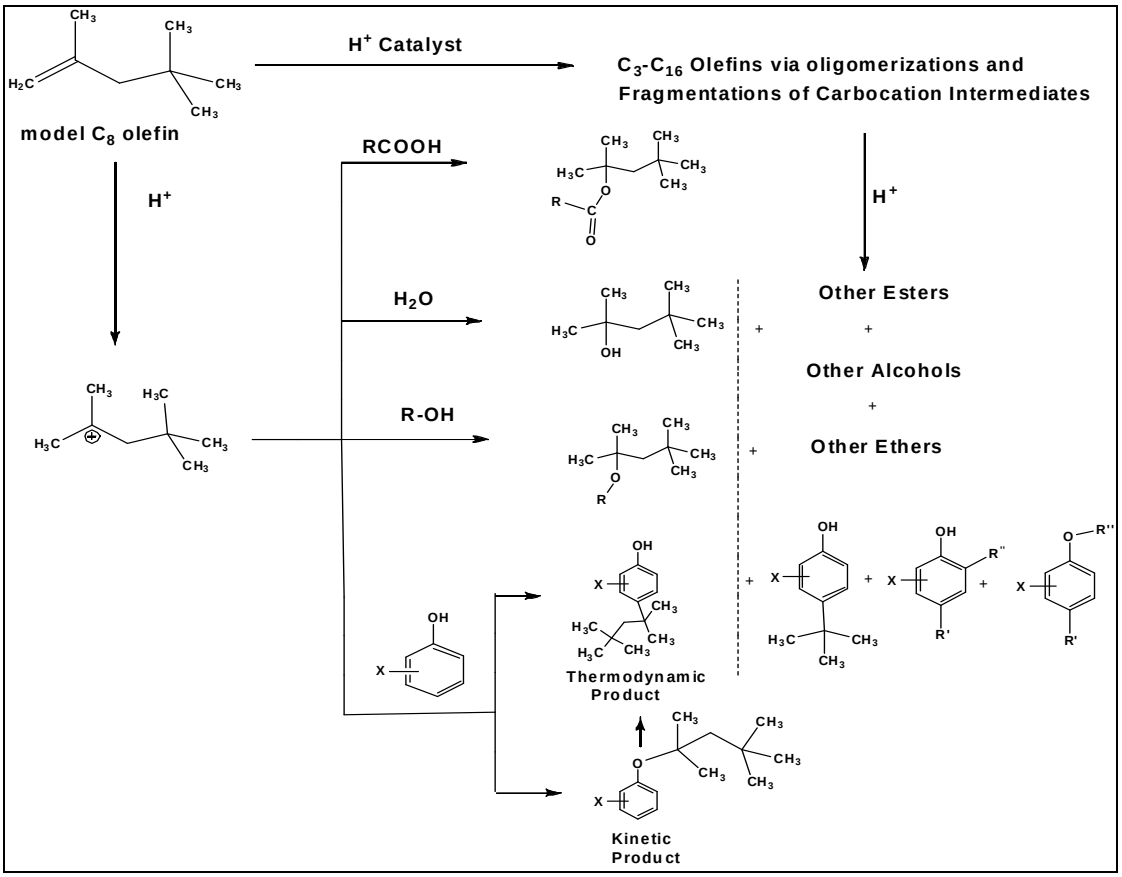


Scheme 5.1 Upgrading of Bio-oil by the Addition of Methanol

An objective of the research presented in this chapter is to upgrade bio-oil using olefins. In the presence of acid catalysts, olefins can react with water, carboxylic acids, alcohols and phenolic compounds as shown in the Scheme 5.2.

The common feature is addition of the –OH (hydroxyl) function across the olefin. These reactions need temperatures between (50-130°C), far below than that of hydrodeoxygenation or cracking processes. Therefore, catalyst coking and bio-oil polymerization can be avoided.[119] Olefins may also undergo both acid-catalyzed oligomerizations and fragmentations to generate larger and smaller olefins via classic carbocation chemistry. These new olefins can also participate in the upgrading reactions.

In contrast to methanol (alcohol) addition to bio-oil (Scheme 5.1), acid-catalyzed additions of olefins to bio-oil components decrease the water content by forming easily burned alcohols from olefins and water. Thus, this process can convert the water present into a valuable fuel without a separate water removal process. Further, all generated alcohols might further react with olefins and form even more hydrophobic ethers, which also add fuel value. Ethers are also formed by the reactions of phenols across olefins (O-alkylation).



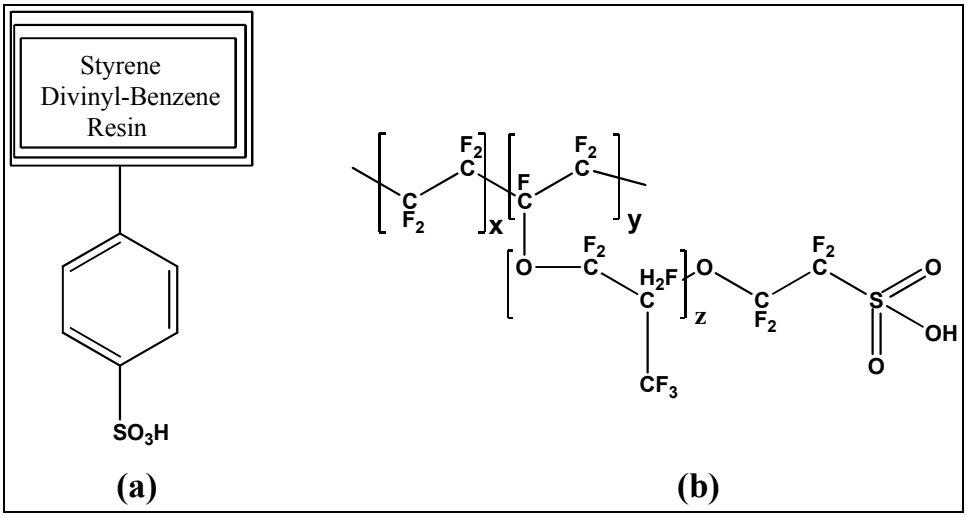
Scheme 5.2 Olefination of Bio-oil Illustrating the Additions of Water/Alcohols/ Carboxylic Acids/ Phenols Across Olefins and C-alkylation and O-alkylation of Phenolic Components. Olefin Oligomerizations and Fragmentations to New Olefin Reagents in this Process are also illustrated

Addition of phenolic compounds across olefins forms the O-alkylate as the kinetic product. These may readily proceed to C-alkylates. For refining purposes, it would be ideal to stop at the O-alkylation stage, since this removes the phenolic hydroxyl from the bio-oil. Acid catalyzed olefinations of carboxylic acids generate the more hydrophobic esters.

All these olefin addition products are less polar than their bio-oil precursors and these products enhance the heating value. These reactions, in total, also increase

hydrophobicity, lower water content and acidity and increase stability and blendibility with heating oils.

In the olefination reactions performed herein, solid acid catalysts were used to aid separation and reduce corrosion problems. Sulfonic acid catalysts have been used commercially for many heterogeneous acid catalyzed reactions.[120] Amberlyst-15 is a heterogeneous acid catalyst[121,122] containing sulfonic acid functions on a styrene-divinylbenzene matrix (Scheme 5.3). Nafion NR-50 is a very strongly acidic fluorinated[123,124,125] sulfonic acid polymeric catalyst. Nafion and Amberlyst show high activities for esterification, etherification, hydration and dehydration.[123,124,125]



Scheme 5.3 Structures of a) Amberlyst-15 and b) Nafion Catalysts

Several olefination reactions of water, methanol, phenol, raw and modified bio-oils were performed over a variety of heterogeneous acid catalysts.[126,127,128] A 'modified'

bio-oil contained water and methanol with lowered carboxylic acid contents versus raw bio-oil.[129] Thus, it could form alcohols, ethers and esters (in smaller amount) upon acid catalyzed olefination reaction. As per previous studies, Amberlyst-15, Amberlyst-70 and Nafion NR-50 were emphasized in this dissertation research. Compositions of the product mixtures were studied by GC/MS (gas chromatography/mass spectrometry). These initial reactions were performed to understand the type of products that could be formed by the olefinations of raw and modified bio-oil using solid acid catalysts. The other goals of examining these reactions were to screen the olefins and catalysts before optimizing the process. Thus, none of the compounds were quantified in these reactions and recovered olefin was not monitored in most of the reactions. However, area percents of most of the peaks are given to show the approximate amount of each product and their area percent values relative to other compounds present in a particular batch. Products were tentatively identified by considering the best match for the corresponding mass fragmentation pattern either to established compound libraries or by individual analysis of these patterns.

Experimental

Materials

Pine wood bio-oil, prepared by fast pyrolysis at 450-470°C in an auger reactor,[115,116,129] was supplied by the Forest Products Laboratory, Mississippi State University. Modified bio-oil was also obtained from the FPL, MSU. Four branched

olefins, which can form tertiary cations on protonation, were used: 2,4,4-trimethyl-1-pentene, 2-ethyl-1-butene, 2,3-dimethyl-1,3-butadiene and 2,3-dimethyl-1-butene (all were obtained from Sigma-Aldrich). Amberlyst-15(16-50 mesh size) was obtained from Fluka and Nafion NR-50 (7-9 mesh size), phenol, methanol were obtained from Sigma-Aldrich. All chemicals were used as received.

Reactions with Model Compounds

Model reactions were all performed with a stoichiometric deficiency of olefin (large excess of the other reagents) at 60°C and 80°C. Using an olefin deficiency would also lower the extraction of bio-oil's hydrophobic components into the remaining unreacted olefin which forms a separate phase by keeping this olefin phase small. Model reactions between olefin/CH_3OH, olefin/H_2O and olefin/phenol were run at mole ratios of 1:6 for 6 h in 50 mL round bottom flasks. In all cases, 1 g of olefin was used. Stirring was performed with a magnetic stirrer. Amberlyst-15 (0.2 g) was used as the catalyst.

Reaction of Olefin with Raw and Modified Bio-oils

Reactions were run for 6 h at different temperatures (60°C, 80°C, 120°C) with different olefins in a 100 mL round bottom flask. Magnetic stirring was used. The olefin/ H_2O (present in raw or modified bio-oil) mole ratio was 1:6, where the water content of raw bio-oil and modified bio-oil were 19% and 16% respectively. All the reactions were performed with 1 g of olefin and 0.2 g of a catalyst (Amberlyst-15 or Nafion NR-50).

Analyses of Product Mixtures

Product mixtures were analyzed in the Forest Products Laboratory, Mississippi State University, using a Hewlett Packard 5890 series II-Gas chromatograph/5971 series A-mass spectrometer (injector temperature 270^{o}C) with a silica capillary column coated with 5% phenylmethylpolysiloxane (30-meter x 0.32 mm internal diameter x 0.25 µ film thickness). An initial column temperature of 40^{o}C (4 min hold) was used followed by heating at 5^{o}C/min to a final temperature of 280^{o}C. A 70 eV electron impact ionization mode was used with a 250^{o}C source (detector) and a 270^{o}C interface.

A 0.2 mg representative product aliquot was diluted with either methanol (in some cases) or dichloromethane (10 mL). This solution (1 mL) was then transferred to the autosampler vial. These reactions were not run under pressure, so C3-C5 olefins, if produced by fragmentation reactions could have been lost. Products were tentatively identified by using NIST mass spectral library.

Results and Discussions

Model Reactions

Model Reactions of 2,4,4-Trimethyl-1-pentene with Water

Alcohols, the recovered starting olefin and some high boiling olefin oligomers (C12, C16) were found in product mixtures catalyzed by Amberlyst-15 (Table 5.1). Amberlyst-15 is a macroreticular sulfonic acid resin crosslinked by divinylbenzene.

Amberlyst-15 was partially destroyed after the reactions at both 60°C and 80°C. Its 16-50 mesh beads are inter-spread by continuous pores and channels, so these hard beads fragment when stirred at 60-80°C. These reactions were two phase reactions (aqueous phase and olefin phase) and the solid catalyst was a third phase. Stirring helps mass transport, but, clearly, crossing phase barriers slow the reactions.

Model Reactions of 2,4,4-Trimethyl-1-pentene with Methanol

Methyl ethers and higher boiling olefin oligomers (C12, C16) were formed in reactions run from 60-80°C (Table 5.2). At higher temperatures more olefin consumption occurred (the GC area % of recovered olefin was less than that of lower temperature reactions). Amberlyst-15 decomposition was more extensive at higher temperatures.

Table 5.1 Model Water Addition Reactions Across 2,4,4-Trimethyl-1-pentene[a]

Temp (°C)	Products		
	Olefin Recovered (area %)	Alcohols (area %)	Olefin Oligomers[b] (area %)
60	47	12	31
80	17	22	53

[a] Reactions of 2,4,4-trimethyl-1-pentene (1 g) with water (0.9 g) were performed using Amberlyst-15 (0.2 g) as the acid catalyst. The 2,4,4-trimethylpentene to water mole ratio was 1:6. Reactions were run for 6 h. The system contained three (water + olefin+ solid catalyst) phases throughout the reaction. GC area % refer to the ion corrents generated in the MS detector and does not represent the true mole percent.
[b] C12 and C16 oligomers.

Note, the goal of this work is to know the product profiles of the olefination of bio-oil. Thus, quantification of the recovered olefin or any other component was not performed.

Table 5.2 Model Methanol Addition Reactions Across 2,4,4-Trimethyl-1-pentene[a]

Temp (°C)	Products		
	Olefin Recovered (area %)	Ethers (area %)	Olefin Oligomers[b] (area %)
60	31	45	20
80	23	33	33

[a] Reactions of 2,4,4-trimethyl-1-pentene (1 g) with methanol (1.6 g) were performed using Amberlyst-15 (0.2 g) as the acid catalyst. The 2,4,4-trimethylpentene to methanol mole ratio was 1:6. Reactions were run for 6 h. Olefin was completely miscible with methanol. GC area % refer to the ion corrents generated in the MS detector and does not represent the true mole percent.
[b] C12, C16 oligomers.

Note, the goal of this work is to know the product profiles of the olefination of bio-oil. Thus, quantification of the recovered olefin or any other component was not performed. Product mixtures consisted of one (liquid) phase and one solid (catalyst) phase.

Model Reactions of 2,4,4-Trimethyl-1-pentene with Phenol

Amberlyst-15 was used as the catalyst (Table 5.3). Only *para*-substituted C-alkylated phenols were obtained. The kinetic product, O-alkylated phenol, was formed first but was further converted very rapidly to the thermodynamically favored C-alkylated phenol. The high stability of the tertiary carbocations formed reversibly upon protonation of these O-alkylated phenols facilitated the conversion of the kinetically controlled

product to the thermodynamically controlled product. The catalyst, Amberlyst-15, a fragile macroreticular resin, was partially destroyed. The added alkyl group was derived from the starting olefin and added to the *para*-position of phenol. The system contained three (two liquid and one solid) phases.

Table 5.3 Model Phenol Addition Reactions Across 2,4,4 Trimethyl-1-pentene[a,b]

Temp (°C)	Products	
	O-alkylation (area %)	C-Alkylation (area %)
60	0	29
80	0	50

[a] Reactions of 2,4,4-trimethyl-1-pentene (1 g) with phenol (5 g) were performed using Amberlyst-15 (0.2 g) as the acid catalyst. **T**he 2,4,4-trimethyl-1-pentene to phenol mole ratio was 1:6. Reactions were run for 6 h. The 2,4,4-trimethyl-1-pentene was not completely miscible with phenol. GC area % refer to the ion corrents generated in the MS detector and does not represent the true mole percent.
[b] The recovered olefin (2,4,4-trimethyl-1-pentene) was not identified by the detector.

Note, the goal of this work is to know the product profiles of the olefination of bio-oil. Thus, quantification of the recovered olefin or any other component was not performed.

Reactions with Bio-oil

Reactions of 2,4,4-Trimethyl-1-pentene with Raw Bio-oil

When Amberlyst -15 was used as the catalyst, alcohols and higher boiling olefin oligomers were formed at both 60°C and 80°C (Table 5.4). After these reactions, two

phases were present. Most of the components were found in the bottom (bio-oil) phase. However, a major fraction of the olefin oligomers formed moved to the olefin (top) phase. When the reaction was run at 120°C, a lot of black tar-like products were found on the catalyst beads. Nafion NR-50 gave similar results. However, char-like buildup was less in this case. Amberlyst-15 was destroyed after the reaction (even at 60°C) but Nafion NR-50 survived after the reaction at 60°C. These reactions are 'olefin deficient' since only 1 mole of olefin was added to every six moles of water in the bio-oil (this does not count the organic HO-containing bio-oil components that could react). The reaction mixture consisted of two liquid phases and one solid (catalyst) phase. Figure 5.1 (page 193) shows the GC chromatograms of the raw bio-oil and bio-oil phase of the product mixture. These chromatograms demonstrate that some of the peaks in the raw bio-oil have disappeared and many new peaks have appeared in the olefinated bio-oil. The comparison of the chromatograms of the olefinated bio-oils at 60°C and 80°C (Figure 5.2, page 194) shows that similar types of new products are formed in both cases. Tentative identifications of some peaks in the chromatogram of the olefinated bio-oil are given in the Tables 5.4 and 5.5 at the end.

Reactions of 2-Ethyl-1-butene with Raw Bio-oil

Both Amberlyst-15 and Nafion NR-50 were used as catalysts in different reactions. Reactions were performed at 80°C and 120°C (Table 5.5). Several alcohols (3-methyl-3-pentanol, 2,2-dimethyl-1-pentanol, 3-ethyl-3-methyl-2-pentanol, etc) and higher boiling olefin oligomers were formed (Figure 5.3, page 195). Amberlyst-15 was

partially destroyed but Nafion NR-50 survived after most of these reactions. With Amberlyst-15, a C-alkylated phenol (*p*-t-butyl phenol) is tentatively identified in the product mixture. GC-MS analyses of the bio-oil phases of product mixtures are shown in the Table 5.6 (for the Amberlyst-15 catalyzed reaction) and Table 5.6 (for the Nafion NR-50 catalyzed reaction) .

Reactions were also performed with the olefins, 2,3-dimethyl-1,3-butadiene and 2,3-dimethyl-1-butene. A variety of alcohols and higher boiling oligomers were formed in both the cases.

Reactions of 2,4,4-Trimethyl-1-pentene with Modified Bio-oil

A few Amberlyst-15 and Nafion NR-50 catalyzed olefination reactions of modified bio-oils were performed. The olefination reaction of modified bio-oil resulted in formation of several alcohols, methyl ethers and higher boiling olefin oligomers in the reactions at 60°C, 80°C and 120°C (Tables 5.8 and 5.9). Methyl ether was formed by the reactions of olefins with excess methanol present in the modified bio-oil.

Conclusions

Acid catalyzed olefinations of bio-oils are extremely complex reaction systems. Most of these systems contain multiple phases. These reactions resulted in a variety of alcohols (2,4-dimethylpentan-2-ol, but-3-en-1-ol, 2,2-dimethylbutan-1-ol, etc) and C12-C16 oligomeric mixtures of the starting olefins. Some of these new compounds were also generated during the model olefination reactions conducted with water and methanol.

Similar model reactions performed with phenol demonstrated C-alkylated phenols were formed. However, C-alkylated phenols were not identified in most of the bio-oil olefination product mixtures. No O-alkylated phenolics were seen in model reactions and were not likely obtained in any of the reactions. These observations can be explained considering the deficiency of olefins in these reactions. Besides phenol alkylation, a few other competitive reactions (e.g. esterification, alcohol formation, oligomerization, fragmentations, etc) occur simultaneously, which decreases the phenol alkylation reactions to a certain degree. Alkylated phenol amounts were too low to be identified by the detector in most of the cases.

Model reactions also showed that olefination reactions at 80°C or higher temperatures give higher amounts (approximated, as solely based on the area percent of the corresponding peak) of alcohols and higher boiling olefin oligomers than the olefination reactions at 60°C with the same catalyst. Amberlyst-15 decomposed during reactions in water or bio-oil, especially at 80°C and this catalyst will not be a commercially viable catalyst for olefination upgrading processes. Nafion NR-50 is more efficient than Amberlyst-15 in most of the cases. Nevertheless, all these reactions showed acid catalyzed olefination of bio-oil as a potential upgrading technique.

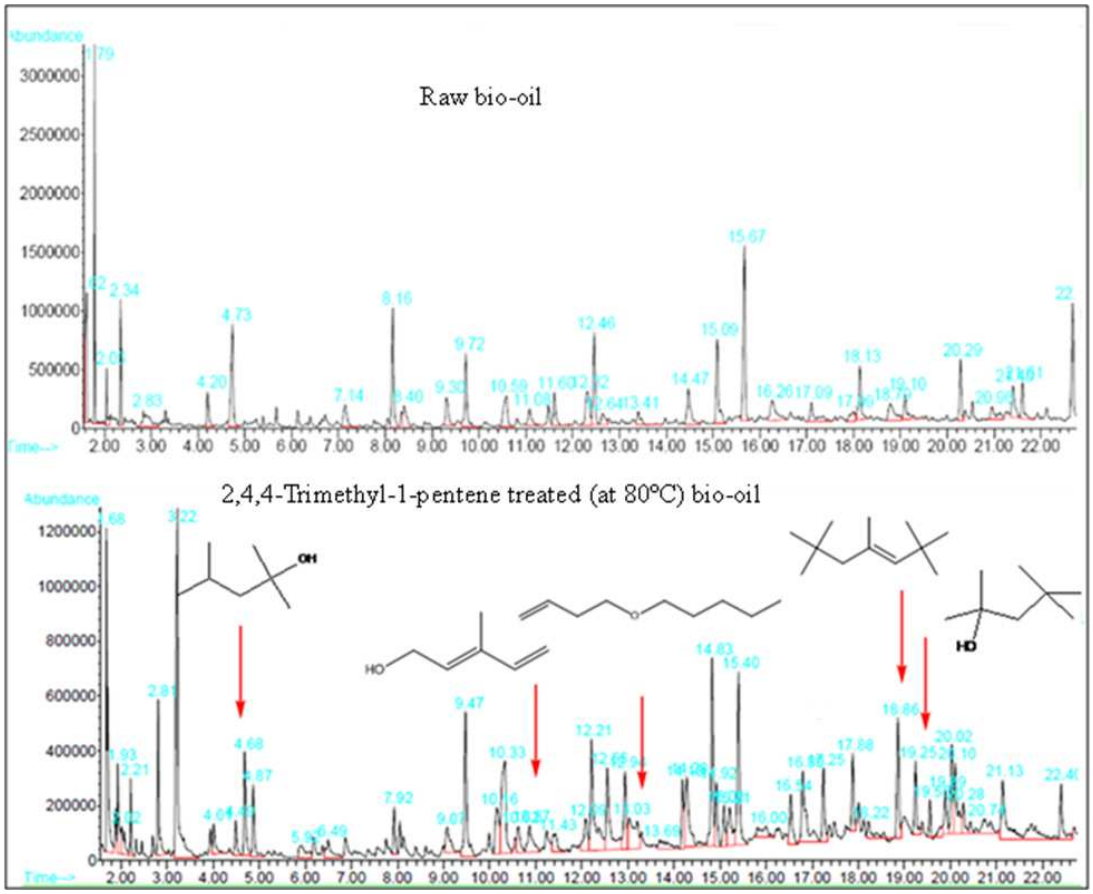


Figure 5.1 Chromatograms of the Raw Bio-oil (Top) and of the Bottom Phase (Bio-oil) obtained after the Reaction of 2,4,4-Trimethyl-1-pentene (1 g) with Raw Bio-oil (4.7 g) using Amberlyst-15 (0.2 g) as the Acid Catalyst at 80°C for 6 h (Bottom)

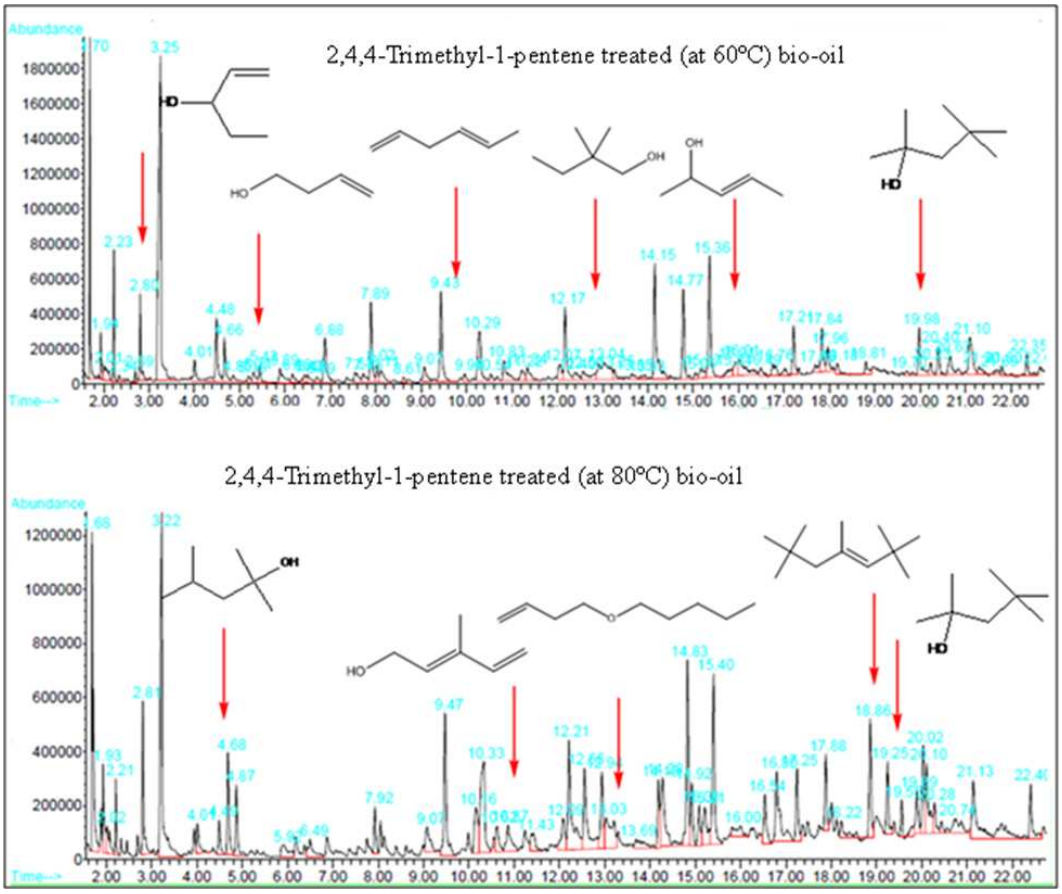


Figure 5.2 Chromatograms of the Bottom (Bio-oil) Phases obtained after the Reactions of 2,4,4-Trimethyl-1-pentene (1 g) with Raw Bio-oil (4.7 g) using Amberlyst-15 (0.2 g) as the Acid Catalyst at 60°C (Top) and 80°C (Bottom) for 6 h

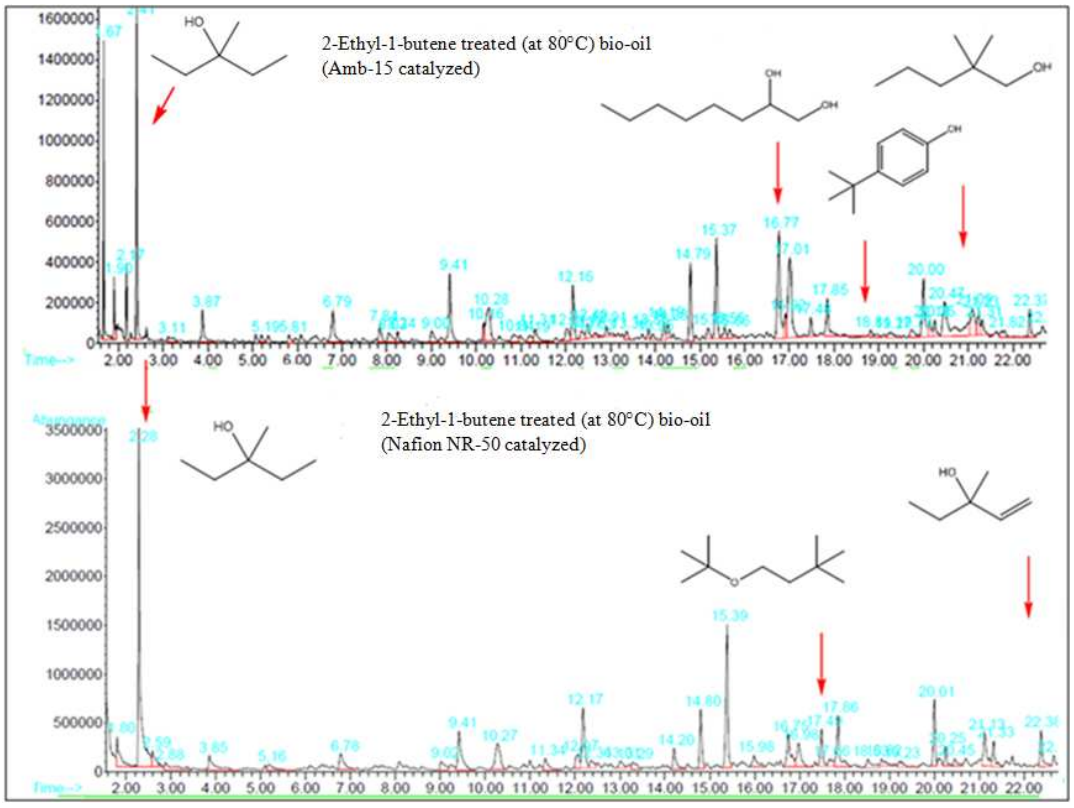


Figure 5.3 Chromatograms of the Bottom (Bio-oil) Phases Obtained after the Reactions of 2-Ethyl-1-butene (1 g) with Raw Bio-oil (6.2 g) using Amberlyst-15 (0.2 g) at 80°C (Top) and Nafion NR-50 at 80°C (Bottom) for 6 h

Table 5.4 Compositions of Raw Bio-oil and Bio-oils after Treatment with 2,4,4-Trimethyl-1-pentene at 60, 80 and 120°C after 6 h over Amberlyst-15[a,b,c]

			Olefin-treated Bio-oil					
R.T. (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	(60°C) Olefin Phase (area %)	(60°C) Bio-oil Phase (area %)	(80°C) Olefin phase (area %)	(80°C) Bio-oil phase (area %)	(120°C) Olefin phase (area %)	(120°C) Bio-oil phase (area %)
1.74	2,4,4-Trimethyl-1-pentene	0	34.24	-	20.04	-	87.30	-
1.79	1-Hydroxy-2-propanone	2.91	-	2.50	-	3.10	-	-
2.02	2-Ethoxy Propane	-	-	-	-	0.54	-	-
2.05	Hydroxy methyl acetate	0.72	-	-	-	0.75	-	-
2.82	3-Methoxy-2,2-dimethyl-Oxirane	1.37	-	-	-	-	-	-
2.84	Pentene—3-ol	-	-	2.56	-	-	-	-
4.01	Furfural	1.39	-	-	-	0.47	-	-
4.20	1-Methoxy-2,2-dimethyloxirane	1.00	-	-	-	-	-	-
4.68	2,4-Dimethyl-2-pentanol	-	-	-	-	1.26	-	1.12
4.73	2,2-Dimethoxy--2-butanone	3.08	-	-	-	0.93	-	-
5.68	3-Butene-1-ol	-	-	0.22	-	-	-	-
6.42	3-Buten-1-ol	-	-	0.20	-	-	-	-
7.13	2-Hydroxy-2-cyclopenten-1-one	1.08	-	-	-	-	-	-

Table 5.4 (Continued)

			Olefin-treated Bio-oil					
R.T. (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	(60℃) Olefin Phase (area %)	(60℃) Bio-oil Phase (area %)	(80℃) Olefin phase (area %)	(80℃) Bio-oil phase (area %)	(120℃) Olefin phase (area %)	(120℃) Bio-oil phase (area %)
9.30	Phenol	1.06	-	-	-	0.68	-	-
9.90	1,4-Hexadiene	-	-	0.17	-	-	-	-
10.16	1,1,2-Trimethoxy ethane	-	-	-	-	1.13	-	-
10.54	1,4-Hexadiene	-	-	0.21	-	-	-	-
10.58	2-Hydroxy-3-methyl-2-cyclopenten-1-one	1.64	-	-	-	2.54	-	-
10.87	3-methylpenta-1,3-diene-5-ol	-	-	-	-	0.79	-	-
11.08	1,1-Dimethoxy-3-methyl -pentanone	0.83	-	-	-	-	-	-
11.60	3-Methylphenol	1.12	-	-	-	-	-	-
12.32	4-Methyl Phenol	1.86	-	-	-	0.78	-	-
12.45	2-Methoxy phenol	2.43	-	0.19	-	2.61	-	- .
12.64	3-Methylbutanal	0.63	-	-	-	-	-	-
13.00	2,2-Dimethylbutan-1-ol	-	-	0.24	-	-	-	-
13.03	3-Butenyl pentyl ether	-	-	-	-	1.50	-	-
13.05	4-Ethoxy-2-butanol	-	-	1.93	-	-	-	-
13.40	2,3-Dihydroxypropyl butanoic acid	0.63	-	-	-	-	-	-
13.65	2,2-Dimethyl-1-butanol	-	-	0.26	-	-	-	-
14.46	2,4-Dimethyl phenol	1.65	-	-	-	-	-	-

Table 5.4 (Continued)

			Olefin-treated Bio-oil					
R.T. (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	(60℃) Olefin Phase (area %)	(60℃) Bio-oil Phase (area %)	(80℃) Olefin phase (area %)	(80℃) Bio-oil phase (area %)	(120℃) Olefin phase (area %)	(120℃) Bio-oil phase (area %)
14.92	Isobutyl propionate	1.06	-	-	-	0.84	-	-
15.21	1-Ethenyloxy-pentane	-	-	-	-	0.95	-	-
15.67	2-Methoxy-4-methylphenol	4.68	-	0.37	-	2.54	-	-
15.99	Pent-3-en-2-ol	-	-	0.20	-	-	-	-
16.21	3-penten-2-ol	-	-	1.22	-	-	-	-
16.26	1,2-Benzenediol	-	-	-	-	0.79	-	-
16.54	5-Methyl-5-Nonanol	-	-	-	0.84	-	-	-
17.09	2-Ethyl-4-methyl phenol	1.13	-	-	1.81	-	-	-
17.98	2-Ethoxy-4-methyl Phenol	0.69	-	-	-	-	-	-
18.78	3-Methyl-1,2-benzenediol	1.37	-	-	-	-	-	-
18.86	2,2,4,6,6-Pentamethyl-3-heptene	-	34.49	-	38.31	1.66	4.70	-
19.10	2-Methoxy-4-vinyl phenol	1.13	-	-	-	-	-	-
19.30	2,4,4-Trimethylpentanol	-	13.34	1.93	20.04	-	2.21	-
19.49	2,4,4,6,6,8,8-Heptamethyl-1-nonane	-	-	-	25.41	0.68	2.21	-
20.28	Eugenol	1.50	-	-	-	1.19	-	-
20.40	4-Methyl-tridecane	-	-	0.67	-	-	-	-

Table 5.4 (Continued)

			Olefin-treated Bio-oil					
R.T. (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	(60°C) Olefin Phase (area %)	(60°C) Bio-oil Phase (area %)	(80°C) Olefin phase (area %)	(80°C) Bio-oil phase (area %)	(120°C) Olefin phase (area %)	(120°C) Bio-oil phase (area %)
20.40	4-Methyl-tridecane	-	-	0.67	-	-	-	-
20.96	1-Methoxy butane	0.87	-	-	-	-	-	-
20.74	4-methyl octane	-	-	-	-	1.05	-	-
21.40	Vanillin	1.27	-	-	-	2.82	-	-
20.40	4-Methyl-tridecane	-	-	0.67	-	-	-	-
20.96	1-Methoxy butane	0.87	-	-	-	-	-	-
21.60	2-Methoxy-4-(1-propenyl) phenol	1.09	-	0.38	-	0.92	-	0.51
22.67	Homovanillyl Alcohol	3.76	-	12.83	-	4.48	-	-
24.71	Acetamide-2-(4-hydroxy-3-methoxyphenol)	12.70	-	-	-	-	-	-
27.49	Benzene acetic acid	2.94	-	-	-	0.55	-	-
27.31	3-Butenyl pentyl ether	-	-	3.89	-	-	-	-
21.60	2-Methoxy-4-(1-propenyl) phenol	1.09	-	0.38	-	0.92	-	0.51
22.67	Homovanillyl Alcohol	3.76	-	12.83	-	4.48	-	-
24.71	Acetamide-2-(4-hydroxy-3-methoxyphenol)	12.70	-	-	-	-	-	-

[a] Reactions of 2,4,4-trimethylpentene (1 g) with raw bio-oil (4.7 g) were performed using (Amberlyst-15 (0.2 g). 2,4,4-Trimethyl-1-pentene to water 19%, present in bio-oil) mole

ratio was 1:6. Reactions were run for 6 h. GC area % refer to the ion corrents generated in the MS detector and does not represent the true mole percent.

[b] The goal of this work is to know the product profiles of the olefination of bio-oil and catalyst or olefin screening to optimize the process. Thus, quantification of the recovered olefin or any other component was not performed.

[c] The system contained three phases (olefin + bio-oil + Amberlyst-15). '–' indicates the ion-current for the corresponding compound was not detected. Retention time is expressed as 'R.T.'

Table 5.5 Compositions of the Bio-oil Phase of Raw Bio-oil Olefinated with 2,4,4-Trimethyl-1-pentene over Nafion NR-50 at 60, 80 and 120°C for 6 h[a,b]

Retention Time (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	Olefin treated Bio-oil		
			(60°C) (area %)	(80°C) (area %)	(120°C) (area %)
1.74	2,4,4-Trimethyl-1-pentene	0	75.99	55.09	-
1.79	1-Hydroxy-2-propanone	2.91	3.52	-	-
2.02	2-Ethoxy propane	-	1.16	-	-
2.05	Hydroxy-methyl acetate	0.72	-	-	-
2.35	1-Ethoxy-2-propanol	-	0.26	-	-
2.71	1-penten-3-ol	-	0.25	-	-
2.82	3-Methoxy-2,2-dimethyl-oxirane	1.37	-	-	-
4.01	Furfural	-	-	-	-
4.20	1-Methoxy-2,2-dimethyloxirane	1.00	-	-	-
4.52	3-Octanol	-	-	0.62	-
4.67	2,3-Dimethyl-2-hexanol	-	0.65	-	-
4.68	2,4-Dimethyl-2-pentanol	-	0.21	-	-
4.73	2,2-Dimethoxy--2-butanone	3.08	-	-	-

Table 5.5 (Continued)

Retention Time (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	Olefin treated Bio-oil		
			(60°C) (area %)	(80°C) (area %)	(120°C) (area %)
8.16	4-Hydroxypyridine -1-oxide	2.90	-	-	-
9.30	Phenol	1.06	-	-	-
10.58	2-Hydroxy-3-methyl-2-cyclopenten-1-one	1.64	1.82	-	0.33
11.08	1,1-Dimethoxy-3-methyl -pentanone	0.83	-	-	-
11.60	3-Methylphenol	1.12	0.48	-	-
12.32	4-Methyl Phenol	1.86	0.80	-	-
12.45	2-Methoxy phenol	2.43	2.00	0.68	-
12.64	3-Methylbutanal	0.63	-	-	-
13.05	4-Ethoxy-2-butanol	-	-	-	-
13.40	2,3-Dihydroxypropyl butanoic acid	0.63	-	-	-
14.46	2,4-Dimethyl phenol	1.65	-	-	-
15.21	1-Ethenyloxy pentane	-	-	-	-
15.67	2-Methoxy-4-methyl phenol	4.68	1.55	0.61	1.18

Table 5.5 (Continued)

Retention Time (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	Olefin treated Bio-oil		
			(60°C) (area %)	(80°C) (area %)	(120°C) (area %)
15.78	3-penten-2-ol	-	-	0.41	-
16.26	1,2-Benzenediol	1.55	-	-	-
16.50	3-Methyl-3-butene-2-ol	-	-	-	0.27
16.54	5-Methyl-5-Nonanol	-	-	-	-
16.84	4-(1-methylethyl) phenol	0.46	-	-	-
17.09	2-Ethyl-4-methyl Phenol	1.13	-	-	-
17.98	2-Ethoxy-4-methyl phenol	0.69	0.99	-	-
18.78	3-Methyl-1,2-benzenediol	1.37	-	-	-
19.10	2-Methoxy-4-vinyl phenol	1.13	-	-	-
19.13	2,2,4,6,6-Pentamethyl -3-heptane	-	-	38.31	4.70
19.49	2,4,4,6,6,8,8,-Heptamethyl--1-nonene	-	-	25.41	2.21
20.28	Eugenol	1.50	1.02	-	-

Table 5.5 (Continued)

Retention Time (min)	Tentative Identification Of Present Compounds	Raw Bio-oil (area %)	Olefin treated Bio-oil		
			(60°C) (area %)	(80°C) (area %)	(120°C) (area %)
20.96	1-Methoxy butane	0.87	-	-	-
20.74	4-methyl octane	-	-	0.21	-
21.40	Vanillin	1.27	1.14	-	0.33
21.60	2-Methoxy-4-(1-propenyl) phenol	1.09	1.32	0.35	-
22.67	Homovanillyl Alcohol	3.76	-	-	1.35
24.37	Heptanoic acid	3.09	-	-	-
20.96	1-Methoxy butane	0.87	-	-	-

[a]Reactions of 2,4,4-trimethylpentene (1 g) with raw bio-oil (4.7 g) were performed using Nafion NR-50 (0.2 g). 2,4,4-Trimethylpentene to water (19%, present in bio-oil) mole ratio was 1:6. Reactions were run for 6 h. GC area % refer to the ion corrents generated in the MS detector and does not represent the true mole percent.
[b] Only the bio-oil phase was analyzed.

Table 5.6 Representative New Products Found in the Bio-oil Phase after Treating Raw Bio-oil with 2-Ethyl-1-butene at 80 and 120°C for 6 h over Amberlyst-15[a,b]

80 ℃		120℃	
Retention Time (min)	Tentative detection of new compounds found	Retention Time (min)	Tentative detection of new compounds found
2.41	3-Methyl-3-pentanol	16.15	2,2,3,3,5,6,6-Heptamethyl-heptane
16.77	1,2-Octandiol	19.01	*para*-Tertiary-butyl phenol
18.89	*para*-Tertiary-butyl phenol		
21.07	2,2-Dimethyl-1-pentanol		

[a] Reactions of 2-ethyl-1-butene (1 g) with raw bio-oil (6.2 g) were performed for 6 h using Amberlyst-15 (0.2 g) as the acid catalyst. 2-Ethyl-1-butene to water (19 %, present in bio-oil) mole ratio was 1:6.
[b] Only the bio-oil phase was analyzed.

Table 5.7 Representative New Products Found in the Bio-oil Phase after Treating Raw Bio-oil with 2 Ethyl-1-butene at 80 and 120°C for 6 h over Nafion NR-50.[a,b]

80 ℃		120 ℃	
Retention Time (min)	Tentative detection of new compounds found	Retention Time (min)	Tentative detection of new compounds found
2.28	3-methyl-3 pentanol	2.41	3-Methyl-3-pentanol
17.49	1-(Tert-butoxy)-3,3 -dimethylbutane	18.92	2,3-Dimethyl-1-pentanol

[a] Reactions of 2-ethyl-1-butene (1 g) with raw bio-oil (6.2 g) were performed for 6 h using Nafion NR-50 (0.2 g) as the acid catalyst. 2-Ethyl-1-butene to water (19 %, present in bio-oil) mole ratio was 1:6.
[b] Only the bio-oil phase was analyzed.

Table 5.8 Representative New Products Found in the Bio-oil Phase of Methanol Modified Bio-oil Olefinated with 2,4,4 Trimethyl-1-pentene and Amberlyst-15[a,b,c]

60°C		80 °C		120 °C	
Retention Time (min)	Tentative detection of new compounds found	Retention Time (min)	Tentative detection of new compounds found	Retention Time (min)	Tentative detection of new compounds found
2.33	3-Methyl-2-hexanol	1.93	2-Methyl-2-pentanol	4.52	3-Heptanol
4.67	2,5-Dimethyl-2-hexanol	4.67	2,4-Dimethyl-2-pentanol	5.35	2,4-Dimethyl-2-pentanol
5.46	2,4-Dimethyl-2-pentanol	5.48	2-Methoxy-2,4,4-trimethyl pentane	16.49	2,4-Dimethyl-4-octanol
19.30	2,4,4-Trimethyl-2-pentanol	17.25	2-Methyl-1-propionate	19.20	2,4,4-Trimethyl -2-pentanol
		18.66	2,2,4,6,6-Pentamethyl-3-heptane		

[a] Modified bio-oil is made by heating raw bio-oil and methanol in the presence of sulfuric acid. Modified bio-oil contains water and methanol with lowered carboxylic acid contents.

[b]Reactions of 2,4,4-trimethyl-1-pentene (1 g) with modified bio-oil (5.8 g) were performed for 6 h using Amberlyst-15 (0.2 g). Olefin to water (16 %, present in modified bio-oil) mole ratio was 1:6.

[c] Quantification of the recovered olefin or any other component was not done.

Table 5.9 Representative New Products Found in the Bio-oil Phase of Methanol Modified Bio-oil Olefinated with 2,4,4-Trimethyl-1-pentene and Nafion NR-50[a,b,c]

60 °C		80 °C		120 °C	
Retention Time (min)	Tentative detections of new compounds found	Retention Time (min)	Tentative detections of new compounds found	Retention Time (min)	Tentative detections of new compounds found
1.68	2-Methyl-1-propanol	4.53	4-Methyl-3-heptanol	15.01	3,7-Dimethyl-2,6-octadien-1-ol
2.14	1-Methoxy-2,3-dimethl-2-butene	5.35	2-Methoxy-2,4,4-trimethyl butane		
4.66	2-Methyl-heptanol	13.03	2,3-Dimethyl-1-butanol		
7.34	5-Methyl-3-heptanol				
		16.50	2,4-Dimethyl-4-octanol		

[a] Modified bio-oil is made by heating raw bio-oil and methanol in the presence of sulfuric acid. Modified bio-oil contains water and methanol with lowered carboxylic acid contents.

[b]Reactions of 2,4,4-trimethylpentene (1 g) with modified bio-oil (5.8 g) were performed using Nafion NR-50 (0.2 g). Olefin to water (16 %, present in bio-oil) mole ratio was 1:6. Reactions were run for 6 h.

[c] Quantification of the recovered olefin or any other component was not done.

CHAPTER VI

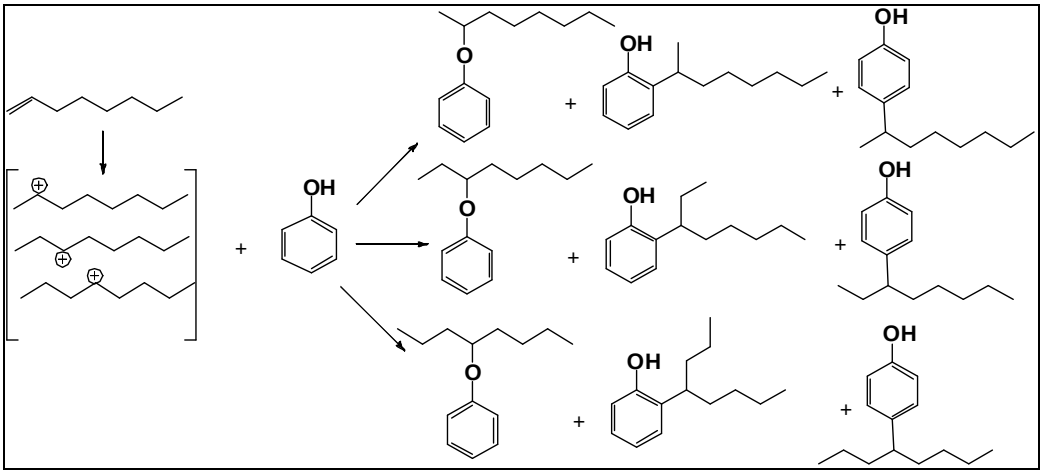
REACTIONS OF RAW BIO-OIL WITH A LARGE EXCESS OF OLEFINS

Introduction and Objective

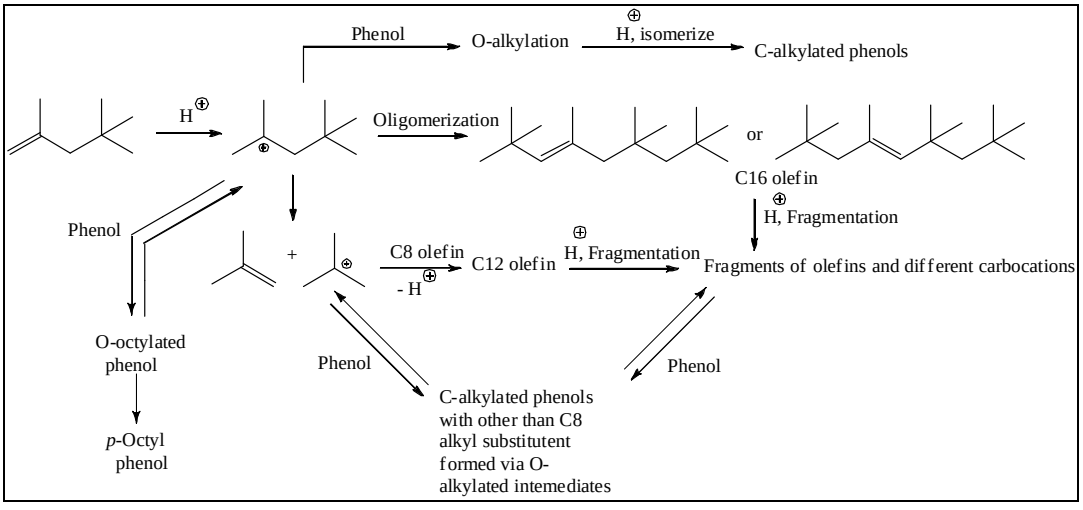
Acid catalyzed olefination of pine wood fast pyrolysis oil or bio-oil is being investigated as a potential upgrading technique to improve bio-oil's fuel quality. Recently, our group reported several model compound studies and preliminary bio-oil reactions to develop this process.[126-128] Some of these reactions and a background about bio-oil olefination were described in the chapter V of this dissertation.

Initial reports from our group[126-128] revealed that a straight chain olefin like 1-octene was more effective at forming phenolic ethers compared to a branched olefin like 2,4,4-trimethyl-1-pentene, where a tertiary carbocation can form on protonation. The olefination of bio-oil in the presence of an acid catalyst goes through the formation of a carbocation (Schemes 6.1 and 6.2).[127] Branched olefins like 2,4,4-trimethyl-1-pentene generate a tertiary carbocation in presence of an acid. This reacts with a phenolic hydroxyl group to initially form the kinetically controlled product, an O-alkylated phenol, which is further converted into the thermodynamically controlled C-alkylated phenol via the regenerated tertiary carbocation. The stability of the tertiary carbocation facilitates the conversion of the kinetic to the thermodynamic product. In the case of the olefination of bio-oil using 1-octene, the O-octyl phenol cannot regenerate the secondary carbocation

as easily. Thus, O-alkylated phenol can be formed as the main product at higher temperatures. This straight chain olefin also generated less olefin and carbocation fragments than branched olefins. Thus, fewer oligomeric olefins and their products appear.[127]



Scheme 6.1 Various Modes of the Alkylation of Phenol with 1-Octene[127]



Scheme 6.2 Different Modes of the Alkylation of Phenol with 2,4,4-Trimethyl-1-pentene[126,127]

All these olefinations consisted of two liquid and one solid (catalyst) phase systems throughout the reaction. Higher temperature reactions (80°C and above) led to higher olefin conversions versus those at lower temperature in the same time period. In most of these olefinations, Amberlyst-15 beads fragmented into tiny particles after the reaction. Nafion NR-50 was found to be more stable than Amberlyst-15.

This chapter will report acid catalyzed olefinations of bio-oil where 1-octene was used in excess, to maximize the uptake of olefin into the products. Amberlyst-70 and Nafion NR-50 were used as catalysts. Amberlyst-70 is a heterogeneous acid catalyst containing sulfonic acid functiontions on a chlorinated styrene-divinyl benzene matrix.[130,131] This macroporous catalyst can withstand higher temperatures than Amberlyst-15 because of the presence of the halogen[131] and it is much less fragile. Amberlyst-70 is particularly useful for catalyzing reactions such as olefin hydrations, aromatic alkylations, etc.[132]

The weight percent of the recovered olefin, the upgraded bio-oil's acid value and water content of each phase of the product mixtures were measured to find out the changes in bio-oil composition and properties.

A series of bio-oil olefinations were performed using 1-octene in presence of ethanol. Ethanol was added to make the two separate phases (olefin and bio-oil) more (partially) miscible. This could enhance the interaction between the compounds in the bio-oil phase with the olefin, improving mass transport rates and reaction rates. Secondly, ethanol will react with carboxylic acids to form esters and aldehydes and ketones to form acetals. These reactions stabilize bio-oil, increase fuel value and reduce hydrophilicity.

The weight percent of recovered olefin, the acid value, water content and heating values of some of these upgraded samples are reported.

Experimental

Materials

Pine wood bio-oil, prepared by fast pyrolysis at 450-470°C in an auger reactor, [118-120] was supplied by the Forest Products Laboratory, Mississippi State University. 1-Octene was the only olefin used. It was purchased from Sigma-Aldrich. Nafion NR-50 and ethanol (HPLC grade) were also purchased from Sigma-Aldrich and Amberlyst-70 was obtained from Rohm and Haas. All chemicals were used as received.

Reactions

Bio-oil olefinations without ethanol were run at three different temperatures (80°C, 100°C, 120°C controlled by an external oil bath) in a 100 mL sealed high pressure glass vessel. Magnetic stirring was used in all these reactions. In all cases, the olefin/ bio-oil H_2O mole ratio was 2:1, where the water content of the raw bio-oil was 30%. Since water is by far the most abundant compound in raw bio-oil, this amount of olefin is sufficient to react with all the carboxylic acids, phenols and water present. Olefinations without ethanol were conducted on 5 g of bio-oil in a high pressure glass vessel to which 18.7 g of 1-octene was added. After the addition of 1 g of the catalyst (Amberlyst-70 or Nafion–NR-50) and a magnetic stirrer, each reaction was run for 6 h.

Olefinations of bio-oil in the presence of ethanol were performed similarly. However, considering the low boiling point of ethanol and the use of glass pressure vessels, the reactions were performed at 80, 90 and 100°C. Higher temperatures (e.g. 120°C) were avoided to keep the pressure below the rupture pressure of the vessel. Reactions were performed with 1 g of ethanol (20% of bio-oil weight). All of these reactions were run with 18.7 g of 1-octene.

Analyses of Product Mixtures

GC/MS Analyses of Product Mixtures obtained by the Olefination of Bio-oil without Ethanol

After cooling product mixtures to room temperature, the two phases present were separated and stored in glass vials. These phases were analyzed separately using a Hewlett Packard 5890 series II-Gas chromatograph/5971 series A-mass spectrometer (injector temperature 270^{o}C) with a silica capillary column coated with 5% phenylmethyl-polysiloxane (30-meter x 0.32 mm internal diameter x 0.25 µ filmthickness). An initial temperature of 40^{o}C (4 min. hold) was followed by heating at 5^{o}C /min to a final temperature of 280^{o}C.

A 70 eV electron impact ionization mode was used with a 250^{o}C source (detector) and a 270^{o}C interface temperature. A 0.2 mg representative aliquot of the product was diluted with dichloromethane (10 mL). This solution (1 mL) was then transferred to the autosampler vial and 10 µL of internal standard (40.00 µg/mL concentrations) was added.

Then 2.0 µL of this sample was injected into the GC to acquire each chromatogram. A mixture of six isotopically labeled compounds (US 108N, Ultra Scientific) were employed as internal standards including: 1,4-dichlorobenzene-d_4, naphthalene-d_8, acenapthene-d_{10}, phenanthrene-d_{10}, chrysene-d_{12} and perylene-d_{12}. Internal standards were used to verify the retention times and to quantitate the recovered olefin in product mixtures using equation 6.1. The GC/MS analyses of these reaction sets were performed in the Forest Product Laboratory, Mississippi State University using their equipment.

GC/MS Analyses of the Product Mixtures obtained in Raw Bio-oil Upgrading with 1-Octene and Ethanol

After cooling product mixtures to room temperature, the two phases present (1-octene top and bio-oil bottom layers) were combined into one single phase using the co-solvent, THF. This single phase was analyzed using a SHIMADZU QP 2010S-Gas chromatograph-mass spectrometer (injector temperature 300^{o}C) with a SHRXI-5MS 30 m x 0.25 mm i.d. x 0.25 µm film capillary column. Helium was used as the carrier gas. An initial temperature of 40^{o}C (3 min. hold) was used followed by heating at 5^{o}C/ min to a final temperature of 250^{o}C and then holding at 250°C for 10 min. A 70 eV electron impact ionization mode was used with a 200^{o}C source (detector) and a 275^{o}C interface temperature.

$$R_f = \frac{(\text{Peak area of the olefin in the standard})(\text{Conc. of the I.S.})}{(\text{Peak area of the I.S. in standard})(\text{Conc. of the olefin})}$$

Equation 6.1

$$\text{Concentration of the olefin (wt. \% of olefinated bio-oil)} = \frac{(\text{Peak area of the olefin in the sample})(\text{Conc. of the I.S.})(100)}{(\text{Peak area of the I.S. in the sample})(R_f)\ (\text{Wt. of the sample})}$$

Equation 6.2

I.S.: Internal standard

R_f : Retention Factor

A representative amount of each sample was taken into a 100 mL volumetric flask and then diluted with 100 mL of THF. This solution (1 mL) with internal standard dodecane was taken into an auto sampler vial. This sample (2.0 µL) was injected to acquire each chromatogram. The weight percent of the recovered olefin in the total product mixture was calculated using equation 6.2. The total olefin consumption in each reaction was calculated using equation 6.3 by subtracting the amount of olefin recovered from both phases from the weight of initial olefin (18.7 g).

$$\%\ \text{Consumption of olefin} = ((18.7\text{-}X) / 18.7)100$$

Equation 6.3

X: Olefin recovered from combined phases or the sum of recovered olefin from two phases

Physical Analyses

The weight percent of water and acid values of the upgraded product mixtures were obtained on samples treated only with 1-octene and those treated with 1-octene plus ethanol. These quantities were determined in the Forest Products Laboratory, Mississippi State University, with their equipment. Samples upgraded with ethanol and 1-octene were run few times under identical conditions. Then, each of the phases in each batch were analyzed. Percent water was determined using Karl Fisher titration with a Cole-Parmer Model C-25800-10 titration apparatus. The acid value was determined by titrating 1 g of product mixture dissolved in 50/50 v/v isopropanol/water with 0.1 N standardized NaOH to a pH 8.5, where phenolphthalein gave a strong red color while titrating with a strong base. (heating) values of the samples (for olefination with 20% ethanol) were measured in the Forest Products Lab, Mississippi State University.

Results and Discussions

Olefination of Raw Bio-oil with Excess 1-Octene Catalyzed by Amberlyst-70

These two phase reaction mixtures (1-octene phase and a bio-oil phase) gave two phase product mixtures after reaction for 6 h at all three temperatures (80°C, 100°C, 120°C). In all reactions, the color of the 1-octene phase changed from clear to dark yellow during the reaction due to the extraction of some bio-oil components into 1-octene (Figure 6.1). At higher reaction temperatures, this color change was more intense. Both original bio-oil components and new products generated from the reaction could have

moved into the olefinic phase. All of these reactions were run in sealed high pressure glass vessels and they were cooled before transfer to minimize any gas loss. In all cases, both 1-octene and bio-oil phases lost some weight during the separation of the phases, due to the hold up of bio-oil or 1-octene phase in the separatory funnel and glassware used in the workups (Table 6.1). The swollen catalyst also adsorbed some small quantities of these components. At 120°C, darkening of Amberlyst-70 catalyst was observed. The average weight loss of the olefinated bio-oil was about 11.9 %.

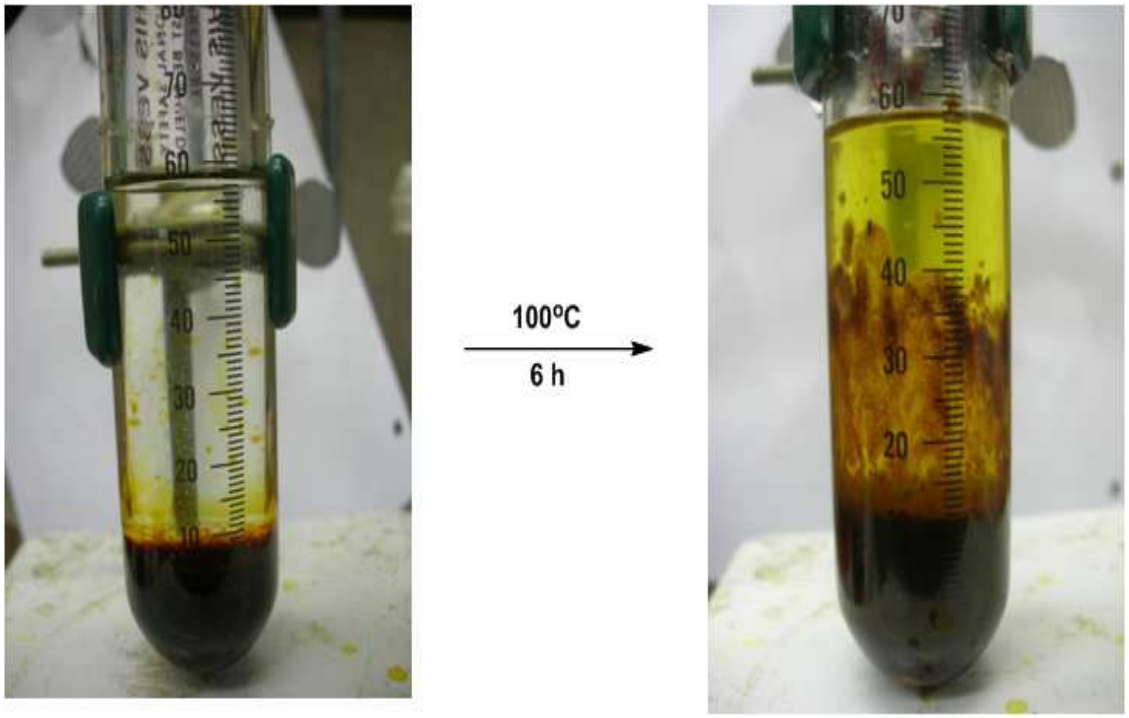


Figure 6.1 A 1-Octene and Bio-oil Mixture Before and After Reaction[a]

[a]1-Octene (18.7 g) was reacted with 5 g of raw bio-oil. The mole ratio of 1-octene to water (present in the raw bio-oil) was 2:1 in every case. Amberlyst-70 (1 g) was employed in each reaction. Reactions were run for 6 h at 100°C.

The percent consumption of 1-octene increased with temperature (Table 6.2). The total percent consumption of olefin in each case was calculated considering the olefin consumption in each phase separately and then adding them. Olefination of raw bio-oil could change the phase weights as different components and reaction products can move from one phase to another. In the calculation of 1-octene consumption, the lost mass due to the hold ups was not incorporated. Thus, the reported percent 1-octene consumptions reflect the maximum amount of olefin that could be incorporated into bio-oil. It is important to determine the trend in olefin consumption in reactions of raw bio-oil with excess 1-octene. The maximum consumption of 1-octene was 67% at 120°C.

Table 6.1 Mass Losses During the Olefination of Raw Bio-oil with 1-Octene Catalyzed with Amberlyst-70 at 80, 100 and 120°C[a]

Temp (°C)	1-Octene Layer (g)	Change %	Bio-oil Layer (g)	Change %	Amberlyst -70 (g)	Change %	Total (all phases) (g)	Change %
Room Temp (Initial)	18.7	-	5.0	-	1.0	-	24.7	-
80 (After Reaction)	16.3	(-) 12.8	4.7	(-) 6	1.3	(+) 30	22.3	(-) 9.9
100 (After Reaction)	15.7	(-) 15	4.5	(-)10	1.3	(+) 30	21.4	(-) 13.3
120 (After Reaction)	15.9	(-) 15	4.3	(-)14	1.4	(+) 40	21.6	(-) 12.5

[a] 1-Octene (18.7 g) was reacted with 5 g of raw bio-oil. The mole ratio of 1-octene to water (present in the raw bio-oil) was 2:1 in every case. Amberlyst-70 (1 g) was

employed in each reaction. Reactions were run for 6 h. Mass loss accompanies the separation of layers with hold up occurring in the separatory funnel etc.

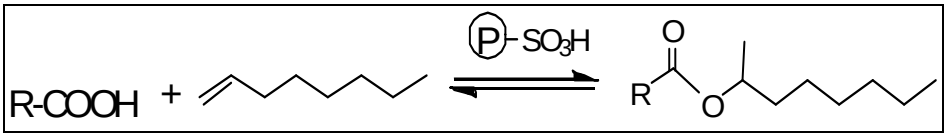
Table 6.2 Weight Percent of 1-Octene Present after Conducting Raw Bio-oil Olefination Reactions Catalyzed by Amberlyst-70 at 80, 100 and 120°C[a,b,c]

Reaction Temp (°C)	1-Octene in the top layer (g)	1-Octene in the bio-oil layer (g)	1-Octene consumed [b] (g)	1-Octene Consumed (wt. % of orig. olefin)[c]
80	10.2	0.6	7.5	40.0
100	7.5	0.2	10.9	59.0
120	5.7	0.4	12.6	67.0

[a]1-Octene (18.7 g) was treated with 5 g of raw bio-oil in sealed high pressure glass Vessel. Amberlyst-70 (1 g) was employed. Reactions were run for 6 h.
[b] The 1-octene consumed was determined by summing the weight of 1-octene found in the top and bottom layers and subtracting this from the original 18.7 g of 1-octene charged into the reaction.
[c] This represents the highest possible 1-octene consumption because the calculation does not include the mass loss during the workup. Lower mass loss could decrease the value of the 1-octene consumed.

The water content of the bio-oil phase was lowered the most (from 1.5 to 1.11 g), in the upgrading reaction run at 100°C (Table 6.3). This indicates that 1-octene was able to take out water by conversion to octanols. This result supports the assumption that in presence of a suitable acid catalyst, 1-octene can react with water present in bio-oil and form alcohols and decrease bio-oil's water content. The olefination of raw bio-oil using 1-octene was able to decrease the water content in all the reactions attempted in this work.

There was a modest overall decrease of acid value in each case. The acid value of the olefinated bio-oil was lowest (75.66) when the reaction temperature was 80°C (Table 6.3). This acid value is noticeably lower than that of the raw bio-oil (98.5). In the olefinations of bio-oil, 1-octene reacts with various carboxylic acids (Scheme 6.3) and acidic phenolics (Scheme 6.3) to form esters and ethers, respectively. These reduce acidity of the system. O-Alkylation of phenols are more favorable at 80°C compared to 120°C because more kinetic product is captured. At higher temperatures more equilibrium from O- to C-alkylated product (thermodynamic product) occurs.



Scheme 6.3 Reactions of 1-Octene with Carboxylic Acids

Table 6.3 Comparison of Percent Water and Acid Values of Bio-oil after Reactions with 1-Octene Catalyzed by Amberlyst-70 at 80, 100 and 120°C[a,b,c]

Reaction Temperature (°C)	Product	Water Content (g)	Water Consumed (wt. % of original water)	Acid Value	Total 1-Octene Consumed (g)	Total 1-Octene Consumed (wt. % of orig. olefin)
80	Top Layer	-	9.3	0.81	7.8	40.0
	Bottom Layer	1.36		75.66		
100	Top Layer	-	6.0	2.15	10.9	59.0
	Bottom Layer	1.11		85.17		
120	Top Layer	-	14.6	2.19	12.5	67.0
	Bottom Layer	1.28		89.67		
Raw Bio-oil		1.5		98.5		

[a] 1-Octene (18.7 g) was treated with 5 g of raw bio-oil in sealed high pressure glass vessel. Amberlyst-70 (1 g) was employed. Reactions were run for 6 h.
[b] The 1-octene consumed was determined by summing the weight of 1-octene found in the top and bottom layers and subtracting this from the original 18.7 g of 1-octene charged into the reaction.
[c] Highest possible 1-octene consumption as the calculation does not include the mass loss during the workup. Lower mass loss could decrease the weight % of 1-octene conversion.
Olefination of Raw Bio-oil by 1-Octene Catalyzed by Nafion NR-50.

Olefination of Raw Bio-oil by 1-Octene Catalyzed by Nafion NR-50

Olefination of bio-oil using the polymeric fluorosulfonic acid catalyst Nafion NR-50[123,124,125] gave results similar to Amberlyst-70-catalyzed reactions. However, catalyst swelling occurred during the reaction and was a maximum at 100° C where these catalyst beads changed their color from clear to black. At higher temperature this swelled catalyst formed char surrounding the particles. Nafion NR-50 catalysts also adsorbed bio-oil and olefin phase components. However, the mass loss of these systems (1-octene + raw bio-oil + Nafion NR-50) was less (average 5.6%) than that of Amberlyst-70 (Table 6.4). This may be due to the lower surface area of Nafion NR-50 versus Amberlyst-70.

Nafion-catalyzed olefinations of raw bio-oil consumed slightly more 1-octene with a rise in temperature from 80°C (41 % 1-octene consumption) to 120°C (47 % consumption) (Table 6.5). However, 1-octene consumption (40.6 %) at 100°C was, within experimental error, was the same as at 80°C. Overall, less 1-octene conversion occurred using the Nafion NR-50 catalyst than using Amberlyst-70. The water content in the product was reduced to 1.00 g at 120°C (Table 6.6). The acid values decreased after treatment at all temperatures and the 100°C reaction again showed the poorest result. The lowest acid value is obtained at 80°C (74.52) which is similar to the acid value trend of Amberlyst-70 catalyzed reactions.

Table 6.4 Mass Losses During the Olefination of Raw Bio-oil with 1-Octene Catalyzed by Nafion NR-50 at 80, 100 and 120°C[a]

Reaction Temp (°C)	1-Octene Layer (g)	Change (%)	Bio-oil Layer (g)	Change (%)	Nafion NR-50 (g)	Total Change all phases (%)	(g)	Change (%)
Room Temp (Initial)	18.7	-	5.0	-	1.0	-	24.7	-
80 (After Reaction)	17.3	(-) 7.4	4.7	(-) 6.0	1.6	(+) 60	23.6	(-) 4.4
100 (After Reaction)	17.2	(-) 8.0	4.2	(-) 16.0	1.9	(+) 90	23.3	(-) 5.6
120 (After Reaction)	17.1	(-) 8.5	4.0	(-) 20.0	1.8	(+) 80	23.0	(-) 6.8

[a] 1-Octene (18.7 g) was reacted with 5 g of raw bio-oil. The mole ratio of 1-octene to water (present in the raw bio-oil) was 2:1 in every case. Nafion NR-50 (1 g) was employed in each reaction. Reactions were run for 6 h. Mass loss accompanies the separation of layers with hold up occurring in the separatory funnel etc.

Table 6.5 Weight Percent of 1-Octene Present after Raw Bio-oil Olefination Reactions Catalyzed by Nafion NR-50 at 80, 100 and 120°C[a,b,c]

Temp (°C)	1-Octene in the top layer (g)	1-Octene in the bio-oil layer (g)	1-Octene Consumed [b] (g)	1-Octene Consumed [c] (wt. % of orig. olefin)
80	10.9	0.1	7.7	41.0
100	10.6	0.5	7.6	40.6
120	9.8	0.1	8.8	47.0

[a]1-octene (18.7 g) was treated with 5 g of raw bio-oil in a sealed high pressure glass vessel. Nafion NR-50 (1 g) was employed. Reactions were run for 6 h.
[b] The 1-octene consumed was determined by summing the weight of 1-octene found in the top and bottom layers and subtracting this from the original 18.7 g of 1-octene charged into the reaction.
[c] These represent the highest possible 1-octene consumption because the calculation does not include the mass loss during the workup. The lower the mass loss closer the percent 1-octene consumed will come to the values.

Table 6.6 Comparison of Percent Water and Acid Values of Olefinated Product Mixtures Catalyzed by Nafion NR 50 at 80, 100 and 120°C[a,b,c]

Reaction Temperature (°C)		Water Content (g)	Water Consumed (wt. % of original water present)	Acid Value	Total 1-Octene Consumed (g)	Total 1-Octene Consumed (wt. % of original olefin)
80	Top Layer	-	12.0	1.67	7.6	41.0
	Bottom Layer	1.32		74.52		
100	Top Layer	-	17.0	1.67	7.5	40.6
	Bottom Layer	1.25		92.38		
120	Top Layer	-	33.0	1.96	8.8	47.0
	Bottom Layer	1.00		83.71		
Raw Bio-oil		1.5		98.5		

[a]1-octene (18.7 g) was treated with 5 g of raw bio-oil in a sealed high pressure glass vessel. Nafion NR-50 (1 g) was employed. Reactions were run for 6 h.
[b] The 1-octene consumed was determined by summing the weight of 1-octene found in the top and bottom layers and subtracting this from the original 18.7 g of 1-octene charged into the reaction.
[c] These represent the highest possible 1-octene consumption because the calculation does not include the mass loss during the workup.

Olefination of Raw Bio-oil with Excess 1-Octene and Ethanol (20% wt of Raw Bio-oil) Catalyzed by Amberlyst-70 or Nafion NR-50

When the olefination of raw bio-oil was conducted with 1-octene in presence of 1 g of ethanol (per 5 g of raw bio-oil), in all of the reactions some mass loss occurred due to hold up of components from product mixture on glass surfaces. When, Nafion NR-50 was used as the catalyst, tar formation on the catalyst was found at 100°C. The catalyst was swelled and gooey. The chromatograms of the raw bio-oil and olefinated bio-oil (catalyzed by Amberlyst-70 and Nafion NR-50 at 90°C) are shown in Figure 6.2.

When Amberlyst-70 was used, the olefin consumptions were similar at 80, 90 and 100°C (20.8, 25.6 and 24% of the initial olefin, respectively). Olefin consumption in the Nafion NR-50 catalyzed reactions were somewhat lower (16-24.7% of the initial olefin amount) than that of Amberlyst-70 (Table 6.8). The water content of the product mixtures varied from 1 to 1.4 g, versus a water content of 1.5 g in the raw bio-oil charged to the reactions (Tables 6.9 for Amberlyst-70 and 6.10 for NR-50). The acid values of the product mixtures decreased noticeably in all cases. The acid values of the upgraded bio-oil's were between 50-60 for Amberlyst-70 catalyzed reactions(Table 6.9) and 48-53 for Nafion NR-50 catalyzed reactions (Table 6.10). These can be compared to the value of 98.5 for raw bio-oil.

The heating values of the samples showed only modest increases in the highest heating values. The largest gain was obtained in the case of the Amberlyst-70 catalyzed reactions performed at 90°C and 100°C (18.2 MJ/kg compared to 14.6 MJ/kg in the case of raw bio-oil) (Table 6.11).

Table 6.7 Weight Percent of 1-Octene Consumed in Bio-oil Upgrading using 1-Octene in Presence of Ethanol (20% of the Weight of Bio-oil) Catalyzed by Amberlyst-70 respectively at 80, 90 and 100°C[a]

Temp (°C)	1-Octene Consumed (g)	1-Octene Consumed (% wt. of orig.)c
80	3.9	20.8
90	4.8	25.6
100	4.5	24.0

[a]1-Octene (18.7 g) was treated with 5 g of raw bio-oil and 1 g of ethanol in sealed high pressure glass vessel. Amberlyst-70 (1 g) was employed. Reactions were run for 6 h.

Table 6.8 Weight Percent of 1-Octene Consumed in Bio-oil Upgrading using 1-Octene in Presence of Ethanol (20% of the Weight of Bio-oil) Catalyzed by Nafion NR-50 respectively at 80, 90 and 100°C[a]

Temp (°C)	1-Octene Consumed (g)	1-Octene Consumed (% wt. of orig.)
80	4.1	21.9
90	4.6	24.7
100	3.0	16.0

[a]1-Octene (18.7 g) was treated with 5 g of raw bio-oil and 1 g of ethanol in sealed high pressure glass vessel. Nafion NR-50 (1 g) was employed. Reactions were run for 6 h.

Table 6.9 Comparison of Percent Water and Acid Values of Bio-oil Treated with 1-Octene and Ethanol (20% of Bio-oil Weight) Catalyzed by Amberlyst-70 at 80, 90 and 100°C[a]

Temperature (°C)	Bio-oil	Water Content (g)	Acid Value
80	Top Layer	-	1.10
	Bottom Layer	1.43	51.06
90	Top Layer	-	1.36
	Bottom Layer	1.04	49.73
100	Top Layer	-	1.19
	Bottom Layer	1.00	59.67
Raw Bio-oil		1.5	98.5

[a]1-Octene (18.7 g) was treated with 5 g of raw bio-oil and 1 g of ethanol in sealed high pressure glass vessel. Amberlyst-70 (1 g) was employed. Reactions were run for 6 h.

Table 6.10 Comparison of Percent Water and Acid Values of Bio-oil Treated with 1-Octene and Ethanol (20% of Bio-oil Weight) Catalyzed by Nafion NR-50 at 80, 90 and 100°C[a]

Temperature (°C)		Water Content (g)	Acid Value
80	Top Layer	-	1.66
	Bottom Layer	1.33	48.26
90	Top Layer	-	1.38
	Bottom Layer	0.91	48.11
100	Top Layer	-	1.67
	Bottom Layer	1.35	52.97
Raw Bio-oil		1.5	98.5

[a]1-Octene (18.7 g) was treated with 5 g of raw bio-oil and 1 g of ethanol in sealed high pressure glass vessel. Nafion NR-50 (1 g) was employed. Reactions were run for 6 h.

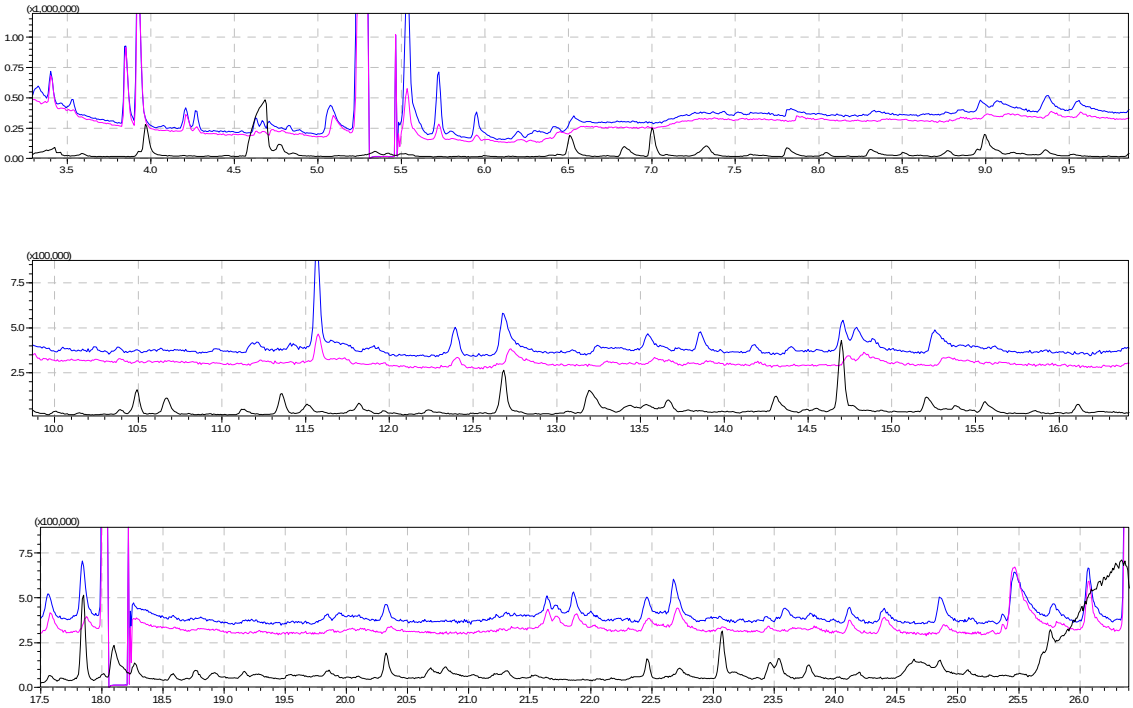


Figure 6.2 Comparison of Chromatograms of 1) Raw Bio-oil (Bottom), 2) Nafion NR-50 Catalyzed Olefinated Bio-oil (Middle) and 3) Amberlyst-70 Catalyzed Olefinated Bio-oil (Top). Both Reactions were performed using 5 g of Raw Bio-oil , 18.7 g of 1-Octene, 1 g of Ethanol and 1 g of the Catalyst. The Reactions were run at 90°C

Table 6.11 Heating Values of the Phases in the Olefination (using 1-Octene in Presence of 20% Ethanol) of Bio-oil Catalyzed with Nafion NR-50 and Amberlyst-70 at 80, 90 and 100°C[a]

Temp (°C)	Nafion NR-50		Amberlyst-70	
	Top Phase (MJ/kg)	Bottom Phase (MJ/kg)	Top Phase (MJ/kg)	Bottom Phase (MJ/kg)
80	44.32	15.52	45.20	14.19
90	45.46	16.73	45.41	18.24
100	44.84	16.66	45.11	18.26
1-Octene	46.52			
Raw Bio-oil	14.67			

[a]1-Octene (18.7 g) was treated with 5g of raw bio-oil and 1 g of ethanol in sealed high pressure glass vessel. Nafion NR-50 or Amberlyst-70 (1 g) was employed. Reactions were run for 6 h.

Conclusions

Acid catalyzed olefination of raw bio-oil induced some changes in the resulting bio-oil. Olefination with excess 1-ocetene showed the decrease of water content and acid values in the olefinated bio-oil. However, the decrease in water content was moderate in most of the cases. The GC-MS analysis of the product mixtures showed the absence of some of the known components like phenol or substituted phenols in some cases. The consumption of olefin was moderate and followed a linear trend in Amberlyst-70 catalyzed reactions. Nafion NR-50 was found to be not suitable for this kind of system.

The addition of ethanol could not transform the three phase (olefin + bio-oil + solid acid catalyst) system into a two phase (liquid + solid) system. However, it made the two liquid phases partly miscible. Olefin consumptions of all the reactions in presence of ethanol were less compared to that of the olefination reactions without ethanol. This may be due to the formation of acetals or esters by the reactions of alcohols and keteones, acids respectively which could not react with olefins anymore.

All the above studies indicate that Amberlyst-70 is a better catalyst than Nafion NR-50 in the acid catalyzed olefination reaction of bio-oil. However, more robust catalyst should be used to get better result. Ethanol was not successful to make the two liquid phases completely miscible. Thus, a suitable co-solvent is needed to make the system one phase (not considering the catalyst).

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