EFFICIENT ROUTES TO OXAZOLINES AND OXAZOLES THROUGH ACTIVATION OF AMIDES

by

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ABSTRACT

EFFICIENT ROUTES TO OXAZOLINES AND OXAZOLES

THROUGH ACTIVATION OF AMIDES

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Oxazolines are nitrogen-containing heterocyclic compounds that are of a special interest due to their applications as active components in a broad range of pharmaceutical products. A challenging task remains in developing reliable and efficient methods that would allow expedient approach to these heterocycles from inexpensive and environmentally friendly substrates and reagents. During preliminary studies, it was unexpectedly found that oxazoline can be produced by reacting *N*,*N*-dichlorobenzamide with styrene. The central goals of this thesis project were:

- to optimize the conditions for the formation of *N*,*N*-dichlorobenzamide by chlorinating benzamide, and

- to optimize coupling of *N*,*N*-dichlorobenzamide with a representative alkene, styrene, leading to the formation of oxazoline. There are no prior literature reports of using chloro amides for the synthesis of these heterocycles.

Trichloroisocyanuric acid (TCCA) belongs to the family of *N*-chloroamides, which are commonly used as bleaching agents and bactericides. In this study, TCCA was used as a chlorinating agent for the amide starting material, following a recent literature report. While a mixture of *N*,*N*-dichlorobenzamide and *N*-monochlorobenzamide was

produced initially in the reaction of benzamide with TCCA, screening of the reaction conditions (varying solvents, temperature, isolation procedure) revealed the set that results in clean formation of the dichloroamide.

Following chlorination, reaction conditions for the coupling of *N,N*-dichlorobenzamide with styrene were optimized. The results of the preliminary investigation confirmed that the oxazoline ring is indeed formed (a transformation not yet described in the literature), albeit with a concurrent formation of an acyclic side product, later assigned as *N*-(2-chloro-2-phenylethyl)benzamide. The two products are close in polarity and not easily separable using column chromatography. After considerable effort, two unique sets of conditions (base-mediated and MnO_2-mediated) were discovered that convert *N*-(2-chloro-2-phenylethyl)-benzamide into the target oxazoline.

A one-pot procedure for oxazoline formation starting from benzamide that does not require the purification of reaction intermediates was subsequently developed and rendered to yield 73% of the desired product, 2,5-diphenyl-2-oxazoline. In addition, applying this procedure to *p*-methylstyrene and *p*-toluamide resulted in formation of two homologous oxazoline products, which were both isolated in a 75% yield (2-(4-methylphenyl)-5-phenyloxazoline and 5-(4-methylphenyl)-2-phenyloxazoline.

Finally, several oxidizing conditions were developed that allow to convert the formed oxazoline into oxazole, using DDQ and/or MnO_2, with up to 65% efficiency.

In summary, preparing oxazolines and oxazoles using the newly developed transition metal-free methods is very promising for future pharmaceutical applications.

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CHAPTER I: INTRODUCTION

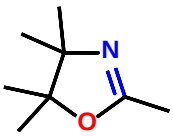
1.1 Introduction

1.1.1 General Description of Heterocyclic Compounds

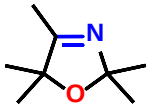
Heterocycles are cyclic compounds incorporating one or more heteroatoms into their ring structure, commonly O, N, P, or S elements. The common building blocks for the construction of heterocycles include: amides, amidines, carboxylic acids, urea, thiols, thioethers, thioketones, and others, as recorded in a number of monographs on the subject [1]. Heterocycles are present in a variety of natural nucleic acids, amino acids, and hormones, as well as synthesized molecules with various biological activity. In fact, out of 200 drugs sold in the US in 2016, 100 have a heterocyclic moiety in their structure [2]. Most commonly studied **nitrogen**-containing heterocycles have five or six-membered rings, examples include pyridine, pyrrole, oxazole, and oxazoline [3].

1.1.2 Oxazolines

Oxazolines are five-membered heterocyclic compounds, which contain one oxygen atom and one nitrogen atom. They are commonly used as ligands, main function of which is to serve as directing groups in organic synthesis [4]. Oxazoline ring is also a commonly encountered motif in pharmaceuticals and bioactive natural products [5]. There are three possible isomers of oxazolines depending on the location of the double bond: 2-oxazolines, 3-oxazolines, 4-oxazolines, and another isomer called isoxazoline. In isoxazoline, the nitrogen atom is adjacent to the oxygen atom as shown below [4].

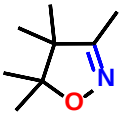


2-oxazoline



3-oxazoline

4-oxazoline



5-oxazoline

1.2 Background

Even though discovered in 1884 [6], interest in the chemistry of oxazoline and its derivatives has not emerged until later, when Gabriel was able to correctly assign its structure [6]. The oxazoline was recognized as one of the key ring structures in heterocyclic chemistry since then, with a wide variety of applications, ranging from food industry, agricultural industry, polymers to pharmaceutics and medicine. Oxazolines are also a part of some natural products.

The oxazoline moiety comprises the core structure in a variety of natural compounds many of which are biologically active. In medicinal chemistry, some oxazoline derivatives show significant levels of biological acitvities: anti-malarial, anti-viral, anti-bacterial, anti-tumour, anti-inflammatory, and anti-pyretic activities.

1.3 Oxazoline Applications and Importance

Organic chemists developed synthetic routes to a variety of oxazoline derivatives, such as compound **1** (see Scheme 1), with pronounced anti-microbial activity.

The analogues of oxazolines are also present in some pain medications, particularly when managing the oncological pain [5]. This is because they show remarkable efficiency as chemotherapeutic agents, having found application as anti-inflammatory and analgesic agents, such as **2** presented in Scheme 1 [5].

Every year, about 1.5 to 2.7 million malaria-infection deaths are reported with over 300 million clinical cases. *Plasmodium falciparum* is responsible for most of these

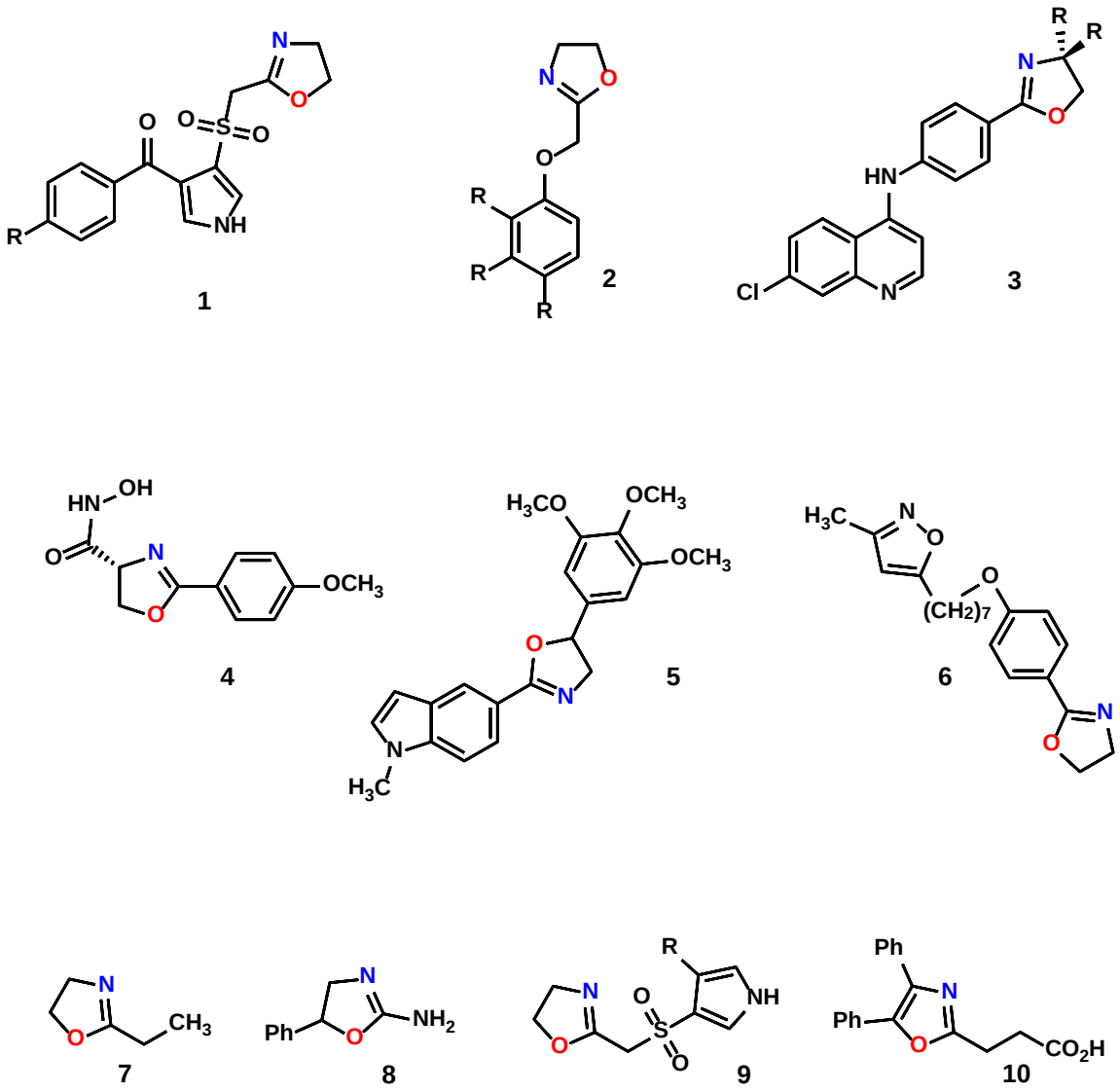
cases being the most virulent malaria species affecting humans. Over time, the cost effectiveness and potent biological activity of 2-oxazolines have been recognized. Investigation of an anti-malarial derivative **3**, as shown in Scheme 1, was carried out by Gordey and coauthors [5].

Humankind faces a lot of health problems due to bacterial infections. Antibiotics-resistant bacteria prompted the research of conceptually novel anti-bacterial agents. One of such agents is compound **4**, an oxazoline showing promising anti-bacterial activity [5].

A number of oxazoline derivatives with anticancer activity have been reported as well. Li and coworkers pioneered the synthesis of indole series containing oxazoline moiety, such as compound **5** [5]. These indoles exerted their active anticancer property via tubulin polymerization inhibition through binding at the sites of colchicines. During the study, it was discovered that the compound was an orally available antimitotic agent showing activity against a variety of cancer cell lines.

Chiral oxazoline-*N*-oxide **6** has been used in the synthesis of a potent antiviral agent. An unusual (-)-carbovir's structure has been found to be effective in the AIDS treatment [5]. Owing to this aspect, a lot of interest in this molecule sparked numerous literature on this subject, including recent report on the isolation of (+)-carbovir, a compound with a new type of antiviral activity [5].

Some other examples of oxazoline-containing products are 2-ethyl-2-oxazoline **7** used for producing water-soluble pharmaceuticals and cosmetics, Aminorex **8** used to treat anorexia, pyrrolyl oxazolines **9** used for their antioxidant properties, and oxaprozin **10** used for juvenile rheumatoid arthritis relief as shown in Scheme 1 [1].



Scheme 1. Substances that Contain Oxazoline Fragment in Their Structure.

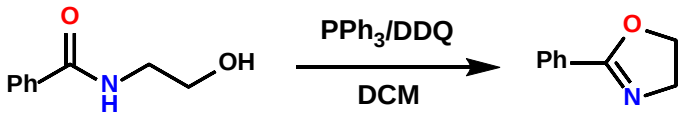
CHAPTER II: LITERATURE REVIEW

2.1 Synthesis of Oxazolines

There has been a number of reported routes to oxazolines. Syntheses starting from amides, nitriles, acids, esters, and aldehydes have been reported, among other methods. This chapter looks into the most commonly used routes to the synthesis of oxazolines.

2.1.1 Using Hydroxy Amides

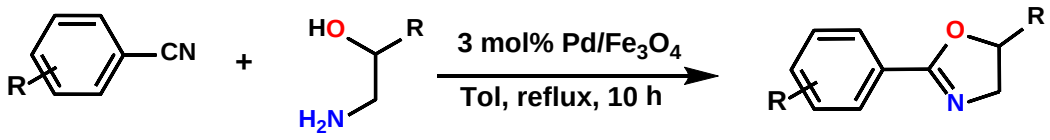
Some hydroxy amides yield oxazolines under moderate heat with no dehydrating agent used while others hardly cyclize, requiring dehydrating agents and high temperatures. For example, 2-oxazolines **12** can be efficiently obtained from *N*-(2-hydroxyethyl) amides **11** by use of triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as shown in the reaction equation below [7]. This unusual intramolecular substitution reaction was carried out under mild conditions obtaining good to excellent yields. However, the use of DDQ makes this method less attractive for pharmaceutical purposes due to the high toxicity of this reagent.



11 **12**

2.1.2 Using Nitriles

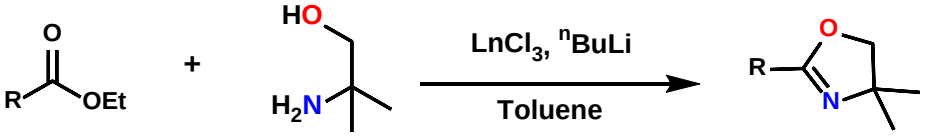
Reaction of amino alcohols with aromatic nitriles in the presence of a number of catalysts results in oxazoline formation. For instance, oxazoline **15** was synthetized from amino alcohol **14** and benzonitrile **13** mixture in toluene at a 100 ^{o}C, in the presence of catalytic Pd/Fe_3O_4 [8]. Amino alcohols for this method can be prepared according to existing literature procedures [8].



13 14 15

2.1.3 Using Esters

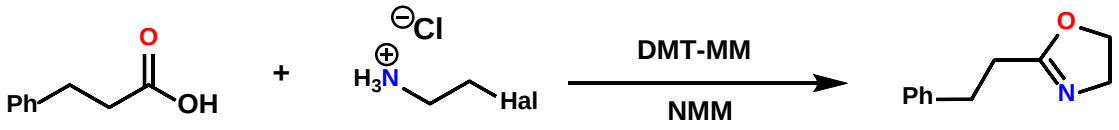
Reacting esters with amino alcohols was shown to yield oxazolines by Zhou and coworkers [9]. Their approach to 2-oxazolines **17** found application in synthetic chemistry due to its efficiency and broad scope. Therein, 2-oxazoline synthesis is carried out from esters and amino alcohols using lanthanide(III) chloride and butyllithium. Use of pyrophoric base (butyllithium) sets limitations on applying this method on industrial scale.



16 17

2.1.4 Using Ammonium Salts

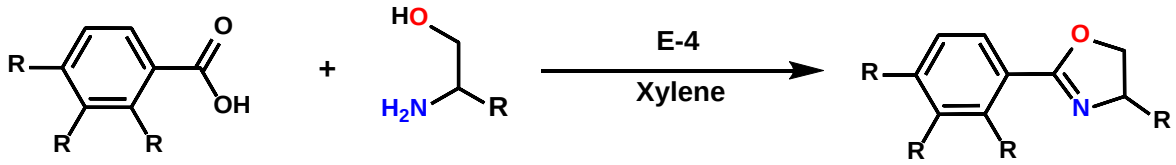
Reaction of 2-haloethylammonium salts **19** and carboxylic acid **18** results in formation of 2-oxazolines, such as **20**. Dehydrocondensation of the two reagents yields *N*-(β-haloethyl)amides, which, through treating with a base, are converted to 2-oxazolines. Ionic liquid (DMT-MM) is used as a solvent in this case [5].



18 19 20

2.1.5 Using Acids

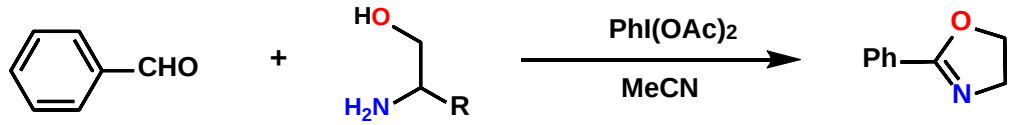
Oxazolines can also be prepared from the reaction of carboxylic acid **21** with an amino alcohol, as demonstrated by **22**. In this simple process, alcohols and amino functionalities can either be aromatic or aliphatic. The process is efficient, for instance, reaction between benzoic acid and 2-amino ethanol in presence of a weak acid zeolite, Ersorb-4 (E-4) in hot xylene or toluene yielded oxazoline **23** in a good yield (76%) [10].



21 **22** **23**

2.1.6 Using Aldehydes

Reaction of β-amino alcohol **24** with aromatic aldehydes produces 2-oxazolines in presence of a variety of catalysts. For instance, in a report by Karade, $PhI(OAc)_2$ was used as a catalyst, which allowed to produce the product **26** in a 65% yield [11].

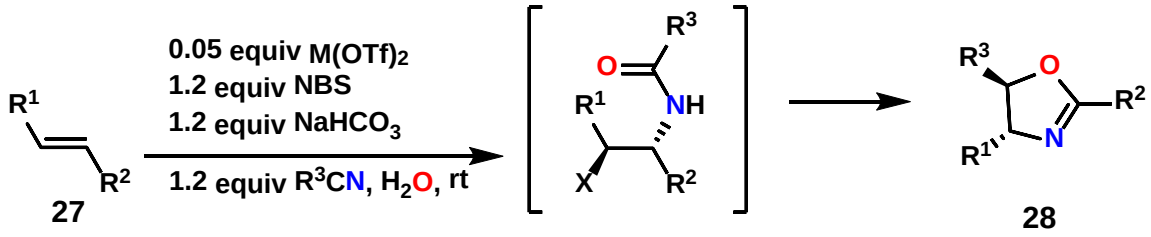


24 **25** **26**

2.1.7 Using One-pot Procedures

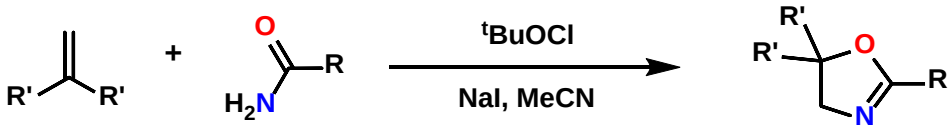
Oxazolines can be produced through stereoselective one-pot synthesis. Hajra and coworkers showed production of oxazolines by treating alkenes with *N*-bromosuccinimide (NBS), a nitrile, $NaHCO_3$, and water in the presence of $Zn(OTf)_2$ or $Cu(OTf)_2$ [12]. These two Lewis acids, among others, were found the most efficient in

producing the desired oxazolines, 66% and 67%, respectively. To minimize the undesired formation of bromohydrin, it was necessary to limit the amount of water to 1.2 equiv. Despite the good yield, scaling up the synthesis of oxazolines according to this approach is problematic due to the usage of the relatively costly NBS.



2.1.8 Using Amides

Coupling of amides and alkenes has been recently reported by Minakata [13]. The activating agent, ^{t}BuOCl, is hazardous and limits the applicability and scale-up of the process. Their team was able to form 2,5-diphenyl-2-oxazoline with a yield of 53%.

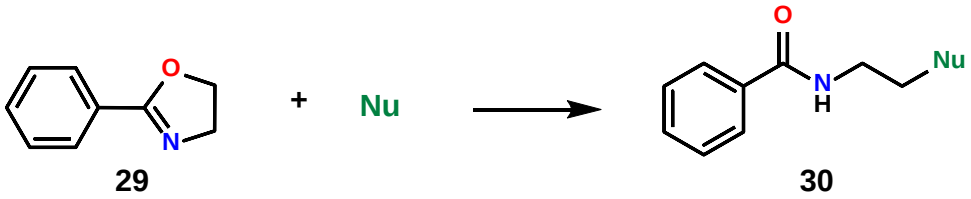


2.2 Nucleophilic Ring-opening of Oxazolines

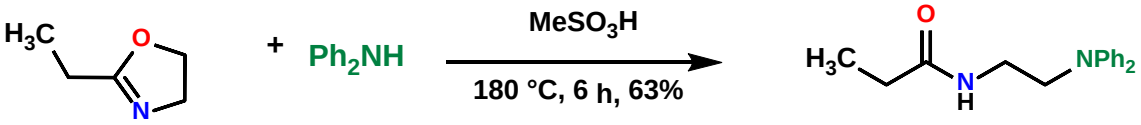
2-Phenyl-2-oxazoline **29** undergoes nucleophilic ring-opening to produce amide products **30** [1], as shown in the scheme below. A variety of nucleophiles have been used in this transformation: thiols and thiophenol as S-nucleophiles; phenols as O-nucleophile; stabilized carbanions as C-nucleophiles. Some other nucleophiles which were used successfully in this approach include tellurium- and selenium- containing nucleophiles.

Imidazoles and azides (such as $TMSN_3$), were successfully employed as *N*-nucleophiles to open oxazolines.

The following equation demonstrates how diphenylamine, in the presence of Lewis or Bronsted-Lowry acids at high temperatures (about 180 ^oC), causes a nucleophilic opening of 2-ethyl-2-oxazoline **31** [14]. Unsymmetrically substituted ethylene-diamines **32** are formed in an 83% yield in this process.

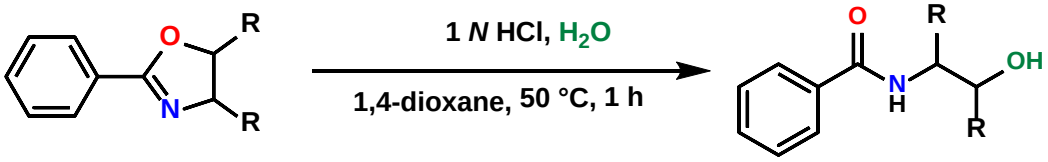


29 30



31 32

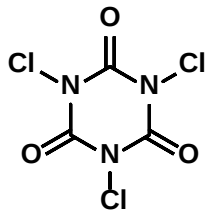
Interestingly, Kuwano and co-workers reported a hydrolysis procedure that allows to transform oxazoline **33** into β–amido alcohol **34,** using 1 *N* hydrochloric acid at 50 ^oC. This ring-opining procedure results in the formation of the products **34** in 67-98% yields.



33 34

2.3 Use of Trichloroisocyanuric Acid (TCCA) in Organic Synthesis

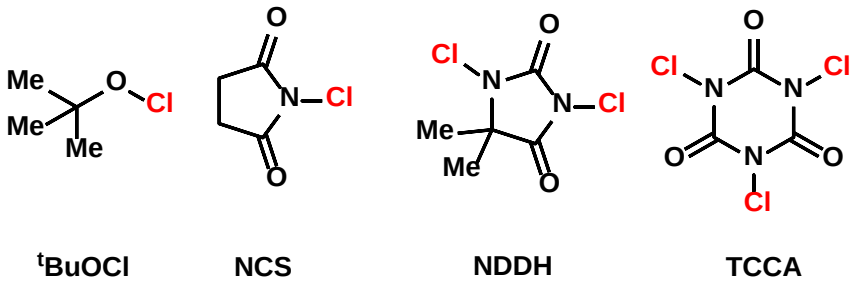
TCCA (Scheme 2) is a white crystalline powder with a strong chlorine odor. It has a melting point of 250 °C and decomposes at elevated temperatures. TCCA is a member of *N*-chloroimides [15].



Scheme 2. Chemical structure of TCCA.

The chlorines in TCCA are “active”, referring to their activity as electrophiles reacting with a wide variety of molecules. One molecule of TCCA provides three chlorine atoms, with comparable potency. The substance has the highest active chlorine content (91.5%) among all the major commercially available *N*-chloroamines. In that regard, 1,3-Dichloro-5,5-dimethylhydantoin (NDDH) has 78%, and *N*-chlorosuccinimide (NCS) has 51%. TCCA has the highest solubility in organic solvents among the *N*-chloroamines. For instance, in ethyl acetate, TCCA has a solubility of 385 g/L in ethyl acetate, 350 g/L in acetone, and 70 g/L in toluene [16]. While several electrophilic halogenating reagents have been described in the literature, trichloroisocyanuric acid (TCCA) has not found broad use, despite its low cost and known ability to chlorinate amides and amines.

Common Electrophilic Chlorinating Agents

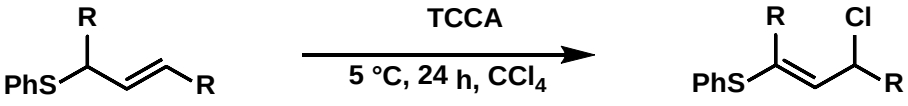


^{t}BuOCl NCS NDDH TCCA

2.3.1 Chlorination Using TCCA

The use of TCCA in organic synthesis for the alkenes' α-chlorination was reported for the first time by Ziegler and co-workers in 1942 [15]. TCCA was later examined in the study of allylic halogenation, using a variety of substrates. According to the authors of the study, a highly exothermic reaction was observed when cyclohexene was added to TCCA. 3-chlorocyclohexene was isolated as the main product in the mixture, with a yield of 29% [15].

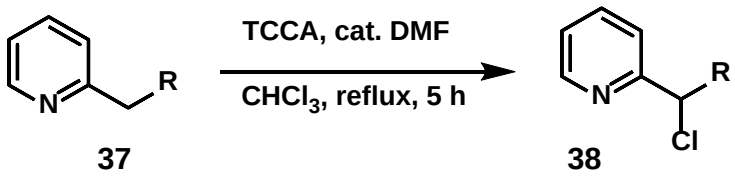
Cohen and coworkers reported in 1975 the application of allylic chlorination for the synthesis of 1-thiophenoxy-3-chloroalkenes, starting from allyl phenyl sulfide [15]. When compared to *N*-chlorosuccinimide (NCS), a more expensive reagent, the yield obtained with TCCA was nearly quantitative, while more commonly used NCS provided the product **36** in a 79% yield.



35 **36**

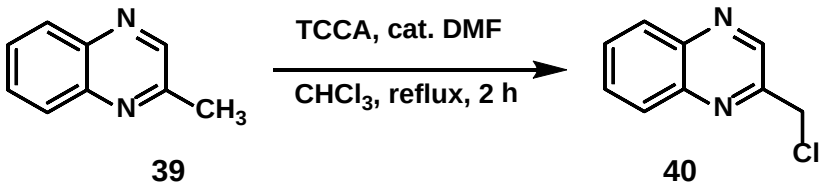
Jeromin and coworkers reported benzylic chlorination of *N*-heterocycles [15]. It should be noted that alkylquinoline and alkylpyridine cannot be easily chlorinated in their benzylic position. However, when TCCA was used, chlorination process provided the

desired products **38** with high efficiency (97% yields). When TCCA was applied in stoichiometric amounts, monochloro-derivative **37** was the major product of the transformation. Under these conditions, no ring chlorination was observed. There was no notable effect on the reaction when a radical initiator was added, eliminating the possible radical pathway for the process. Adding a carboxylic amide, such as DMF or benzamide, however, was crucial for the initiation of the reaction [15].



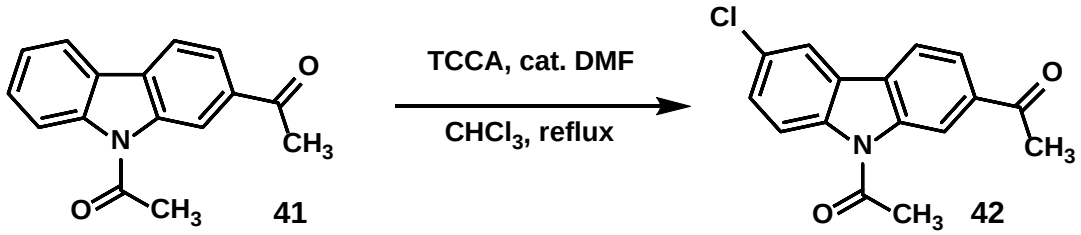
37 **38**

Chlorination of other alkyl-substituted *N*-heterocycles, such as 2-methylchinoxalin, was also performed by **39**, the reaction yielded monochloro derivative **40** in a 90% yield. In the study, only electron-deficient *N*-heterocycles were investigated. Until now, there has been no TCCA-mediated benzylic chlorination reported on electron-rich heterocycles [15].

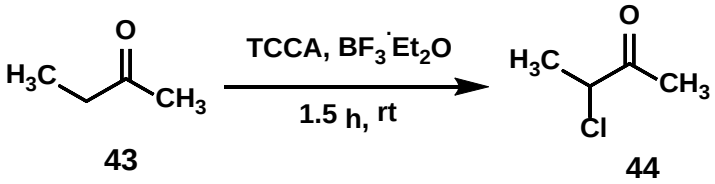


39 **40**

In 1997, Manschand and coworkers reported a selective chlorination process in the carbazole's 7-position in presence of TCCA at room temperature [15]. An expected chlorinated carbazole **42** was formed using these conditions. This procedure provides the chlorinated products with exceptional regioselectivity.



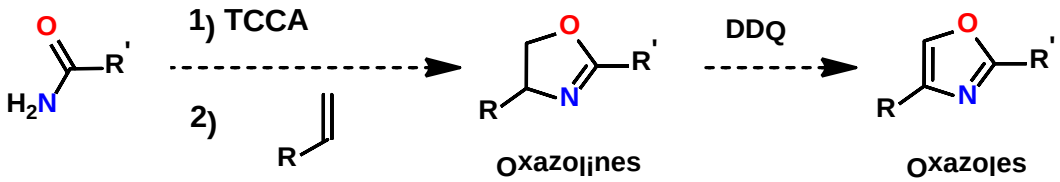
In 1998, H. Suzuki developed a chlorination procedure for phenylphosphonic acid, using TCCA in concentrated sulfuric acid [15]. Preparation of tetrachlorophthalic anhydride proceeded from phthalic anhydride with a yield of 93%. Hiegel and coworkers also reported successful use of TCCA for the α-chlorination of ketones **43** in 1985 [15]. The process was catalyzed with Lewis acids, such as BF_3•Et_2O. Monochlorination of the most substituted chain was observed under these conditions in moderate to high yields [15].



In 1998, R. Roemmele and H. Rayle reported chlorination process of substituted alkenes, such as enamines, enol esters, and enol ethers, with the use of TCCA [17]. Good yields of α-chloroketones were obtained after hydrolysis.

CHAPTER 3: METHODOLOGY

This chapter describes the method used in this study to produce oxazolines. *N*-monochloro and *N*,*N*-dichloro aromatic amides are reactive compounds, which makes them very useful as synthetic intermediates. We have discovered and optimized a procedure that allows to form oxazolines through the coupling of chlorinated amides with alkenes, and further oxidize them to oxazoles.

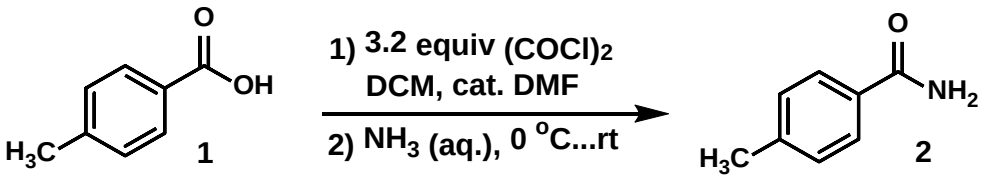


Scheme 1. Summary of the methods to be developed.

3.1 Preparation of *p*-Toluamide

Three experiments were run to prepare the *p*-toluamide, a substrate that is subsequently going to be used for chlorination and coupling reaction.

3.1.1 Method I

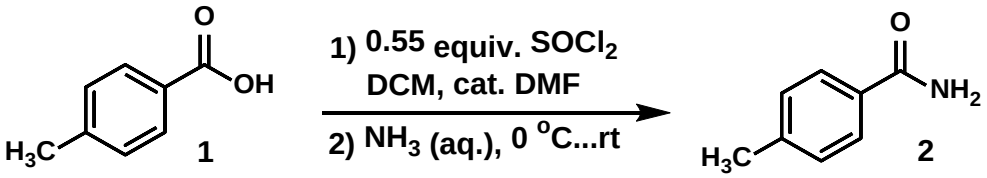


Scheme 2. Formation of *p*-toluamide using method I.

In a 100-mL round-bottom flask 5.013 g (36.82 mmol) of *p*-toluic acid were dissolved in 50 mL of dichloromethane at 0 °C, and 10.20 mL of oxalyl chloride (118.0 mmol, 3.2 equiv.) were then added dropwise, followed by the addition of 1 drop of DMF (catalyst). The flask was equipped with an empty balloon, which was gradually filled with CO and CO_2 as the gases were forming during the reaction. After an overnight

stirring, the reaction mixture was slowly added to 100 mL of 30% aqueous NH_3 solution upon vigorous stirring. Stirring continued for additional 9 hours, then the mixture was filtered to remove the formed white precipitate, and diluted with 100 mL of water. The mixture was transferred into a separatory funnel and washed with DCM. The organic layer was collected and further washed with brine solution, 30 mL. The organic layer was filtered through cotton and the solvent was removed under reduced pressure to produce a crude amide, which was purified by flash chromatography (6:1, hexane: ethyl acetate) to yield 98.5 mg of pure amide (2.2% yield). The ^1H NMR spectroscopy confirmed formation of *p*-toluamide. This method proved very inefficient compared to method II.

3.1.2 Method II

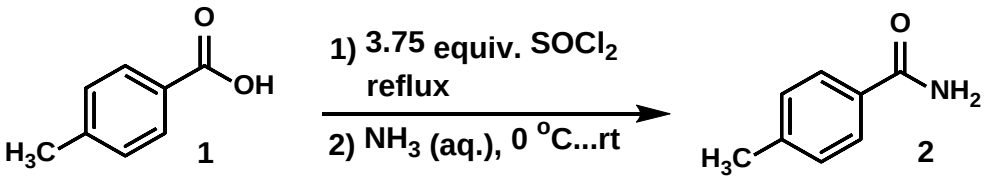


Scheme 3. Formation of *p*-toluamide using method II.

Another procedure, utilizing $SOCl_2$ instead of $(COCl)_2$, was followed to increase the yield of *p*-toluamide. A solution of 1.994 g (14.64 mmol) *p*-toluic acid was prepared in 10 mL dichloromethane at 0 °C, and 0.58 mL of thionyl chloride (8.00 mmol, 0.55 equiv.) was then added dropwise, followed by the addition of 1 drop of DMF. The flask was equipped with an empty balloon, which was gradually filled with CO and CO_2 as the gases were forming during the reaction. After 20 hours of stirring, the reaction mixture was slowly added to 20 mL of 30% aqueous NH_3 solution upon rigorous stirring. Stirring for continued for additional 22 hours, then the reaction mixture was filtered. The reaction was transferred into a separatory funnel, and washed with DCM. The organic layer was

collected and further washed with brine, 30 mL. The organic layer was filtered through cotton and the solvent was removed under reduced pressure to produce 0.883 g of a pure amide (6.53 mmol, 44.6%). The ^{1}H NMR spectrum suggested that there is no need for purification of the product through flash chromatography.

3.1.3 Method III



Scheme 4. Formation of *p*-toluamide using method III.

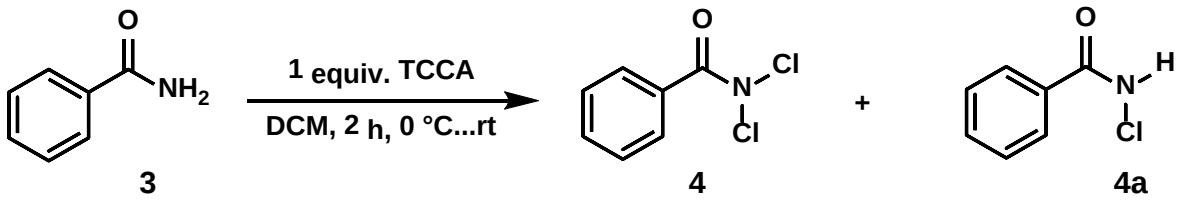
This method utilizes neat $SOCl_2$, with no DCM used. A solution was prepared by adding 10 mL of thionyl chloride (137.8 mmol, 3.75 equiv.) dropwise to 5.006 g (36.75 mmol of *p*-toluic acid), and the resulting mixture was brought to reflux at 100 °C. After 20 minutes, extra 1 mL of $SOCl_2$ was added to the reaction. After one hour, the reaction mixture was cooled to room temperature and the mixture was evaporated under reduced pressure to the volume of ~2 mL. Next, the reaction mixture was added dropwise to a 40 mL of 30% aqueous NH_3 solution in a 200 mL Erlenmeyer flask, upon vigorous stirring which continued for the next 12 hours following the slow addition. The reaction mixture was then washed with EtOAc and filtered. The reaction was transferred into a separatory funnel and extracted with EtOAc, organic layer was separated and additionally washed with brine. The organic layer was filtered through cotton and then the solvent was removed under reduced pressure to produce 0.596 g of the pure amide (4.41 mmol, 12.0%). This procedure was later repeated using only 5 mL of $SOCl_2$ to avoid the cumbersome evaporation part of the procedure, with similar efficiency.

3.2 Chlorination of *p*-Toluic Amide and Benzamide

N,N-dichloroamides are interesting synthetic intermediates due to their unique reactivity. Hiegel recently reported chlorination conditions for a number of amides using trichloroisocyanuric acid (TCCA) [18]. However, they were only able to obtain the monochloroamide product. We explored conditions for the production of *N,N*-dichloroamides.

3.2.1 Preparation of *N,N*-dichlorobenzamide and *N,N*-Dichloro-*p*-toluamide

Reported procedure [16] was applied for the chlorination of both amides and further improved.



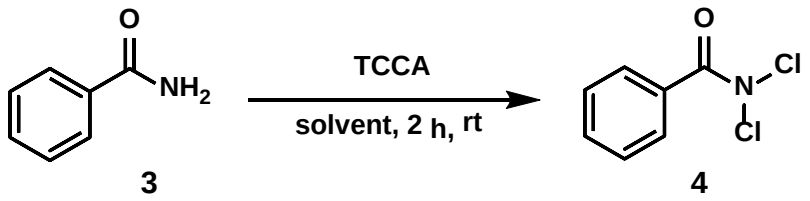
Scheme 5. Chlorination reaction of benzamide using TCCA.

1.284 g (5.5 mmol) of trichloroisocyanuric acid (TCCA) were added at 0 °C to a well stirred solution of 0.6105 g benzamide (5.0 mmol) in 30 mL of dichloromethane. After four hours at room temperature, the TLC (hexane:EtOAc 3:1) showed the reaction's completion. The mixture was filtered using Celite and extracted with distilled water. After that, the solvent was evaporated on the rotary evaporator. The pure *N,N*-dichloroamide **4** was then isolated using column chromatography (hexane:EtOAc 3:1). The concentration on the rotary evaporator produced yellow oil, which was stored in the refrigerator, the dichloroamide decomposes into the form of crystalline solid when it was kept at room temperature (interestingly, these crystals failed to produce oxazoline when reacted with styrene). The NMR spectra show no difference between the product

that was run through a column and the one that was not run, as ^{1}H NMR ($CDCl_3$, 400 MHz) gives the following chemical shifts 7.85 (m, 2H, ArH), 7.45-7.63 (m, 3H, ArH), and ^{13}C NMR ($CDCl_3$, 100 MHz): 127.8, 128.8, 130.1, 133.7, 174.5. Although the TLC (hexane:ethyl acetate 3:1) shows two spots (less polar dichloroamide and more polar monochloroamide, see Figure 3.1), ^{1}H NMR analysis did not reveal any N-H signals (broad singlet at ~8.1 ppm [17]), which suggests that the partial decomposition of the dichloroproduct occurs while the TLC plate is developed.

3.2.2 Examination of Solvent Effect on Chlorination Reaction

The effect of solvent on the chlorination of benzamide was then studied. The solvents that were attempted in the reaction are as follows: dichloromethane (as supplied, as well as dried over molecular sieves), dichloroethane, toluene, butyl acetate, acetonitrile, chloroform, *N*,*N*-dimethylformamide, tetrahydrofuran, and ethyl acetate. The reaction progress was monitored by TLC as shown in Figure 3.1.



3 4

Table 3.1. Chemical properties of the solvents that were used in chlorination reaction.

TLC plate entry	Solvent	Density (g/mL)	Formula	TCCA solubility
1	Dichloromethane	1.33	CH_2Cl_2	not soluble
2	1,2-Dichloroethane	1.25	$CH_3CH_2Cl_2$	not soluble
3	Toluene	0.87	C_7H_8	not soluble
4	Butyl acetate	0.883	$C_6H_{12}O_2$	slightly soluble
5	Acetonitrile	0.786	CH_3CN	soluble
6	Chloroform	1.489	$CHCl_3$	soluble
7	DMF	0.948	$(CH_3)_2NCHO$	soluble
8	Dichloromethane **(predried with sieves)**	1.33	CH_2Cl_2	not soluble
9	Tetrahydrofuran	0.889	C_4H_8O	not soluble
10	Ethyl acetate	0.902	$C_4H_8O_2$	soluble

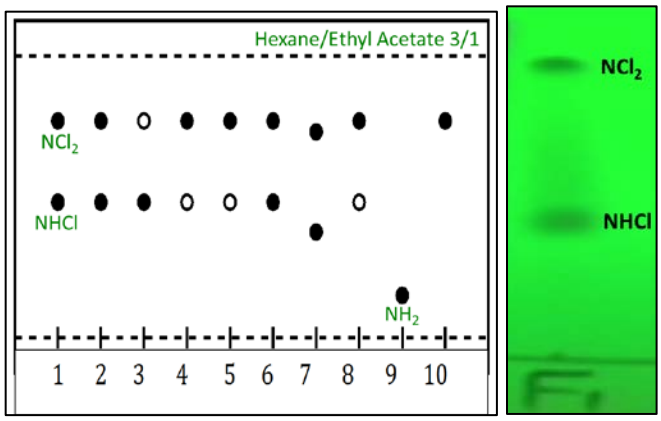
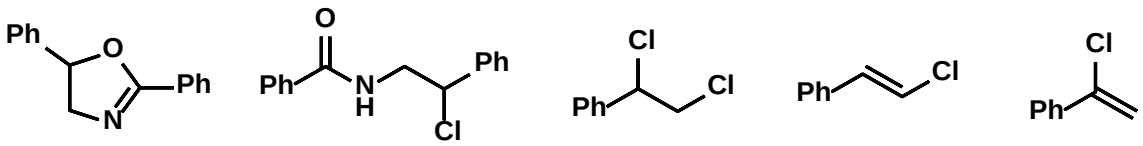


*Figure 3.1 TLC shows the effect of different solvents on N,N-dichlorobenzamide (**4**) formation. Numbers correspond to TLC plate entry from Table 3.1.*

3.3 Study of the Dichloroamide Coupling with Styrene

After purifying the *N*,*N*-dichlorobenzamide **4** through column chromatography, varying amounts of styrene were added to ~100 mg (0.53 mmol) solution of *N*,*N*-dichlorobenzamide in 3 mL of a number of solvents, such as dichloroethane, toluene, and EtOAc. The reactions were placed in tightly sealed 20-mL vials and were let to stir at different temperatures (25 °C, 50 °C and at 100 °C) in order to identify conditions that provide the highest yield of the desired oxazoline.

The ^{1}H NMR of the crude product as shown in Figure 3.3, and GC/MS of the mixture revealed that there are several side products formed in the reaction of *N*,*N*-dichlorobenzamide and styrene. Using literature data in conjunction with GC/MS database and NMR data, the products of the reaction are assigned as follows:



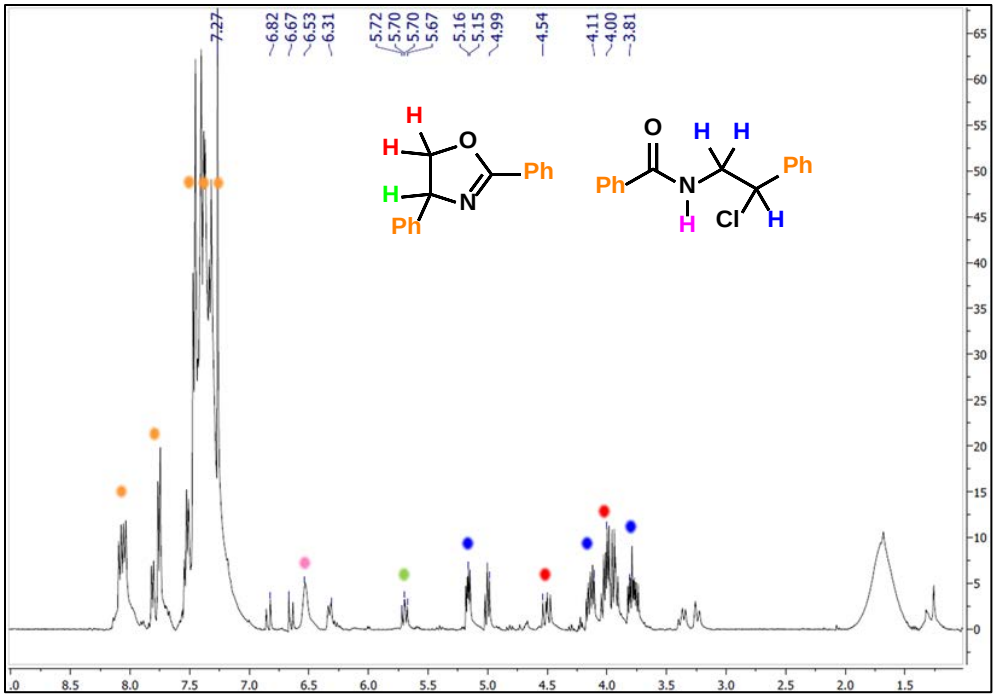


Figure 3.3 Crude ^{1}H NMR Spectrum of the Coupling Reaction.

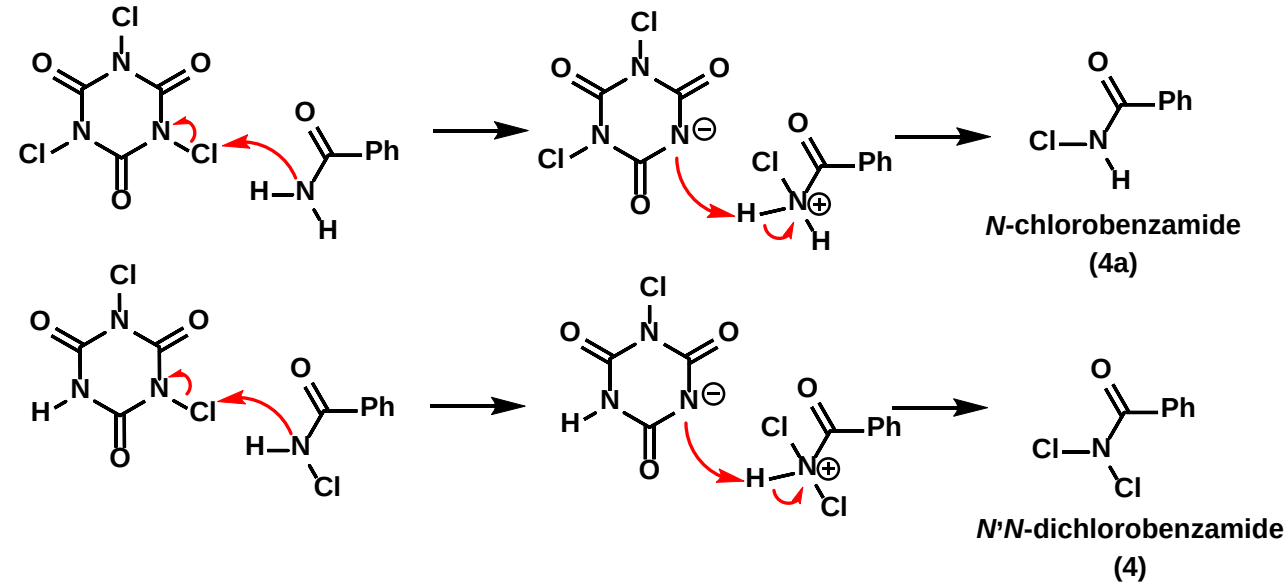
3.3.1 Tentative Mechanism of Oxazoline Formation

The benzamide was first chlorinated using trichloroisocyanuric acid (TCCA), Scheme 6. In benzamide, both the oxygen and nitrogen atoms are potentially nucleophilic. In this case, it is the nitrogen atom in the benzamide that attacks the electrophilic chlorine atom in TCCA which leads to a tetravalent nitrogen salt formation. The imide anion formed during the process immediately acts as a strong base to dequaternize the salt and form the *N*-chlorobenzamide **4a**. The reaction proceeds analogously for installing the second chlorine atom into the molecule.

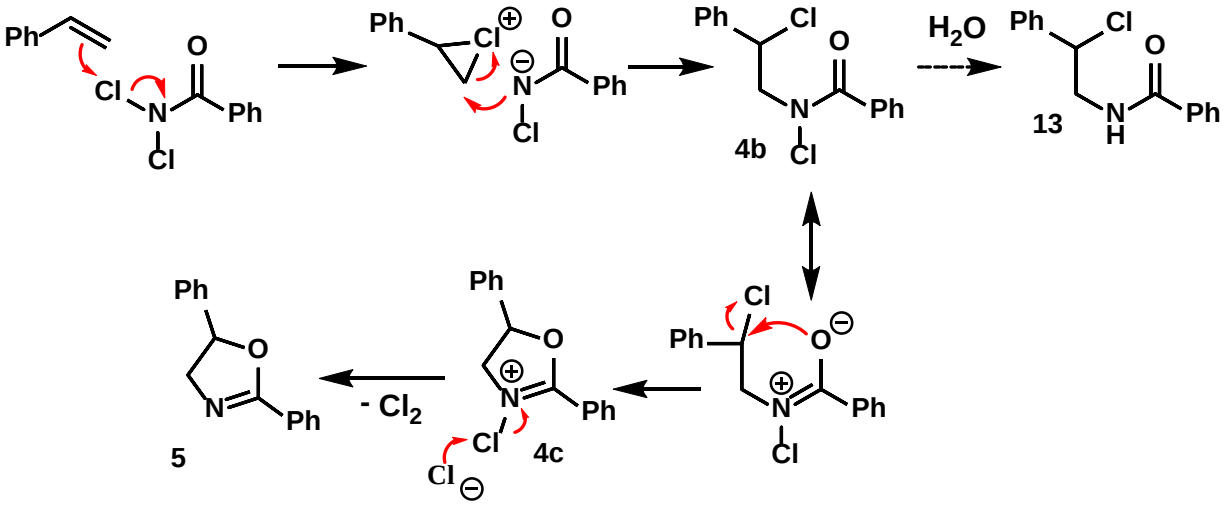
Next, electrophilic chlorine in dichlorobenzamide is thought to activate the double bond of styrene and result in an addition process leading to *N*-chloroamide **4b** (observed regioselectivity is likely due to steric factors). This intermediate can be either hydrolyzed to provide the acyclic **13**, or undergo an intermolecular cyclization to form an iminium cation **4c**. The free chloride anion can subsequently aid dechlorination of the iminium

cation and form the final oxazoline derivative **5** and molecular chlorine as a side-product (which, at least, partially, can be trapped with excess styrene present in the mixture).

Chlorination Mechanism



Coupling Tentative Mechanism

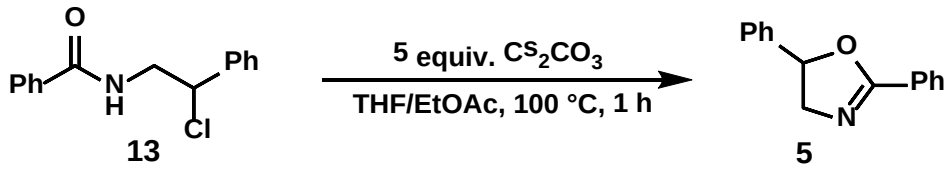


Scheme 6. The mechanism of *N*,*N*-dichlorobenzamide **4** formation, and the tentative coupling and cycloaddition reaction mechanism that produces 2,5-diphenyloxazoline **5**.

The major product that was isolated besides the oxazoline was identified as compound **13**, its formation lowered the yield of the desired cyclic product **5**. We turned our effort into exploring conditions that would efficiently convert it to the desired cyclized product **5**.

3.4 Cyclization Reaction Studies

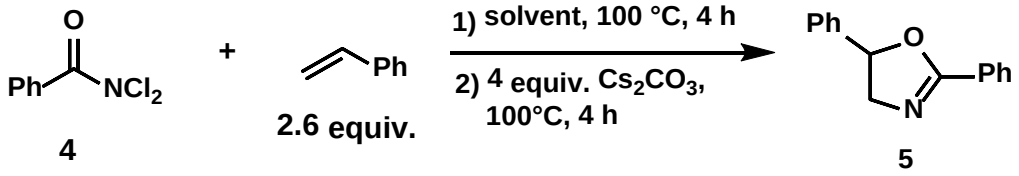
In order to convert the acyclic substrate **13** to oxazoline, it was dissolved in 3 mL of THF/ EtOAc, 5 equivalents of Cs_2CO_3 was added into a sealed vial, and the reaction mixture was stirred for one hour at 100 °C. The same reaction was done for the unpurified batch of the substrate **13** to compare the results with the purified one. In both cases, the reaction mixture was extracted with DCM and purified using a short silica gel column using a mobile phase system of (95:5, hexane; EtOAc). Results of the experiments are discussed in Chapter 4.



3.5 One-pot Process Optimization

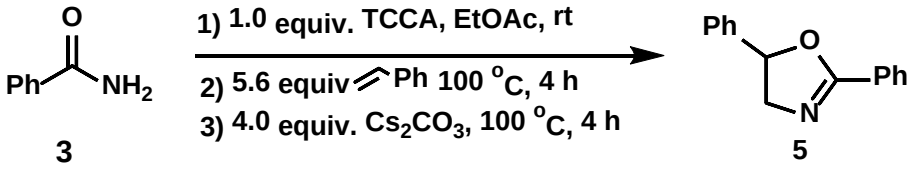
In order to avoid the loss of some of the material that can be caused during filtration/extraction/chromatography/transfer of the cyclized and acyclic product, a one-pot synthesis was attempted, using the dichloroamide as the starting material. Subsequently, we incorporated the TCCA-chlorination step into the one-pot procedure as well, which allowed us to start from benzamide.

3.5.1 One-Pot (2 Steps at Once) Starting from Dichlorobenzamide



In several 20 mL vials, 51.3 mg (0.263 mmol) of dichlorobenzamide was dissolved in varying amounts of EtOAc (2, 3, 4, 6, and 8 mL), and then 120 µL of styrene (4 equiv.) were added to each vial. Reaction mixtures were heated at 100 °C for 4 hours, 4 equivalents of Cs_2CO_3 was added at that point, the reaction mixture was allowed to stir for 6-7 hours at a 100 °C. TLC on silica (9:1, hexane:EtOAc) revealed the complete conversion at that point. The reaction mixture was then filtered and extracted using DCM and water. The solvent was removed from the filtrate using a rotary evaporator. Flash chromatography was performed using silica gel as stationary phase and hexane:EtOAc (93:7) as the mobile phase, to isolate the desired product with R_f value of 0.42. Results of these experiments are discussed in Chapter 4. Repeating the same experimental procedure with varying equivalents of styrene showed little effect upon the yield. In some experiments, MnO_2 was used instead of Cs_2CO_3, but, generally, the product's yield of using Cs_2CO_3 was 23% higher than when using MnO_2.

3.5.2 One-Pot (3 Steps at Once) Starting from Benzamide



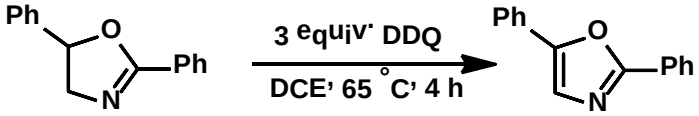
In a 50-mL round-bottom flask, 4 mL ethyl acetate were added to 101.2 mg (0.835 mmol) of benzamide, the mixture was stirred at 0 °C. After 10 minutes, 194.0 mg (0.835 mmol, 1 equiv) of TCCA was added, and stirring continued at room temperature for 2 hours. Then, the reaction was transferred into a 20 mL vial, the round-bottom flask was rinsed with 2 mL EtOAc, 320 µL (2.79 mmol, 5.2 equiv.) of styrene were added, and the mixture was allowed to stir at 100 °C for 4 hours (sealed vial). Next, 1.060 g (3.25 mmol, 4.0 equiv.) of Cs_2CO_3 were added to the reaction vial and heating continued for 3 hours. The reaction mixture was cooled to room temperature, filtered and then extracted using DCM/water. The solvent was removed from the filtrate using a rotary evaporator. Finally, column chromatography on silica (90:10, hexane:EtOAc) allowed to collect the pure oxazoline with a yield of 66%. Similar experiment was run using one-pot synthesis (no transformation was involved) as 97.3 mg (0.803 mmol) of benzamide was dissolved in 4 mL EtOAc. While stirring the mixture at 0 °C, 204.0 mg (0.878 mmol, 1.1 equiv.) of TCCA was added. After stirring at room temperature for 2 hours, TLC showed reaction completion and 304 µL (2.65 mmol, 3.3 equivalents) of styrene were added, then the mixture was allowed to stir at 100 °C for 4 hours (sealed vial). The TLC analysis before addition of Cs_2CO_3 revealed that both the cyclized and acyclic products were present, as well as some other minor compounds. Styrene, one of these compounds, evaporated from the TLC plate within a few minutes. For cyclization step, 1.267 g (3.89 mmol, 5 equiv.) of Cs_2CO_3 was added to the reaction vial and heating continued for 3-6 hours. Then the

reaction mixture cooled to room temperature, filtered, and extracted using DCM/water. The solvent was removed from the filtrate using a rotary evaporator. The pure oxazoline **5** was collected using column chromatography (90:10, hexane:EtOAc), 136.1 mg (0.61 mmol, 73%). The same procedure was applied to benzamide and *p*-methylstyrene coupling which yielded 75% of 5-(4-methylphenyl)-2-phenyloxazoline **15**. *p*-Toluamide was also investigated in the coupling with styrene, it produced 75% of 2-(4-methylphenyl)-5-phenyloxazoline **14**.

3.6 Oxidation of 2,5-Diphenyl-2-oxazoline to Form Oxazole

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a very effective oxidant that has been widely used in chemical transformations, such as cross-coupling, biaryl construction, and removal of protecting group [19]. Oxidation of oxazoline **5** successfully resulted in formation of the corresponding oxazole **16** by using DDQ as an oxidant, as described below.

3.6.1 Method I

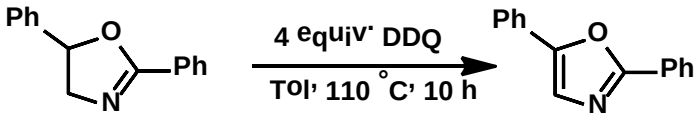


5 **16**

30.0 mg (0.134 mmol) of oxazoline **5** was dissolved in 4 mL of DCE, then 90.0 mg (0.396 mmol, 3.0 equiv.) of DDQ was added to the reaction mixture, and was kept at 65 °C. After 4 hours, TLC revealed that (a) the reaction did not go to completion and (b) traces of the acyclic product **16** were formed. The reaction mixture was then extracted with DCM from a saturated solution of Na_2CO_3. Subsequently, the organic solvent was removed using rotary evaporator, the crude mixture analyzed by ^1H NMR. A short

chromatography column followed using hexane/EtOAc (95:5) as the eluent to yield 8.0 mg (0.036 mmol, 27%) of the oxazole.

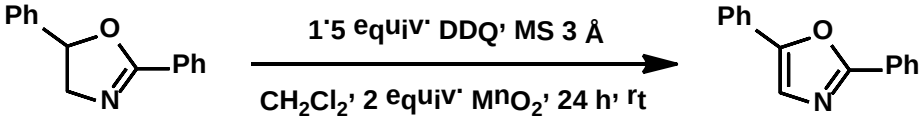
3.6.2 Method II



5 16

19.5 mg (0.087 mmol) of 2,5-diphenyloxazoline was transferred into a 50 mL round-bottom flask and dissolved in 4 mL toluene. Then, 85.6 mg of DDQ (0.377 mmol, 4.3 equiv.) was added to the reaction mixture, and the mixture was allowed to reflux at 110 °C for overnight. The completion of the reaction was monitored by TLC (9:1, hexane:EtOAc). Next, the reaction was filtered, extracted with DCM from saturated solution of Na_2CO_3. The solvent was evaporated and the crude product was purified on a short column using a hexane:EtOAc system (95:5) to yield 9.0 mg (0.040 mmol, 46%) of 2,5-diphenyl-2-oxazole.

3.6.3 Method III



5 16

In a 20 mL scintillation vial, 53.0 mg (0.237 mmol) of oxazoline **5** was dissolved in 3 mL DCM, and 480 mg of 3Å molecular sieves were added. After 10 minutes, 80.7 mg (0.36 mmol, 1.5 equiv.) of DDQ was added to the reaction solution, and the mixture was allowed to stir at room temperature. After 12 hours, 45.4 mg (0.52 mmol, 2 equiv.) of

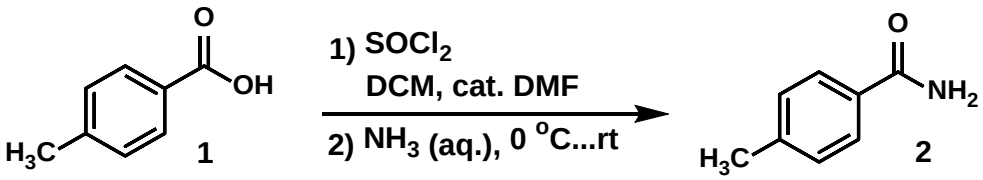
activated MnO_2 was added to push the reaction towards completion. After 48 hours, the TLC analysis revealed that some of the starting material was still present in the mixture. The reaction mixture was filtered, quenched with 10% NaOH, and extracted with DCM. The solvent was evaporated using a rotary evaporator. Pure oxazole product (34.1 mg, 0.154 mmol, 65% yield) was collected after short column chromatography in hexane: EtOAc (95:5).

CHAPTER 4: RESULTS AND DISCUSSION

This chapter presents the results of the experiments discussed in the previous chapter. It further provides analyses of the obtained results in the process of producing oxazolines. The effect of using different solvents on chlorination reaction is analyzed. One-pot reaction optimization is described. In addition, transformation of oxazoline into oxazole will be discussed.

4.1 Formation of *p*-Toluamide using TCCA

Using method II as shown in Scheme 1 produces the highest yield (74.1%) of *p*-toluamide **2** compared with method (I and III) as shown Table 4.1. The low yields of methods I and III may possibly be due to either the quality of the used oxalyl chloride or not slow enough addition of the reagent to the NH_3 solution with controlled temperature (at 0 °C).



Scheme 1. *p*-Toluamide formation according to method II.

Table 4.1. Formation of p-Toluamide. Efficiency of the Process.

Trial	*p*-toluic acid (mg)	*p*-toluamide (mg)	Yield, %	Method
1	5012.7	98.5	2.0	I
2	1199.4	883.1	74.2	II
3	5015.8	374.0	7.5	III
4	5039.5	589.0	11.8	III

For detailed conditions see chapter 3.

The spectrum shown in Figure 4.1 has confirmed that the product isolated was a pure *p*-toluamide **2**, the spectroscopic data matches the one reported in the literature [17]: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.70 ppm (d, 1H), 7.25 ppm (d, 1H), 6.02 ppm (s, -N*H*H), 5.54 ppm (s, -NH*H*), 2.40 ppm (s, -CH_3). *p*-Toluamide is subsequently used in oxazoline synthesis (see page 53).

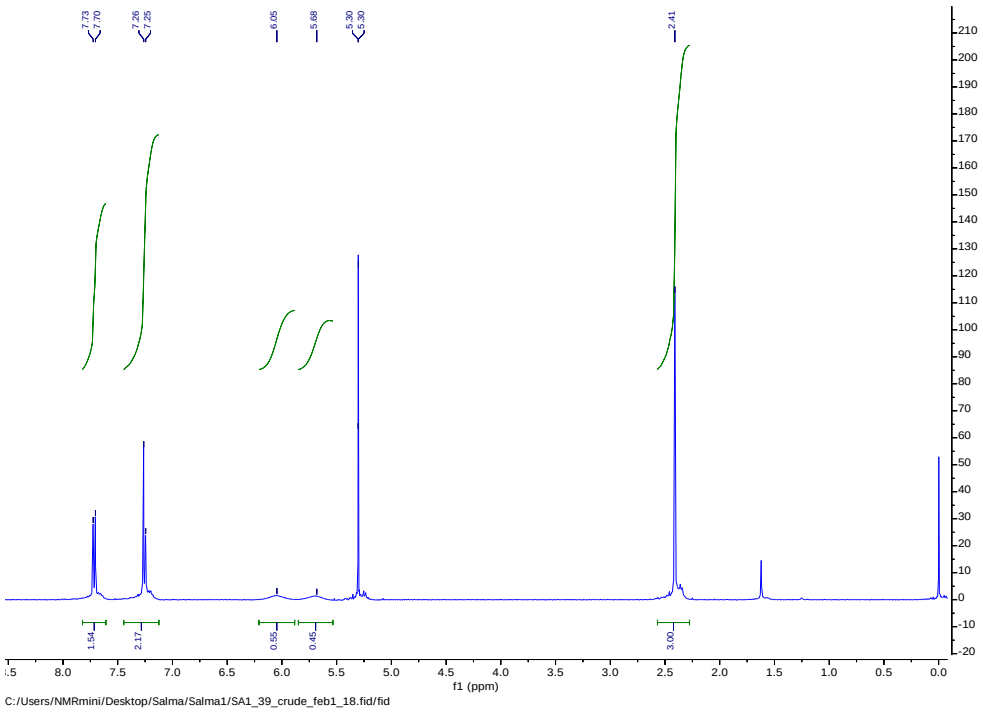
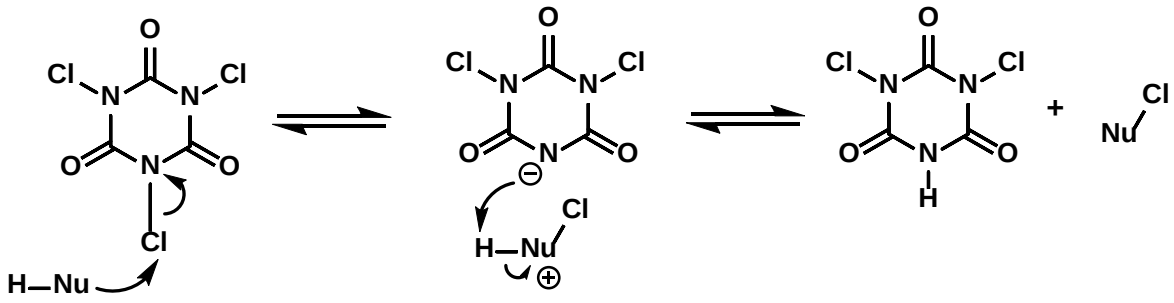


*Figure 4.1. ^{1}H NMR spectrum of the pure p-toluamide (**2**). (DCM at 5.30 ppm). Higher resolution spectra are listed in Chapter 6.*

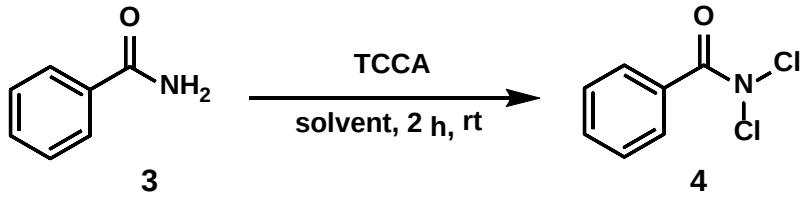
4.2 Activation of Primary Amides with (TCCA)

A general mechanism for using TCCA as a reagent in chlorination reaction is shown in Scheme 2. The nucleophilic atom (in our case, nitrogen) attacks the chlorine and converts TCCA into a base that helps during the following deprotonating step.



Scheme 2. General mechanism of chlorination.

N,N-dichloroamide **4** (yellow oil) is produced from amides upon their chlorination with TCCA as shown in Scheme 3, with yields listed in Table 4.2. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.85 (m, 2H, ArH), 7.45-7.63 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): 127.8, 128.8, 130.1, 133.7, 174.5. From the ^{1}H NMR, it follows that only dichloroamide is formed because of the lack of the broad N-H peak, had the monochlorinated product been present in the mixture. That peak should have been present at 8.09 (s, br, 1H, NH) [20].



Scheme 3. Benzamide chlorination. General scheme.

Table 4.2. Attempts of Benzamide Chlorination. Reaction Yields.

Trial	Benzamide g	TCCA, equiv.	Solvent	Yield (%)	Note
1	0.6105	1.10	DCM	96	With column purification
2	2.0039	0.84	DCM	86	With column purification
3	1.9619	0.85	DCM	91	W/o column purification
4	1.5319	1.00	EtOAc	95	W/o column purification

All reactions were conducted as follow: benzamide dissolved in the solvent at 0 °C with continuous stirring then the TCCA was added and the reaction was allowed to stir at room temperature for 2 h, see the detailed condition in chapter 3.

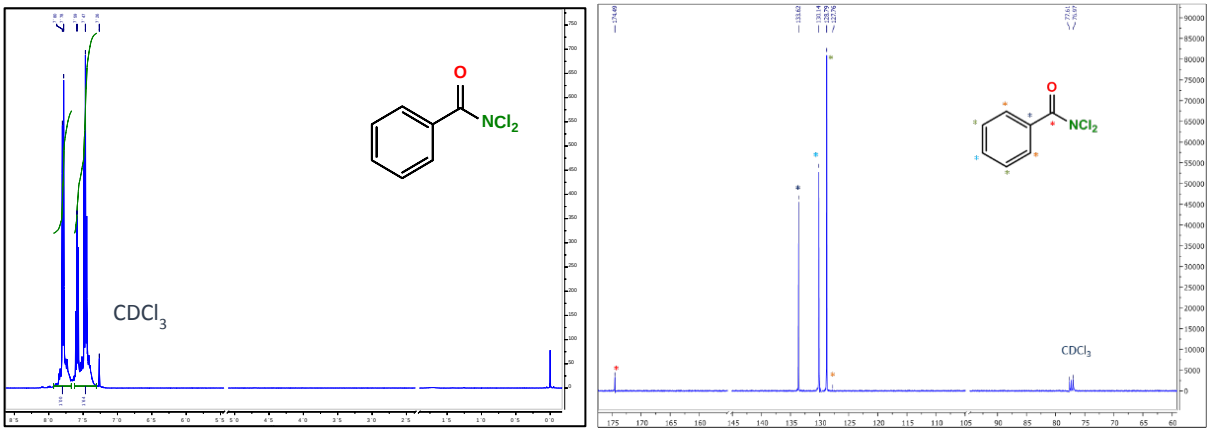


*Figure 4.2. ^{1}H NMR and ^{13}C NMR spectra of obtained N,N-dichlorobenzamide (**4**). Higher resolution spectra are listed in Chapter 6.*

Observation of two spots on TLC of the reaction mixture indicates that some of the dichloroamide product hydrolyzed by moisture either present in the air or in the solvent, Figure 4.2.1. Although the reaction was subsequently repeated using a specially pretreated DCM (placed above molecular sieves (3 Å) for three days), the TLC still shows presence of both mono- and dichloroamides.

It is best to store dichlorobenzamide at 0 ^{o}C to protect it from decomposition. It was observed that oily product partially decomposes (crystal formation) when stored for a month at room temperature.

Flash chromatography with a mobile phase system of hexane:EtOAc (9:1) was attempted to separate the two products, albeit unsuccessfully. Hence, triethylamine Et_3N was added (2% v/v) to the mobile phase system hexane:EtOAc (3:1) to aid the separation (by preventing potential acid-catalyzed hydrolysis of the products). The addition of Et_3N, unfortunately, resulted in formation of additional products (as observed by TLC), (Figure 4.2.1.)

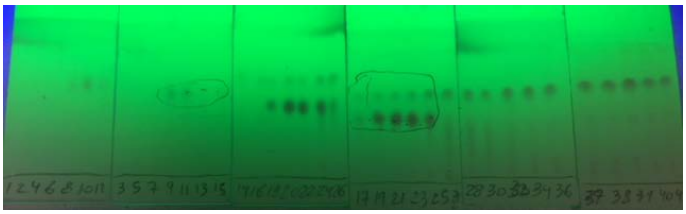


Figure 4.2.1 TLC shows the effect of Et_3N addition to the system of hexane:EtOAc (3:1) on the separation of monochlorobenzamide and dichlorobenzamide.

A procedure reported in literature showed that dichloroamide can be successfully obtained in the absence of light and moisture when the reaction is stirred for 2 hours at 0 °C and then for 1 hour at room temperature [21]. However, that method could not be reproduced – two products were still observed in the reaction mixture (TLC). Various solvents were then screened to examine their effect on clean conversion of the benzamide into dichlorobenzamide.

4.2.1 Solvent Effect on Chlorination Reaction

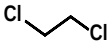
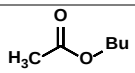
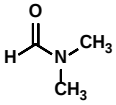
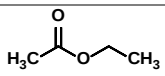
A study of the effect of solvents on the *N*-chlorination of benzamide was carried out using dry and wet dichloromethane, acetonitrile, toluene, ethyl acetate, 1,2-dichloroethane, butyl acetate, chloroform, dimethylformamide, and tetrahydrofuran

(see TLC sketch in Figure 3.1). Complete conversion of the starting material of most of the reactions took 1-2 hours at room temperature.

It has been determined from the TLC (Figure 3.1) that using ethyl acetate as a solvent in the chlorination reaction cleanly produces only one product, the *N*,*N*-dichlorobenzamide. During that trial, the starting material dissolved completely upon addition of TCCA to produce a clear solution. On the other hand, when the reaction was run in DCM, toluene, and DCE, white solid material was observed from the beginning of the reaction upon addition of TCCA. Noteworthy, the reaction solution turned into a white suspension after ~35 minutes, which could mean that the excess of TCCA precipitated. In trial 5, when the reaction was run in acetonitrile, TCCA completely dissolved in the solvent, but when the reaction with styrene followed, a previously unobserved product was produced instead of the desired one. Thus, good solubility is not necessarily associated with a higher yield of the desired dichlorinated product. When methanol was used (entry 11), a clear solution resulted. After 2 hours, the TLC of the extracted product showed formation of the monochloroamide as the minor product and of the dichloroamide as the major product.

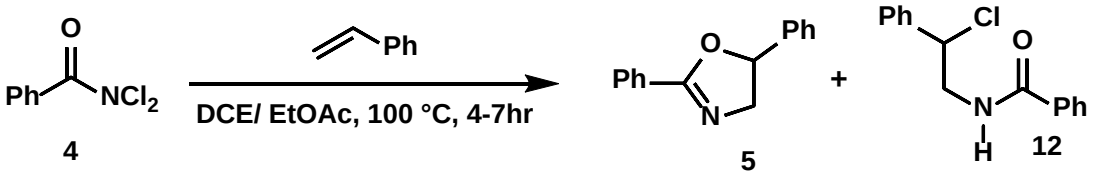
The solvents that did not result in successful product formation are toluene, THF, and DMF. In toluene, the spots (TLC) were faint and the reaction mixture was thick, whereas for the reaction in THF the product formed underwent decomposition within 24 h under the reaction conditions.

Table 4.2.1. The Solvent Effect upon Selectivity in Formation of N,N-dichlorobenzamide (4).

Trial	Solvent	Structure	Starting material	PhC(O)NHCl	$PhC(O)NCl_2$	Miscellaneous
1	DCM (wet)	CH_2Cl_2	N/O	major	major	faint TLC spots
2	Dichloroethane		N/O	major	major	rxn takes >4 hr
3	Toluene		N/O	major	major	thick rxn mixture
4	Butyl acetate		N/O	minor	major	rxn takes >4 hr
5	Acetonitrile	CH_3CN	N/O	minor	major	TCCA dissolves
6	Chloroform	$CHCl_3$	N/O	major	major	rxn takes >4 hr
7	DMF		N/O	major	major	pdts decompose after 1 d
8	DCM (dry)	CH_2Cl_2	N/O	minor	major	rxn takes >1 d
9	Tetrahydrofuran		major	N/O	N/O	no reaction
10	Ethyl acetate		N/O	N/O	major	rxn takes 1 hr
11	Methanol	CH_3OH	N/O	minor	major	Clear rxn solution

4.3 Cycloaddition Reaction Using Styrene

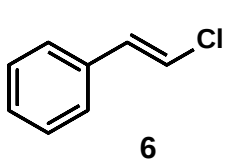
The most known and important type of a process in which a cycle is formed is the Diels-Alder reaction, a concerted [4 + 2] cycloaddition. In our study, a likely stepwise formal [3 + 2] cycloaddition takes place, in which a heterocyclic five-membered ring oxazoline is formed. This process was discovered during our preliminary studies and, to the best of our knowledge, it has not been reported in the literature yet.



Scheme 4. General equation of cycloaddition reaction using styrene.

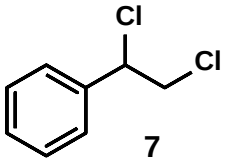
4.3.1 Formation of Oxazoline and Data Analysis

The reaction of *N*,*N*-dichlorobenzamide **4** with styrene produced two major products, oxazoline (more polar spot), followed by another spot that is assigned the structure of acyclic product **12** (even more polar spot), Figure 4.3. Crude ^{1}H NMR revealed (Figure 4.3.1) presence of some additional minor products, besides **5** and **12**, such as *E*-(2-chlorovinyl)benzene **6**, (1,2-dichloroethyl)benzene **7**, and (1-chlorovinyl)benzene **8**, as shown in Scheme 6. These side products were also detected during a GC/MS analysis of the crude mixture.



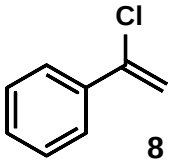
6

(2-chlorovinyl)benzene



7

(1,2-dichloroethyl)benzene



8

(1-chlorovinyl)benzene

Scheme 6. Detected side products derived from styrene.

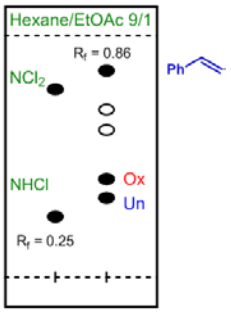


Figure 4.3 TLC of the cycloaddition reaction (Ox = oxazoline, Un = acyclic derivative).

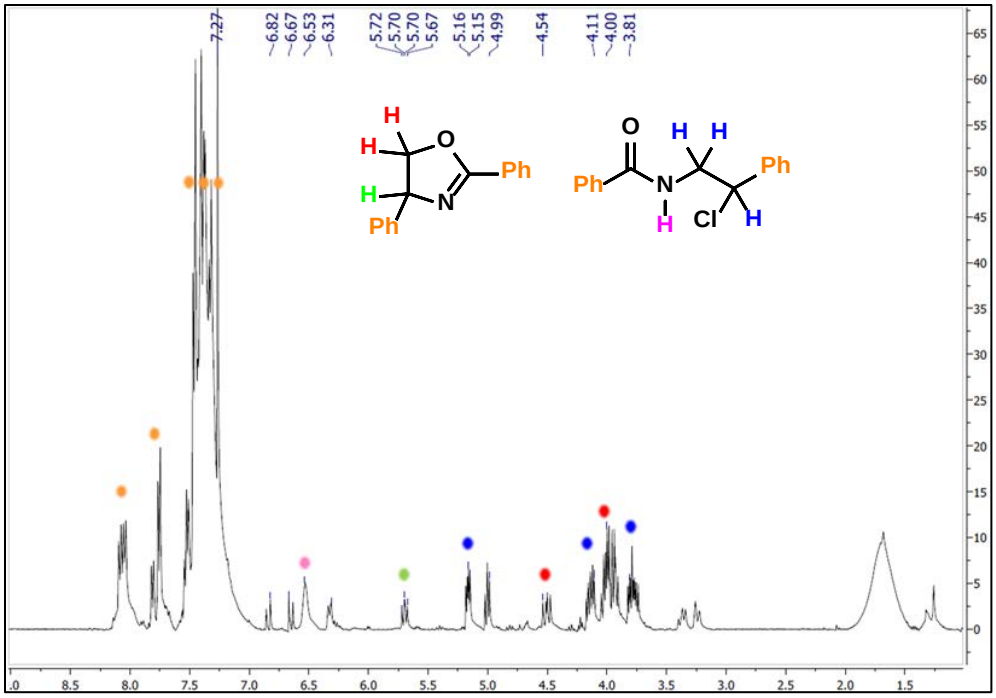
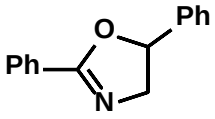
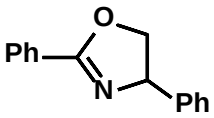


Figure 4.3.1 ^{1}H NMR Spectrum of Crude Mixture, Coupling Reaction with Styrene.



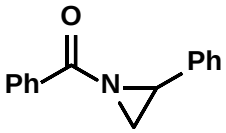
5

2,5-diphenyl-2-oxazoline



9

2,4-diphenyl-2-oxazoline



10

N-benzoyl-2-phenylaziridine

Scheme 7. Possible major products from cycloaddition reaction.

There are at least three possible isomers, with identical molecular weight of 223.3 g/mol and chemical formula $C_{15}H_{13}NO$, which are plausible in the coupling of dichlorobenzamide with styrene. These isomers include 2,5-diphenyl-2-oxazoline **5**, 2,4-diphenyl-2-oxazoline **9**, and *N*-benzoyl-2-phenylaziridine **10**, Scheme 7. Using additional methods of analysis (^{1}H NMR), we could narrow down the list of isomers to just one, oxazoline **5**, while the alternatives (described in the literature and prepared by

other methods) had mismatched chemical shifts. The spectra of proton NMR for the compound **5** were in agreement with the reported data [22]. The purified oxazoline that was obtained as colorless oil, with the following characterization data, ^{1}H NMR ($CDCl_3$, 400 MHz): 3.99 ppm (dd, 1H, -NC*H*HCHO-), 4.48 (dd, 1H, -NCH*H*CHO-), 5.67 (t, 1H, -NCH_2CHO-), 7.31-7.54 (m, 8H, ArH), 8.02 (d, 2H, ArH), Figure 4.3.2.

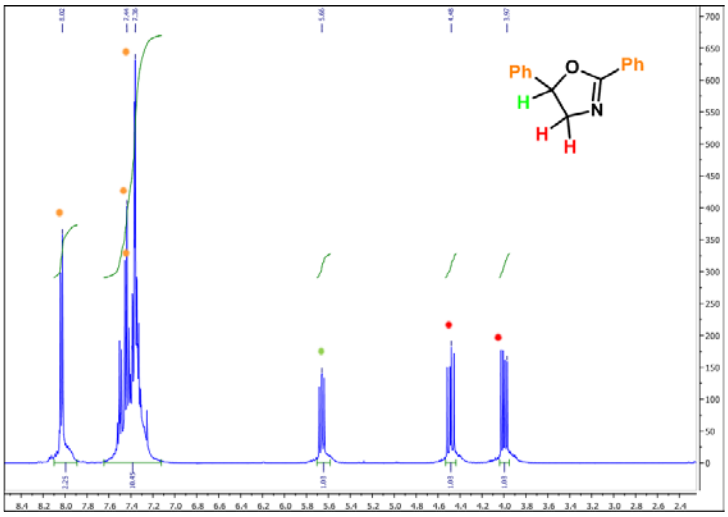


Figure 4.3.2 ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the obtained 2,5-diphenyl-2-oxazoline. Higher resolution spectra are listed in Chapter 6.

Carbon-13 NMR of the purified oxazoline are also consistent with the reported data, as described [22]: ^{13}C NMR ($CDCl_3$, 100 MHz), 164.0, 141.0, 131.5, 128.8, 128.4, 128.3, 125.7, 81.1, 63.2 (ppm), shown in Figure 4.3.3.

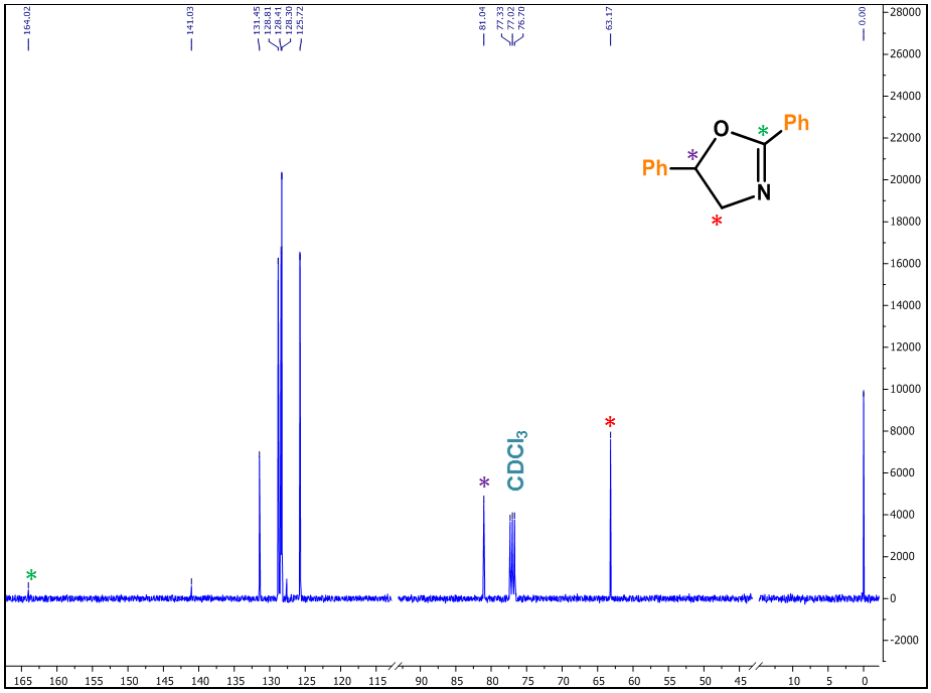
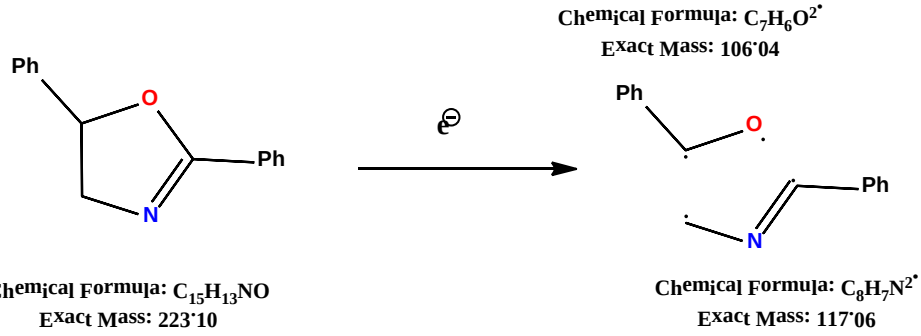


*Figure 4.3.3 [13]C NMR spectrum of 2,5-diphenyl-2- oxazoline (**5**). Higher resolution spectra are listed in Chapter 6.*

Besides the proton and the carbon NMR analysis of oxazoline **(5)**, the total ion GC-MS chromatogram and its mass spectrum (EI) were obtained by running a sample of 1 µL oxazoline dissolved in 1 mL of dry DCM. The molecular ion peak appeared at 223.1 *m*/*z* corresponding to oxazoline's exact molecular mass. In addition, the base peak at 117.1 *m*/*z* indicated a fragmentation forming C_8H_7N as shown in Scheme 8 and Figure 4.3.4.



Scheme 8. Plausible oxazoline fragmentation using GC-MS. Radical cations of the structures above might account for the observed peaks in the GC-MS.

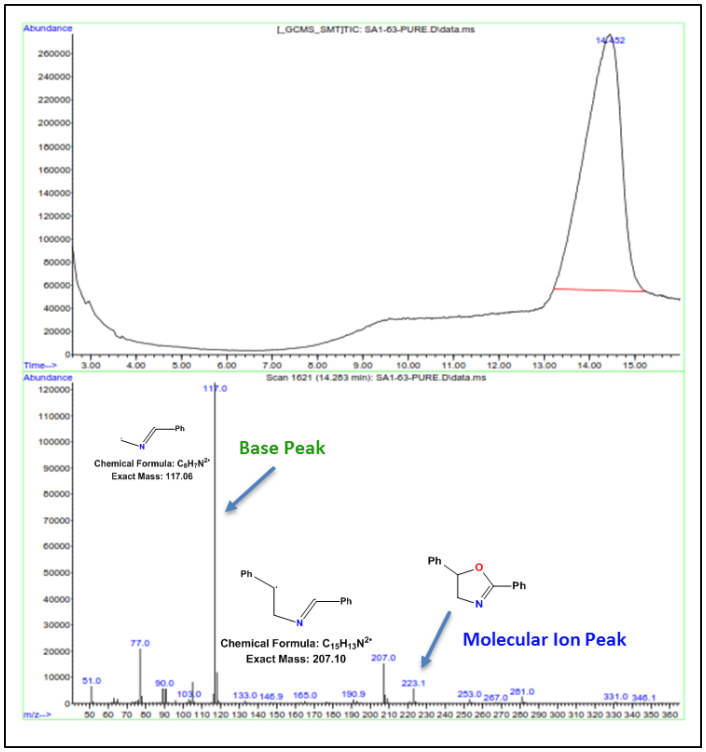
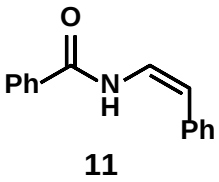


Figure 4.3.4 Total ion chromatogram (TIC) of the isolated 2,5-diphenyl-2-oxazoline (5), and its EI (70 eV) mass spectrum. Higher resolution spectra are listed in Chapter 6.

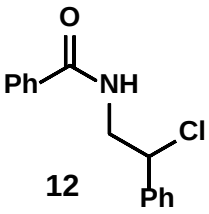
4.3.2 Acyclic Product Data Analysis

Three plausible structures with different molecular weight were initially proposed for the acyclic product. These include *N*-(2-phenylethenyl)benzamide (**11**), *N*-(2-chloro-2-phenylethyl)benzamide (**12**), and *N*-(2-hydroxy-2-phenylethyl)benzamide (**13**) as shown in Scheme 9.



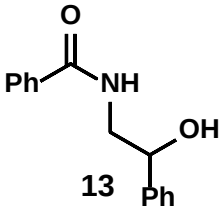
11

(*Z*)-*N*-styrylbenzamide



12

N-(2-chloro-2-phenylethyl)benzamide

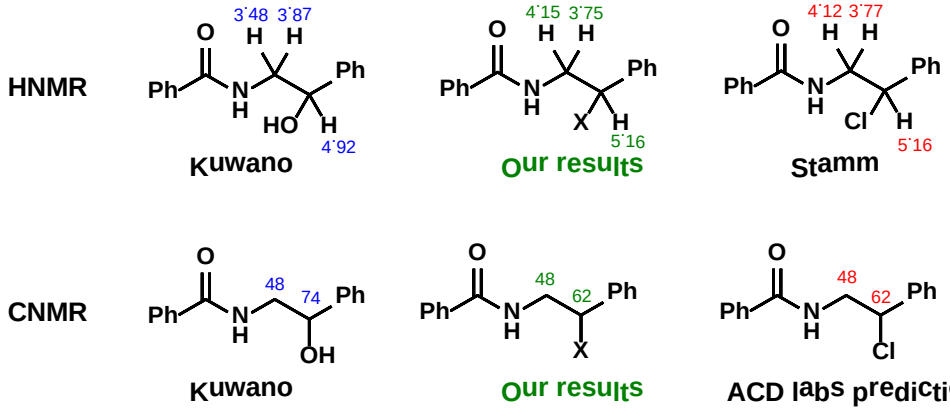


13

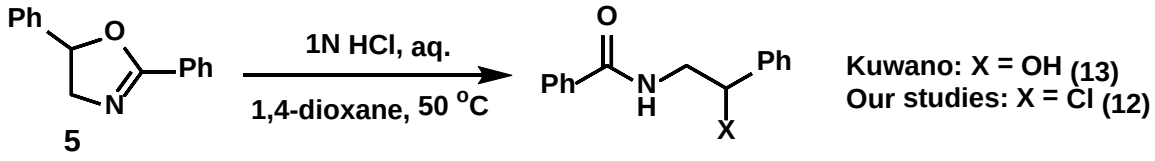
N-(2-hydroxy-2-phenylethyl)benzamide

Scheme 9. Proposed structures of the acyclic product.

The reported ^{1}H NMR of alkenylamide compound **(11)** [23] does not match the obtained product. The reported ^{1}H NMR spectrum of hydroxy compound (**13**) has a close match in the number of peaks and splitting pattern to the isolated product, including the broad peak at 6.52 ppm (1H, brd, N*H*), but all signals appear to be slightly shifted [Kuwano, 22]. The reported ^{1}H NMR spectrum of pure *N*-(2-chloro-1-phenylethyl) benzamide **(12)** has the following spectroscopic data [Stamm, 24]: ^{1}H NMR ($CDCl_3$, 400 MHz) 3.77 (m, 1H), 4.12 (ddd, 1H), 5.16 (dd, 1H), 6.58 (br s, 1H), 7.31-7.55 (m, 8H, ArH), 7.70-7.81 (m, 2H, ArH) (ppm), which closely matches the obtained acyclic product, which has 3.75 ppm (m, 1H), 4.15 (m, 1H), 5.16 (dd, 1H), 6.52 (br s, 1H, N*H*), 7.30-7.55 (m, 8H, ArH), 7.74-7.77 (m, ArH). Thus, it is most likely that the acyclic product is *N*-(2-chloro-1-phenylethyl) benzamide **(12),** see Scheme 10 for the summary of shifts.



Scheme 10. NMR chemical shifts of the hydroxy amide, our results, and the chloro amide.



Scheme 11. Oxazoline ring opening.

Scheme 11 describes oxazoline ring opening, originally reported by Ryoichi Kuwano [22]. We applied Kuwano's reaction conditions to our system to investigate whether the reported hydrolysis product, *N*-(2-hydroxy-2-phenylethyl)-benzamide, is distinct from the acyclic one **12**. Surprisingly, hydrolysis of oxazoline yielded not the literature hydroxy product **13**, but the *N*-(2-chloro-2-phenylethyl)-benzamide, based on ^{1}H NMR. This unexpected result could have been due to the extension of time of Kuwano's procedure. It is plausible that the hydroxy derivative might convert into the chloro derivative **12** in the HCl medium through an S_N1 process.

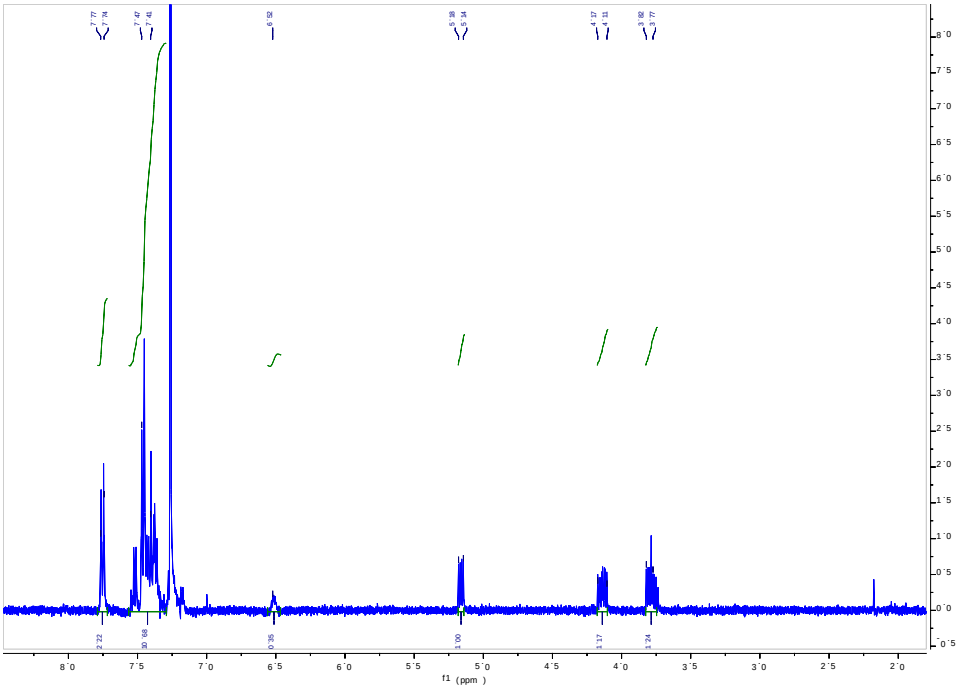


Figure 4.3.5 ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the acyclic product (12). Higher resolution spectra are listed in Chapter 6.

Unfortunately, the GC-MS of the product **12** did not show any peaks aside from the oxazoline **5** peak which could be caused by instability of **12** under the GC/MS method conditions, its conversion in into oxazoline *in situ*, or its lack of volatility.

Additionally, Carbon-13 NMR analysis revealed peaks at 47.8, 62.4, 126.0, 127.2, 127.4, 128.9, 129.1, 132.0, 134.3, 138.9, 167.8 (ppm), which are in agreement with the values predicted for *N*-(2-chloro-2-phenylethyl)-benzamide by ACD Labs software [25].

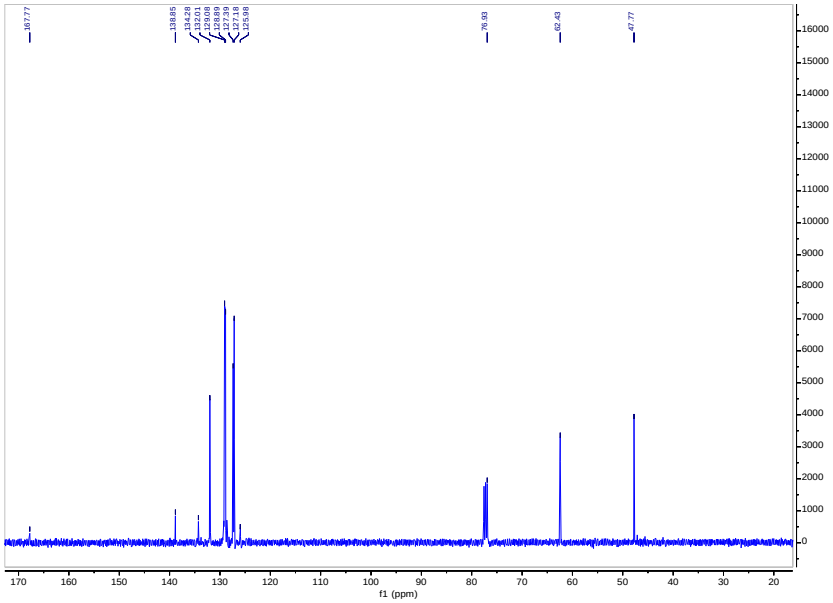


Figure 4.3.6 ^{13}C NMR spectrum of N-(2-Chloro-2-phenylethyl)-benzamide the acyclic product (12). Higher resolution spectra are listed in Chapter 6.

4.3.3 Calculating the Oxazoline Yield via NMR of Crude Product

In the initial stages of the project, product's yield was calculated by integrating the NMR peaks of the crude mixture, in an effort to save time and materials used in column chromatography. When the reaction was extracted, a recorded amount of internal standard, 1,4-dimethoxybenzene, was added to the flask, and then an ^{1}H NMR of the mixture was taken in $CDCl_3$, using extended d1 time. The ^{1}H NMR spectrum was then integrated and the product's yield was calculated. The integral of the proton(s) adjacent to OCH_3 was used in all the cases unless otherwise indicated. Unfortunately, the internal standard procedure was not reliable due to the age of the NMR spectrometer. Also, in

some cases the peaks of the internal standard overlapped with those of the product making the integration not so reliable, further contributing to the inaccuracy in % yield.

Thus, purifying the product after every experiment using column chromatography provided the only plausible solution for analysis during the optimization stage. Since oxazoline and product **12** are difficult to separate on column chromatography, we initially focused on the mixture of the two compounds as our final sample, with ratio determined by NMR (somewhat more accurate than the internal standard technique, this method provided sufficient accuracy to navigate through the optimization studies) (Table 4.3.2).

*Table 4.3.2 Calculated Yield Using NMR ratio of Mixture of Oxazoline (***5***) and N-(2-chloro-2-phenylethyl)benzamide (***12***).*

Trial	Amide (mg)	Styrene, equiv.	Solvent	Temp. (°C)	Oxazoline, %yield*	Chloro amide, %yield*	Combined yield, %
1	188	3.0	CH_3CN	100	N/O	N/O	0
2	36.0	1.0	DCE	50	N/O	N/O	0
3	214	2.0	DCE	100	35	27	62
4	110	3.0	DCE	100	37	21	58

** Based on crude NMR ratio of the characteristic proton peaks.*

4.4 Cyclization Reaction

Conversion of *N*-(2-chloro-2-phenylethyl)benzamide **12** into oxazoline **5** was found to proceed in the presence of Cs_2CO_3 or MnO_2. TLC reveals a major product in the reaction mixture (R_f matches oxazoline) while ^1H NMR of the purified product matches the literature values for oxazoline **5** [22].

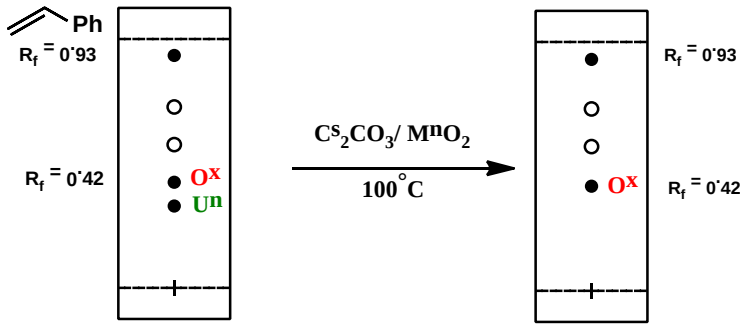
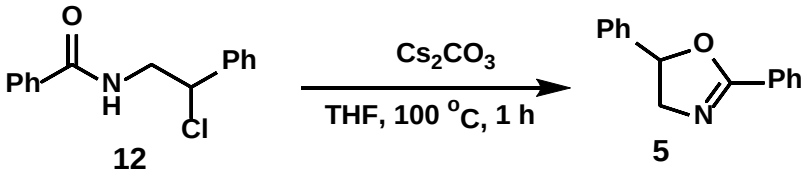


Figure 4.4 TLC shows the cyclization reaction of the isolated mixture of the acyclic and cyclized products.



Scheme 12. Cyclization Reaction of the Mixture of Oxazoline and Chloro Amide.

Table 4.3.3 Cyclization reaction conditions of the N-(2-chloro-2-phenylethyl)-benzamide.

Trial	Benzamide, mg	Acyclic (12), mg*	Oxazoline (5), mg*	Cs_2CO_3, equiv.	%yield
1	109.5	31	48	4	52
2	109.8	50	30	4	46
3	110.7	32	25	4	43
4	213.9	82	85	5	55

** Estimated masses before the cyclization step, based on crude NMR ratio of the characteristic proton peaks.*

All reactions were run as follows: product was placed into 20 mL vial and dissolved in 4 mL THF, Cs_2CO_3 was then added, allowed to stir for 1 hour at 100 °C. The yield of oxazoline and the acyclic product was calculated based on the ratio of characteristic

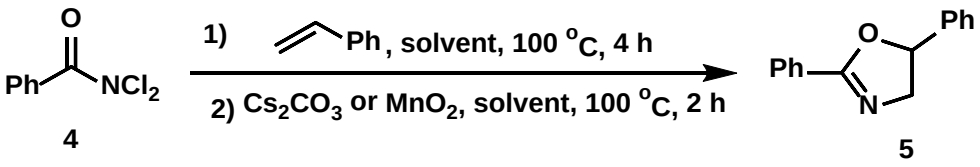
peaks in the HNMR of the mixture. Theoretical yield estimation was based on the mass of the benzamide that was used for the coupling process.

The overall yield of oxazoline obtained after the cyclization reaction was lower than the total yield of the mixture of **12** and **5** that entered the cyclization step (as calculated based on the NMR integration). This might be caused by the loss of the material during transfer in between the flasks or formation of minor amounts of other side-products. We envisioned that avoiding transfer and separation steps (running procedure as a one-pot) could have potentially increased the overall yield of the desired oxazoline.

4.5 Optimization of One-pot Synthesis of Oxazoline

A one-pot synthesis of oxazoline was attempted, starting from either benzamide or purified *N*,*N*-dichlorobenzamide.

4.5.1 Optimization of *N*,*N*-dichlorobenzamide cycloaddition/cyclization sequence



Scheme 13. One-pot equation of cycloaddition/cyclization sequence using dichlorobenzamide **4**.

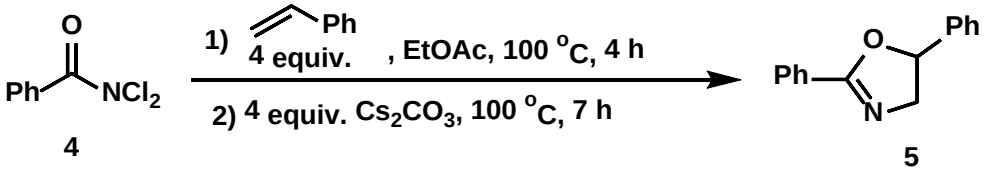
*Table 4.5 One-pot Optimization of Cycloaddition Reaction (**4**).*

Trial	$Ph(O)NCl_2$ (mg)	Solvent	Setup	Styrene equiv	Cs_2CO_3 equiv	MnO_2 equiv	Oxazoline % yield
1	84.9	EtOAc	sealed vial	2.6	5.0	0	43
2	103.3	EtOAc	sealed vial	2.6	0	5.0	35
3	100.7	EtOAc	reflux	2.6	3.0	5.0	38
4	102.0	EtOAc	sealed vial	1.5	4.0	0	46
5	101.8	EtOAc	sealed vial	4.0	4.0	0	46
6	101.1	EtOAc	reflux	2.6	4.0	0	47
7	103.2	EtOAc	sealed vial	2.6	4.0	0	53

All reactions were run as follows: $Ph(O)NCl_2$ for all reactions was isolated using column chromatography (Hexane:EtOAc, 95:5). The dichlorobenzamide was dissolved and styrene was added to a sealed 20 mL vial. After stirring for 4 h at 100 °C, Cs_2CO_3 was added and the reaction was allowed to stir for another 2-4 h at 100 °C.

It was unexpectedly found that using MnO_2 converts the acyclic product **12** into oxazoline as well. However, the efficiency of the Cs_2CO_3 protocol (trial 1) was somewhat higher than when using MnO_2 (trial 2), and there is no advantage from the simultaneous use of both (trial 3). Varying amount of styrene does not have much effect on the oxazoline's yield (trials 4, 5). Running reaction under reflux conditions versus in a sealed vial did not show a drastic change in the product's yield either (trials 6, 7).

4.5.2 Concentration Effect on the Yield of Oxazoline



Scheme 14. One-pot Synthesis of Oxazoline Starting from Dichloroamide.

Next, we varied substrate's concentration to see if it has an effect on the oxazoline's yield (Table 4.5.2). It follows that the yield is somewhat higher when the initial dichlorobenzamide's concentration is 0.07 M. The reaction was monitored via TLC (9:1, hexane: EtOAc).

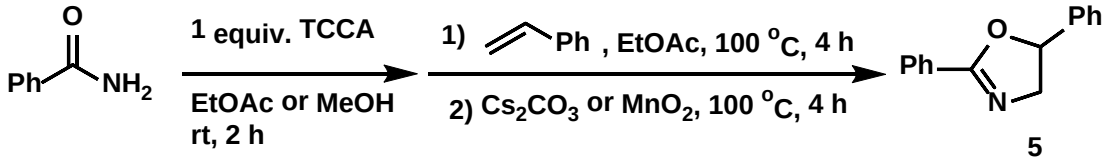
Table 4.5.2 Concentration Effect on the Yield of Oxazoline (One-pot Procedure).

Trial	**$Ph(O)NCl_2$ (mg)**	**EtOAc (mL)**	**Substrate Concentration (M)**	**% Yield**
1	103.2	3	0.18	53
2	53.5	2	0.14	56
3	50.2	4	0.07	**63**
4	51.0	6	0.05	57
5	50.6	8	0.03	53

All reactions were run as follows: in a sealed vial, the dichloroamide was dissolved in EtOAc and 4 equivalents of styrene were added. After running the reaction for 4 hours at 100 °C, 4 equivalents of Cs_2CO_3 were added at the room temperature reaction mixture, which was allowed to stir for another 6-7 h at 100 °C. The mixture was filtered and extracted with DCM/H_2O, and purified (hexane:EtOAc, 95:5).

4.6 One-pot Synthesis of Oxazoline Using Benzamide

Before running the one-pot procedure, separate steps of the process were investigated individually to determine, for instance, the effect of filtration and extraction upon the product's yield as shown in Table 4.6.



Scheme 15. The Effect of Filtration and Extraction on the Yield of Oxazoline.

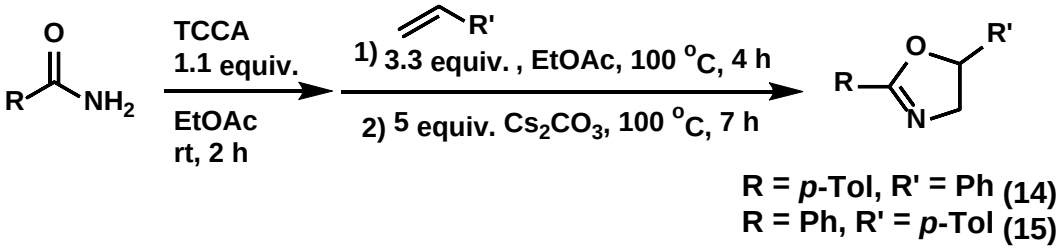
Table 4.6 Optimization of Cycloaddition Reaction Conditions.

Trial	Benzamide (mg)	Solvent, mL	Styrene equiv.	Cs_2CO_3/MnO_2	Conditions	% yield
1	100.2	EtOAc, 4	1.8	4 equiv. **MnO_2**	The reaction mixture was filtered and extracted*	traces
2	99.5	CH_3OH, 4	1.8	2 equiv. **Cs_2CO_3** + 2 equiv. **MnO_2**	Extracted and then extra EtOAc was added*	44
3	100.5	EtOAc, 4	1.8	4 equiv. **Cs_2CO_3**	Only filtration*	50
4	101.2	EtOAc, 4	5.2	4 equiv. **Cs_2CO_3**	No filtration, no extraction. The reaction mixture was transferred to a vial*	66

** The filtration/extraction was performed after the chlorination steps in all the trials. All chlorination reactions were run at room temperature for 2 hours. For the coupling reaction, all trials were allowed to stir at 100 °C for 4 h. Then Cs_2CO_3 was added and stirring continued for 4 h at 100 °C. The reaction was then filtered through Celite, extracted with DCM/H_2O, and purified via column chromatography (hexane: EtOAc, 9:1).*

It seems that using 4 equivalents of MnO_2 for the cyclization step is not efficient, more equivalents are needed to push the reaction to completion. From Table 4.6 one can

see that the yield increased to 66% without the filtration/extraction steps. It was thus ensured that running the reaction without filtration/extraction has no negative effect upon the formation of the oxazoline. In addition, we found that EtOAc is the best solvent that can be used with a concentration of 0.07 M, providing the highest yield of the product (Table 6.1).

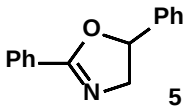
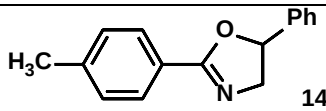
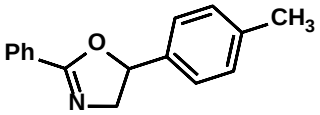


Scheme 16. Reaction Scheme for the One-pot Synthesis of Oxazolines.

As table 4.6.1 reveals (below), the one-pot synthesis went successfully with improved percentage yield (73%) for 2,5-diphenyl-2-oxazoline **5**. This time, the increase in yield from 66% (Table 4.6, entry 4) to 73% (Table 4.6.1, entry 1) is likely due to running all three steps in the same vial with no transfer of material involved, and extended time for the Cs_2CO_3-mediated cyclization step (increased from 4 to 7 hours). In addition, we were able to apply this condition using *p*-toluamide with styrene which produces 75% of 2-(4-methylphenyl)-5-phenyloxazoline **14.** The recorded data is as follows: ^{1}H NMR ($CDCl_3$, 400 MHz), 2.41 ppm (s, CH_3), 3.99 ppm (dd, 1H, -NC*H*HCHO-), 4.48 (dd, 1H, -NCH*H*CHO-), 5.66 (t, 1H, -NCH_2C*H*O-), 7.25-7.35 (m, 8H, ArH), 7.90 (d, 2H, ArH), for supporting information see Figure 6.9. Carbon-NMR for compound **14** shows the following data: ^{13}C NMR ($CDCl_3$, 100 MHz), 21.8, 63.4, 125.0, 126.0, 128.5, 128.5, 129.0, 129.4, 141.4, 142.1, 164.3 (ppm), as shown in Figure 6.10.

Finally, when *p*-methylstyrene was used with the benzamide, the reaction yielded 75% of 5-(4-methylphenyl)-2-phenyloxazoline **15** with recorded data as follows: ^{1}H NMR ($CDCl_3$, 400 MHz), 2.36 ppm (s, CH_3), 3.99 (dd, 1H, -NC*H*HCHO-), 4.48 (dd, 1H, -NCH*H*CHO-), 5.65 (t, 1H, -NCH_2C*H*O-), 7.20-7.26 (dd, 4H, ArH), 7.43-7.50 (m, 3H, ArH), 8.02 (d, 2H,ArH) see SI, Figure 6.11; ^{13}C NMR ($CDCl_3$, 100 MHz), 21.8, 63.3, 81.3, 126.1, 128.5, 128.6, 129.7, 131.6, 138.2, 138.4 (ppm) (Figure 6.12). There are no literature spectra reported for either of the two oxazolines.

Table 4.6.1 One-pot Synthesis of Oxazolines.

Trial	Amide (mg)	Alkene	Product	% yield
1	97.3	styrene	 **5**	73
2*	66.3	styrene	 **14**	75
3	100.9	*p*-methylstyrene	 **15**	75

** p-Toluamide was used.*

All reactions were run as follows: chlorination reaction was allowed to stir for 2 hours at room temperature in a sealed vial. Next, 3.3 equivalents of styrene were added to the reaction and allowed to stir for 4 h at 100 °C. Once the reaction mixture was brought to room temperature, 5 equivalents of Cs_2CO_3 were added and the mixture was allowed to stir overnight at 65 °C, and then for 4-7 h at 100 °C. The mixture was filtered and extracted with DCM/H_2O. Column chromatography (hexane: EtOAc, 9:1) allowed to purify the produced oxazolines.

4.7 Oxidation of Oxazoline

The dehydrogenation of oxazolines into oxazoles was reported using the following oxidants: DDQ, O_2, H_2O_2, KNO_3, activated MnO_2 [19]. Specifically, DDQ

(2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is one of the highly effective oxidants that have been used in this transformation.

4.7.1 Oxazole data analysis

The reaction of oxazoline with DDQ (DCE, 65 ^{o}C) resulted (based on TLC) in the formation of a new product. Conversion was not complete and a small amount of the starting material partially decomposed, overall resulting in a low yield (27 %) of the oxazole. The new product's identity was determined by NMR, as shown in Figure 4.7. The recorded data is as follows: ^{1}H NMR ($CDCl_3$, 400 MHz), 8.11 (2H, d), 7.72 (2H, d), 7.37-7.48 (6H, m, ArH), 7.26 (1H, t, ArH) (ppm); ^{13}C NMR ($CDCl_3$, 100 MHz), 123.7, 124.4, 126.5, 127.7, 128.2, 183.7, 129.0, 129.0, 129.2, 130.6, 151.5, 161.4 (ppm), (Figure 4.7.1) are in agreement with the literature data [26].

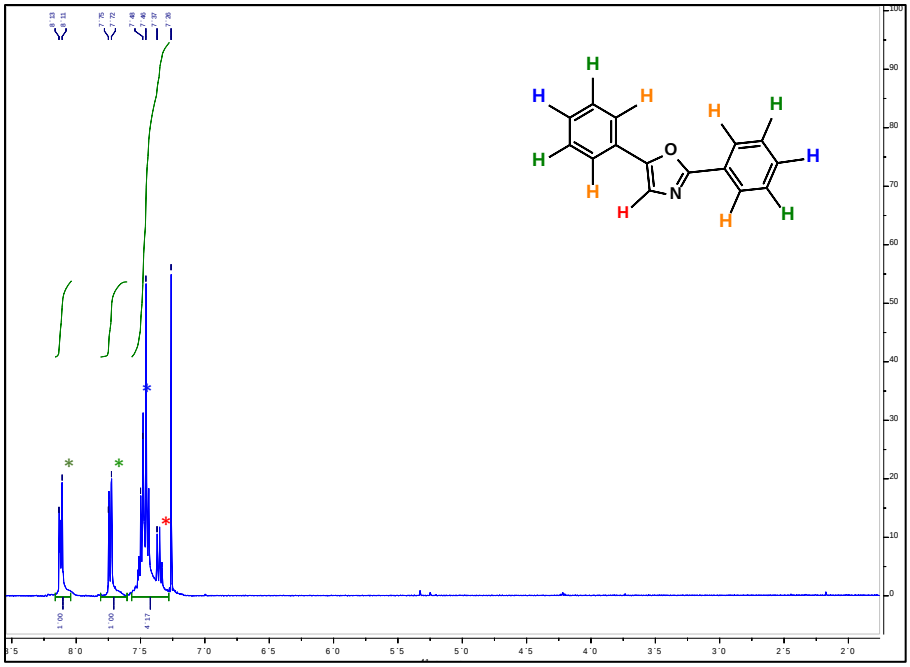


*Figure 4.7 ^{1}H NMR spectrum of obtained 2,5-diphenyl-2-oxazole (**16**). Higher resolution spectra are listed in Chapter 6.*

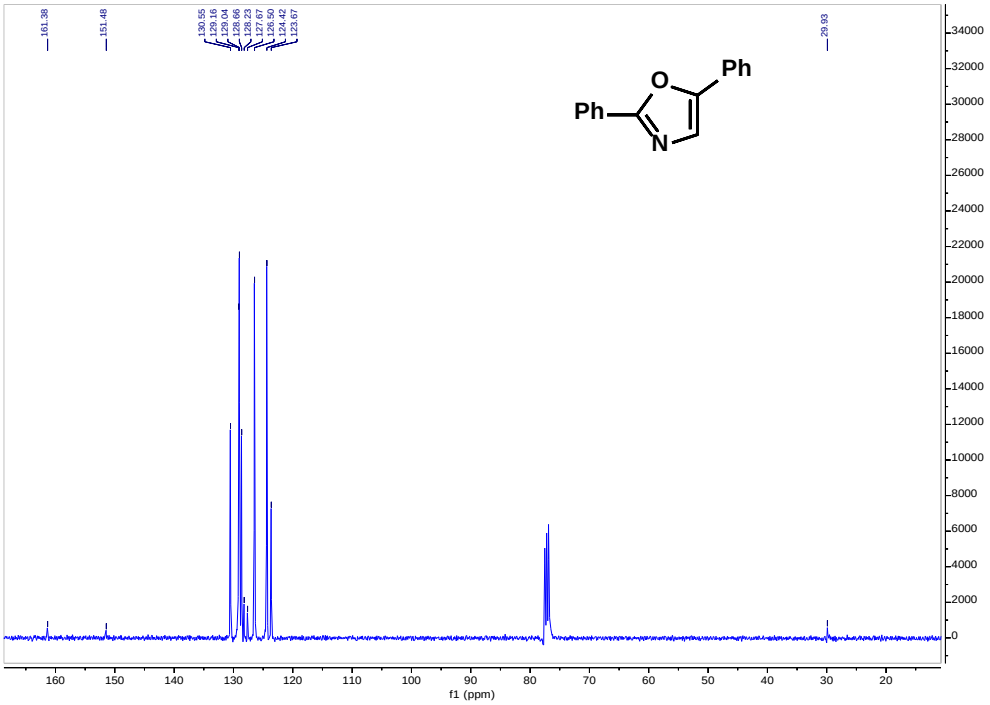
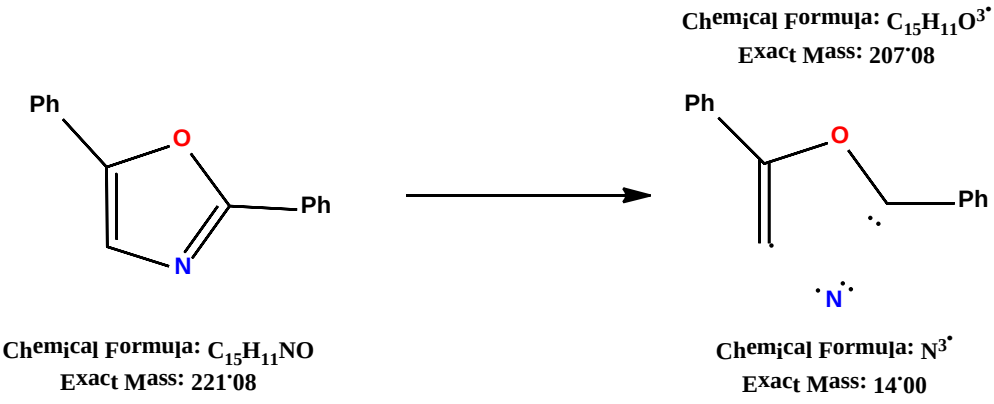


*Figure 4.7.1 ^{13}C NMR spectrum of 2,5-diphenyl-2-oxazole (**16**) (impurity at 30 ppm). Higher resolution spectra are listed in Chapter 6.*

In addition to the analysis of HNMR and CNMR, a GC-MS sample was prepared by dissolving 1 µg of oxazole in 1 mL of dry DCM. As shown in the obtained spectrum in Figure 4.7.2, the molecular ion peak is located at 221.0 *m*/*z*, which corresponds to the oxazole's molecular mass. The base peak appears at 207.1 *m*/*z*, which indicates a possible fragmentation of the molecule at the nitrogen atom, forming $C_{15}H_{11}O^{3\bullet}$ related ion.



Scheme 17. Proposed Fragmentation of the Oxazole.

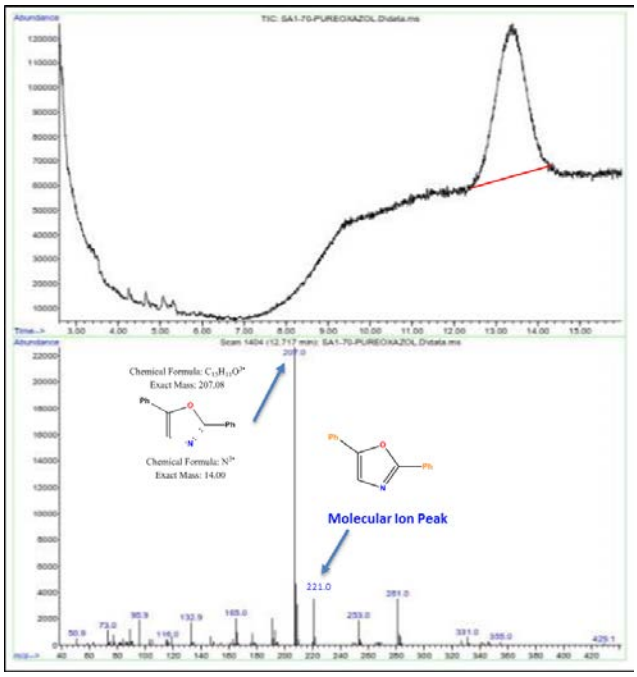
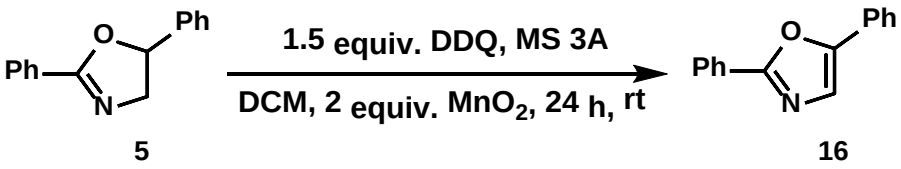


*Figure 4.7.2 TIC of 2,5-diphenyloxazole (**16**) and its mass spectrum (the peaks above 221.0 match the background noise).Higher resolution spectra are listed in Chapter 6.*

4.7.2 Reaction Optimization of Oxazole Formation

We varied several solvents, reaction time, temperature, relative amounts of DDQ or MnO_2 for the formation of oxazole **16** (see Scheme 18 and Table 4.7).



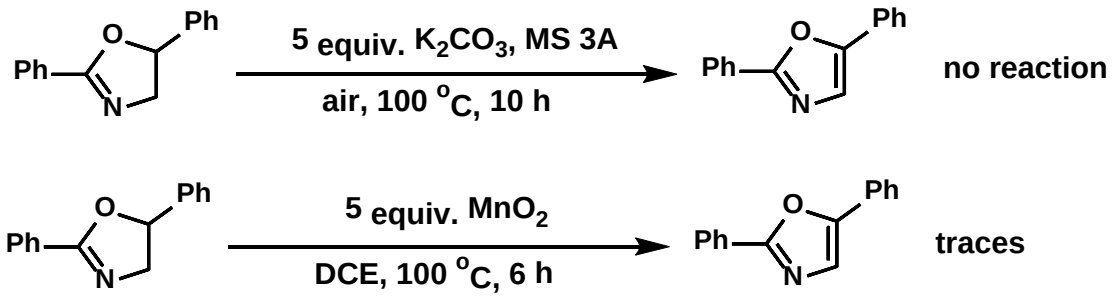
Scheme 18. Reaction Conditions that Provide the Highest Yield of Oxazole**.**

Table 4.7 Optimization of the Oxidation Reaction.

Trial	Oxazoline (mg)	Solvent, mL	DDQ (equiv)	Time, h	T (°C)	MnO_2 (equiv)	% Yield
1	15	DCE, 4 mL	0	5	100	5	traces
2	30	DCE, 4 mL	3.0	3	65	0	27
3	50	DCE, 4 mL	4.0	7	100	4	29
4	77	Toluene, 4 mL	4.0	7	100	4	31
5	51	Toluene, 3 mL	4.0	4	reflux	0	39
6	20	Toluene, 4 mL	3.0	10	reflux	0	46
7	53	DCM, 4 mL	1.5	48	rt	2	65

All reactions were isolated using column chromatography (hexane: EtOAc, 95:5).

Several more oxidation reactions were conducted in order to increase the yield of oxazole formation, including the following:



Scheme 19. Additional Attempts of the Oxazoline Oxidation.

These two reactions did not result in the desired conversion of the oxazoline to oxazole. When K_2CO_3 was used, the TLC showed no reaction. When 5 equivalents of activated MnO_2 was used (Scheme 18), a trace amount of the product was detected by TLC. Noteworthy, by using 1.5 equivelints of DDQ with the addition of (3 Å) molecular sieves, 65% of the desired oxazole **16** was formed (entry 7, Table 4.7).

CHAPTER 5: CONCLUSION AND FUTURE DIRECTIONS

In conclusion, procedure for the dichlorination of benzamide by TCCA was optimized. Even though the undesired monochloro-derivative is observed in DCM (traces, TLC analysis), it may be due to the decomposition of the material on the plate, as HNMR data points to a clean formation of the desired product.

Upon screening of other solvents in the chlorination procedure, it was discovered that ethyl acetate provides clean dichloroamide product in 91-95% yields.

N,*N*-dichloroamide reacts with excess styrene to form 2,5-diphenyl-2-oxazoline **(5)**, this transformation has not been previously reported in the literature. The crude ^{1}H NMR of the reaction mixture revealed formation of the *N*-(2-chloro-2-phenylethyl)benzamide in addition to the desired oxazoline, with other minor side products identified as *E*-(2-chlorovinyl)benzene (**6**), (1,2-dichloroethyl)benzene (**7**), and (1-chlorovinyl)benzene (**8**).

A one-pot procedure that provides oxazoline starting from available benzamide was subsequently developed. Three steps were implemented without intermediate separation/purification steps: chlorination of the amide, coupling with the alkene, cyclization of the side-product into oxazoline. Parent benzamide yields 2,5-diphenyl-2-oxazoline **(5)** in a 73% overall yield. The reaction was additionally evaluated using *p*-toluamide and *p*-methylstyrene substrates – the corresponding oxazolines were produced with similar efficiency of 75%. Finally, oxazoline was oxidized into oxazole using DDQ as an oxidant, providing the product in a 65% yield.

In summary, efficient procedures for converting aromatic amides into medicinally valuable heterocycles, oxazolines and oxazoles, have been developed. We are looking forward to extending the scope of these processes to more functionalized amides and alkenes.

CHAPTER 6: SUPPORTING INFORMATION

All NMR spectra were measured with Varian Unity Inova NMR spectrometer (400 MHz), using $CDCl_3$ as a solvent (0.1% v/v TMS). In ^{1}H NMR spectra, chemical shifts (ppm) are referenced to internal tetramethylsilane (0.00 ppm in $CDCl_3$). In ^{13}C NMR spectra, chemical shifts (ppm) are referenced to the carbon signal of the deuterated solvent ($CDCl_3$ 77.0 ppm).

Flash chromatography separation was performed with silica gel (60 Å, 70-90 μm), using compressed nitrogen gas, and, in some cases, a portable air pump to increase the flow rate. The mobile phase system used for the purification of oxazolines is hexane:ethyl acetate, 90:10. Oxazoles were purified using hexane:ethyl acetate, 95:5. TLC was implemented using silica-gel GF254 plates (200 × 200 mm from Agela Technologies) using hexane:ethyl acetate in variable ratios as the solvent system.

The Gas chromatography-mass spectrometry analyses were performed on Agilent GC-MS system consisting of 7890 GC system and 5975C VL mass selective detector (MSD) with Triple Axis Detector. HP-5MS UI GC column (30 m long, internal diameter 0.25 mm, stationery phase thickness 0.25 μm) was used. The GC-MS system was controlled by MSD ChemStation software (Agilent, ver. 02.00.493) with W8N08 Library. The carrier gas was He (1.2 mL/min). The temperature program was set at 100 ℃ for 1 min, followed by a ramp from 100 to 310 ℃ in 16 min (30 ℃/min), and then 310 ℃ for 8 min. The sample was dissolved in 1mL DCM and then 1 μL of it was injected. The solvent delay time was 2.50 min. The detection was accomplished using EI (70 eV) mass spectrometry.

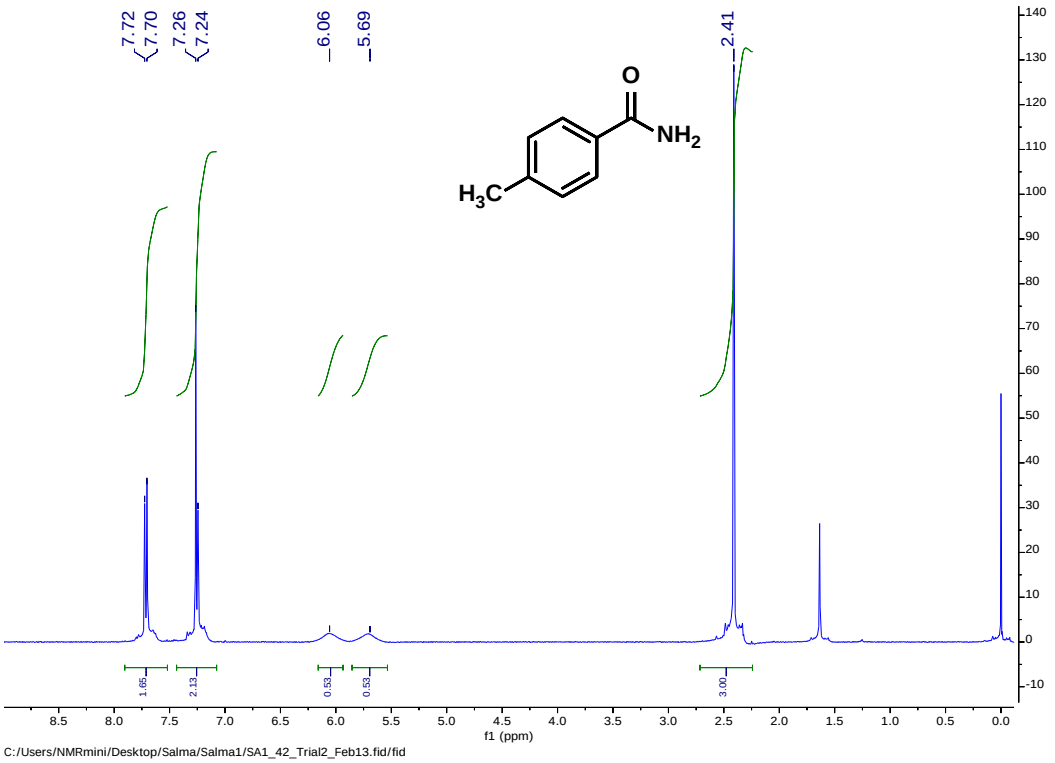


*Figure 6.1 ^{1}H NMR spectrum of the pure p-toluamide (**2**). (DCM at 5.30 ppm)*

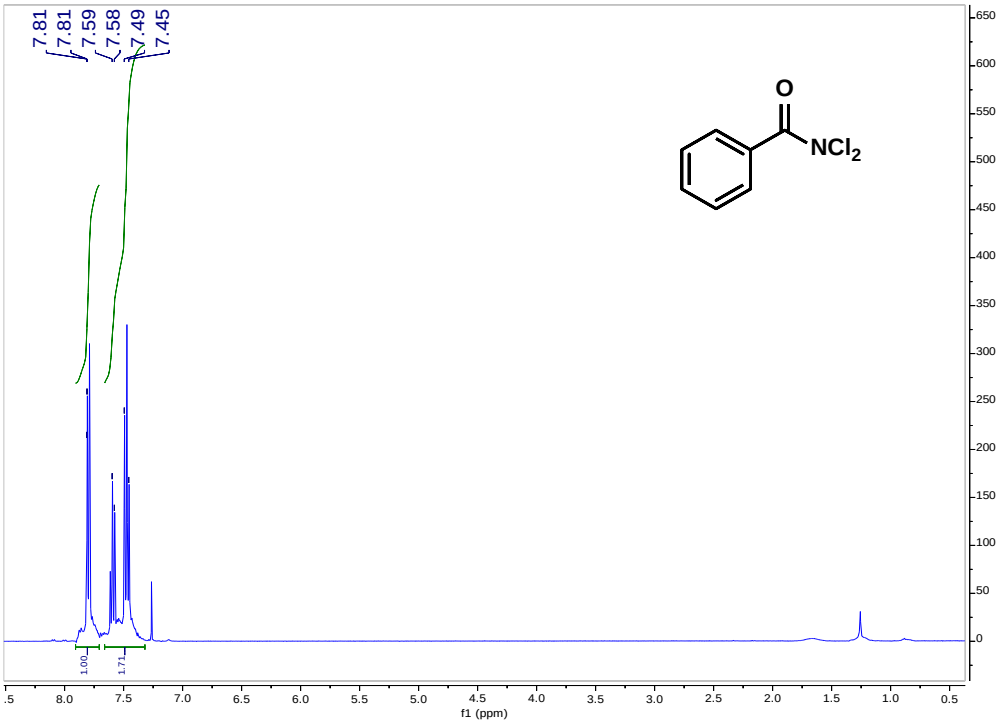


*Figure 6.2 ^{1}H NMR spectrum of the pure N,N-dichlorobenzamide (**4**).*

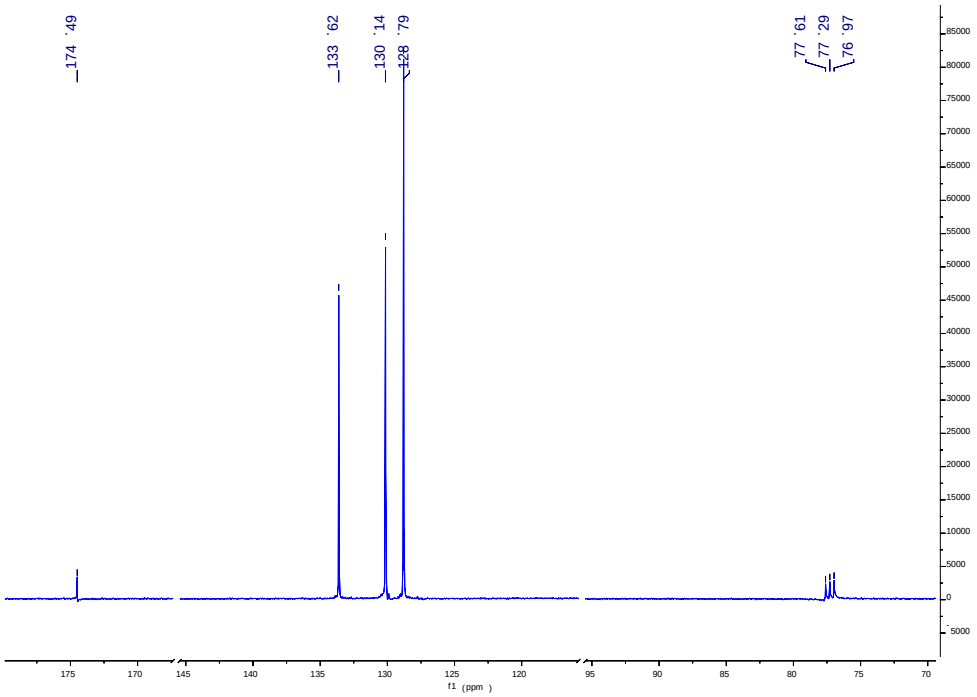


*Figure 6.3 ^{13}C NMR spectrum of the pure N,N-dichlorobenzamide (**4**).*

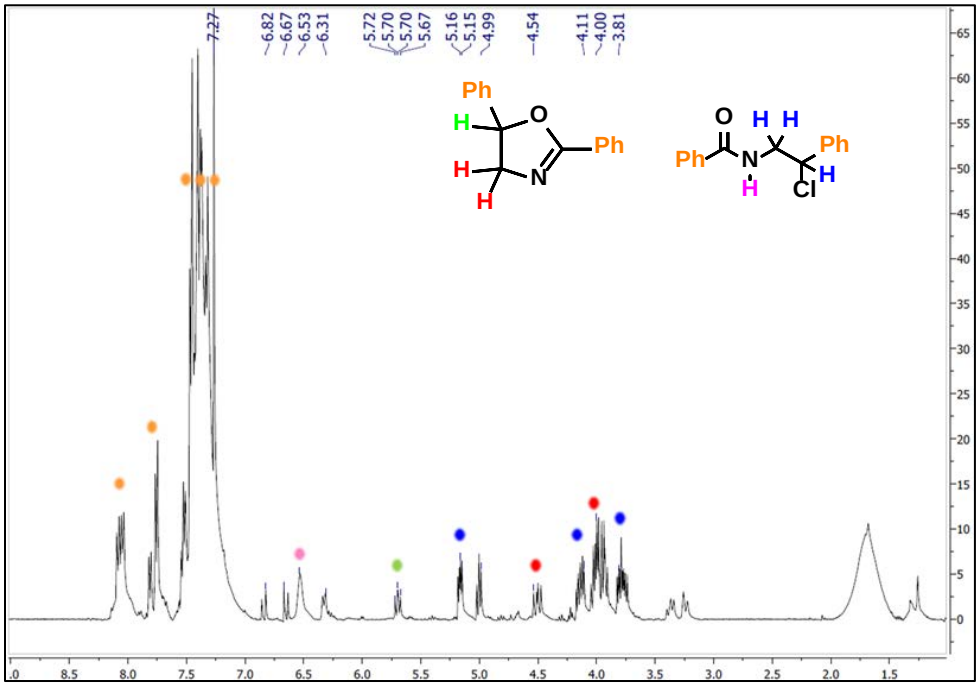


Figure 6.4 ^{1}H NMR Spectrum of Crude Mixture, Coupling Reaction with Styrene.

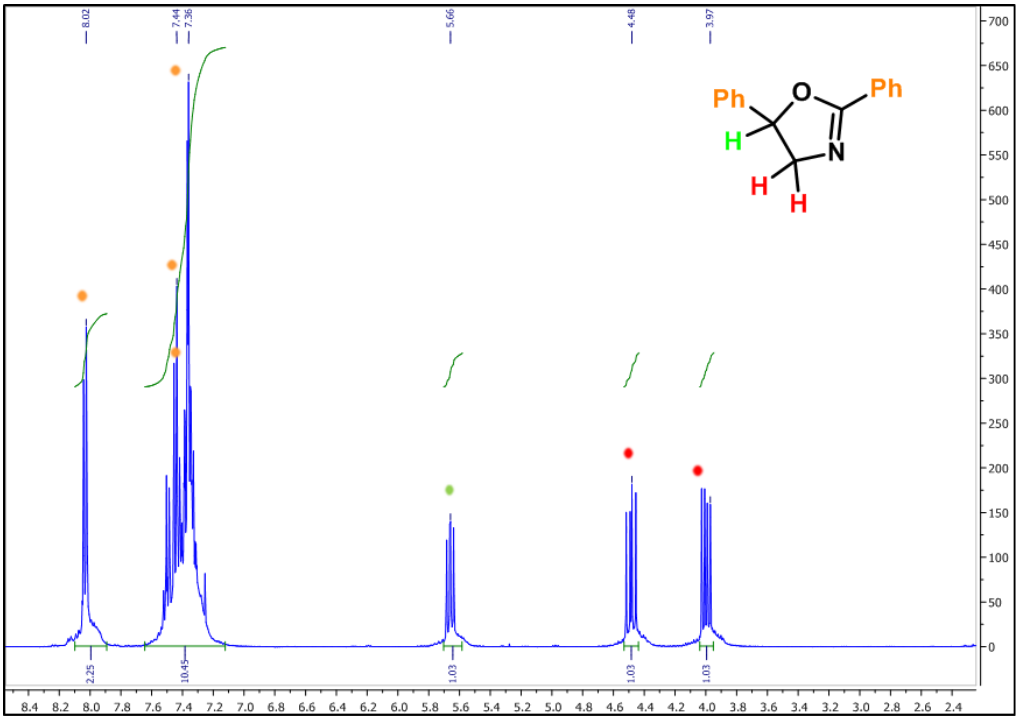


*Figure 6.5 ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the obtained 2,5-diphenyl-2-oxazoline(**5**).*

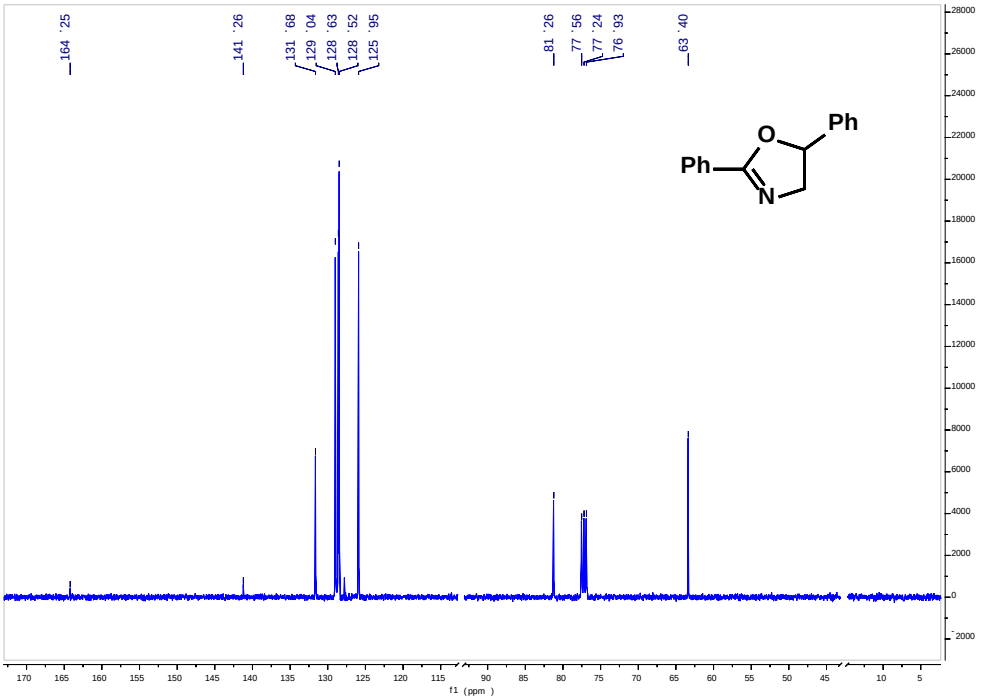


*Figure 6.6 ^{13}C NMR spectrum of 2,5-diphenyl-2- oxazoline (**5**).*

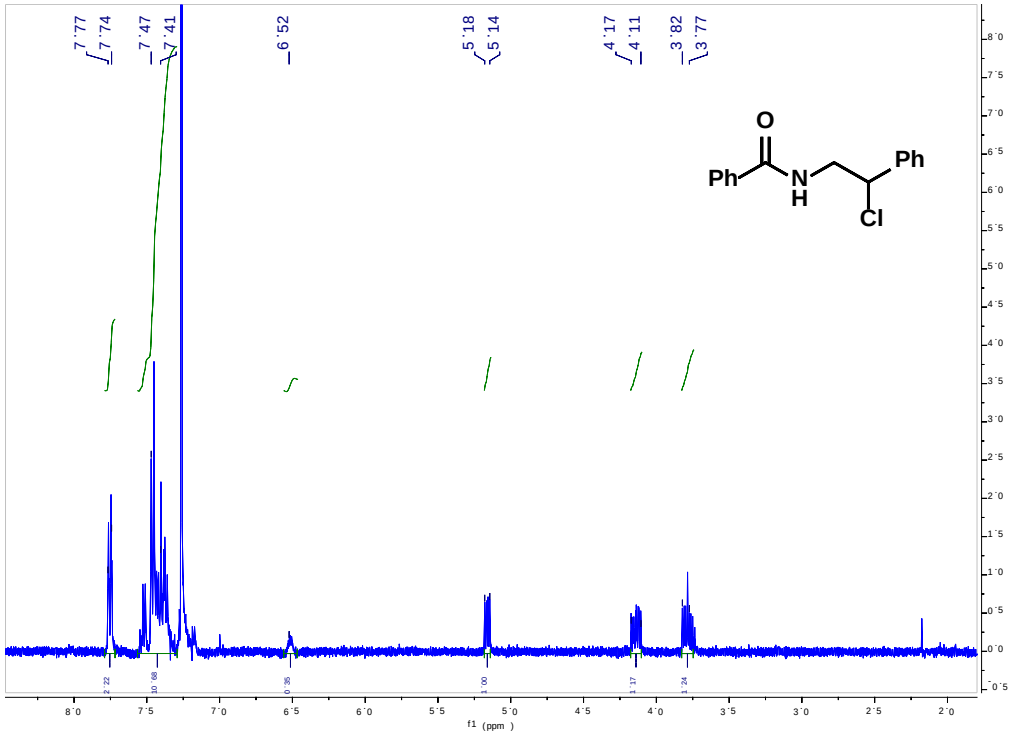


*Figure 6.7 ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the acyclic product (**12**)*

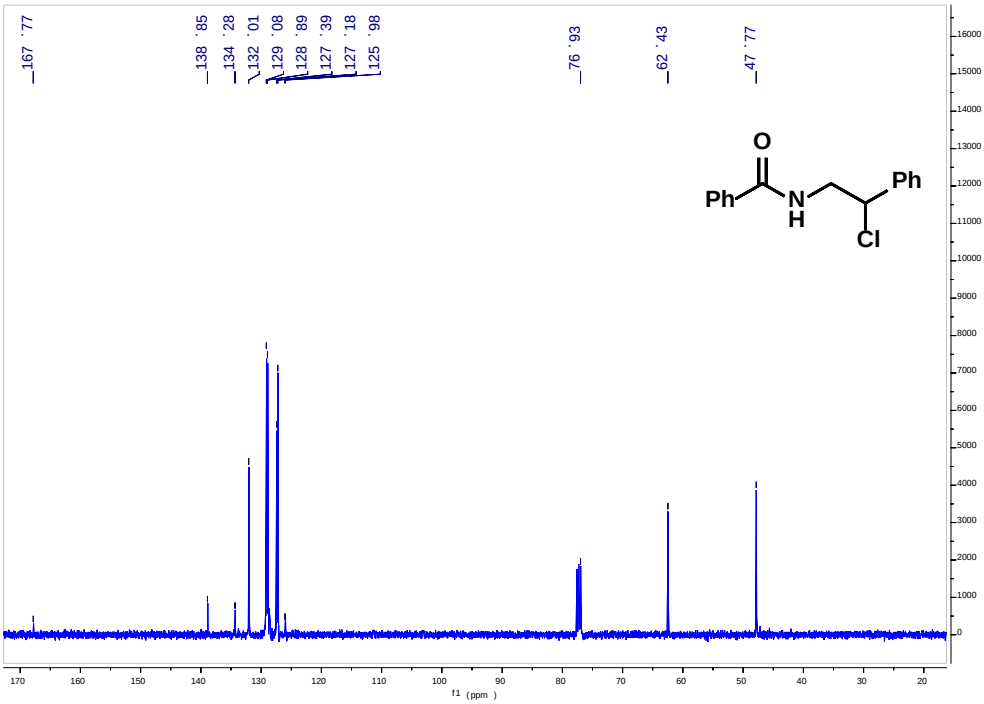


*Figure 6.8 ^{13}C NMR spectrum of N-(2-Chloro-2-phenylethyl)-benzamide the acyclic product (**12**).*

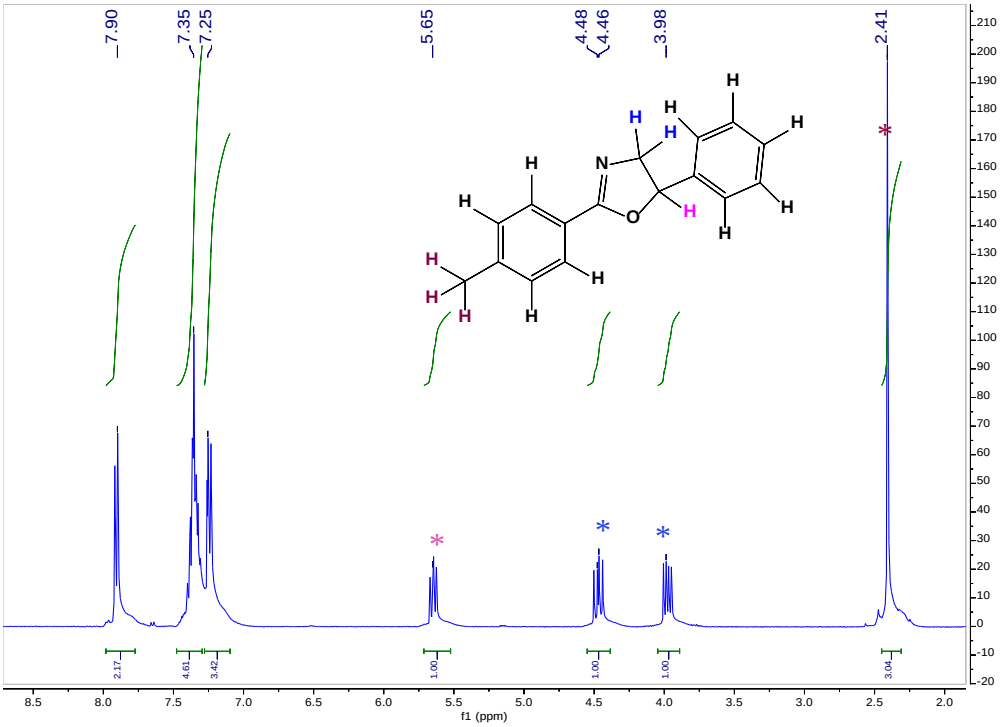


*Figure 6.9 [1]H NMR spectrum of 2-(4-methylphenyl)-5-phenyloxazoline (**14**).*

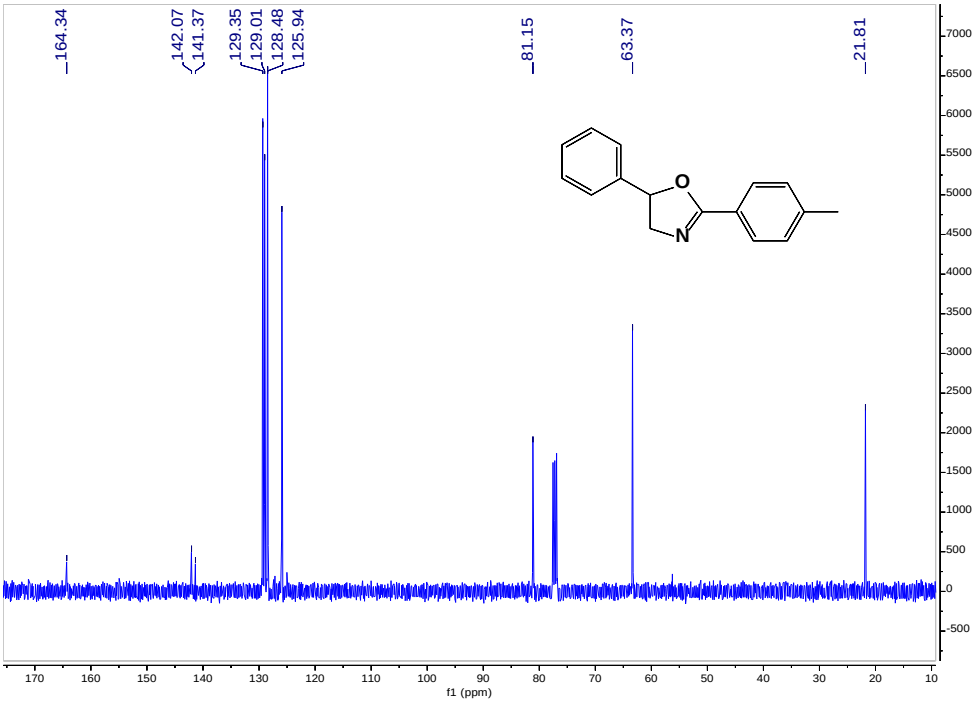


*Figure 6.10 [13]C NMR spectrum of 2-(4-methylphenyl)-5-phenyloxazoline (**14**).*

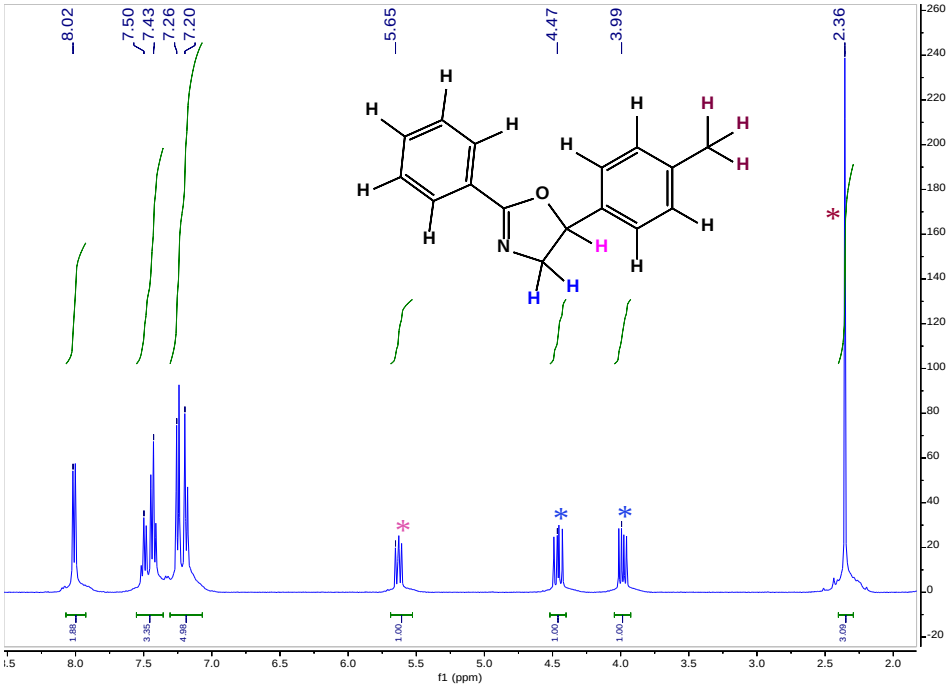


*Figure 6.11 [1]H NMR spectrum of 5-(4-methylphenyl)-2phenyloxazoline (**15**).*

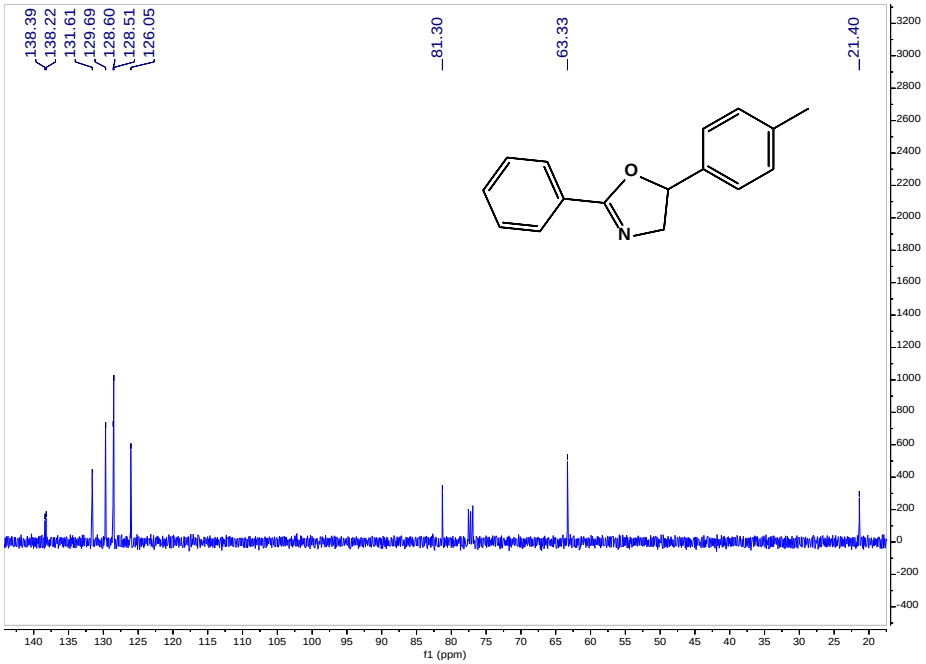


*Figure 6.12 [13]C NMR spectrum of 5-(4-methylphenyl)-2phenyloxazoline (**15**).*

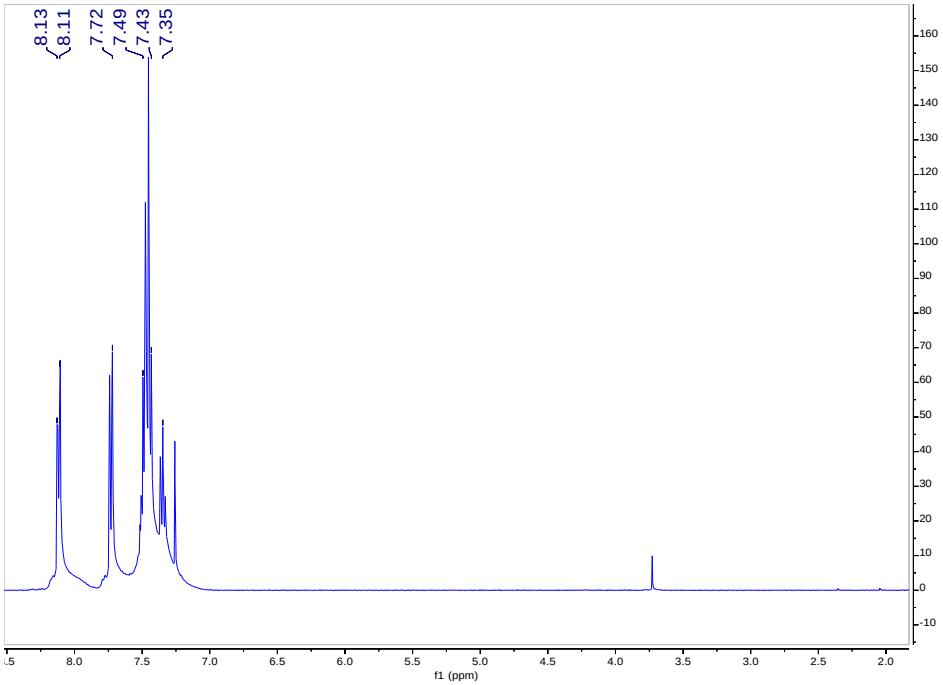


*Figure 6.13 [1]H NMR spectrum of obtained 2,5-diphenyl-2-oxazole (**16**).*

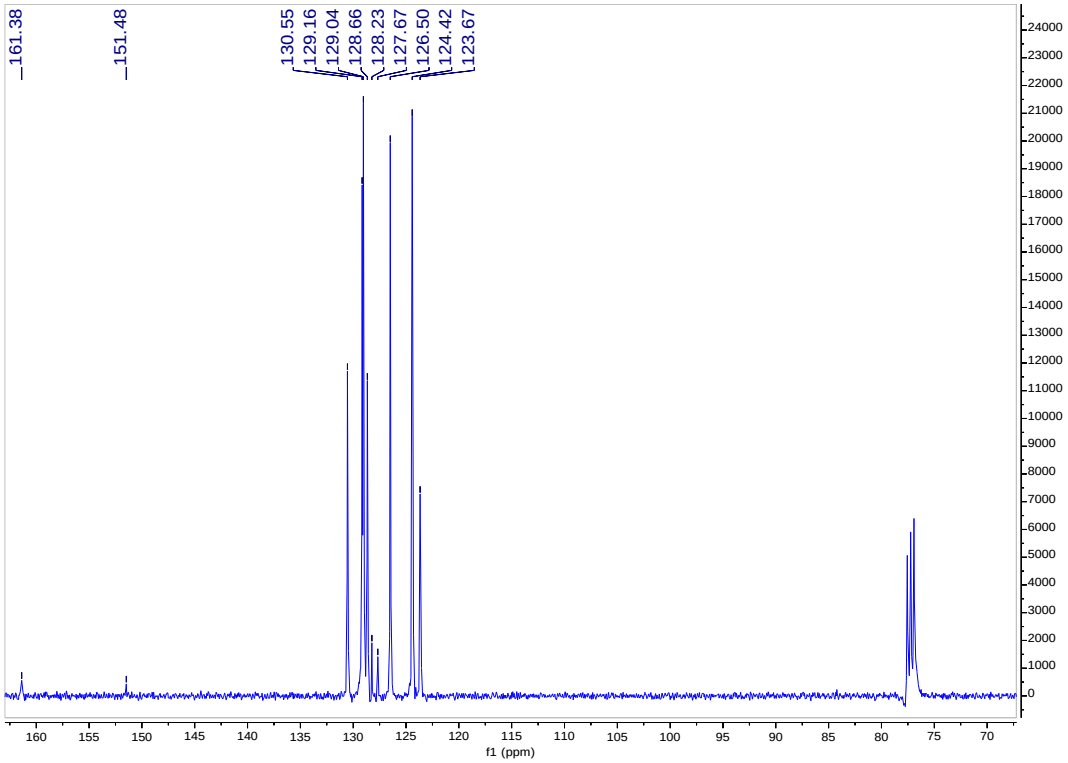


*Figure 6.14 [13]C NMR spectrum of 2,5-diphenyl-2-oxazole (**16**).*

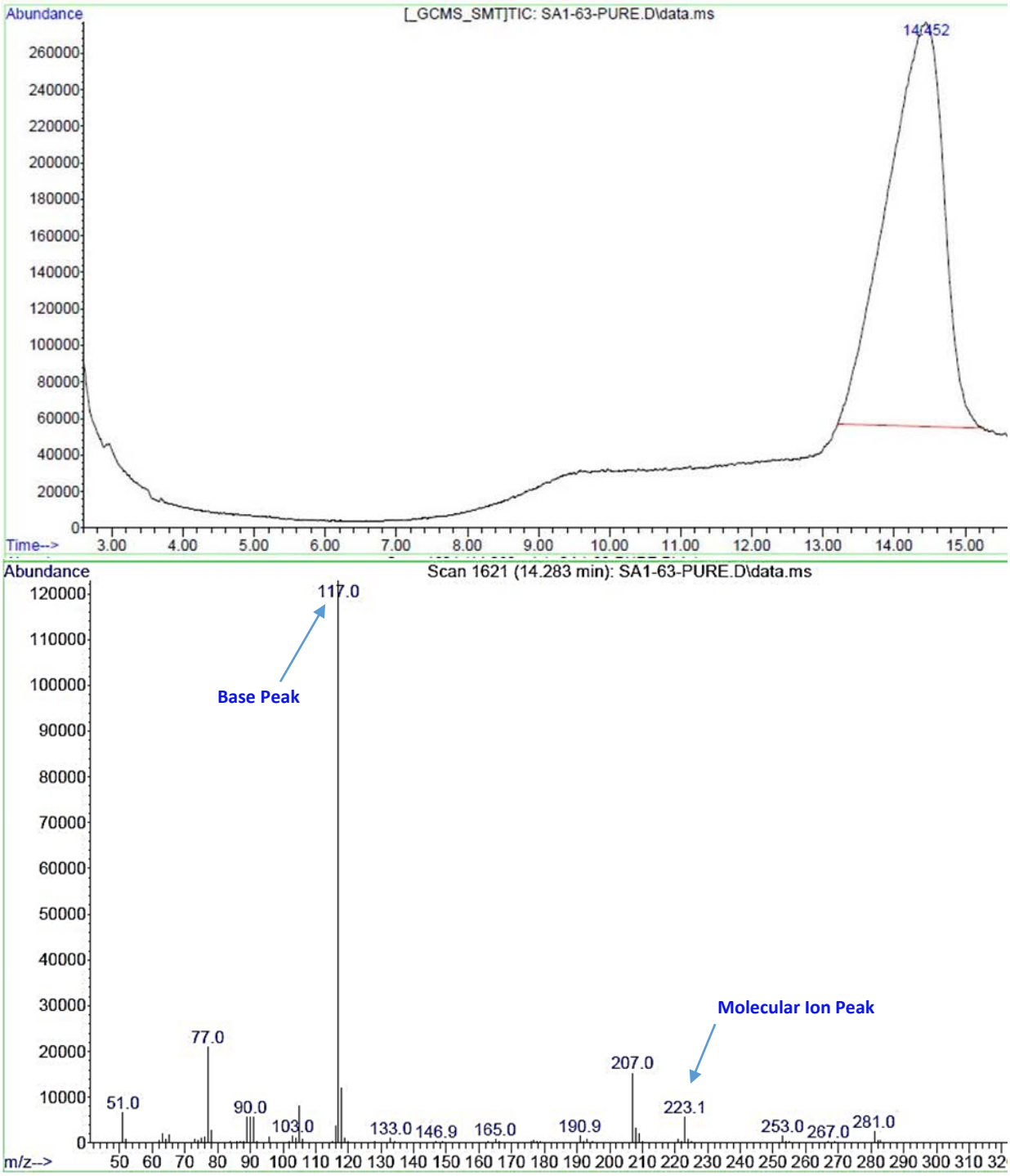


*Figure 6.15 Total ion chromatogram (TIC) of the isolated 2,5-diphenyl-2-oxazoline (**5**), and its EI (70 eV) mass spectrum.*

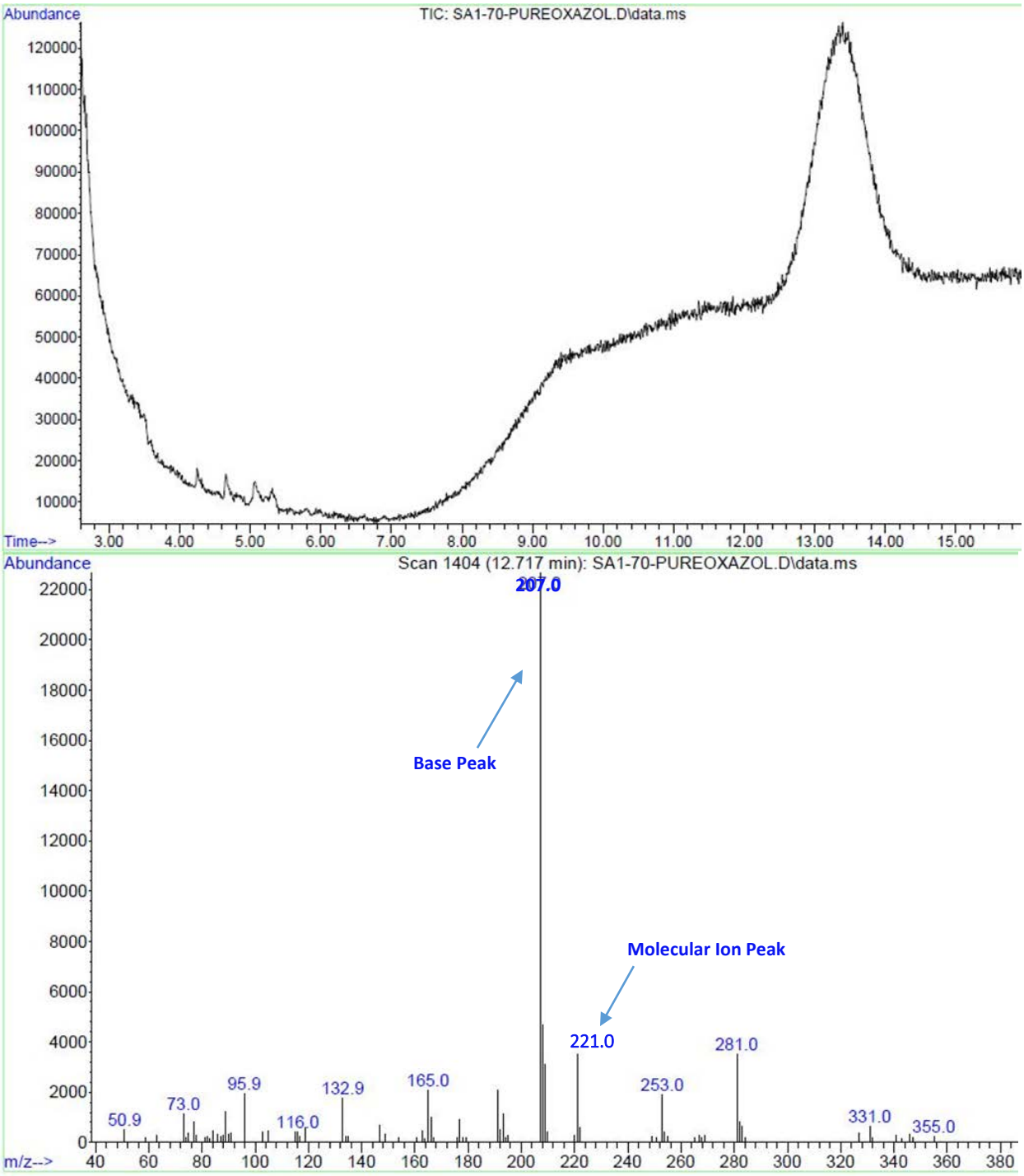


*Figure 6.16 TIC of 2,5-diphenyloxazole (**16**) and its mass spectrum (the peaks above 221.0 match the background noise).*

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