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STUDIES TOWARDS THE TOTAL SYNTHESIS OF KOTTAMIDES (A-D)
ONE-POT FRIEDEL-CRAFT/ROBINSON-GABRIEL SYNTHESIS OF OXAZOLES USING OXAZOLONE TEMPLATES

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STUDIES TOWARDS THE TOTAL SYNTHESIS OF KOTTAMIDES (A-D) ONE-POT FRIEDEL-CRAFT/ROBINSON-GABRIEL SYNTHESIS OF OXAZOLES USING OXAZOLONE TEMPLATES

By

Manasi Keni

A THESIS

Submitted to
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Department of Chemistry

2005

ABSTRACT

STUDIES TOWARDS THE TOTAL SYNTHESIS OF KOTTAMIDES (A-D)
ONE-POT FRIEDEL-CRAFT/ROBINSON-GABRIEL SYNTHESIS OF OXAZOLES
USING OXAZOLONE TEMPLATES

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The initial studies towards total synthesis of Kottamides (A-D), a biologically active alkaloids isolated from the New Zealand endemic ascidian *Pycnoclavella kottae,* is presented. Kottamides have been shown to exhibit anti-inflammatory, anti-metabolic activity and cytotoxicity toward tumor cell lines. The kottamides (A-D) are novel imidazol-4-one bearing alkaloids possessing a unprecedented substitution pattern and exist in nature as the Z-isomer. The key to the synthesis of the kottamides is synthesis of the 2,2,5-trisubstituted imidazol-4-one and the Z-enamide.

The synthesis of oxazoles is discussed in which oxazoles are synthesized, starting with oxazol-5-ones, using a general protocol. A one-pot synthesis of 2,4,5-trisubstituted oxazoles is reported via a Friedel-Crafts/Robinson-Gabriel synthesis using a general oxazolone template. Treatment of the oxazol-5-one template with a range of aromatic nucleophiles provided the highly substituted oxazoles in good yields. The oxazole nucleus is present in a wide variety of natural and unnatural biologically active compounds and is a useful reagent in the synthesis of a range of biologically active scaffolds. As part of our program to develop diverse classes of small molecule libraries containing potential biological properties, we have developed a substrate controlled diversity-oriented synthesis (DOS) using a general oxazolone template.

Dedicated with love to mummy and baba for their love and care.

ACKNOWLEDGMENTS

I am grateful to Dr. Jetze Tepe for his guidance as my advisor. He has been very supportive, understanding and patient during my stay in his lab. I am glad I worked with him as his drive and dedication was inspiring to me. I think working for him helped me grow as a chemist. I would like to thank Dr. Maleczka for his help mainly for CEM 852, which is one of the most helpful courses I have taken. I would like to thank Prof. Wulff and Prof Pinnavai for serving on my committee and for their helpful comments.

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I am blessed with amazing parents and brother who always helped me in anyway that they could. I especially thank my dad for always finding time to coach me in chemistry. I am thankful to my best friend Nikhil, whom I have known all these years growing up, for always standing by me in good times as well as bad. I consider myself lucky to have been friends with such an amazing person.

Finally I thank Abhi for whom I came to Michigan State University and for whom I am leaving. His love for chemistry and sincerity to work is inspirational.

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ABBREVIATIONS

NMR = nuclear magnetic resonance

Tf_2O = trifluoromethanesulfonic anhydride

TFAA = trifluoroacetic anhydride

KHMDS = potassium hexamethyldisilazane

Pyr, Py = pyridine

TsCl = *p*-toluenesulfonic chloride

Et_2O = diethyl ether

EWG = electron withdrawing group

TLC = thin layer chromatography

i-Pr_2NH = diisopropyl amine

PTSA, TfOH = trifluoromethanesulfonic acid

LiHMDS = lithium hexamethyldisilazane

p-TsOH = *p*-toluenesulfonic acid

KO*t*-Bu = potassium tert-butoxide

DIBAL = diisobutylaluminium hydride

EtOH = ethanol

Boc = tert-butoxycarbonyl

DMAP = 4-dimethylaminopyridine

NEt_3, TEA = triethyl amine

Ph = phenyl

TMSCl = trimethylsilyl chloride

Ac_2O = acetic anhydride

THF = tetrahydrofuran

NOESY = nuclear overhauser effect spectroscopy

DMSO = dimethyl sulfoxide

DBU = 1,8-diazabicyclo[5.4.0]undec—7-ene

NH_4OAc = ammonium acetate

NBS = N-bromosuccinimide

Me = methyl

LA = Lewis acid

AgOAc = silver acetate

Et = ethyl

EDCI = 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide

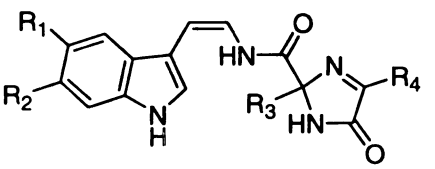
Bt = benzatriazole

CHAPTER 1

STUDIES TOWARDS THE SYNTHESIS OF KOTTAMIDES

Introduction

Kottamides (Figure 1.1) are 2,2,5-trisubstituted imidazolone-containing alkaloids which have been isolated from the New Zealand endemic ascidian *Pycnoclavella kottae* and they exhibit anti-inflammatory, anti-metabolic activity and cytotoxicity toward tumor cell lines.[1] The kottamides are the first example of 2,2,5-trisubstituted imidazolone natural products and this is the first reported study on chemistry from an ascidian of the genus *Pycnoclavella*.



A: R_1=Br, R_2=Br, R_3=^{i}Pr, R_4=^{i}Bu

B: R_1=Br, R_2=H, R_3=^{i}Pr, R_4=^{i}Bu

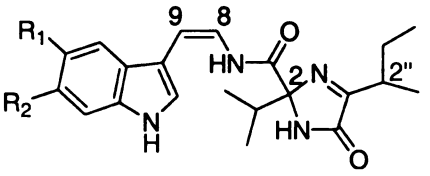
C: R_1=H, R_2=Br, R_3=^{i}Pr, R_4=^{i}Bu

D: R_1=Br, R_2=Br, R_3=^{i}Bu, R_4=Me

Figure 1.1: Kottamides A-D.

Structure analysis

The kottamides (A-D) are novel imidazol-4-one bearing alkaloids possessing an unprecedented substitution pattern. While imidazol-4-one bearing alkaloids have been reported as synthetic precursors,[2] only the rhopaladins from ascidians,[3] and the fused examples luciferin[3] and coelenterazine,[3] have been reported from natural sources. The kottamides are the first example of 2,2,5-trisubstituted imidazolone natural products. The kottamides were structurally characterized using ^{15}N natural abundance 2-D NMR in addition to standard spectroscopic methods. Kottamides (A-D) exist in nature as *Z* (C_8-C_9 double bond) isomers (Figure 1.2). The stereochemistry at C-2, C-2'' and the quaternary sp^3 carbon of the imidazolone is unknown in kottamides-A,B,C. The stereochemistry at C-2' and the quaternary sp^3 carbon of the imidazolone is unknown in kottamide-D.



A: R_1=Br, R_2=Br, R_3=^{i}Pr, R_4=^{i}Bu

B: R_1=Br, R_2=H, R_3=^{i}Pr, R_4=^{i}Bu

C: R_1=H, R_2=Br, R_3=^{i}Pr, R_4=^{i}Bu

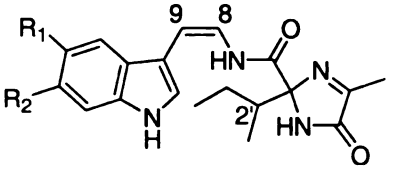


Figure 1. 2: Structural analysis of kottamides (A-D)

The synthetic strategy towards the total synthesis of kottamides (A-D) involved:

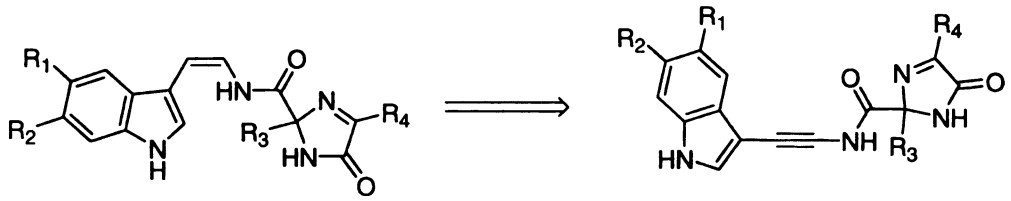
1. *Z*-Enamide synthesis.
2. 2,2,5-trisubstituted imidazol-4-one synthesis.

Studies on *Z*-enamide synthesis

Enamides have been previously synthesized using a number of methods, including N-acylation of imines,[4] elimination of α-substituted amides,[5] isomerization of *N*-allyl amides,[6] palladium(II)-catalyzed amidation of alkenes,[7] Peterson olefination,[8] and *N*-acylation of protected enamines.[9] Other recent enamide formation methods have also been developed, including organometal addition to vinyl isocyanates,[10] oxidative decarboxylation-elimination,[11] Ru-catalyzed chain extension,[12] and rearrangement of *N*-(α-silyl)allyl amides.[13]

Synthesis of *Z*-enamide linkage

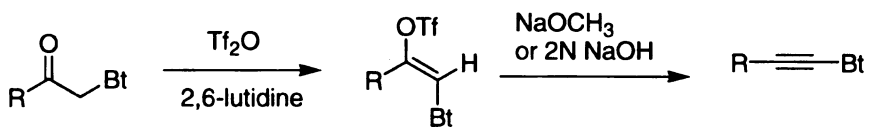
To enable the synthesis of kottamides we require a general method to synthesize enamides. One of the methods to synthesize a *Z*-enamide **1.1** could be using palladium catalyzed asymmetric hydrogenation of the corresponding ynamide **1.2** (Figure 1.3).



1.1 1.2

Figure 1.3: Retrosynthesis of *Z*-enamide from ynamide.

Carbon-carbon triple bond can be reduced to a carbon-carbon cis double bond by catalytic methods.[14] A good catalyst for this purpose is the Lindlar catalyst (Pd-$CaCO_3$-PbO). In considering a potential new method for synthesizing the ynamide we focused our efforts on using a route similar to one developed by Katritzky.[15] Treating a ketone **1.3** with triflic anhydride in the presence of 2,6-lutidine afforded enol triflates **1.4**. These enol triflates could be converted into alkynes **1.5** after treatment in situ with sodium methoxide or sodium hydroxide (Scheme 1.1).



1.3 1.4 1.5

Scheme 1.1: Synthesizing an alkyne from ketone.

Retrosynthetically the kottamides could be synthesized from their ynamide analogue **1.7**. The ynamide **1.7** could be synthesized from the amide **1.9** via intermediate

1.8 by treating the amide with a base in the presence of Tf_2O. The amide can be synthesized from the indoles **1.10** and 2-substituted oxazol-5-one **1.11**, via Friedel-Craft acylation reaction. The oxazol-5-one **1.11** can be synthesized from the corresponding acid **1.12** via cyclization (Figure 1.4).

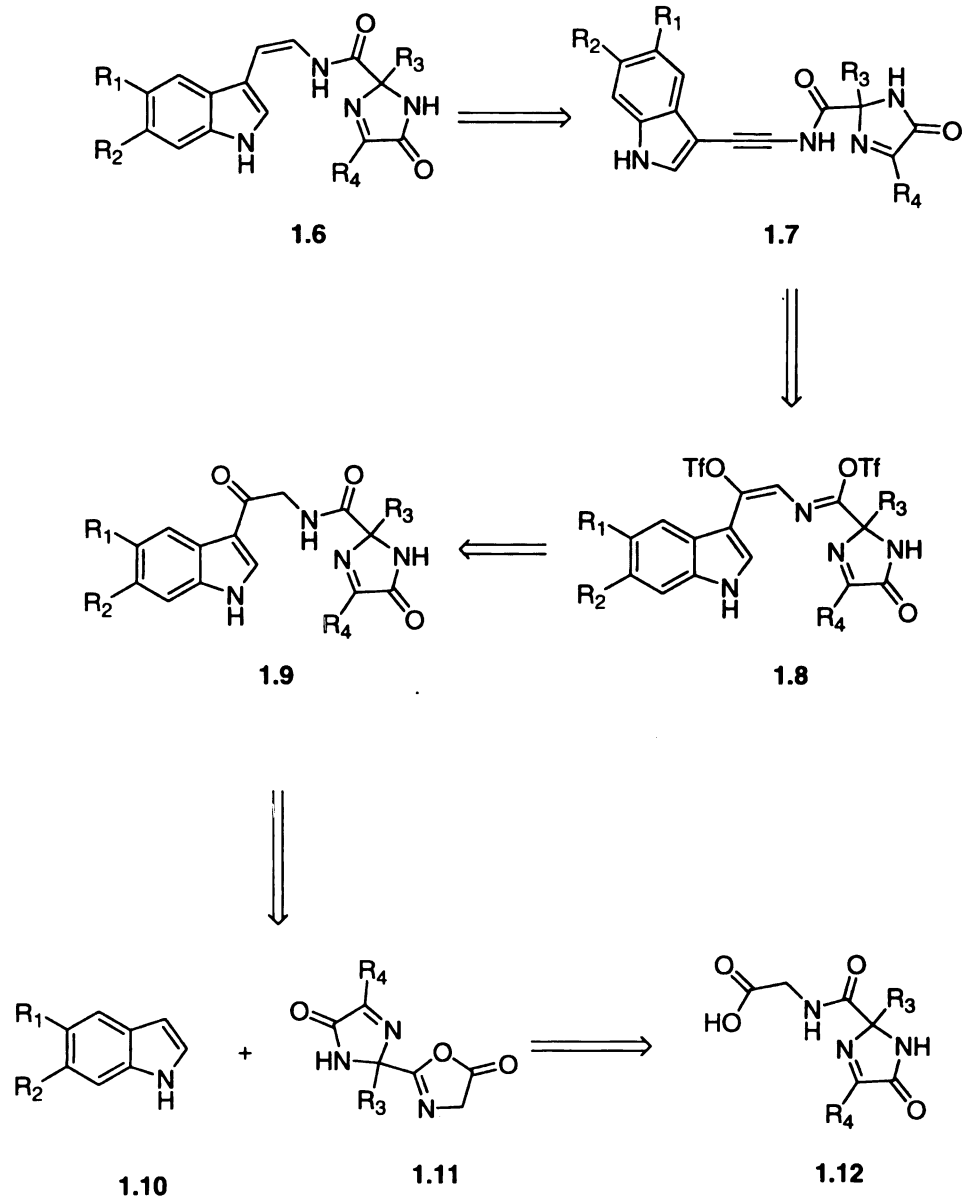
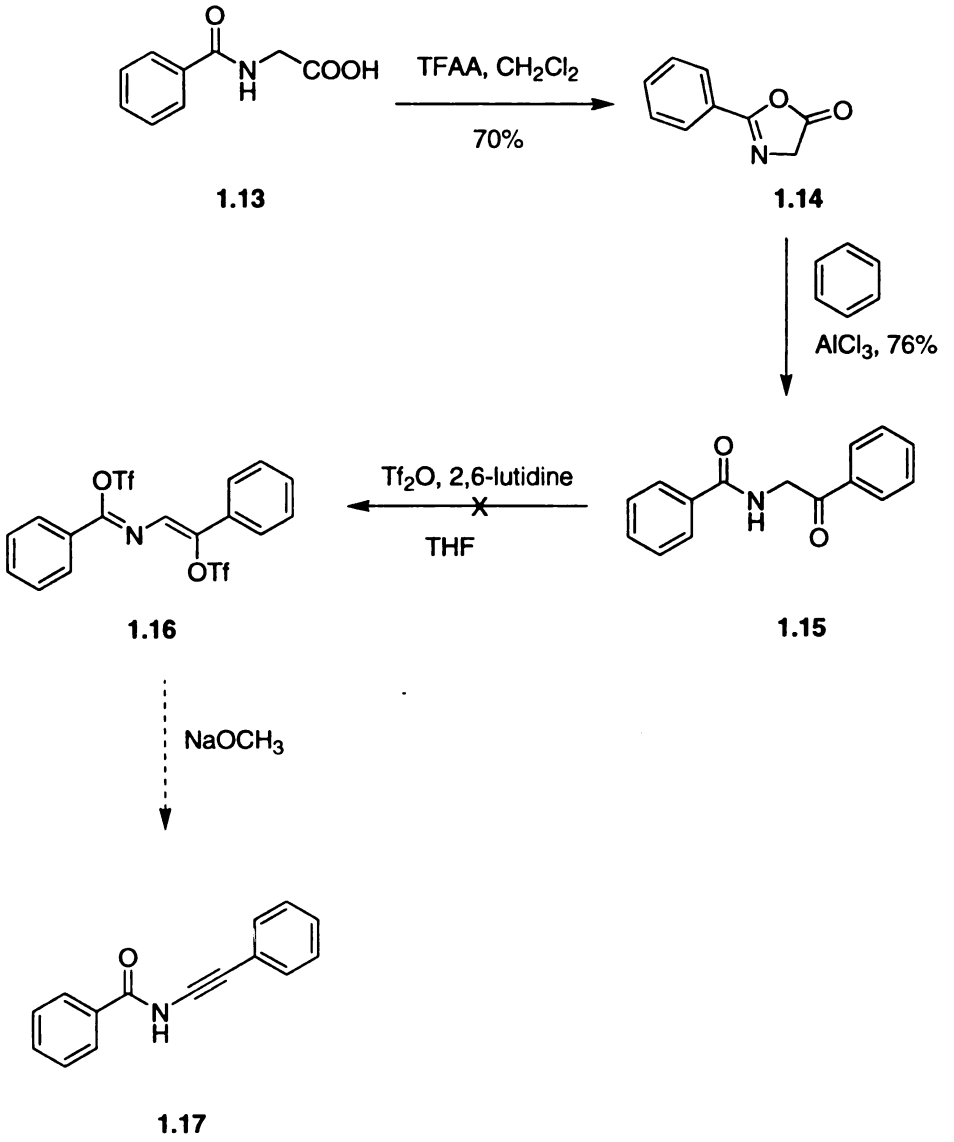


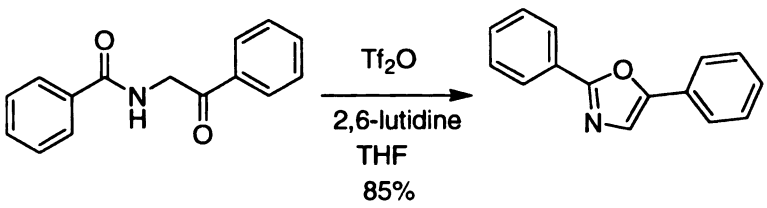
Figure 1.4: Retrosynthesis of kottamides (I).

To confirm the feasibility of this route a model system was devised using readily available starting materials. Benzene was used instead of indol and hippuric acid was used instead of the acid **1.12** (Scheme 1.2). Upon treating hippuric acid **1.13** with

used instead of the acid **1.12** (Scheme 1.2). Upon treating hippuric acid **1.13** with trifloroacetic anhydride the corresponding oxazol-5-one **1.14** was obtained via dehydrative cyclization. The oxazol-5-one **1.14** undergoes a Friedel-Craft acylation to give *N*-(2-oxo-2-phenyl-ethyl)-benzamide **1.15**. Treating *N*-(2-oxo-2-phenyl-ethyl)-benzamide **1.15** with triflic anhydride and excess of base (2,6-lutidine) did not afford the ynamide. This reaction resulted in the formation of 2,5-diphenyl oxazole **1.18** via Robinson-Gabriel synthesis instead (Scheme 1.3). This synthesis would be further elaborated on in chapter 2.



Scheme 1.2: Model system for synthesizing the ynamide.

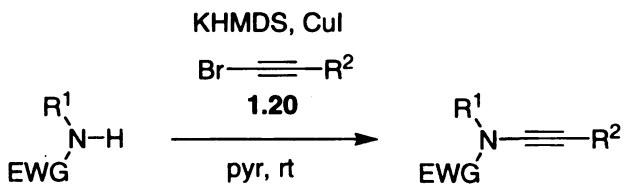


1.15 1.18

Scheme 1.3: Synthesis of 2,5-oxazole via Robinson-Gabriel synthesis.

Copper catalyzed coupling to synthesize *Z*-enamide via ynamide.

It has been reported that ynamides can be synthesized via copper catalyzed coupling of amides with alkynyl bromides.[16] A amination strategy for the *N*-alkynylation of carbamates, sulfonamides, oxazolidinones and imidazolidinones is described by which a variety of ynamides **1.21** are available. Ynamides **1.21** are synthesized by deprotonation of amides **1.19** with KHMDS followed by reaction with CuI and alkynyl bromide **1.20** (Scheme 1.4).



1.19 1. 21

Scheme 1.4: Copper-mediated *N*-alkynylation for synthesis of ynamides.

Retro-synthetically kottamides **1.1** could be synthesized from the corresponding ynamide **1.2**. The ynamide can be synthesized from the *N*-protected-3-bromoethynyl indol **1.23** and the corresponding *N*-protected amide **1.24** via copper catalyzed coupling

(Figure 1.5). Copper-mediated coupling has been used for N-alkynylation to synthesize ynamides.[16,17,18]

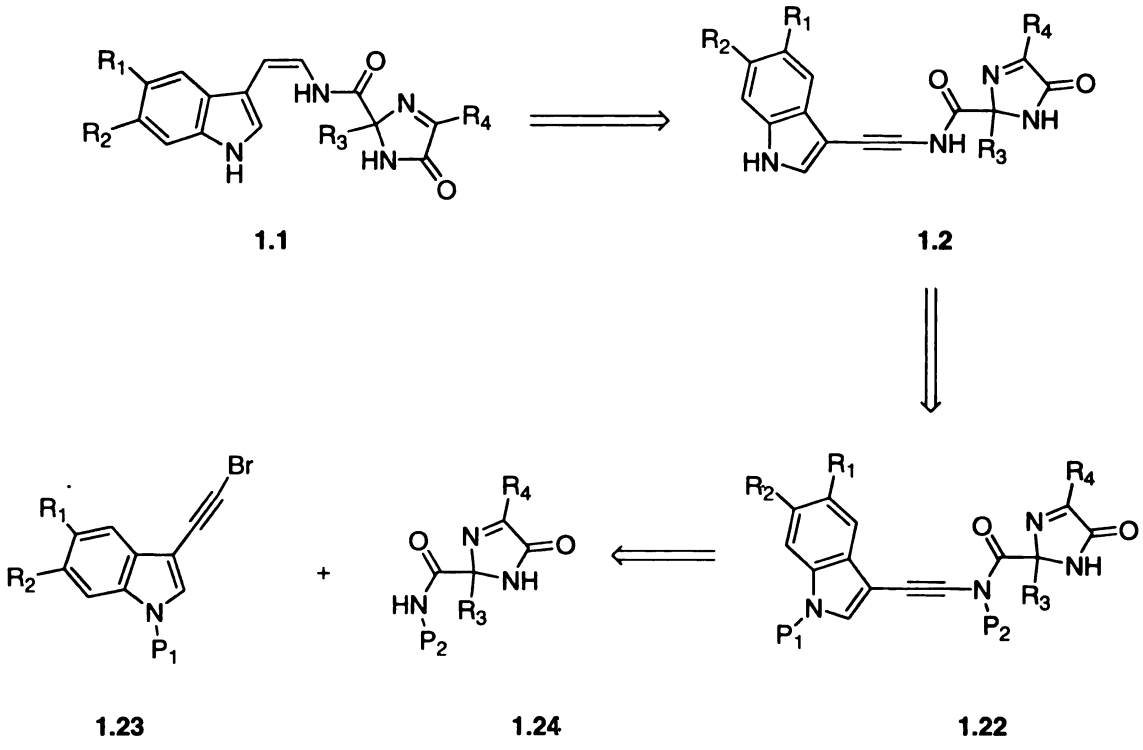
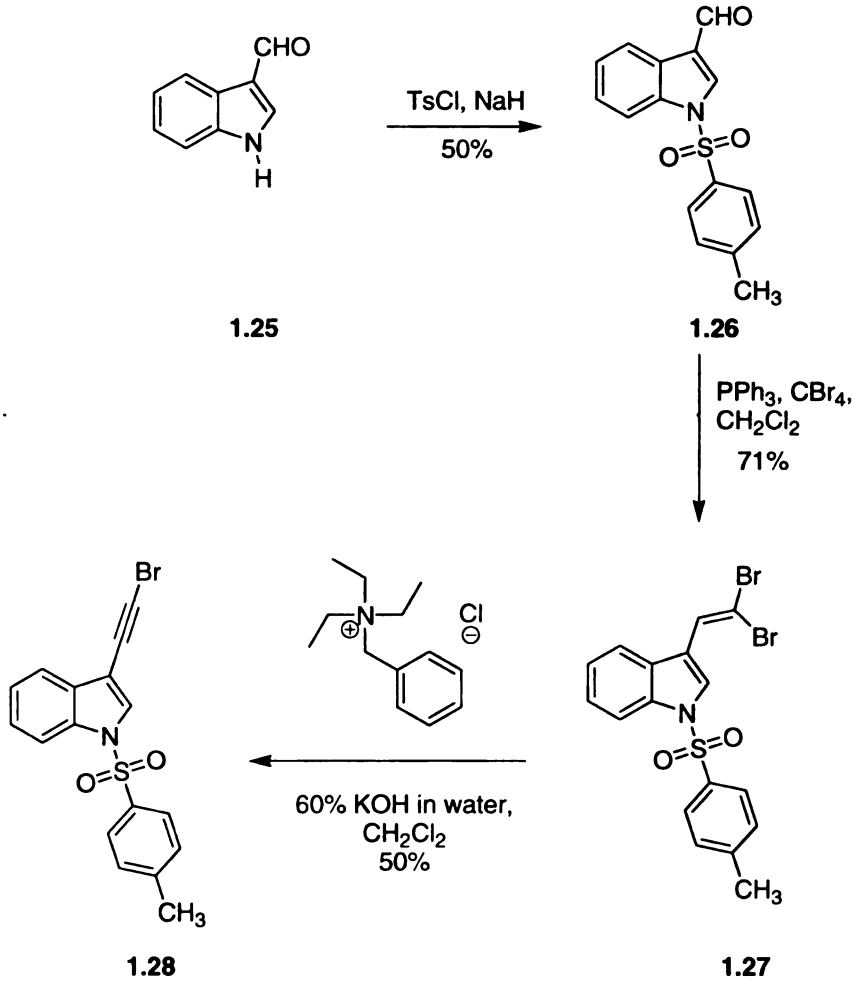


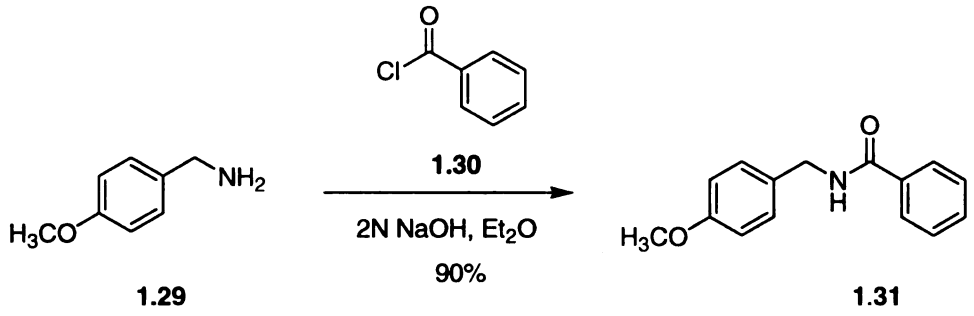
Figure 1.5: Retrosynthesis of kottamides (II)

Since the starting materials were not readily available to check the feasibility of this reaction, the following model system was used. The alkynyl bromide **1.28** and *N*-(4-methoxy-benzyl)-benzamide **1.31** are used to check the feasibility of the copper catalyzed reaction (Scheme 1.7). The *N*-protected-3-bromoethynyl indol **1.28** was synthesized from commercially available indol-3-carboxaldehyde **1.25**. The carboxaldehyde was tosylated using tosyl chloride to synthesize the N-tosylated carboxaldehyde **1.26** which on treating with carbon tetrabromide and triphenyl phosphene afforded the dibromo alkene **1.27**.

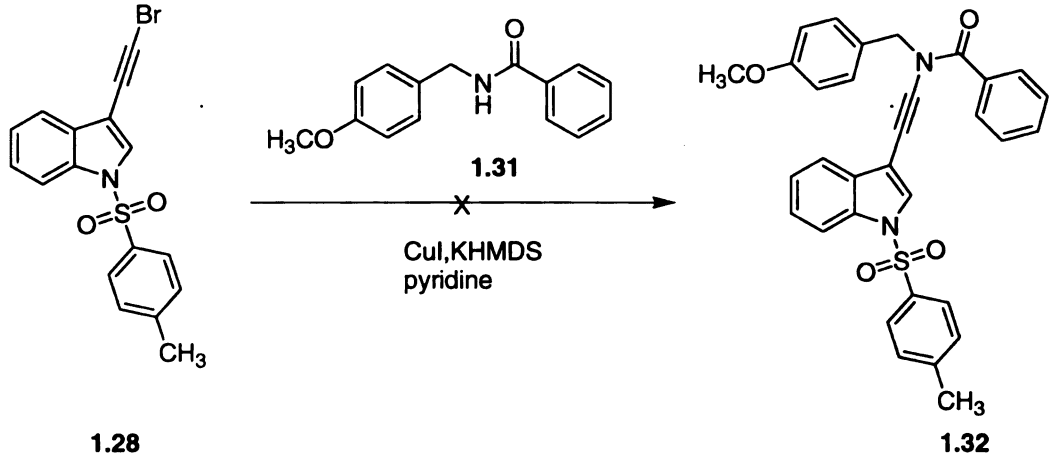
This on treating with a base produces alkynyl bromide **1.28** (Scheme 1.5). The *N*-(4-methoxy-benzyl)-benzamide was synthesized from benzoyl chloride and 4-methoxy-benzylamine (Scheme 1.6).



Scheme 1.5: Synthesis of 3-bromoethynyl-1-(toluene-4-sulfonyl)-indol.

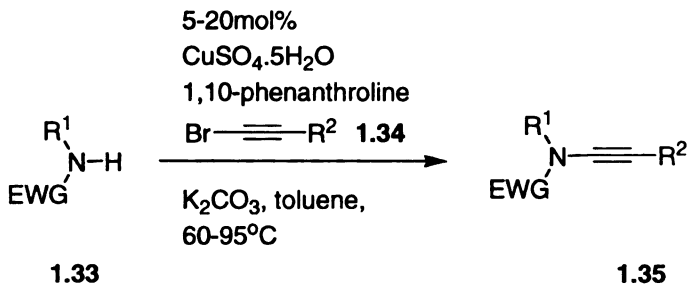


Scheme 1.6: Synthesis of *N*-(4-methoxy-benzyl)-benzamide.



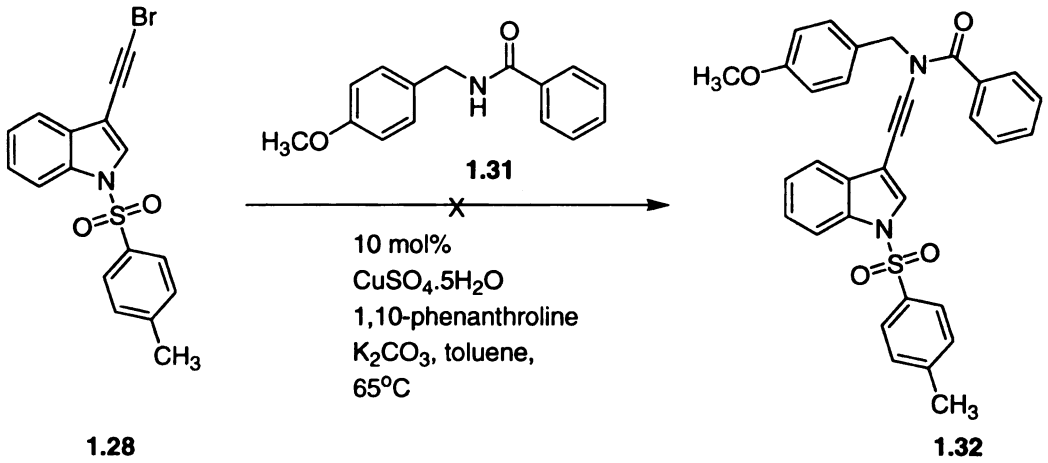
Scheme 1.7: Copper (I) mediated *N*-alkynylation of amide to generate ynamide on model system.

The ynamide **1.32** was not obtained on using similar conditions on a model system (Scheme 1.7). From crude ^{1}H NMR only the starting materials were observed. According to another report, ynamides **1.35** were synthesized via a cross-coupling of amides **1.33** with alkynyl bromides **1.34** using catalytic $CuSO_4.5H_2O$ and 1,10-phenanthroline (Scheme 1.8).[17]



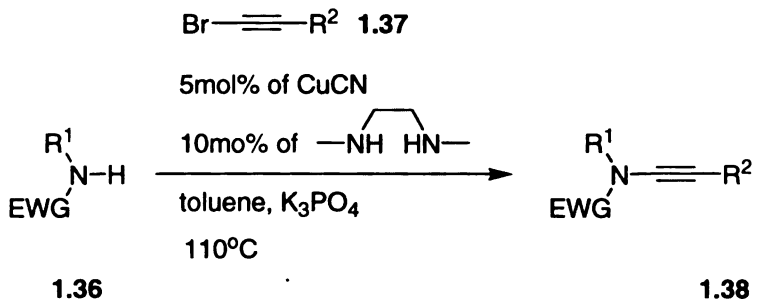
Scheme 1.8: Copper sulfate pentahydrate, 1,10-phenanthroline catalyzed amidation of alkynyl bromides.

Using the same model system as used in scheme **1.7**, this copper sulfate pentahydrate catalyzed system was applied to 3-bromoethynyl-1-(toluene-4-sulfonyl)-indol **1.28** and *N*-(4-methoxy-benzyl)-benzamide **1.31** (Scheme 1.9).



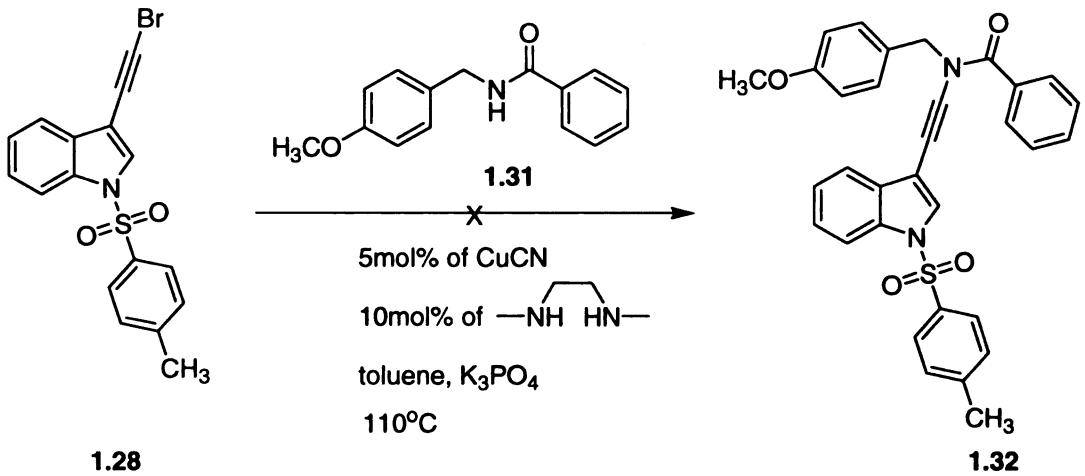
Scheme 1.9: Copper sulfate pentahydrate mediated *N*-alkynylation of amide to generate ynamide on model system.

The ynamide **1.32** was not obtained on using similar conditions on a model system (Scheme 1.9). A negligible amount of byproduct isolated in this reaction seemed to be from the homocoupling of the alkynyl bromide. Referring to another report ynamide **1.38** synthesis could be achieved using copper cyanide catalyzed coupling resulting in new C-N bond formation involving sp-hybridized carbon (Scheme 1.10).[18]



Scheme 1.10: Copper cyanide mediated *N*-alkynylation of amide to generate ynamide.

Using the similar model system as scheme 1.**7,** 3-bromoethynyl-1-(toluene-4-sulfonyl)-indole **1.28** was used for the alkynyl bromide and *N*-(4-methoxy-benzyl)-benzamide **1.31** was used as the amide (Scheme 1.11). The ynamide was not synthesized in this reaction. From the crude ^{1}H NMR and TLC only the starting materials were isolated after the work up of this reaction. None of the copper catalysts that have been reported represent a general protocol that could be used for coupling with the given substrate (amides). Despite the encouraging results that were reported, most of these catalytic systems were seen to be inconsistent, and homocoupling of the alkynyl iodides continued to compete. This reaction required further research.



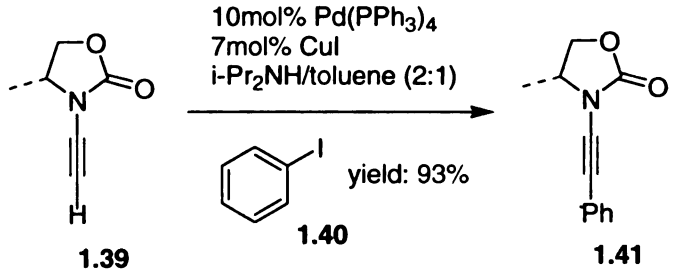
Scheme 1.11: Copper cyanide mediated *N*-alkynylation of amide to generate ynamide on model system.

In the case of ynamide formation where copper cyanide was used, oxazolidinone based amides, lactams and urea based auxiliaries were used as substrates.[18] When copper iodide was used as the catalyst, various acyclic carbamates were used as substrates.[16] When copper sulfate pentahydrate was used as the catalyst, several acyclic carbamates, oxazolidinone based amides, aza-camphor, imidazolidinone, acyclic urethanes, lactams, and sulfonamides were used as substrates.

Z-enamide synthesis using Sonogashira cross-coupling via ynamide.

Sonogashira coupling could be utilized to synthesize the ynamide, which in turn could be reduced to form the *Z*-enamide of the kottamides. According to a report, a

ynamide **1.39** and aryl iodide **1.40** could be utilized in transition metal-mediated cross-coupling reaction to form the ynamide **1.41** (Scheme 1.12).[19] Retrosynthetically kottamides could be synthesized from substituted 3-iodo-indole **1.42** and ynamide **1.43** (Figure 1.6).



Scheme 1.12: Sonogashira coupling of ynamide and aryl iodide.

As discussed before the Z-enamide in Kottamides could be synthesized from their ynamide analogues **1.2**. This ynamide could be potentially synthesized from the ynamide **1.43** and iodo-indol **1.42** via Sonogashira coupling. Alkynyl iodonium triflate salt **1.45** could be utilized with various amides to provide ynamide **1.43** required for Sonogashira coupling (Figure 1.7).[17] Since at this point the amide required to synthesize the kottamides was not available a model system was devised for the synthesis of ynamide **1.48** with readily available amide **1.31** (Scheme 1.14). The alkynyl iodoniumtriflate salt **1.45** was synthesized from 1,2-bis-trimethylsilanyl-ethyne **1.47** (Scheme 1.13). The alkynyl iodoniumtriflate salt can be synthesized from 1,3-bis-trimethylsilanyl-propyne **1.47** (Scheme 1.13).

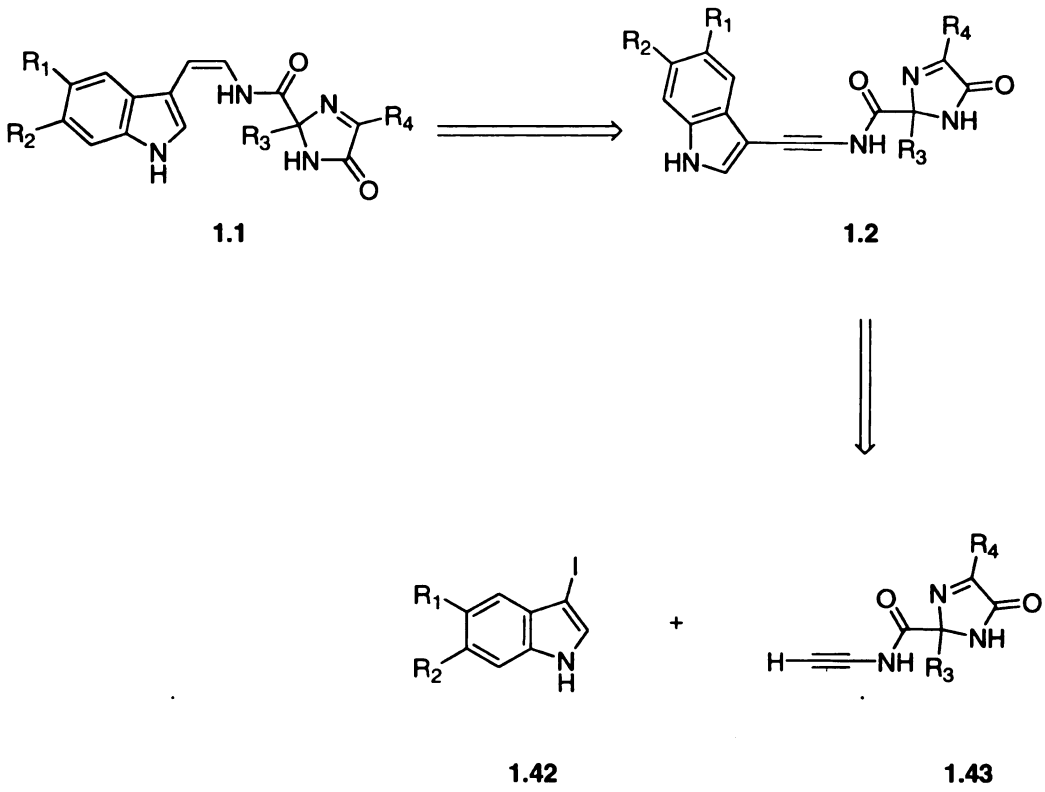


Figure 1.6: Retrosynthesis of kottamides using Sonogashira coupling.

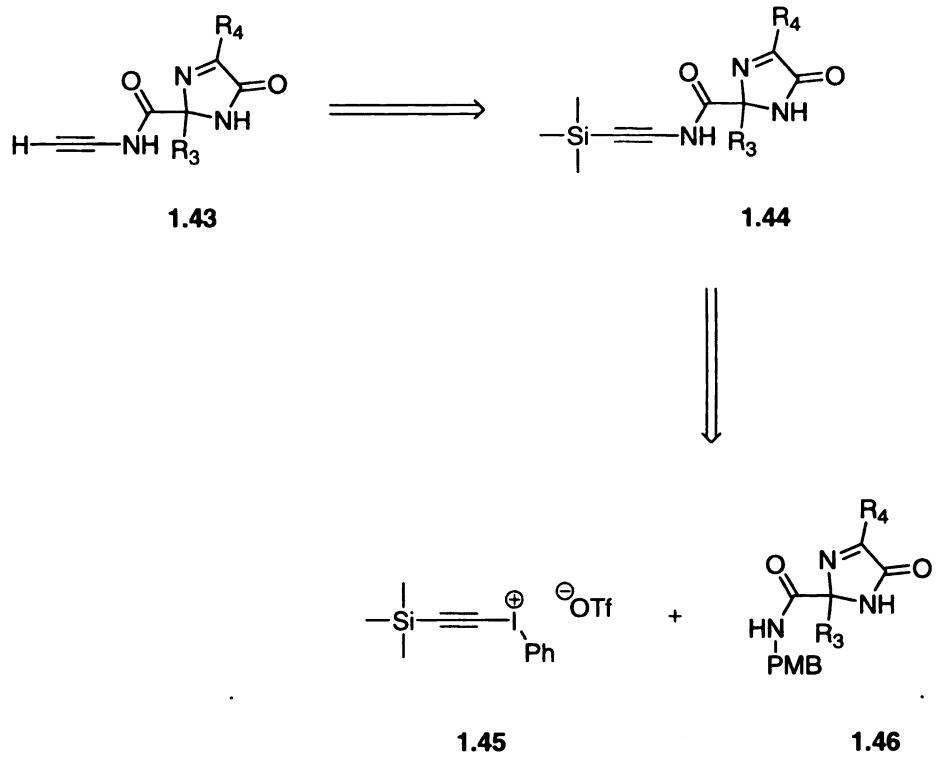
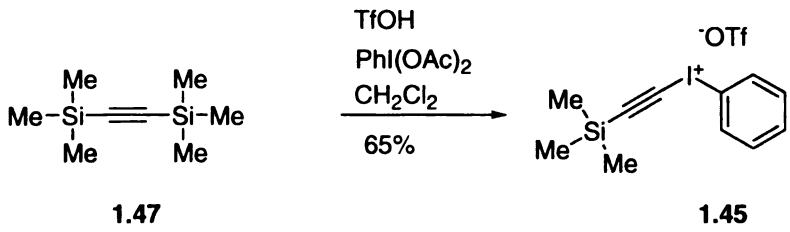
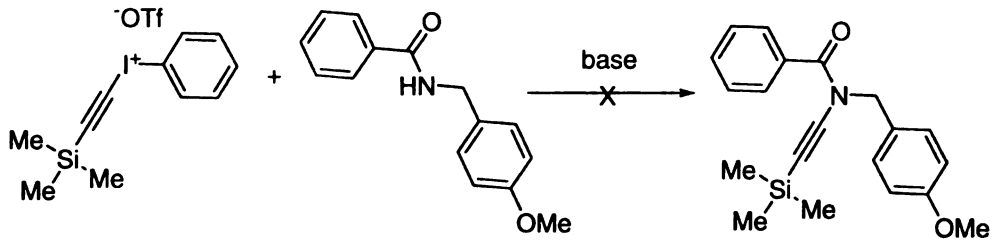


Figure 1.7: Synthesis of ynamide utilizing alkynyl iodoniumtriflate salt.



Scheme 1.13: Synthesis of alkynyl iodonium triflate salt.



1.45 **1.31** **1.48**

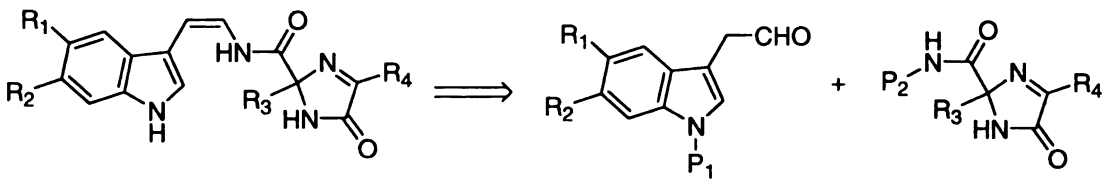
Scheme 1.14: Synthesis of ynamide utilizing alkynyl iodonium triflate salt on model system.

The base used in this reported reaction is *N*-butyl lithium.[20] When *N*-butyl lithium was used it was observed that the ynamide was not synthesized. Along with the majority of starting material a trace amount of hex-1-ynyl-trimethyl-silane was isolated. LiHMDS was used as a base under the same reaction conditions as reported instead of *N*-butyl lithium. No product was formed in this reaction. The next base to be used was NaH. No product was observed to be formed. At this point this method was abandoned since the reported conditions did not seem to generate the ynamide in this model system.

Z-enamide formation via dehydrative condensation of aldehyde and amide.

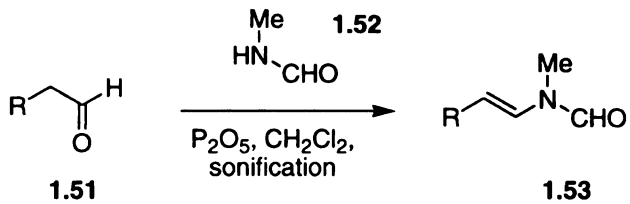
The *Z*-enamide of the kottamides was pursued using dehydrative condensation of aldehyde **1.49** and amide **1.50** (Figure 1.8). One of the methods of synthesizing an enamide **1.53** is via dehydrative condensation of aldehyde **1.51** and amide **1.52**. It has been reported that phosphorus pentoxide was the reagent of choice for this reaction as it promotes condensation by removing water that is a bi-product of this reaction (Scheme 1.15).[21] Acid catalyzed condensations of aldehydes **1.55** and amides **1.54** have also been

reported.[22] A wide variety of lactams and aldehydes have been shown to go through acid catalyzed dehydrative condensation to form *N*-alkenyl lactams or enamides **1.56** (Scheme 1.16).[23]



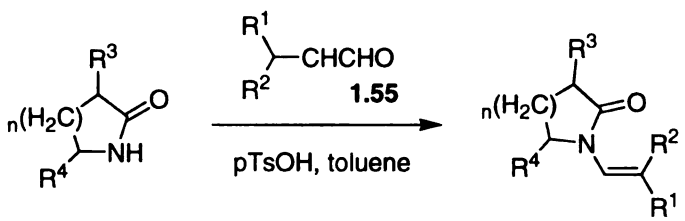
1.1 **1.49** **1.50**

Figure 1.8: Retrosynthesis of *Z*-enamide of kottamides using dehydrative condensation.



1.51 **1.53**

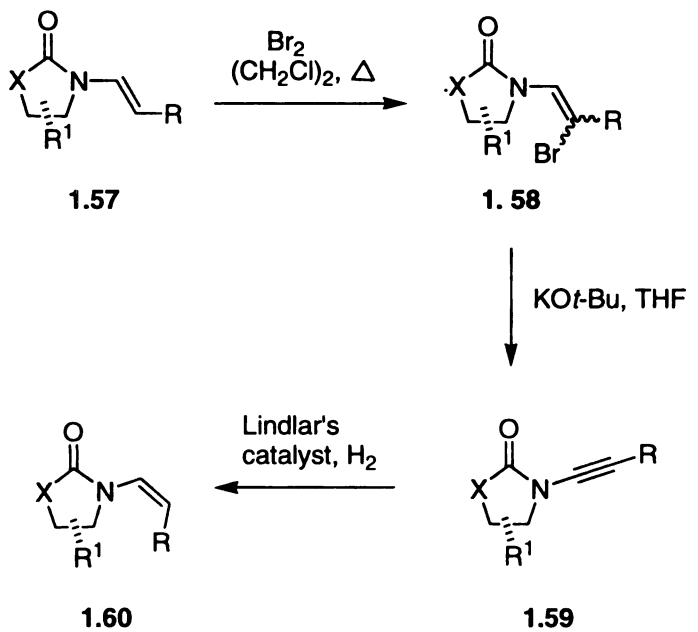
Scheme 1.15: Dehydrative condensation of aldehyde and amide.



1.54 **1.56**

Scheme 1.16: Enamide synthesis from lactams and aldehydes.

In all these cases *E*-enamide **1.57** is the major product. The *E*-enamide **1.57** can be treated with bromine in 1,2-dichloroethane to derive *β*-bromoenamide **1.58.** The *β*-bromoenamide **1.58** on being treated with potassium *t*-butoxide yields the ynamide **1.59**.[24] The ynamide **1.59** on catalytic stereoselective reduction with Lindlars catalyst would give the *Z*-enamide **1.60** (Scheme 1.17).

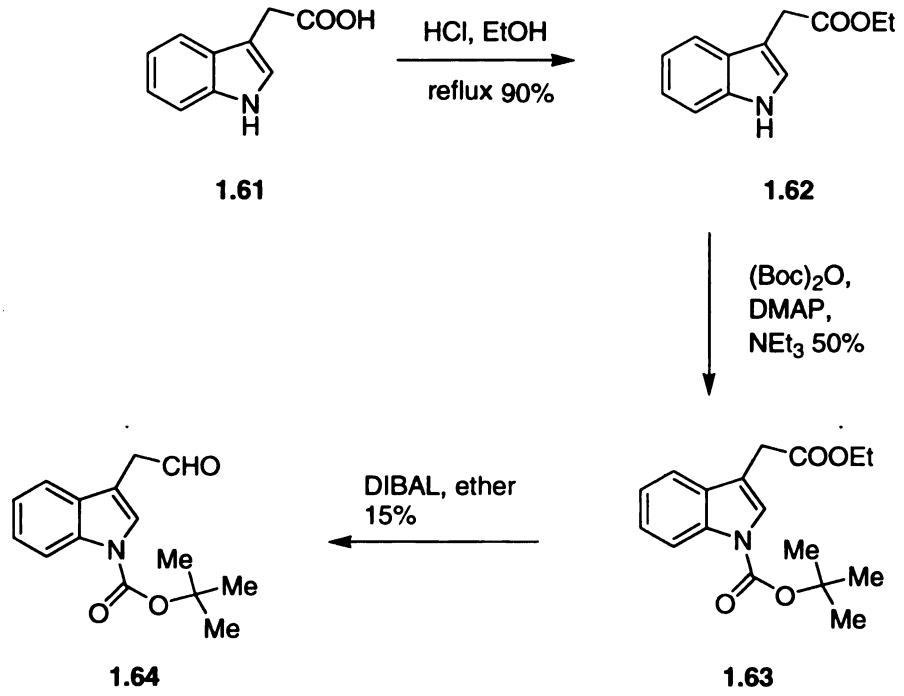


1.57 **1. 58** **1.59** **1.60**

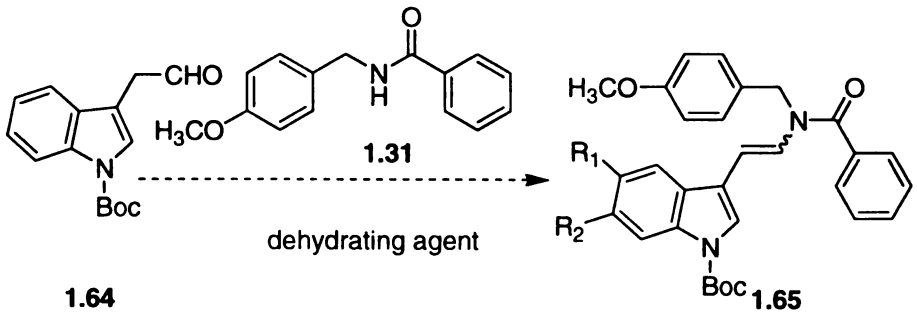
Scheme 1.17: Synthesis of *Z*-enamide from E-enamide.

To check the feasibility of this system a model system was used. Indol-3-acetaldehyde **1.64** was the aldehyde and *N*-(4-methoxy-benzyl)-benzamide **1.31** was the amide (Scheme 1.19). Indol-3-acetaldehyde was made from indol-3-acetic acid **1.61**

(Scheme 1.18). Commercially available indol-3-acetic acid was used to synthesize indol-3-acetic acid ester **1.62** via Fischer esterification. The indol-3-acetic acid ester **1.62** was *N*-protected with the Boc group. The *N*-protected indol-3-acetic acid ester **1.63** was reduced using DIBAL to afford the indol-3-acetaldehyde **1.64**.



Scheme 1.18: Synthesis of Boc-protected Indol-3-acetaldehyde.



Scheme 1.19: Dehydrative condensation to synthesize enamide.

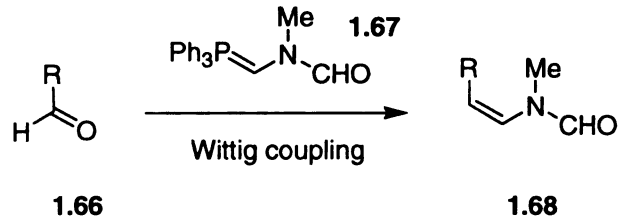
The conditions used on the model system along with the dehydrating agents have been listed (Table 1.1). Both the substrates, amide and aldehyde, do not resemble the ones used in the reports mentioned above when dehydrative condensation to synthesize enamide was attempted. This condensation was attempted on pyrrolidinones, lactams and *N*-methylformamide. The reason for this unsuccessful attempt to synthesize the enamide might be the sterics of both the substrates, amide and aldehyde.

Sr. No.	Dehydrating agent	Conditions	Product
1.	P_2O_5	CH_2Cl_2, sonification	No product
2.	molecular sieves	toluene, dean stark	No product
3.	*p*TsOH	toluene, dean stark	No product

Table 1.1: Dehydrative condensation to synthesize enamide.

Z-enamide formation using Wittig reaction.

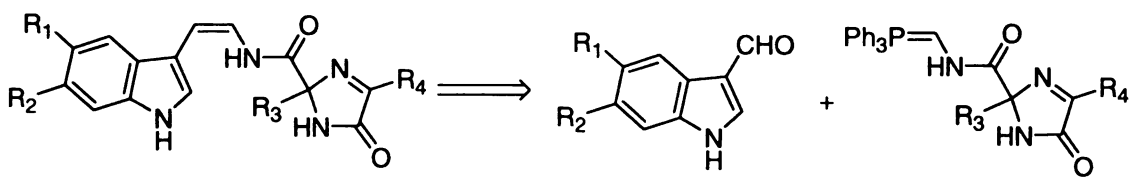
Another method that could be pursued for the formation of *Z*-enamide is Wittig reaction which predominantly gives the *Z*-enamide. According to a published report Wittig reaction of phosphonium salt **1.67** and *N*-methyl formamide **1.66** were explored which resulted in the formation of *cis*-alkenyl-*N*-methyl-formamide **1.68** (Scheme 1.20).[21]



1.66 1.68

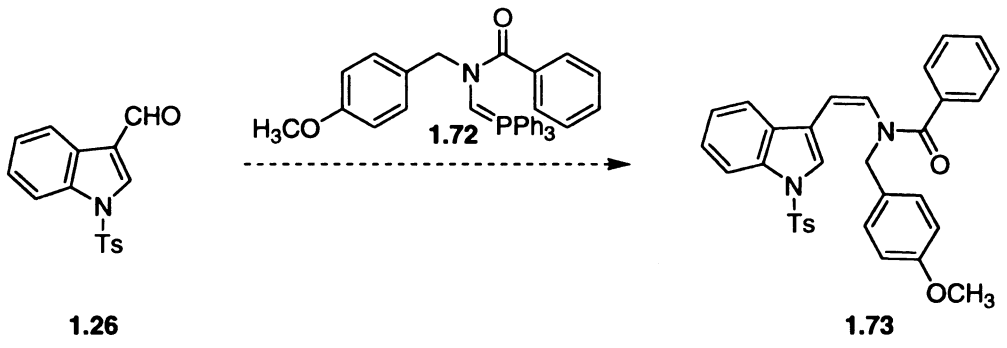
Scheme 1.20: *Z*-enamide synthesis via Wittig coupling.

Using this same methodology for the synthesis of *Z*-enamide of kottamides **1.1** retrosynthetically the aldehyde **1.69** and phosphonium salt **1.70** can be used as starting materials (Figure 1.9). Before using this method on the kottamides it was tried on a model system first (Scheme 1.21). Indol-3-carbaldehyde **1.71** and the phosphonium salt **1.72** could be used to construct the *Z*-enamide **1.73**. The *N*-tosylated indol-3-carbaldehyde **1.26** is synthesized from the corresponding indol-3-carboxaldehyde **1.71** using tosyl chloride in the presence of base (Scheme 1.22).

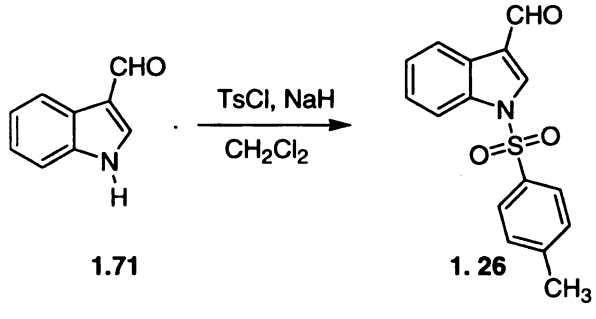


1.1 1.69 1.70

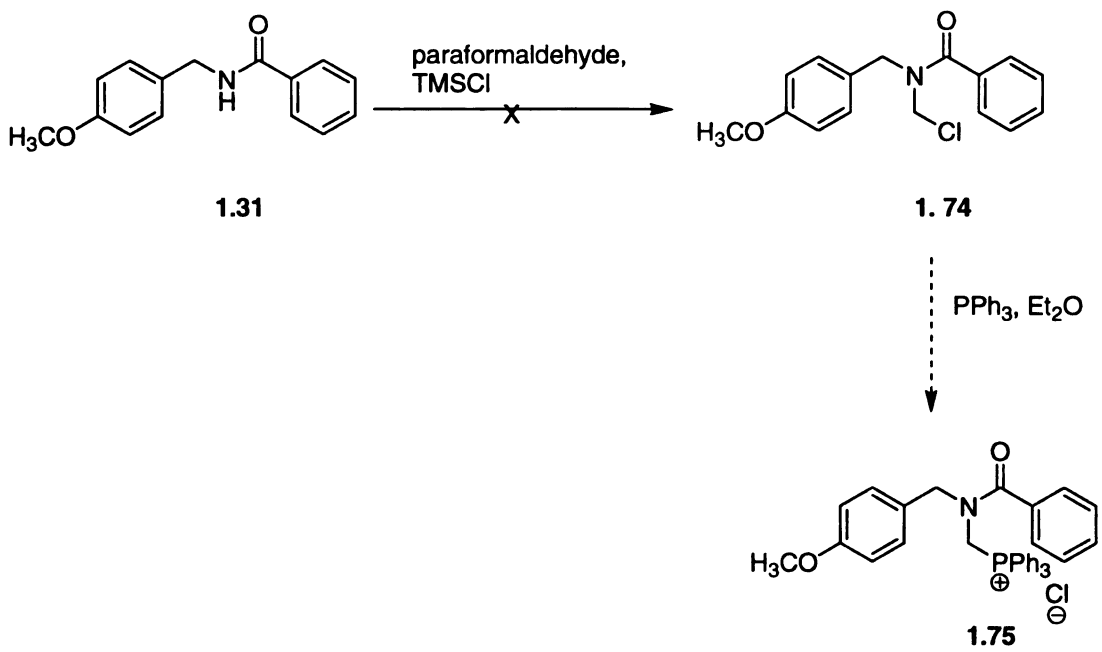
Figure 1.9: Retrosynthesis of *Z*-enamide of kottamides using Wittig reaction.



Scheme1.21: Model Wittig reaction to synthesize *Z*-enamide moiety.



Scheme 1.22: Synthesis of *N*-tosylated indol-3-carbaldehyde.



1.31 1.74 1.75

Scheme 1.23: Synthesis of phosphonium salt.

The synthesis of the phosphonium salt **1.75** was attempted. Synthesizing the phosphonium salt **1.75** requires the synthesis of the chloromethyl-amide **1.74**. This has been synthesized before by refluxing the amide **1.31** with paraformaldehyde in the presence of TMSCl which is used as a solvent.[25] Only the starting material was isolated after work-up of this reaction. Different conditions were tried to construct the chloromethyl-amide (Table 1.2). Since the paraformaldehyde has a solubility problem only the starting material, amide **1.31**, was obtained in all these cases. Next another form of formaldehyde, trioxane, which is a trimer of formaldehyde was used.[26] A range of reaction conditions were evaluated using this reagent but still the starting material was recovered without the formation of any product (Table 1.2).

Sr. No.	Formaldehyde source	Conditions Catalyst/temp.	Time (hours)	solvent	Product
1.	Paraformaldehyde	TMSCl/reflux	2	TMSCl	SM
2.	Paraformaldehyde	TMSCl/reflux	8	TMSCl	SM
3.	Paraformaldehyde	Reflux*	8	toluene	SM
4.	Paraformaldehyde	TMSCl/reflux	8	CH_2Cl_2**	SM
5.	Trioxane	TMSCl/rt	8	TMSCl	SM
6.	Trioxane	Reflux*	8	toluene	SM
7.	Trioxane	TMSCl/reflux	8	TMSCl	SM
8.	Trioxane	TMSCl/reflux	8	THF	SM

Table 1.2: Different conditions tried for synthesizing chloromethyl-amide.

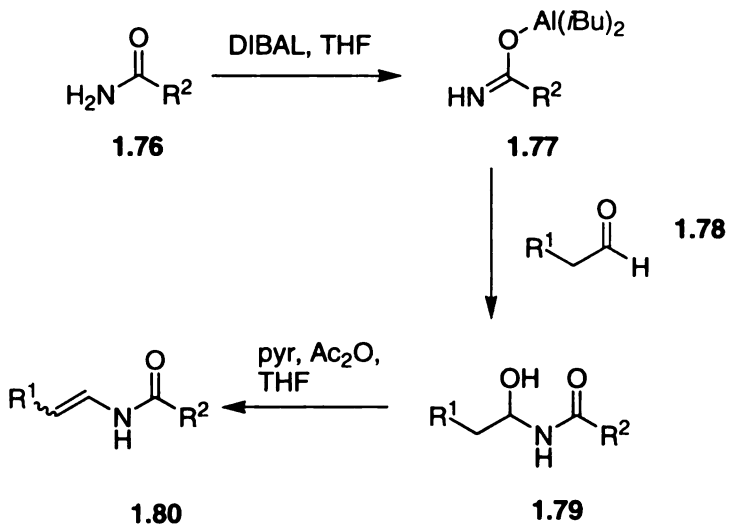
* No catalyst (TMSCl) was used.

**1 eq. of triphenyl phosphene was also used in this reaction.

SM: starting material.

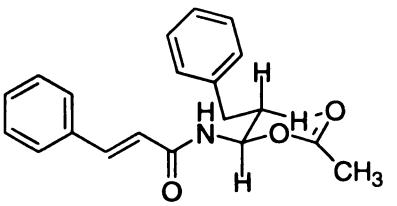
Synthesis of *Z*-enamide through hemiaminal formation and elimination of water.

A simple strategy towards enamides **1.80** would involve the elimination of water from *N*-acylhemiaminal **1.79**.[27] The *N*-acylhemiaminal **1.79** could be synthesized by treating aldehyde **1.78** with aluminum carboximidoate **1.77** derived from amide **1.76** and DIBAL (Scheme 1.24). Formation of the enamide **1.80** could be affected by refluxing the hemiaminal **1.79** in a solution of THF containing acetic anhydride and pyridine.



Scheme 1.24: Synthesis of *Z*-enamide through hemiaminal formation and elimination of water.

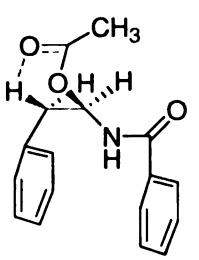
Applying this to a model system where benzamide is used as the amide and phenyl acetaldehyde as the aldehyde *Z*-enamide, *Z*-*N*-styryl-benzamide was obtained via *N*-(1-hydroxy-2-phenyl-ethyl)-benzamide (Scheme 1.25). The *Z*-conformation was confirmed by the coupling constant of the alkene protons, NOESY and homocoupling experiment. Regarding the mechanism of elimination it has been seen that enamide formation proceeds via dehydration of hemiaminal, which usually gives the trans isomer as the major product.[27] The reason for the observed stereochemistry is the chair like transition state **1.81** (TS) of the intermediate (Figure 1.10).



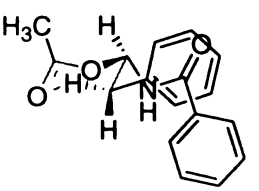
1.81

Figure 1.10: TS leading to *E*-enamide.

The transition state in the case of the model system used is boat like (Figure 1.11). This is due to the fact that the transition state can be more stabilized by π stacking of the aromatic benzene rings, which would be only possible in case of the boat like transition state. Thus it is observed that only *Z*-enamide was synthesized in this model reaction.

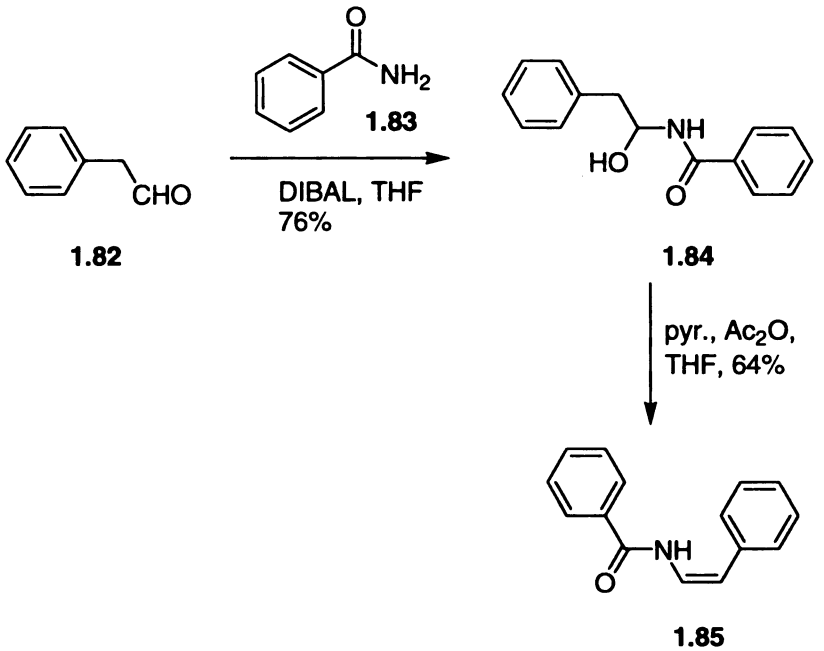


boat like TS=*Z*-enamide



chair like TS=*E* enamide

Figure 1.11: *Z*-enamide vs *E*-enamide.



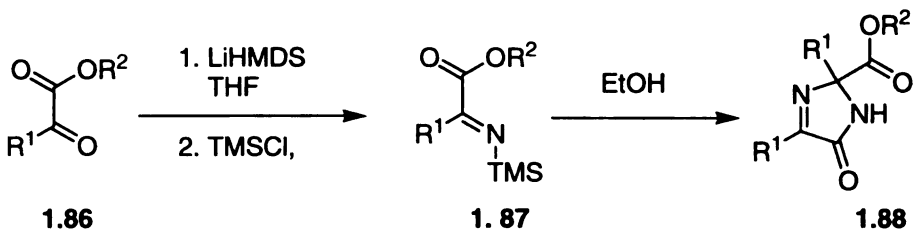
Scheme 1.25: Successful synthesis of *Z*-enamide on model system.

Studies on 2,2,5-trisubstituted imidazol-4-one synthesis

The kottamides are the first example of natural products that contain a 2,2,5-trisubstituted imidazol-4-one heterocycle. Very few examples have been reported on their synthesis[28,29] and there are very few reports dealing with their structure.[30] Some 2,2,5-trisubstituted-2*H*-imidazol-4-one are prepared by oxidation of the corresponding 2*H*-imidazol-5-thiones,[29] which in turn are prepared by reaction of acetophenones, ammonia and excess sulfur,[31] or by condensation of ketones and aldehydes with α-oxothionamides.[29,32] Another approach for synthesizing 2,2,5- trisubstituted-2*H*-imidazol-4-one is the reaction of the amide of phenylglyoxylic acid with acetophenone and ammonia, as well as peracid oxidation of 2,2,5 trisubstituted-2*H*-imidazoles, or the reaction of their *N*-oxides with sodium cyanide in DMSO.

Synthesis of 2,2,5-trisubstituted imidazol-4-one.

It has been reported that α-keto ester **1.86** when treated with lithium 1,1,1,3,3,3-hexamethyldisilazide in THF, affords α-(*N*-trimethylsilyl)imino ester 1.**87** which when treated in methanol/ethanol produces 2,2,5-trisubstituted imidazol-4-one 1.**88** via dimerization (Scheme 1.26).[33]



1.86 **1. 87** **1.88**

Scheme 1.26: Dimerization of α-keto ester.

The imidazolone in kottamides resembles the imidazolone **1.88**. Hence this could be a methodology that could be used for synthesizing the 2,2,5-imidazol-4-one. Kottamides- A, B, C all have the same imidazol-4-one **1.89** which can be synthesized from the α-keto ester **1.92** and **1.93** using the above methodology (Figure 1.12). Kottamide- D has the imidazol-4-one **1.90**, which can be potentially synthesized from the α-keto ester **1.95** and **1.96** using the above methodology (Figure 1.13).

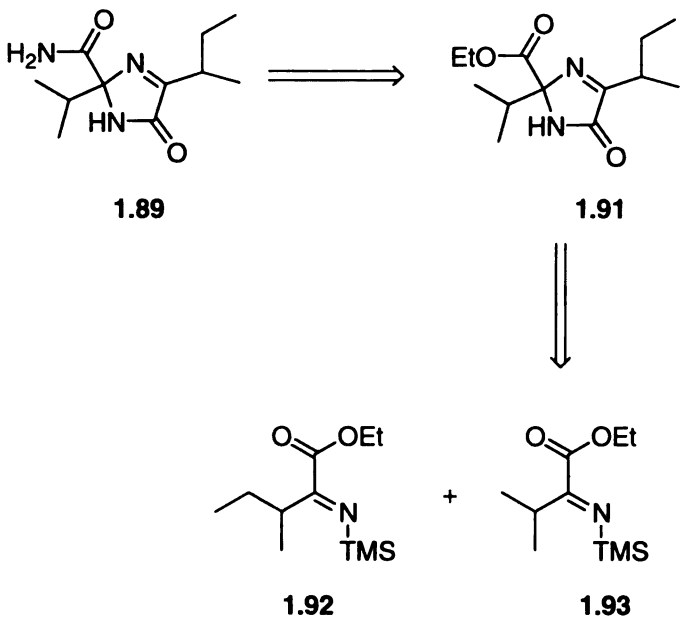


Figure 1.12: Retrosynthesis of imidazol-4-one in kottamides-A, B, C.

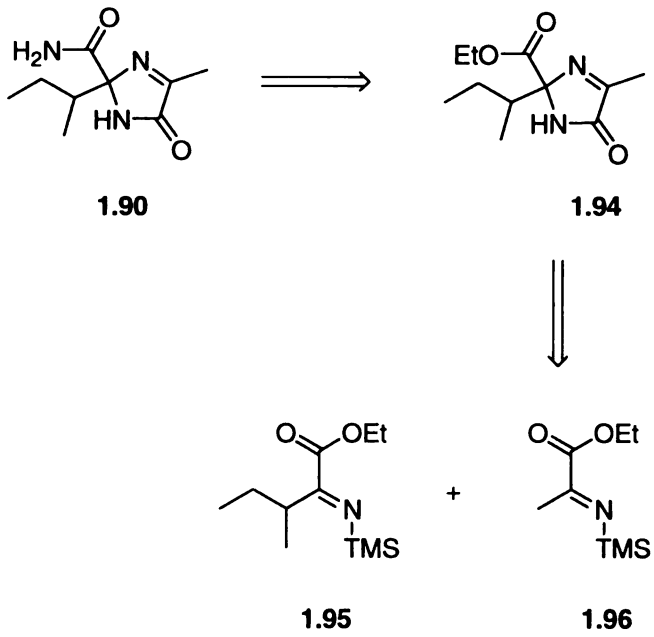
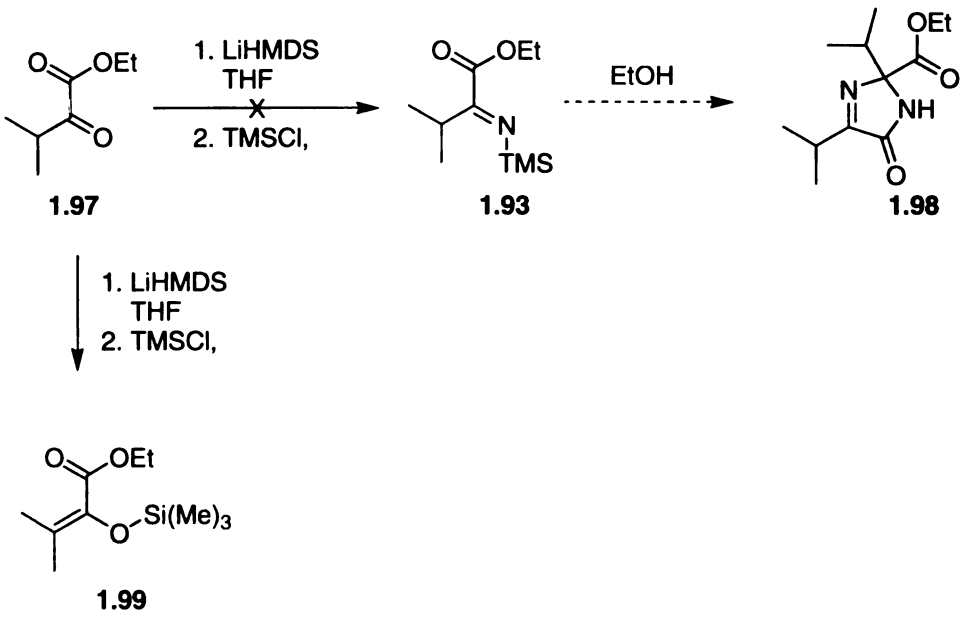


Figure 1.13: Retrosynthesis of imidazol-4-one in kottamides-D.

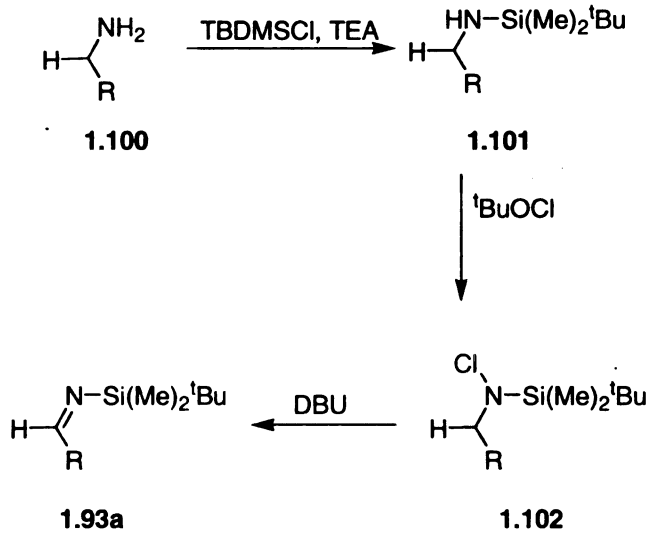
To check the feasibility of this reaction, it was initially evaluated on just one of the α-keto ester **1.97**. The α-keto ester **1.97** was treated with 1,1,1,3,3,3-hexamethyldisilazide in THF. This reaction was thought to afford α-(N-trimethylsilyl)imino ester **1.93** which after treating with methanol/ethanol would produce the corresponding 2,2,5-trisubstituted imidazol-4-one **1.98** via dimerization (Scheme 1.27). This reaction did not give the desired product. Instead the silyl enol ether **1.99** was synthesized. Thus this methodology cannot be used to synthesize the imidazol-4-one **1.98** and could only work with α-keto ester which has no enolizable hydrogen. From the method shown above the synthesis of the imidazol-4-one can potentially be used if the imine **1.92**, **1.93**, **1.95**, **1.96** or their desilylated analogues could be synthesized. Different routes to synthesize these imines where attempted.



Scheme 1.27: Reaction of α-keto ester with 1,1,1,3,3,3-hexamethyldisilazanide.

Synthesizing the imine for synthesis of 2,2,5-imidazol-4-one.

An alternative synthesis of *N*-(trialkylsilyl)imines **1.93** can be starting with a parent amine **1.100**. This procedure involves oxidation of *N*-silylamines **1.101** by tert-butyl hypochlorite followed by base induced elimination (Scheme 1.28).[34] The amine substrates used in this method reported formation of *N*-(trimethylsilyl)aldimines. *N*-(trimethylsilyl)ketoimines that were synthesized had been obtained from ketones lacking α-hydrogen.

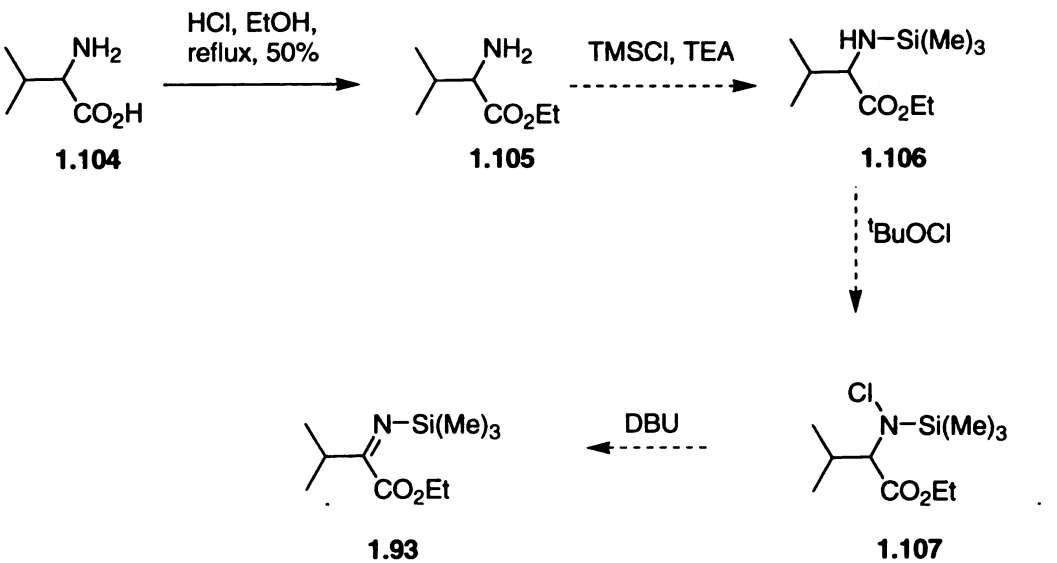


R=Ph, 2-furyl, CO_2Et, $CH{=}CH_2$

Scheme 1.28: Synthesis of *N*-(trialkylsilyl)imines.

To use this method, valine **1.104** could be used as the starting material for the synthesis of imine **1.93a**. This involved protecting the carboxylic acid, *N*-silylation and then oxidation and finally base induced elimination (Scheme 1.29). But this method would not have been able to give the imine needed as the last step involves use of base

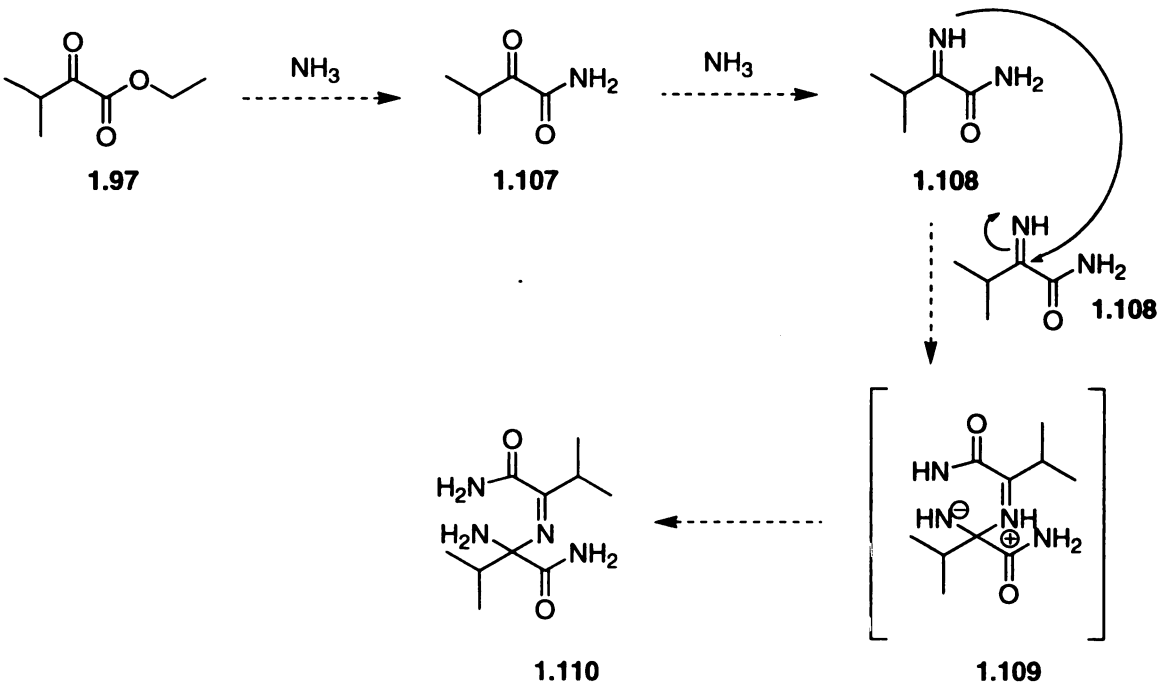
which might afford the corresponding enamide similar to the one **1.99** isolated using the previous method.



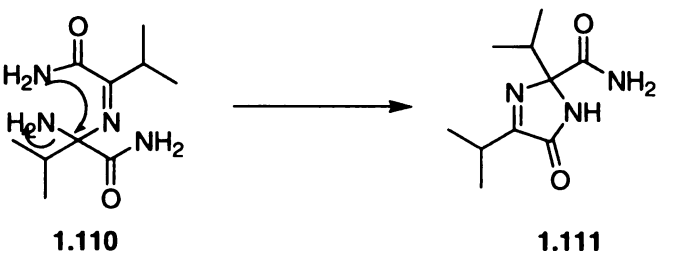
Scheme 1.29: Synthesis of *N*-(trimethylsilyl)ketoimines.

Another method that could be used to synthesize the imine could be the use of inorganic catalysts such as $Mg(ClO_4)_2$[35] or $TiCl_4$[36], which could be used to derive imines from ketones and mono-substituted amine. But the main drawback here was isomerization of imines to enamines. It was thought that if these imines could be synthesized in situ, the isolation of these labile intermediates could be avoided. Thus if the α-keto ester **1.97** were treated with excess of ammonium hydroxide solution (Scheme 1.30) they would produce the amide **1.107** which on further reacting with ammonia would form the α-imido ester **1.108**. This on undergoing an aldol-type condensation with the α-imido ester **1.108** would produce the intermediate **1.109** which would form the dimer **1.110** on proton-transfer. A similar report shows the aldol-type condensation

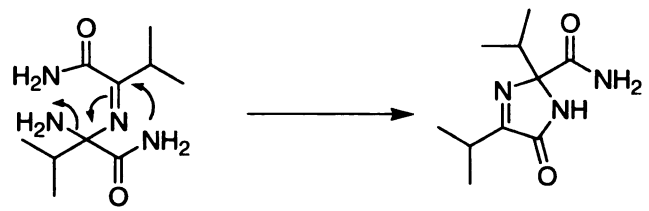
between aldehyde and quinonimine.[37] The dimer **1.110** could then undergo intramolecular cyclization via nucleophilic substitution (Scheme 1.31) or indirect nucleophilic substitution (Scheme 1.32) reaction to afford the 2,2,5-imidazol-4-one **1.111**.



Scheme 1.30: Synthesis of 2,2,5-imidazol-4-one using *α*-keto ester.



Scheme 1.31: Direct intramolecular nucleophilic substitution reaction.



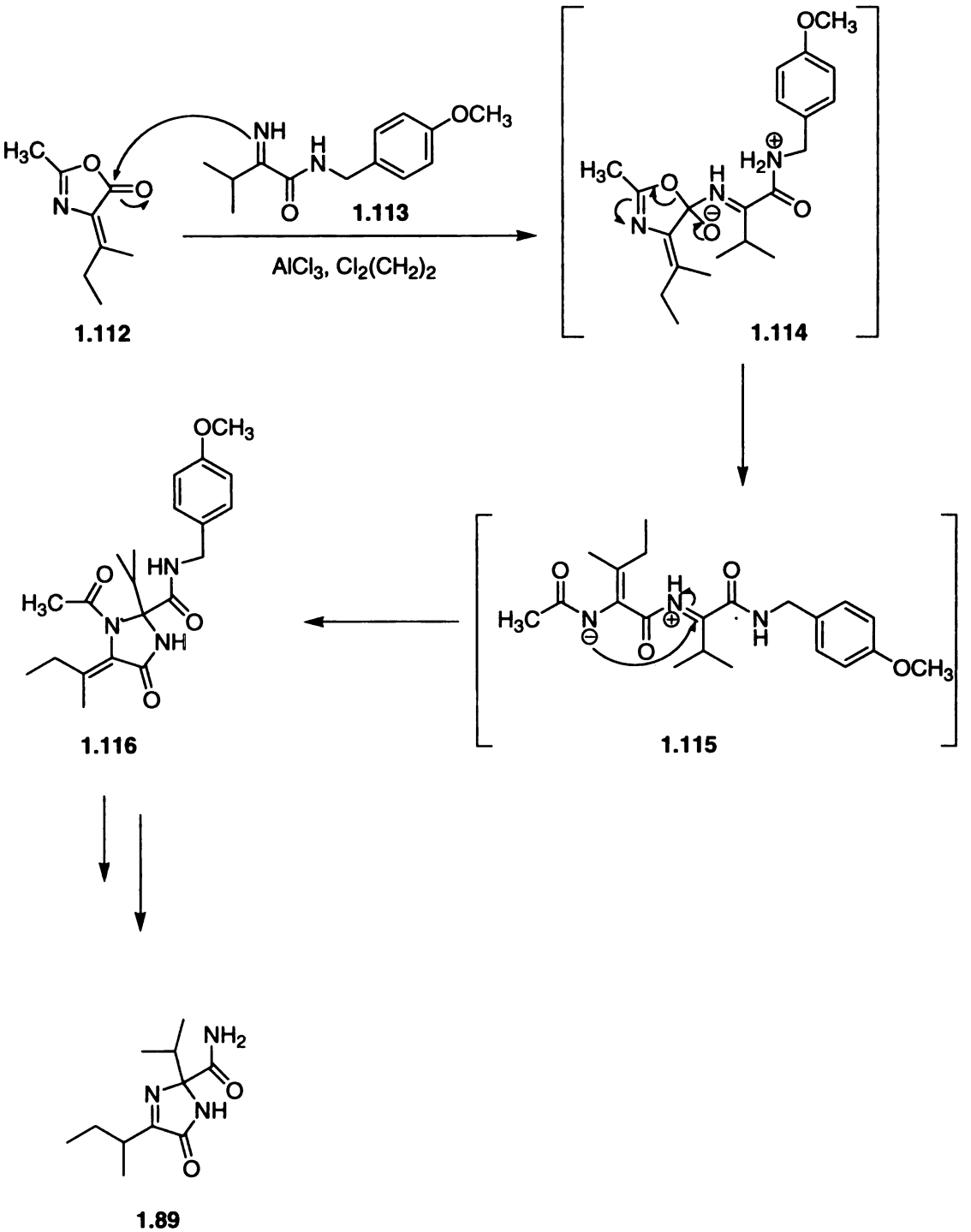
1.110 **1.111**

Scheme 1.32: Indirect intramolecular nucleophilic substitution reaction.

2,2,5-trisubstituted imidazol-4-one has been synthesized before using a similar mechanism.[38] Here 2-aza-1,3-butadienes were used which on hydrolysis would undergo intramolecular cyclization to form the 2,2,5-trisubstituted imidazol-4-one. Thus the α-keto ester **1.97** was treated with excess of ammonium hydroxide solution. After 5 minutes of stirring at room temperature a thick white precipitate would be formed which after 30 minutes would disappear. On isolating the precipitate it was found to be the α-keto amide **1.107** which on further reaction with ammonia produced a compound, the structure of which did not match the imidazol-4-one **1.111** or the dimer **1.110**. This unknown compound is still under analysis. The same compound is synthesized if the the α-keto ester **1.97** and ammonium hydroxide are refluxed for 2 hrs. When α-keto ester **1.97** was treated with 2N solution of ammonia in methanol only the amide **1.107** was synthesized. Thus this method could not be used to afford the 2,2,5-trisubstituted imidazol-4-one.

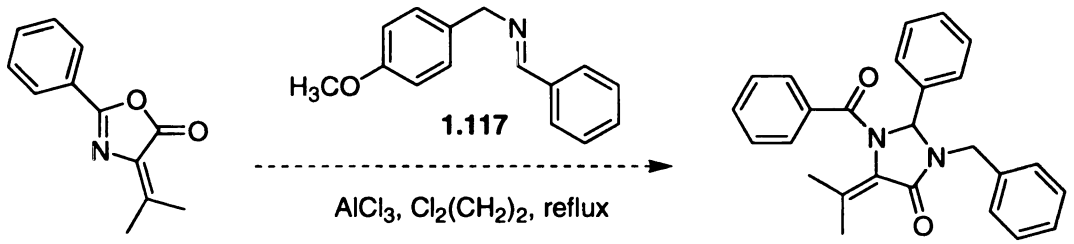
Using oxazol-5-ones for synthesis of 2,2,5-trisubstituted imidazol-4-one.

It is known that oxazol-5-ones can be activated with aluminum chloride, which upon reacting with aromatic nuclei produce α-(acyl-amino)-ketones.[39] Similarly it was thought that activated oxazol-5-one could react with a nucleophile to produce imidazol-5-one (Scheme 1.33). The oxazol-5-one **1.112** could be activated by aluminum chloride and then reacted with the imine **1.113** to produce a zwitterionic intermediate **1.115** which undergoes cycloaddition to afford imidazol-4-one **1.116**. Imidazol-4-one **1.116** can potentially be further converted to the required imidazol-4-one **1.89**.

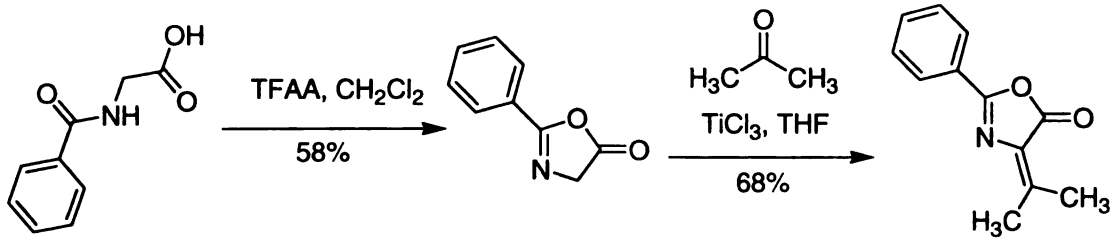


Scheme 1.33: Synthesizing imidazol-4-one using oxazol-5-one.

The imine **1.113**, and the oxazol-5-one **1.112** were not readily available Thus a model reaction was conducted to check the feasibility of this reaction (Scheme 1.34). The oxazol-5-one **1.116** was synthesized from hippuric acid **1.13** via oxazol-5-one **1.14** (Scheme 1.35). The imine **1.117** was synthesized from the corresponding benzaldehyde and p-methoxy benzamine. The imidazol-4-one **1.118** was formed but was difficult to purify with column chromatography but from the ^{1}H NMR of the crude mixture and from the mass spectrometry analysis it was seen that the imidazol-4-one **1.118** was formed. Thus it was thought that the nucleophilic addition followed by cycloaddition did work and afforded the imidazol-4-one **1.118**.



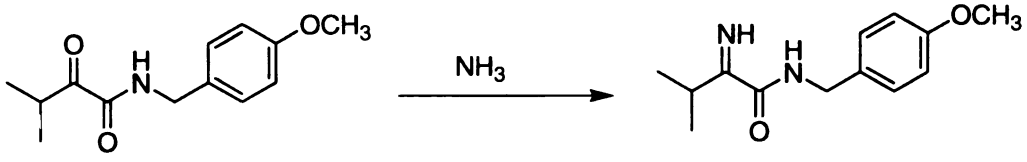
Scheme 1.34: Synthesis of imidazol-4-one via oxazol-5-one using model system.



1.13 **1.14** **1.116**

Scheme 1.35: Synthesis of oxazol-5-one.

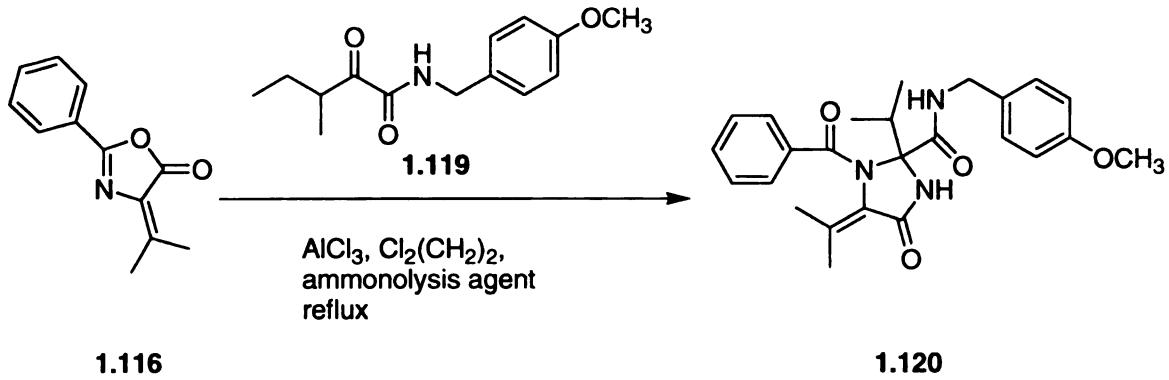
Oxazol-5-one **1.112** which would be needed to synthesize the imidazol-4-one **1.89** can be synthesized similarly. The imine **1.113** would also be required for applying this methodology, the synthesis of which can be achieved using α-keto amide **1.119** (Scheme 1.36).



1.119 **1.113**

Scheme 1.36: Synthesis of imine 113.

Different methods were used to synthesize the imines as have been discussed before. Since it was seen that the imines were too labile to be synthesized and separated it was thought that they could be synthesized in situ (Scheme 1.37). Different reagents for ammonolysis were used (Table 1.3).



1.116 1.120

Scheme 1.37: Synthesis of imidazol-4-one using model system.

Sr. No.	Ammonolysis agent	Product 120
1.	NH_4CO_3	X
2	NH_4OAc	X

Table 1.3: Use of ammonolysis reagents for synthesizing imidazol-4-one in model system.

Ammonium acetate did not show any product formation at all. Ammonium carbonate did form negligible amount of imidazol-4-one **1.120** which could only be verified by mass spectroscopy. Until there would be an effective ammonolysis reagent to synthesize the imine in situ to generate the required imidazol-4-one for the kottamides this method was not seen to be as productive in achieving the synthesis of the imidazol-4-ones.

Synthesis of imidazol-4-one via imidazolidi-4-one.

In potentially considering a new methodology imidazol-4-ones **1.121** could be synthesized on oxidation of imidazolidi-4-ones **1.122**. The imidazolidi-4-ones **1.122** could be synthesized from ketone **1.125** and amino acid amide **1.124** via condensation

and oxidation reaction (Figure 1.14). The condensation of amino acid amides and ketones has been attempted before to synthesized spiroimidazolidinones.[40,41,42,43,44,45]

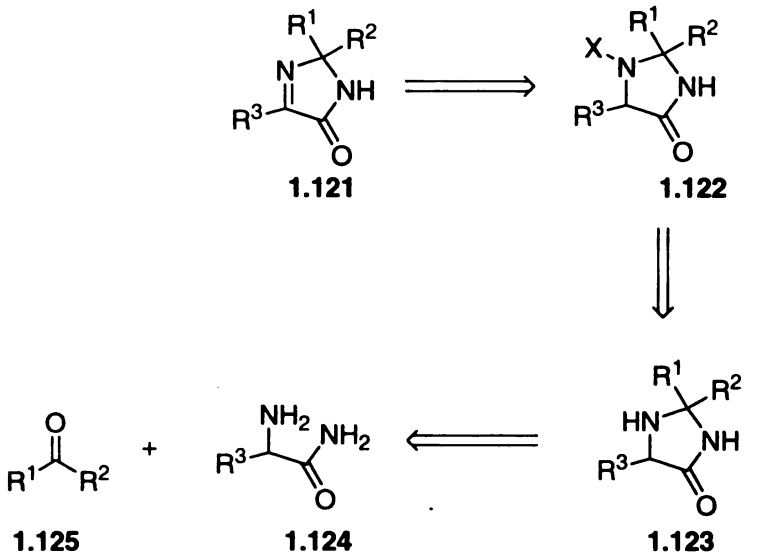
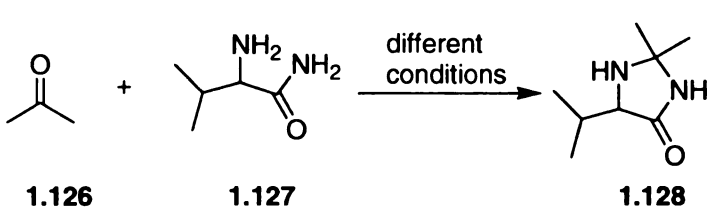


Figure 1.14: Synthesis of imidazol-4-ones via of imidazolidi-4-ones.

For testing this methodology readily available starting materials were used (Scheme 1.38). Acetone **1.126** and valinamide **1.127** were used for the condensation reaction using different conditions to synthesize imidazolidi-4-one **1.128** (Table 1.4).



Scheme 1.38: Synthesis of 5-isopropyl-2,2-dimethyl-imidazolidin-4-one.

Sr. No.	Conditions	Product 128 yield (%)
1.	PTSA	0
2.	TEA/molecular sieves	25

Table 1.4: Different conditions used for synthesizing imidazolidi-4-one.

PTSA was most commonly used as the acid catalyst for this reaction.[41,44,45] Imidazolidi-4-ones were not synthesized when PTSA was used. The reason for this maybe that under acidic conditions, direct hydrolysis of the imidazolidi-4-one to amino acid would occur (Figure 1.15).[43] Thus this method was only shown to have worked with 1,2-diamines and cyclic ketones to afford spiro compounds and there were no reports where acyclic ketones were used. In the case of kottamides the imidazolidi-4-one is not a spiral compound. Eventually the imidazolidi-4-one **1.128** was synthesized under conditions using TEA and molecular sieves.[40]

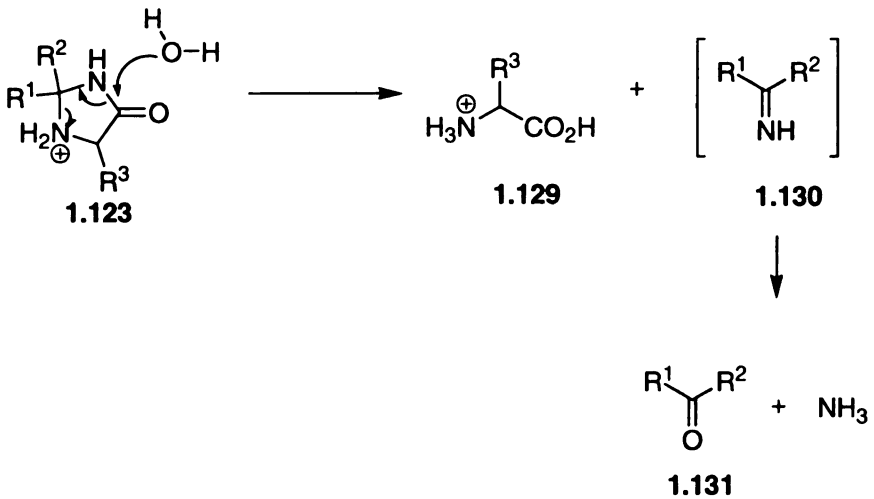
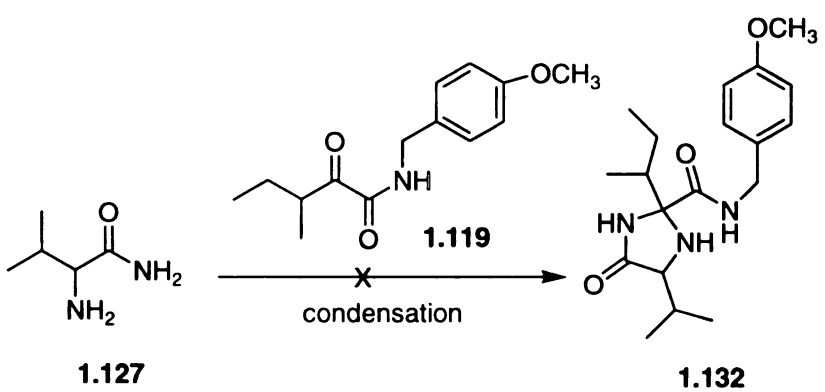


Figure 1.15: Acid catalyzed hydrolysis of imidazolidi-4-one.

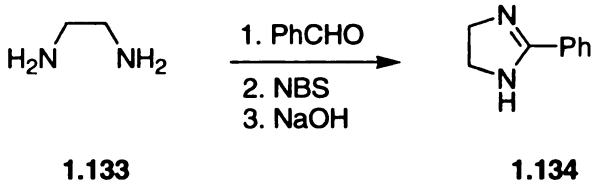
The same reaction conditions were used to see if the amino acid amide **1.127** would condense with the ketone **1.119** having similar substituents as those found in the natural product. The reaction did not amount to the predicted products maybe because of the steric bulk of the ketone used for condensation.



Scheme 1.39: Synthesis of imidazolidi-4-none.

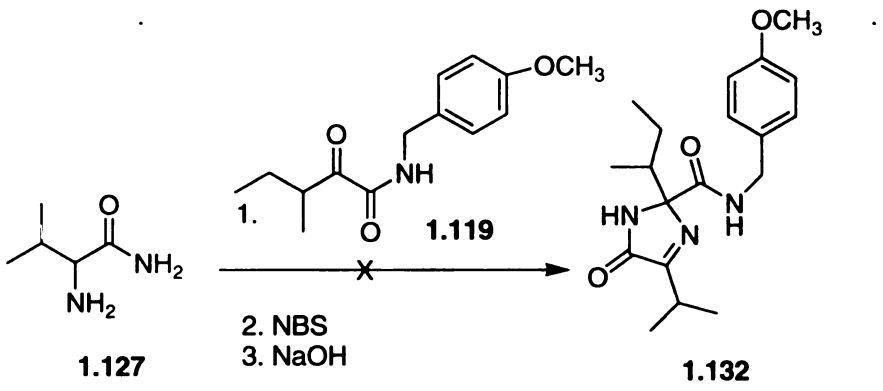
It was seen that reactions of various aldehydes and 1,2-diamines **1.133** followed by NBS treatment gave the corresponding dihydroimidazoles **1.134** (Scheme 1.40).[46]

This same method can be applied for synthesizing the imidazol-4-one via imidazolidi-4-one.



1.133 1.134

Scheme 1.40: Synthesis of 2-dihydroimidazoles.

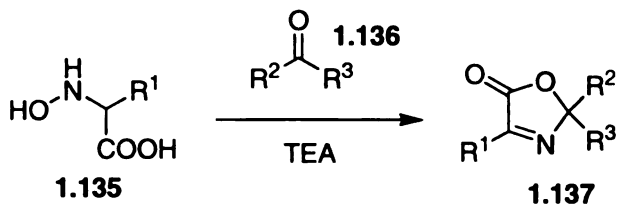


1.127 1.132

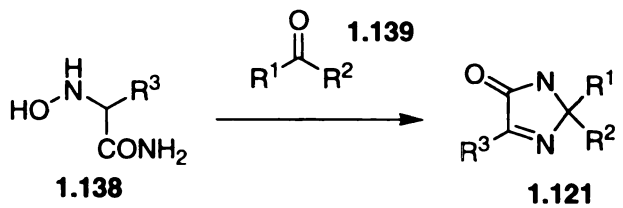
Scheme 1.41: One-pot synthesis of imidazol-4-one.

The imidazol-4-one could not be synthesized using this methodology. The reactivity of the amino acid amide depends on the electrophilicity and the bulkiness of the substituent of the carbonyl group.[41] Thus the reason for this method not being useful could be because the ketone used is very sterically bulky and could be hindering the amino group of the amino acid amide to react with it. Thus a less sterically hindered ketone **1.97** could be used to afford the imidazol-4-one needed.

Another method that could be applied is the substituent on nitrogen could be changed. Instead of bromine which later gets dehydrohalogenated the hydroxyl group could be used. It was reported that when α-hydroxyamino acids **1.135** were reacted with carbonyl compounds **1.136** they afforded 3-oxazolin-5-ones **1.137**.[47] Using the same concept, α-hydroxyamino acid amides **1.138** could be used to synthesize the imidazol-4-one **1.121** (Scheme 1.43).

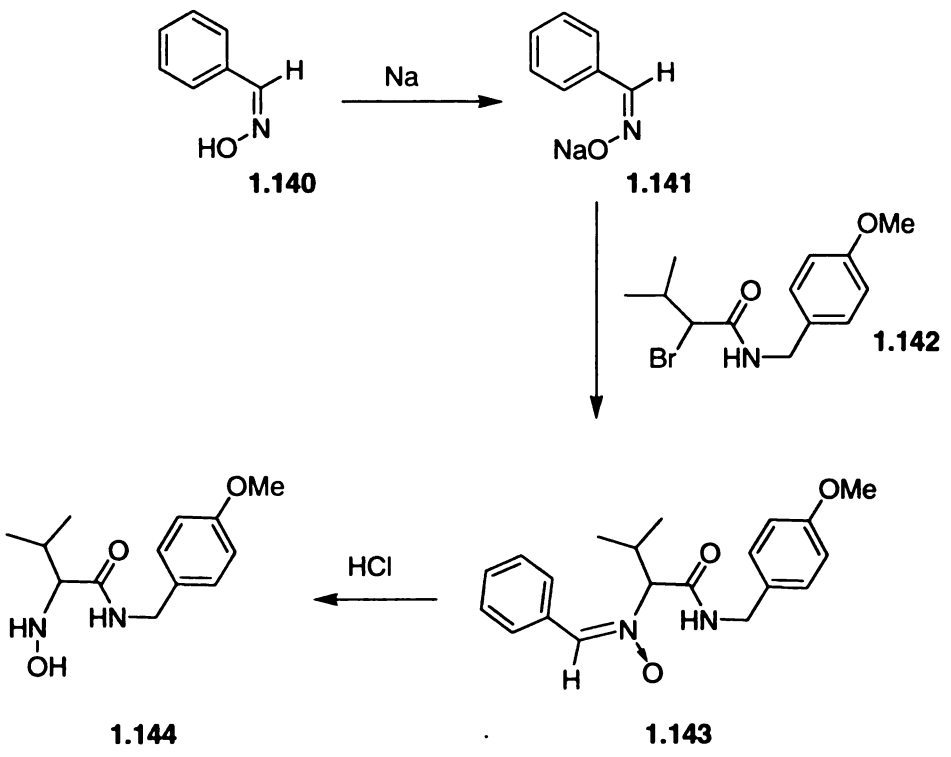


Scheme 1.42: Synthesis of 3-oxazolin-5-one using α-hydroxyamino acids.



Scheme 1.43: Synthesis of imidazol-4-ones using α-hydroxyamino acid amides.

The α-hydroxyamino acid amide **1.144** could be synthesized from *Z*-benzaldehydoxime **1.140**. This yields a nitrone **1.143**, which is synthesized from α-bromo amide **1.142**. The nitrone can be transformed into the α-hydroxyamino acid amide **1.144** (Scheme 1.44).

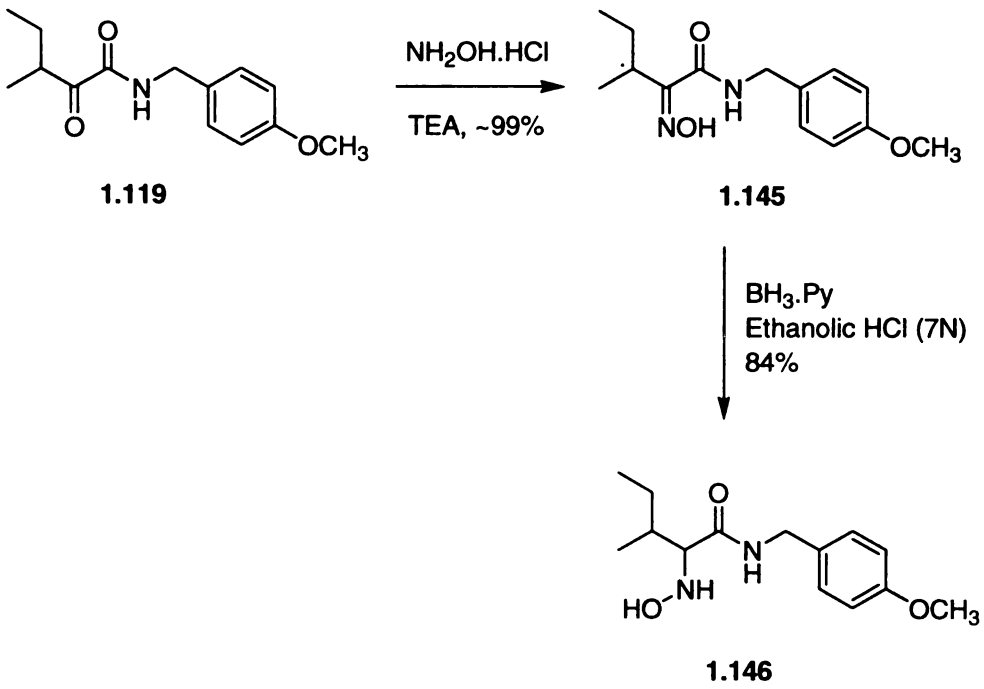


Scheme 1.44: Synthesis of α-hydroxyamino acid amides.

In this method only a *Z*-oxime can be converted into the α-hydroxyamino acid amide.[48] If the *E* isomer of the oxime were to be used, instead of getting the nitrone, *O*-alkylation occurs.[48,49] Thus it was essential to get the *Z*-isomer. Since the *E* isomer is the most stable it was the only isomer synthesized and it was difficult getting the *E*-isomer needed for this reaction.[50]

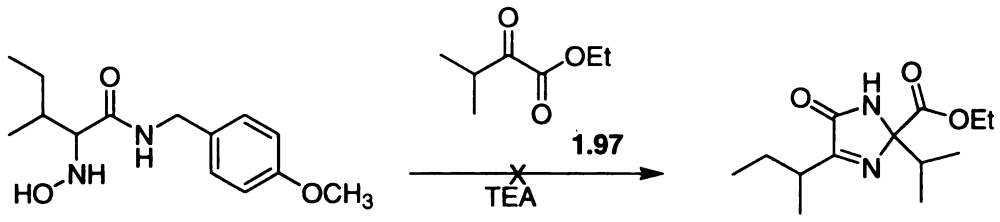
In a different approach, to avoid the stereochemistry issue, the oxime **1.145** can be synthesized from α-keto amide **1.119** (Scheme 1.45). The oxime can be reduced into the α-hydroxyamino acid amide **1.146**. During the conversion of the ketone **1.119** into the oxime **1.145** it was seen that TEA was the reagent of choice due to its quantitative conversion.[51] Pyridine is not a good choice as the reaction does not go to completion and

since the Rf values of the reactant and product are very close it is very difficult to separate the two.[52] TfOH gave many coproducts.[53] Both *E* and *Z* isomers are produced. These did not need to be separated as in the next step they both would be reduced. On keeping these in a solution of $CDCl_3$ overtime (3 weeks) the Z isomer is converted completely into the E isomer, which is preferred as the E isomer is capable of intramolecular hydrogen bonding. During the reduction both reducing agents, $BH_3.Py$[54] and $BH_3.NMe_3$[55], worked though the first one take 30 minutes and the second takes 24 hrs for quantitative conversion.



1.119 **1.145** **1.146**

Scheme 1.45: Alternative synthesis of *α*-hydroxyamino acid amide.



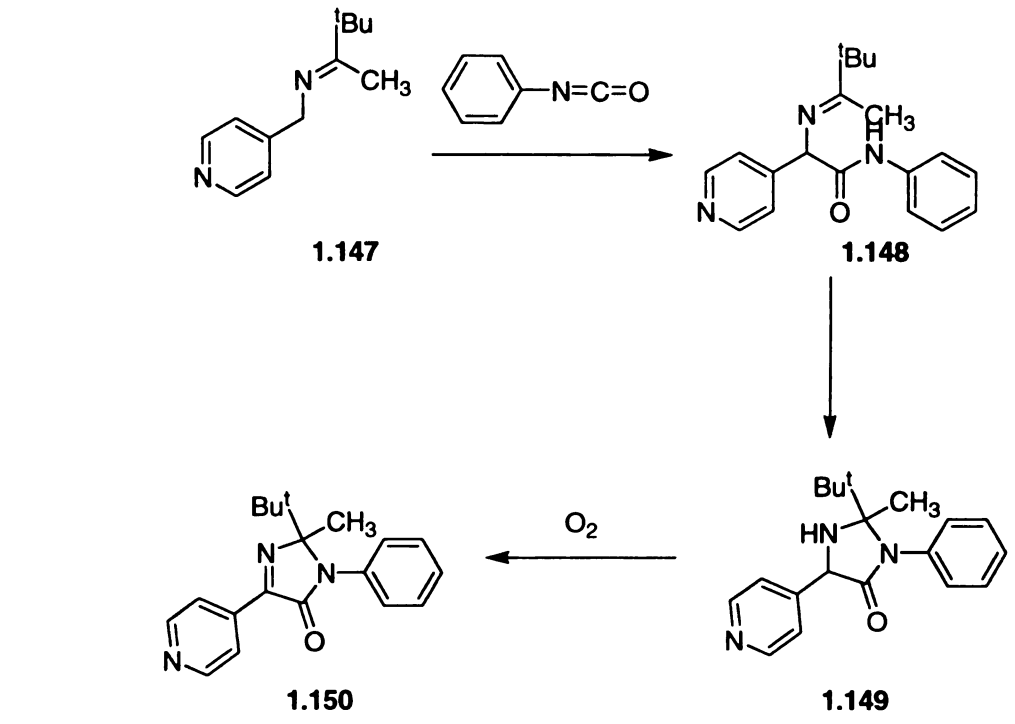
1.146 1.91

Scheme 1.46: Synthesis of 2,2,5-trisubstituted imidazol-4-one of kottamides A, B, C.

After using the conditions used in the reported reaction for the synthesis of 3-oxazolin-5-one **1.137**, α-hydroxyamino acid amide **1.146** was treated with α-keto ester to synthesize the required imidazol-4-one **1.91** (Scheme 1.46).This reaction did not result in the formation of the required imidazol-4-one. Only the starting materials were seen on TLC and in crude ^{1}H NMR. Thus the α-hydroxyamino acid amide **1.146** was concluded to be less reactive due to the sterics of the ketone **1.97**, even though electronically this reaction should be favorable.

Synthesis of imidazol-4-ones via azamethines.

The addition of phenyl isocyanate to azamethine **1.147** followed by oxidation was reported to synthesize imidazol-4-ones **1.150** (Scheme 1.47).[56] The imidazol-4-ones could be synthesized using the same methodology (Figure 1.16). The imidazol-4-one **1.89** could be synthesized from the azamethine **1.152**.



Scheme 1.47: Synthesis of imidazol-4-one via azamethinine.

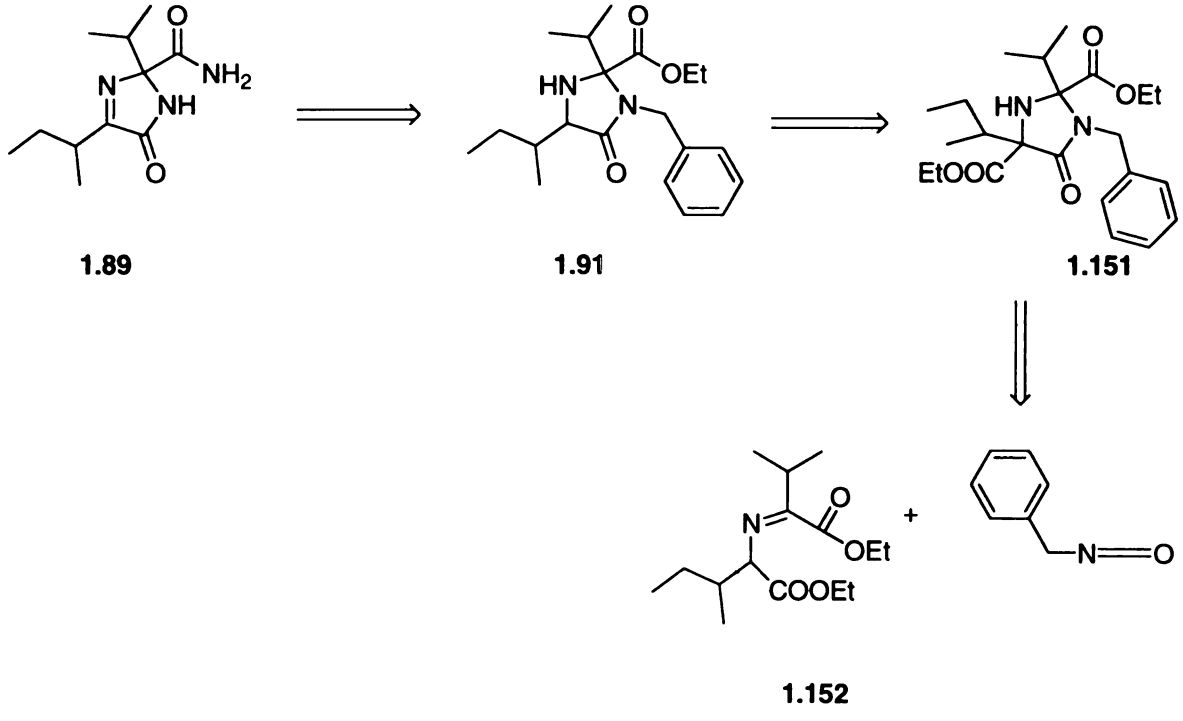
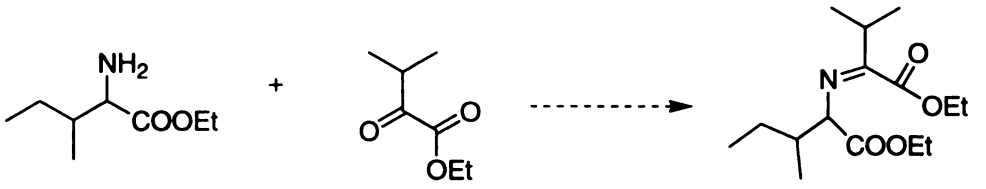


Figure 1.16: Retrosynthesis of the imidazol-4-one to azamethine.

The azamethine **1.152** could be synthesized from the protected amine acid **1.153** and the α-keto ester **1.97** (Scheme 1.48). The synthesis of this imine **1.152** was difficult to achieve. Thus this methodology could not be used in successfully synthesizing the 2,2,5-trisubstituted imidazol-4-one of kottamides.



1.153 **1.97** **1.152**

Scheme 1.48: Synthesis of azamethine required for synthesis of imidazol-4-one.

Conclusion and future Work.

The *Z*-enamide synthesis was achieved successfully on the model system (Scheme 1.25). After the synthesis of the 2,2,5-trisubstituted imidazol-4-one the total synthesis of kottamides could be achieved via hemiaminal formation and elimination of water as described before. For the synthesis of the 2,2,5-trisubstituted imidazol-4-one moiety a couple of problems were encountered. It has been seen in previous reports that the synthesis of these compounds has been done via imines which in the case of kottamides is difficult since imine formation always competes with the more stable enamide formation. Thus if a method was developed whereby the imine could be synthesized successfully the synthesis of 2,2,5-tribuststituted imidazol-4-one would be simple.

Enamide synthesis could also be achieved via oxazoles. According to reports a similar type of reaction has been attempted with furans where reaction of 2,5-diaryl-3-

bromofurans with butyl lithium gave corresponding acetylenes.[57] Thus the *Z*-enamide of kottamides could be synthesized from oxazole **1.154** via ynamide **1.2**. The oxazole **1.154** could be synthesized from the oxazol-5-one **1.11** and the corresponding substituted indol **1.10** (Figure 1.17). The oxazol-5-one could be synthesized from the corresponding acid **1.12** as described before.

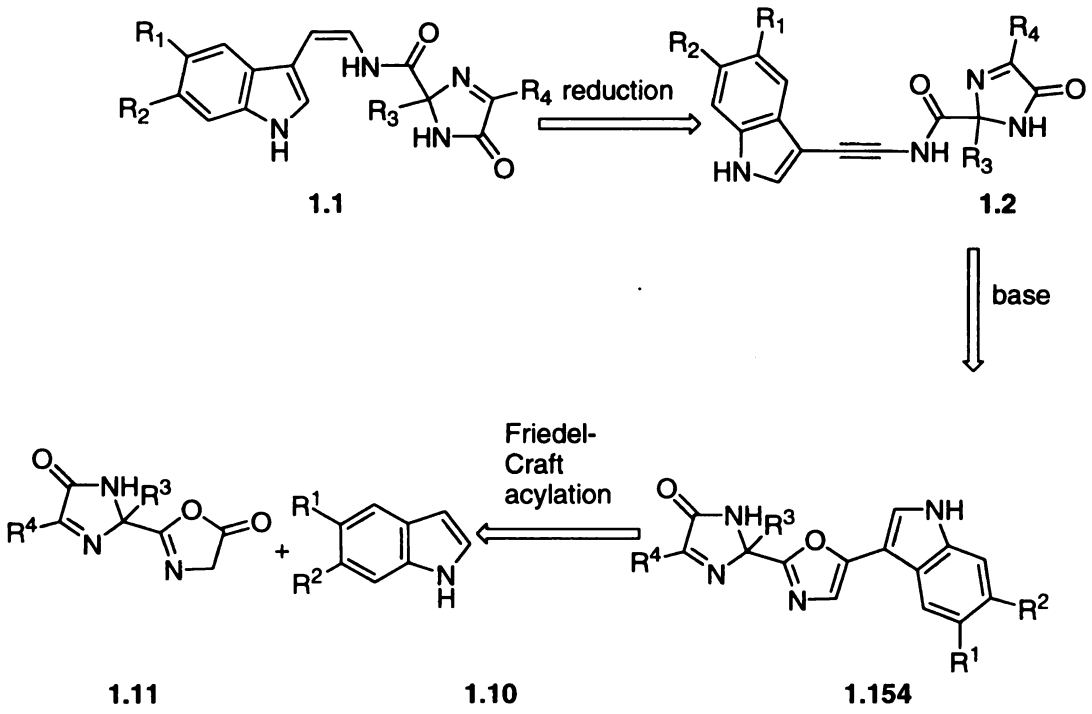


Figure 1.17: Retrosynthesis of kottamides using oxazole.

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Experimental

Reactions were carried out in oven-dried glassware under nitrogen atmosphere, unless otherwise noted. All commercial reagents were used without further purification. All solvents were reagent grade. Anhydrous solvents were dispensed from a delivery system, which passes the solvents through packed columns (tetrahydrofuran, methylene chloride: dry neutral alumina). All reactions were magnetically stirred and monitered by thin layer chromatography with Analtech 0.25-mm pre-coated silica gel plates. Column chromatography was carried out on silica gel (230-400 mesh) supplied by EM Science. Yields refer to chromatography and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Mel-Temp (Laboratory device) apparatus with a microscope attachment. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton, carbon, and fluorine NMR spectra were recorded on a Varian Gemini-300 spectrometer or a varian VXR-500 spectrometer. Chemical shifts were reported relative to the residue peaks of the solvent chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). HRMS were obtained at the mass spectrometry facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer. Combustion analysis was carried out in house on a CHNS/O mass spectrometer. All chemicals were obtained from Aldrich Chemical Co. and used as received. *Caution: Trifluoromethanesulfonic acid is a corrosive and hygroscopic liquid that should be handled with care under dry atmosphere.*

2-phenyl-4H-oxazol-5-one (1.14): Synthesis of this oxazo-5-one will be described in chapter 2.

N-(2-oxo-2-phenyl-ethyl)-benzamide (1.15): The azolactone **1.14** (0.5 g, 3.11 mmol) is introduced gradually into the stirred solution of the aluminium chloride (1.65 g, 12.44 mmol) and benzene under external ice cooling. Stirring was continued for 2 hours in ice under nitrogen and the stirred overnight at room temperature. After hydrolysis with ice, (some HCl is added) then treated with sodium bicarbonate, dried over brine and sodium sulfate and evaporated off. The compound was purified by column chromatography to give **1.15** as a white solid. ^{1}H NMR (300MHz) ($CDCl_3$) δ 4.95 (2H, d, J = 8.2Hz), 7.44-7.56 (5H, m), 7.6 (1H, t, J = 7.2 Hz), 7.9 (2H, d, J = 7.0 Hz), 8.1 (2H, d, J = 7.0 Hz); ^{13}C NMR (75 MHz) ($CDCl_3$) 46.6, 127.0, 128.1, 129.9, 130.9, 132.0, 134.1, 134.5, 135.1, 167.5, 196.2; $M^{+\cdot}$= 239, IR (cm^{-1}): 1689, 1635.0, 1577.2, 1556 .8; Melting Point: 118°C-120°C. Yield: 76%.

2,5-diphenyl-oxazole (1.18): Synthesis of this oxazo-5-one will be described in chapter 2.

3-(2,2-dibromo-vinyl)-1-(toluene-4-sulfonyl)-1H-indole (1.27): A solution of triphenyl phosphene (1183.9 mg, 4.359 mmol) and carbon tetrabromide (720.96 mg, 2.17 mmol) was made in dichloromethane. To this was added via a cannula a solution of aldehyde **1.26** (500 mg, 1.67 mmol) at 0°C. This solution was stirred at 0°C for an hour. Hexanes were added to the solution and stirred for 30 min. at 0°C and this solution was then

filtered through a silica bed. The solution was concentrated under reduced pressure and purified using column chromatography which yielded the solid white product. ^{1}H NMR (500MHz) (DMSO) δ 8.49 (1H, s), 8.12 (1H, d, *J* = 7.2 Hz), 8.10 (1H, s), 8.09 (2H, d, *J* = 7.3 Hz), 8.02 (1H, d, *J* = 7.2 Hz), 7.50-7.58 (3H, m), 7.50 (1H, t, *J* = 7.2 Hz), 2.321 (3H, s); ^{13}C NMR (125MHz) (DMSO) δ 146.6, 134.3, 134.0, 131.1, 129.7, 127.8, 127.6, 126.5, 125.2, 124.6, 120.7, 118.1, 113.8, 91.6, 21.7; IR (cm^{-1}) 2980.19, 1732.11, 1577.3, 1434.84, 1229.45, 785.26; LRMS m/e 455.0 (M^+). Yield: 71%.

3-bromoethynyl-1-(toluene-4-sulfonyl)-1H-indole (1.28): A solution of the alkene **1.27** (30 mg, 0.0659 mmol), was made in THF. To this was added BH_3.toluene solution (0.2 mL, 0.0136 mmol) at -23°C dropwise via a syringe. After stirring at -23°C for 60 hrs. 4mL of methanol was added followed by the simultaneous addition of 5 mL of 3M NaOH and 5mL of 30% H_2O_2. The resulting mixture was stirred at room temperature for 2 hours. The product was isolated as a light yellow solid which was purified using column chromatography. ^{1}H NMR (500MHz) (DMSO) δ 8.24 (1H, s), 7.95 (1H, d, *J* = 7.2 Hz), 7.91 (2H, d, *J* = 7.3 Hz), 7.58 (1H, d, *J*=7.3 Hz), 7.40-7.51 (3H, m), 7.33 (1H, t, *J*=7.2 Hz), 2.31 (3H, s); ^{13}C NMR (125 MHz) (DMSO) δ 145.9, 133.6, 133.2, 130.9, 130.4, 129.9, 126.9, 125.9, 124.2, 119.9, 113.4, 103.7, 70.9, 56.7, 21.0; IR (cm^{-1}) 3068.21, 2923.57, 1595.81, 1539.89, 1447.32, 1374.04, 1174.44, 757.89; LRMS m/e 375 (M^+). Anal. Calcd for $C_{18}H_{17}NO$: C, 54.55; H, 3.21; N, 3.74. Found: C, 54.75; H, 3.74; N, 3.48; Yield: 50%.

N-(4-methoxy-benzyl)-benzamide (1.31): To a solution of para- methoxy benzylamine (5 g, 35.5 mmol) in 100 mL of diethyl ether was added benzoyl chloride (4.88 g, 35.5

mmol). To this was added 2N sodium hydroxide solution in water (20 mL). This was stirred at room temperature for 12 hours. After an aqueous work up the product was purified using column chromatography and characterized. ^{1}H NMR (500 MHz) ($CDCl_3$) : δ 7.77 (2H, d, *J* = 6.8 Hz), 7.31-7.49 (3H, m), 7.22 (2H, d, *J* = 7.1 Hz), 6.80 (2H, d, *J* = 6.8 Hz), 6.55 (1H, bs), 4.48 (2H, d, *J* = 6.1 Hz), 3.79 (3H, s); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 167.2, 159.0, 134.4, 131.4, 130.2, 129.2, 128.5, 126.9, 114.1, 55.2, 43.5; IR (cm^{-1}) 3451.2, 1654.1, 1646.9; Yield: 90%.

Phenyl(trimethylsilylethynyl)iodonium triflate (1.45): To a stirred solution of $PhI(OAc)_2$ (1g, 3.11mmol) in CH_2Cl_2 was added TfOH (0.3 mL, 1.56 mmol) dropwise at 0^0 C and the mixture was stirred for 30 minutes. To the resulting solution was added bis(trimethylsilyl)acetylene (0.535 g, 3.11 mmol) at 0°C and the resulting mixture was stirred for 2 hours. The solvent was then evaporated affording the final product, which was a white solid, that was characterized by NMR. ^{1}H NMR (500 MHz) ($CDCl_3$): δ 0.22 (9H, s), 7.49-7.54 (2H, m), 7.62-7.68 (1H, m), 8.06(2H, d, *J* = 8.7 Hz); ^{13}C NMR (125 MHz) (DMSO) δ 0, 54, 114, 120, 132, 132.5, 138. IR: 2143.0 cm^{-1}; melting point 132-134°C. Yield: 60%.

(1H-indol-3-yl)-acetic acid ethyl ester (1.62): To a mixture of 3-acetic acid indole **1.61** (5 g, 28.60 mmol) in ethanol (100 mL) was added 15 mL conc. hydrochloric acid. This mixture was refluxed for 15 hours and then extracted with sodium bicarbonate and dried with brine and sodium sulfate. The product was isolated as a white solid. ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.16 (1H, bs), 7.66 (1H, d, *J* = 7.4 Hz), 7.34 (1H, d, *J* = 7.2 Hz), 7.22

(1H, t, J = 7.4 Hz), 7.18 (1H, t, J = 7.2 Hz), 7.11 (1H, s), 4.42 (2H, q, J = 6.5 Hz), 3.81 (2H, s), 1.41 (3H, t, J = 6.5 Hz); ^{13}C NMR (125MHz) ($CDCl_3$) δ 172.9, 135.6, 130.2, 128.4, 121.5, 120.8, 115.7, 111.3, 109.9, 61.9, 40.1, 11.9; IR (cm^{-1}) 3379.7, 3002.9, 2980.1, 1740.1, 1567.9; Yield: 90%.

3-ethoxycarbonylmethyl-indole-1-carboxylic acid tert-butyl ester (1.63): To the solution of the ester **1.62** (4.5 g, 22.20 mmol) in dichloromethane was added $(Boc)_2O$ (7.3 g, 33.30 mmol) dimethylamino pyridine (4.07 g, 33.30 mmol) and triethylamine (4.28 mL, 33.30 mmol) and this mixture is stirred at room temperature for 2.5 hours. The dichloromethane is then evaporated and purified via column chromatography and the product was isolated as a white solid. ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.13 (1H, d, J = 7.3 Hz), 7.53-7.61 (2H, m), 7.31 (1H, t, J = 7.1 Hz), 7.25 (1H, t, J = 7.3 Hz), 4.16 (2H, q, J = 6.2Hz), 3.69 (2H, s), 1.66 (9H, s), 1.31 (3H, t, J = 6.2 Hz); ^{13}C NMR (125MHz) ($CDCl_3$) δ 172.5, 159.2, 140.2, 132.9, 124.5, 122.2, 120.1, 120.1, 119.2, 111.1, 70.4, 60.1, 32.1, 29.1, 11.1; IR (cm^{-1}) 2980.4, 1736.1, 1680.0, 1477.6, 1452.5, 1369.6, 1155.5, 746.5; Yield: 50%.

3-(2-oxo-ethyl)-indole-1-carboxylic acid tert-butyl ester (1.64): 1N solution of the ester **1.63** (200 mg, 0.33 mmol) in ether was prepared and cooled to -78°C. To this was added DIBAL dropwise and stirred for an hour at 78°C. To the reaction mixture is the added methanol and water in the ratio of 3:5 respectively and stirred for 10 minutes. Sodium potassium tartarate is added to this and this mixture is stirred overnight. This is worked up with water and purified using column chromatography. The product is a

colorless gel. ^{1}H NMR (500 MHz) ($CDCl_3$) δ 9.80 (1H, t, *J* = 3.5 Hz), 8.19 (1H, s), 7.60 (1H, s), 7.47 (1H, d, *J* = 7.2 Hz), 7.39 (1H, t, *J* = 7.2 Hz), 7.281 (1H, t, *J* = 7.2 Hz), 3.782 (2H, d, *J* = 3.5 Hz), 1.698 (9H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 193.5, 186.0, 130.5, 126.4, 124.6, 122.8, 122.6, 119.5, 117.5, 115.2, 111.3, 83.8, 18.4; IR (cm^{-1}) 2918.6, 1734.2, 1653.2, 1425.5, 1369.6, 1157.4, 746.5; Yield: 15%.

N-(1-hydroxy-2-phenyl-ethyl)-benzamide (1.84): To the well stirred solution of the amide **1.83** (2 g, 8.82 mmol), in dry THF (16 mL) was added DIBAL (1M in toluene) (20.80 mmol), dropwise at 0°C. After the mixture was stirred for 30 minutes at 0°C, the aldehyde **1.82** (1g, 4.16 mmol) was added. The resulting solution was stirred overnight at 0 °C, before it was diluted with ethyl acetate (10 mL/mmol) and quenched with water (10 mL/mmol) at 0 °C. Afetr separation of the layers, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sufate, filtered and concentrated under vacuo. The product, which was a white solid, was characterized after purification using column chromatography. ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.63 (2H, d, *J* = 7.6 Hz), 7.47 (1H, t, *J* = 7.6), 7.25-7.38 (7H, m), 6.82 (1H, bs), 5.75-5.78 (1H, m), 3.01-3.11 (2H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 168.2, 135.7, 131.9, 129.5, 128.7, 128.6, 127.0, 126.9, 75.1, 41.3; $(M-H_2O)^+$ 223.0 (100%); IR (cm^{-1}) 3335.7, 1643.7, 1522.3, 1076.6, 1039.4. Yield: 76%.

***Cis*-N-styryl-benzamide (1.85):** To a stirred solution of the hydroxy-amide **1.84** (200 mg, 0.83 mmol), in dry THF (12 mL) was added dry pyridine (2.0 mL, 24.90 mmol), and dry acetic anhydride (1.2 mL, 12.45 mmol). After refluxing the mixture for 24 hours, it

was cooled to room temperature, and diluted with ethyl acetate (200 mL/mmol) and water (100 mL/mmol). The layers were separated and the organic layer was washed with saturated ammonium chloride solution, water and brine, dried over sodium sulfate, filtered and concentrated in vacuo. The product, which was a white solid, was characterized after purification using column chromatography. ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.36 (1H, d, J = 9.0 Hz), 7.75 (2H, d, J = 8.1 Hz), 7.15-7.55 (9H, m), 5.87 (1H, d, J = 9.6 Hz); ^{13}C NMR (125 MHz) (CDCl3) δ 164.3, 135.7, 133.3, 132.1, 129.2, 128.8, 127.8, 127.0, 122.3, 110.9; LRMS m/e 223.1 (50.2%) (M^+); IR (cm^{-1}) 1665.5, 1648.2, 1510.5. Yield: 64%.

2-amino-3-methyl-butyric acid ethyl ester (1.105): A solution of valine **1.104** (5 g) in ethanol (100 mL) with HCl (2N) was refluxed overnight. The reaction mixture was then treated with $NaHCO_3$. This is extracted with ether and the ether layer is evaporated off after drying it with sodium sulfate.The product was isolated as a colorless gel. ^{1}H NMR (500MHz) ($CDCl_3$): δ 4.11 (2H, q, J = 6.0 Hz), 3.18 (1H, d, J = 5.8 Hz), 1.88-1.98 (1H, m), 1.37 (2H, s), 1.19 (3H, t, J = 6.0 Hz), 0.90 (3H, d, J = 5.7 Hz), 0.83 (3H, d, J = 5.8 Hz); ^{13}C NMR (125MHz) ($CDCl_3$): δ 175.4, 60.4, 59.8, 32.0, 19.1, 17.0, 14.1. Yield: 50%.

4-isopropylidene-2-phenyl-4H-oxazol-5-one (1.116): A solution of $TiCl_4$ (4 equivalents) in dichloromethane, (1M), was added into THF at -10°C. acetone (1 equivalent) and 2-phenyl-4H-oxazol-5-one **1.14** (2 equivalents) were added and stirred at 0°C for 20 minutes. Pyridine (6 equivalents) was then added over a 30 minutes period.

The reaction mixture was then stirred at 0°C for 2 hours and then allowed to stir overnight at room temperature. A saturated solution of NH_4Cl was added and the mixture was stirred for 10 minutes and extracted with ethyl acetate. This was purified further using column chromatography and the product isolated was a yellow solid. ^1H NMR (500MHz) ($CDCl_3$): δ 8.12 (2H, d, *J* = 7.6 Hz), 7.55 (1H, t, *J* = 7.6 Hz), 7.41(2H, t, *J* = 7.6 Hz), 2.35 (3H, s), 2.25 (3H, s); ^{13}C NMR (125MHz) ($CDCl_3$): δ 169.1, 159.5, 153.1, 133.5, 132.8, 129.1, 128.1, 127.5, 22.2, 18.6. Yield: 68%.

Benzylidene-(4-methoxy-benzyl)-amine (1.117): A solution of benzaldehyde (1equivalent) and p-methoxy benzylamine (1equivalent) in benzene was refluxed for 6 hours. The benzene was then evaporated. No further purification was required as product had no impurities.The product was a pale yellow liquid. ^1H NMR (500MHz) ($CDCl_3$): δ 8.36 (1H, s), 7.77 (2H, d, *J* = 7.2 Hz), 7.39-7.41 (3H, m), 7.25 (2H, d, *J* = 7.4 Hz), 6.88 (2H, d, *J* =7.4Hz), 4.76 (s, 2H), 3.78 (s, 3H); C^{13}NMR (125MHz): δ 161.5, 158.5, 136.1, 131.2, 130.8, 129.1, 128.3, 128.0, 113.9, 62.1, 54.9. Yield: ~100%.

3-methyl-2-oxo-pentanoic acid benzylamide (1.119): The sodium salt of 3-methyl-2-oxo-pentanoic acid (1 equivalent) is taken in some dichloromethane. To this is added oxalyl chloride (1.4 equivalents) and then a drop of DMF at 0°C. This is stirred at room temperature overnight. To this reaction mixture is added some p-methoxybenzylamine (1.2eq) at 0°C and this is stirred for another 4 hours After an aqueous work up the dichloromethane is evaporated off to give the product which looks like a colorless gel. H^1NMR (500MHz) ($CDCl_3$): δ 7.18, (2H, d, *J* = 7.4 Hz), 6.85 (2H, d, *J* = 7.4 Hz), 4.39

(2H, d, J = 5.5 Hz), 3.78 (3H, s), 3.50 (1H, h, J = 5.8 Hz), 1.68-1.78 (2H, m), 1.35-1.44 (2H, m), 1.09 (3H, d, J = 5.5 Hz), 0.89 (3H, t, J = 5.8 Hz); ^{13}C NMR (125MHz) ($CDCl_3$): δ 202.2, 159.7, 130.8, 129.3, 129.1, 114.2, 55.3, 42.9, 40.4, 25.4, 15.1, 11.5; IR (cm^{-1}) 3379.7, 2968.8, 1759.3, 1684.0, 1514.31, 1250.0; MS (EI) m/e 249.1 (5.88) (M+). Yield: 55%.

5-isopropyl-2,2-dimethyl-imidazolin-4-one (1.128): Solution of valinamide hydrochloride (100 mg, 0.65 mmol) was taken in acetone (10 mL) in activated molecular sieves. This was stirred overnight. To this was added NBS (87.12 mg, 0.65 mmol). This was stirred for 12 hours. The molecular sieves were filtered off and acetone was evaporated off. The reaction mixture was taken in dichloromethane and stirred in a solution of 2N NaOH till alkaline. The dichloromethane was extracted and the crude product was purified using column chromatography in dichloromethane and acetone. The product was isolated as a white solid. ^1H NMR (500 MHz) ($CDCl_3$) δ 6.32 (1H, s), 3.53 (1H, d, J = 8 Hz), 2.20-2.09 (1H, m), 1.43 (3H, s), 1.39 (3H, s), 1.23 (1H, s), 1.02 (3H, d, J = 6Hz), 0.92 (3H, d, J = 6.5 Hz); MS (EI) m/e 156.2 (6.57) (M+). Yield 25%.

2-bromo-N-(4-methoxy-benzyl)-3-methyl-butyramide (1.142): EDCI.HCl (1.27 g, 6.24 mmol) was added to a solution of 2-bromo-3-methyl-butyric acid (1g, 5.52 mmol). After stirring for one hour para-methoxy benzyl amine (0.82 mL, 6.24 mmol) was added to the reaction mixture and it was stirred for 12 hours. After an aqueous work up the product was purified using column chromatography and the product was separated as a white solid. ^1H NMR (500 MHz) ($CDCl_3$) δ 7.18 (2H, d, J = 7.4Hz), 6.85 (2H, d, J =

7.4Hz), 6.75 (1H, bs), 4.29-4.39 (3H, m), 3.78 (3H, s), 2.37-2.43 (1H, m), 1.03 (3H, d, *J* = 6 Hz), 0.92 (3H, d, *J* = 6.2Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 167.9, 159.6, 129.6, 129.1, 114.1, 61.7, 55.3, 43.6, 32.3, 20.9, 18.34. MS (EI) m/e 299.0 (0.05) (M^+). IR (cm^{-1}) 3278.4, 2964.1, 1646.9, 1542.8, 1513.8, 1461.8, 1303.7, 1251.6, 1037.5, 823.5, 777.2. Melting Point: 89-91°C.

2-hydroxy-imino-3-methyl-pentanoic acid 4-methoxy-benzylamide (1.145): The keto amide **1.119** was dissolved in MeOH and $NH_2OH.HCl$ followed by addition of TEA. The reaction is refluxed for 5 hours. This reaction mixture was worked up with water, HCl and then $NaHCO_3$. The product, which was a white solid, looked clean so there was no reason for column chromatography. Both the E, Z isomers are isolated here in the ratio of 1:2 respectively. ^1H NMR (500 MHz) ($CDCl_3$) δ 7.22 (1H, d, *J* = 8Hz), 7.17 (2H, d, *J* = 8Hz), 6.81-6.86 (3H, m), 4.52 (1H, d, *J* = 5Hz), 4.37 (2H, d, *J* = 5 Hz), 3.775 (1.5H, s), 3.77 (3H, s), 3.21-3.33 (1H, m), 2.72-2.83 (0.5H, m), 1.81-1.91 (1H, m), 1.56-1.70 (1.5H, m), 1.34-1.44 (0.5H, m), 1.23 (3H, d, *J* = 7.2), 1.10 (1.5H, d, *J* = 7.0), 0.83-0.91 (4.5H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 163.2, 15.9, 158.4, 130.1, 129.1, 114.1, 55.3, 42.9, 42.8, 37.4, 32.6, 27.1, 26.1, 17.4, 16.5, 12.5, 11.6. MS (EI) m/e 264.3 (0.19) (M^+)247.0 (21.5) (M^+ -17). IR (cm^{-1}) 3334.3, 2966.0, 1714.4, 1681.6, 1612.2, 1513.8, 1459.9, 1301.7, 1249.7, 1176.4, 1035.6, 831.2. Yield: ~100%.

Stable isomer: ^1H NMR (500 MHz) ($CDCl_3$) δ 7.18 (2H, d, *J* = 7.3Hz), 6.84 (2H, d, *J* = 7.3Hz), 4.37 (2H, d, *J* = 5.4 Hz), 3.77 (3H, s), 3.23-3.31 (1H, m), 1.83-1.85 (1H, m), 1.55-1.70 (1H, m), 1.23 (3H, d, *J* = 7.2Hz), 0.86 (3H, t, *J* = 6.2 Hz).

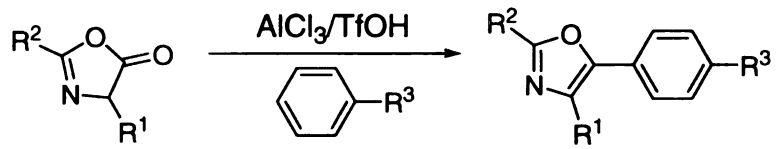
2-hydroxyamino-3-methyl-pentanoic acid 4-methoxy-benzylamide 1.146: A 7N ethanolic HCl solution was added dropwise at 0°C to a stirred solution of hydroxime **1.145** synthesized above mixed with borane-pyridine complex in EtOH. Stirring was continued for an hour. The reaction mixture was evaporated and dissolved in dichloromethane washed with $NaCO_3$ and dried. The yield of this reaction was 84%. Product was a white solid, isolated as a mixture of diastereomers. ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.16 (2H, d, *J* = 7.2Hz), 6.80 (2H, d, *J* = 7.2Hz), 4.37 (2H, d, *J* = 5Hz), 3.74 (3H, s), 3.34 (1H, dd, *J* =15Hz, 3Hz), 1.75-1.64 (1H, m), 1.39-1.49 (1H, m), 1.09-1.22 (2H, m), 0.82-0.89 (7H, m); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 172.7, 158.9, 149.5, 136.2, 130.3, 129.0, 123.8, 113.9, 113.4, 71.18, 70.6, 55.2, 42.6, 35.8, 35.5, 26.5, 25.7, 15.8, 15.0, 11.7, 11.9. IR (cm^{-1}) 3304.5, 2963.0, 1647.4, 1612.7, 1514.3, 1462.2, 1250.0, 1176.7, 1035.9, 819.8. Yield: 84%.

CHAPTER 2

ONE-POT FRIEDEL-CRAFT/ROBINSON-GABRIEL SYNTHESIS OF OXAZOLES USING OXAZOLONE TEMPLATES.

Introduction

The synthesis of oxazoles was discussed briefly in chapter **1**, where we chanced upon molecules with oxazole structure. We tried to develop a reaction where we could synthesize the oxazoles starting with oxazol-5-ones using a general protocol. We reported a one-pot synthesis of 2,4,5-trisubstituted oxazoles via a Friedel-Crafts/Robinson-Gabriel synthesis using a general oxazolone template. Treatment of the oxazolone template **2.1** with a range of aromatic nucleophiles **2.2** provided the highly substituted oxazoles **2.3** in good yields (Scheme 2.1).[1]

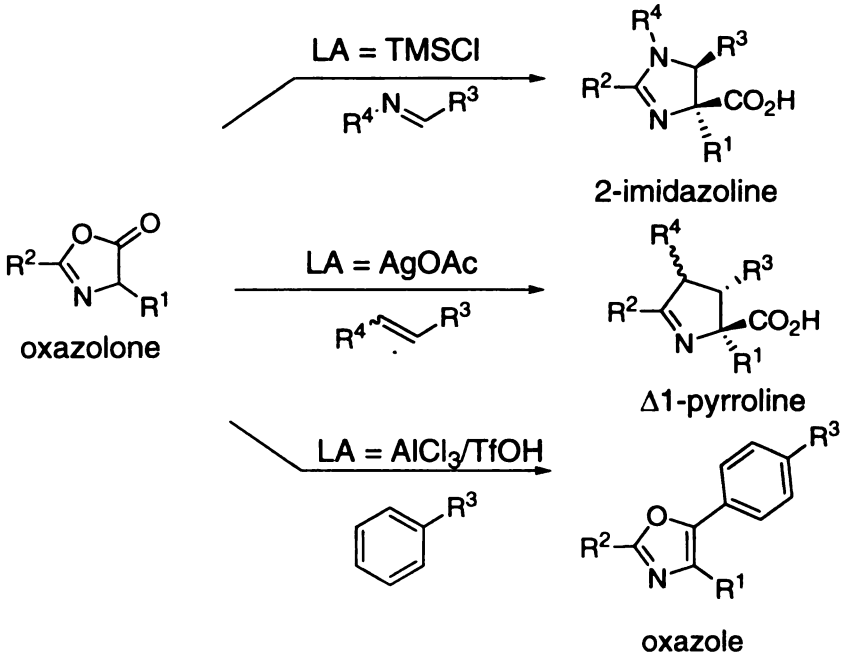


2.1 **2.2** **2.3**

Scheme 2.1: One-pot synthesis of oxazoles.

The development of small molecular weight scaffolds containing a high degree of diversity has become a leading focus in modern drug discovery.[2,3,4,5,6] As part of our program to develop diverse classes of small molecule libraries containing potential biological properties, we have developed a substrate controlled diversity-oriented synthesis (DOS) using a general oxazolone template. Recently, we reported the use of the

oxazolone template for the cycloaddition reactions with imines and alkenes to provide the corresponding imidazolines and Δ^1-pyrrolines.[7,8,9] As an extension of this approach, we report herein a one-pot synthesis of 2,4,5-trisubstituted oxazoles via a Friedel-Crafts/Robinson-Gabriel synthesis (Scheme 2.2).



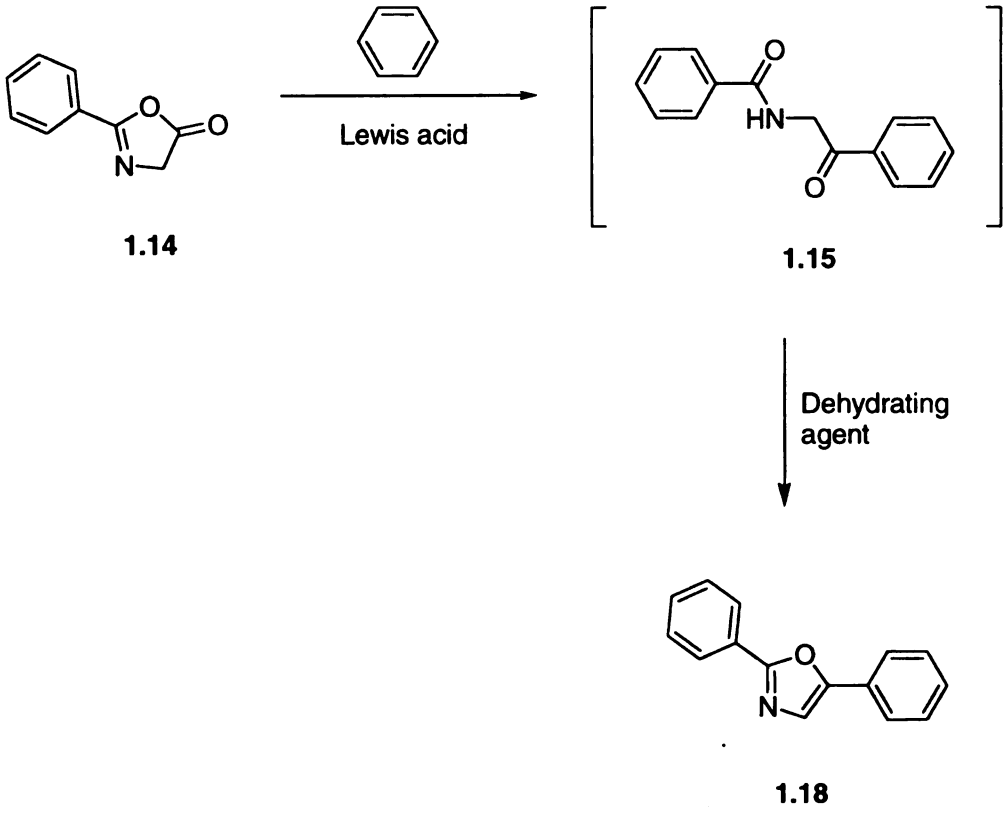
Scheme 2.2: Substrate controlled diversity synthesis of heterocycles using oxazolones.

The oxazole nucleus is present in a wide variety of natural and unnatural biologically active compounds[10,11,12] and is a useful reagent in the synthesis of a range of biologically active scaffolds.[13,14,15,16] A number of methods exist in the literature for the synthesis of oxazoles,[15,17,18,19,20] however due to its abundant representation as a synthetic and medicinal scaffold, new methods for the facile production of oxazoles continue to be of interest.[21,22,23,24] One of the oldest yet most versatile methods to generate 2,5-di and

2,4,5-trialkyl, aryl-, heteroaryl-, and alkyloxazoles is the Robinson-Gabriel cyclo-dehydration of 2-acylamino ketones.[25,26] The latter can be generated via an aluminum chloride mediated Friedel-Crafts acylations of oxazol-5-ones and aromatics.[27] In contrast, Friedel-Craft acylations with the traditional acid chloride derivatives of amino acids are often cumbersome.[28]

Combining Friedel-Crafts reaction and Robinson-Gabriel cyclodehydration reaction in a one-pot synthesis.

We investigated the possibility of combining the Friedel-Crafts reaction and Robinson-Gabriel cyclodehydration reaction in a one-pot synthesis of 2,4,5-trisubstituted oxazoles using a general oxazol-5-one template. After screening a small number of Lewis acids on 2-phenyl-oxazol-5-one **1.14**, aluminum chloride was found to be the most successful in producing the Friedel-Crafts products. The 2-acylaminoketone **1.15** formed was subsequently evaluated for its ability to cyclize and dehydrate in situ to the corresponding oxazoles **1.18** (Scheme 2.3). A number of dehydrating agents were evaluated in combination with $AlCl_3$ for their ability to provide a one-pot oxazole synthesis (Table 2.1). We found that trifluoromethanesulfonic acid was the reagent of choice generating the desired product in a one-pot sequence with the aluminum chloride.



1.14 1.15 1.18

Scheme 2.3: One-pot synthesis of 2,5-diphenyl oxazole.

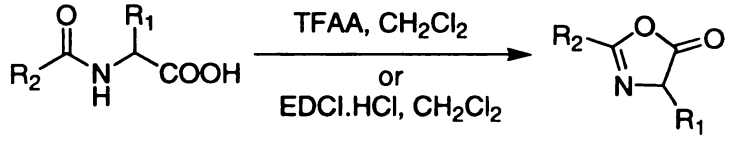
Sr. No.	Lewis acid/dehydrating agent	Intermediate 2.4 (%)	Product 2.5 (%)
1.	$AlCl_3$	85%	0%
2.	$AlCl_3$/ TfOH	0%	76%
3.	TfOH	X	X
4.	$AlCl_3$/ TFAA	X	X
5.	TFAA	X	X
6.	$AlCl_3$/ Tf_2O	X	X
7.	Tf_2O	X	X
8.	$AlCl_3$/ P_2O_5	85%	0%
9.	$AlCl_3$/ $POCl_3$	85%	0%
10.	$BF_3.OEt_2$/ TfOH	X	X
11.	$P_2O_5.CH_3SO_3H$/ TfOH	X	X

Table 2.1: Screening of Lewis acids for one-pot Friedel-Craft/Robinson-Gabriel synthesis.

Other common dehydrating reagents used in Robinson-Gabriel cyclodehydration reactions are phosphorous pentoxide, phosphorous oxychloride, trifluoroacetic anhydride and triflic anhydride, which were all found to be unsuccessful in generating the oxazoles in this one-pot sequence (Table 2.1).

Synthesis of oxazol-5-ones.

The oxazolones **2.5** were prepared from 2-acylamino acids **2.4** by dehydration with 1-ethyl-3- (3'dimethylaminopropyl) carbodiimide·HCl (EDCI.HCl) or trifluoroacetic anhydride to provide the pure oxazol-5-ones in high yields.[29,30,31]



2.4 **2.1**

Scheme 2.4: Synthesis of oxazol-5-ones.

The following table of oxazol-5-ones was prepared starting with *N*-acylated amino acids using trifloroacetic anhydride (TFAA) (Table 2.2).

Series No.	**R_1**	**R_2**	**% yield of oxazol-5-one.**
1.14.	H	C_6H_5	70
2.5.	CH_3	C_6H_5	83
2.6.	$CH_2\ C_6H_5$	C_6H_5	69
2.7.	$CH(CH_3)_2$	C_6H_5	87
2.8.	CH_3	$pC_6H_5OCH_3$	85

Table 2.2: Synthesis of oxazol-5-ones using TFAA.

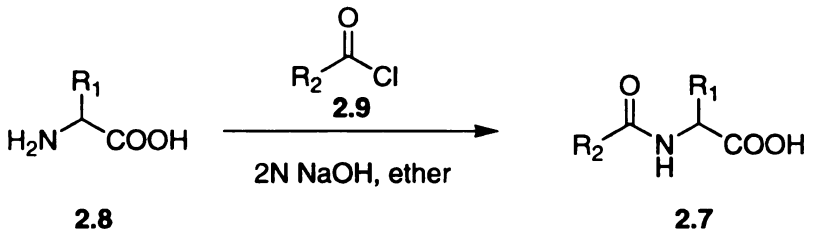
Some oxazol-5-ones were synthesized using a different procedure using 1-ethyl-3-(3-dimethyllaminipropyl)carbodiimide hydrochloride (EDCI.HCl) (Table 2.3). This was because they were seen to be more sensitive and formed ketenes if treated with sodium bicarbonate in the workup which is the required workup procedure when trifloroacetic anhydride is used. For these cases a different procedure is followed in which case EDCI.HCl is used.

Series. No.	**R_1**	**R_2**	**% yield of oxazol-5-one.**
2.9.	H	CH_3	48
2.10.	H	$CH_2C_6H_5$	60
2.11.	CH_3	$CH_2C_6H_5$	67
2.12.	CH_3	CH_3	66

Table 2.3: Synthesis of oxazol-5-ones using EDCI.HCl.

Synthesis of the *N*-acylated amino acids.

The *N*-acylated amino acids **2.14** were synthesized via *N*-acylation of commercially available amino acids **2.13** using acid chlorides **2.15** (Scheme 2.5).[7]



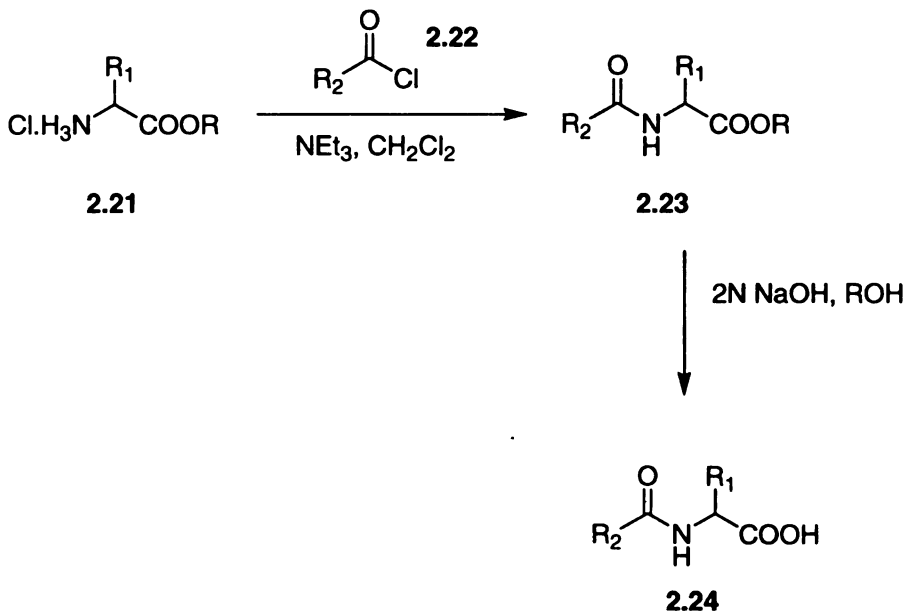
Scheme 2.5: *N*-acylation of amino acids to afford *N*-acylated amino acids using Schotten-Bauman procedure.

Using this procedure, Schotten-Bauman procedure, afforded the *N*-acylated amino acids (Table 2.4).

Series No.	R_1	R_2	% yield of *N*-acylated amino acids
2.16.	CH_3	C_6H_5	70
2.17.	CH_3	$pC_6H_4O\ CH_3$	68
2.18.	$CH_2C_6H_5$	C_6H_5	68
2.19.	$CH(CH_3)_3$	C_6H_5	68
2.20.	C_6H_5	C_6H_5	71

Table 2.4: Synthesis of *N*-acylated amino acids using Schotten-Bauman procedure.

The procedure used for some acid chlorides (substituted acetyl chloride) **2.22** is different as they are sensitive to moisture (react rapidly with water to afford HCl and acetic acid).[32] In this case a different procedure is followed (Scheme 2.6).



Scheme 2.6: Alternative *N*-acylation of amino acids.

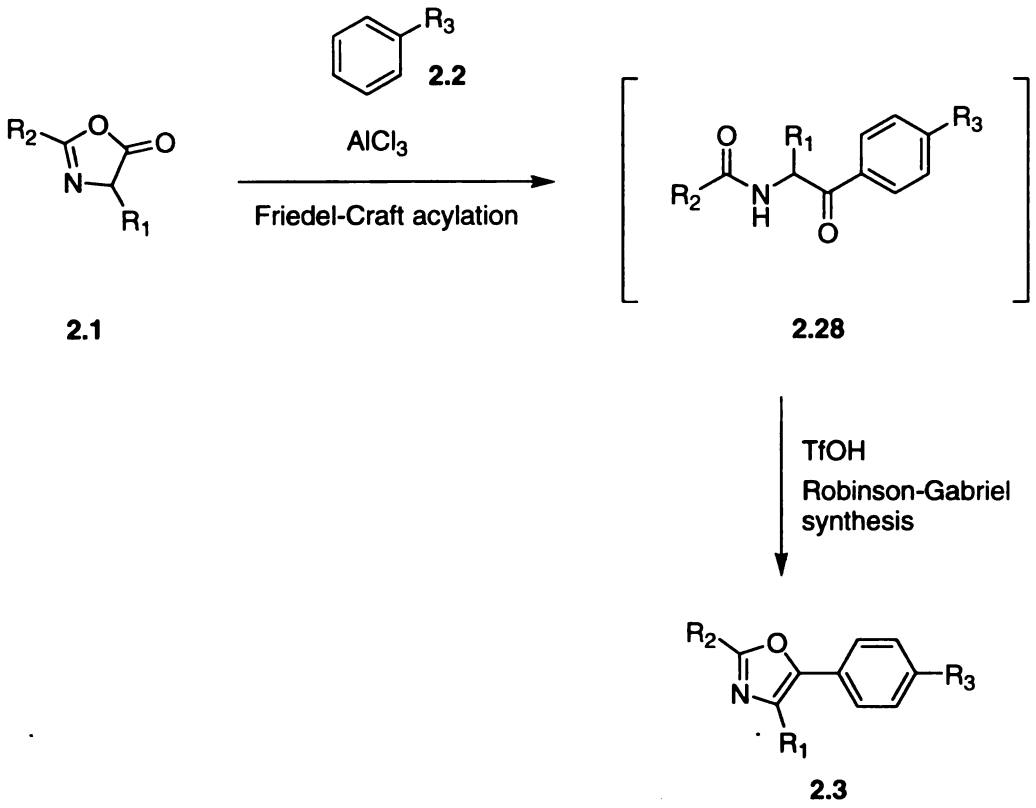
The *N*-acylated amino acids **2.24** were synthesized in this case starting from amino acid ester hydrochlorides **2.21** (Table 2.5).

Series No.	R_1	R_2	% yield of *N*-acylated amino acids
2.25.	H	$CH_2C_6H_5$	55
2.26.	CH_3	$CH_2C_6H_5$	93
2.27.	CH_3	CH_3	57

Table 2.5: Synthesis of *N*-acylated amino acids using alternative procedure.

Synthesis of oxazoles with various substitutes.

Once the oxazol-5-ones **2.1** were synthesized they were treated to Friedel-Craft acylation followed by a Robinson-Gabriel type reaction to synthesize the oxazole **2.3** in a one-pot synthesis (Scheme 2.7). The efficacy of various oxazol-5-ones **2.1**, containing different substituents at C-2 (R^2) and C-4 (R^1) positions, to undergo this Friedel-Craft/Robinson-Gabriel reaction with different aromatic substrates **2.2** to synthesize the oxazoles **2.3** is illustrated (Table 2.6).

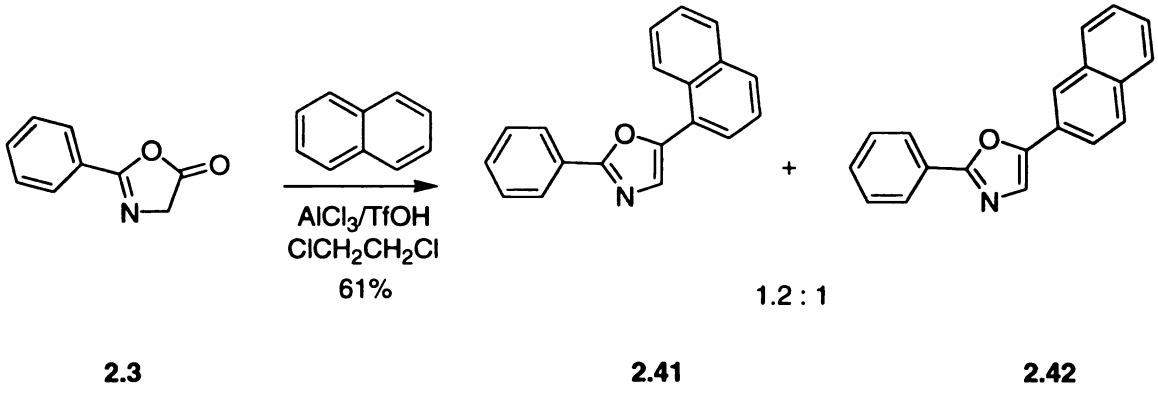


Scheme 2.7: One-pot synthesis of oxazoles using Friedel-Craft/Robinson-Gabriel synthesis.

Series No.	R^1	R^2	R^3	% yield of oxazoles
1.18.	H	C_6H_5	H	76
2.29.	H	$CH_2C_6H_5$	H	38
2.30.	H	CH_3	H	55
2.31.	CH_3	C_6H_5	H	81
2.32.	$CH_2\ C_6H_5$	C_6H_5	H	51
2.33.	$CH(CH_3)_2$	C_6H_5	H	82
2.34.	C_6H_5	C_6H_5	H	87
2.35.	CH_3	C_6H_5	CH_3	65
2.36.	CH_3	C_6H_5	OCH_3	78
2.37.	H	C_6H_5	OCH_3	73
2.38.	H	C_6H_5	C_6H_5	81
2.39.	H	C_6H_5	Br	63
2.40.	H	C_6H_5	NO_2	0

Table 2.6: Yields of oxazoles with various substituents.

In case of oxazoles with R^3=H and R^3= CH_3 dry benzene and toluene are used respectively. Exposure of the oxazole template **1.14** to naphthalene provided a 1.2:1 mixture of **2.41**:**2.42** (Scheme 2.8) with 61% yield.



Scheme 2.8: Synthesis of naphthalene-substituted oxazoles.

All reactions proceeded smoothly with various aromatic substrates in moderate to good yields (Table 2.6), with the exception of the electron deficient nitrobenzene (Table 2.6, entry 13). Treatment of the oxazolones with $AlCl_3$ (3 eq.) with either benzene or toluene as solvent followed by the exposure of the reaction mixture to trifluoromethanesulfonic acid (10 eq) resulted in the formation of the oxazoles. Alternatively, 1,2 dichloroethane was used as solvent with a stoichiometric quantity of the aromatic substrate.

Mechanism of one-pot synthesis of oxazoles from oxazol-5-ones.

The mechanism of the Robinson-Gabriel synthesis has been elucidated by oxygen labeling studies.[33] A possible mechanism consistent with these studies involves the

activation of the oxazolones by $AlCl_3$ followed by the nucleophilic addition of the aromatic substrate generating the 2-acylamino ketones in situ. Protonation of the aryl ketone by the super acid results in the formation of an electrophilic carbonyl carbon, which is attacked by the amide oxygen generating a five membered dihydro-oxazolol (Figure 2.1). Dehydration of the dihydro-oxazolol subsequently forms the oxazole.

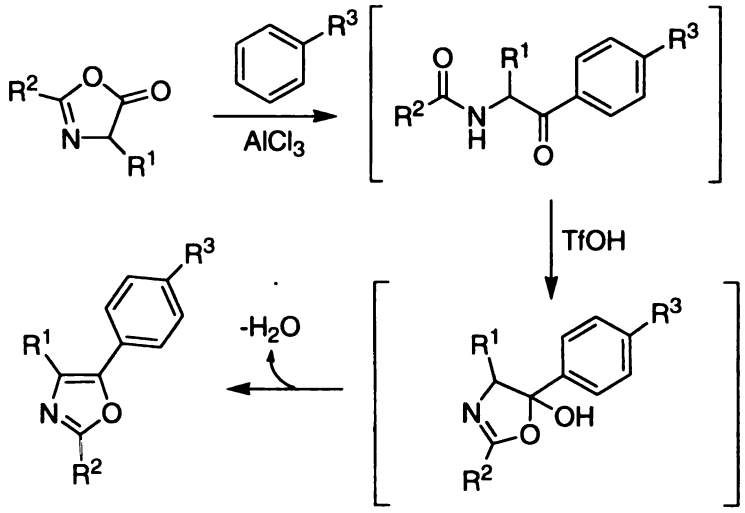


Figure 2.1: Mechanism of one-pot synthesis of oxazoles from oxazol-5-ones.

Conclusion.

In summary, we report an efficient method of generating 2,4,5-trisubstituted oxazoles via a one-pot Friedel-Craft/Robinson-Gabriel reaction using a general oxazolone template. This one-pot oxazole reaction adds to the repertoire of the Lewis acid mediated substrate-controlled diversity-oriented synthesis using the oxazolone template.

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Experimental

Reactions were carried out in oven-dried glassware under nitrogen atmosphere, unless otherwise noted. All commercial reagents were used without further purification. All solvents were reagent grade. Anhydrous solvents were dispensed from a delivery system, which passes the solvents through packed columns (tetrahydrofuran, methylene chloride: dry neutral alumina). All reactions were magnetically stirred and monitered by thin layer chromatography with Analtech 0.25-mm pre-coated silica gel plates. Column chromatography was carried out on silica gel (230-400 mesh) supplied by EM Science. Yields refer to chromatography and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Mel-Temp (Laboratory device) apparatus with a microscope attachment. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton, carbon, and fluorine NMR spectra were recorded on a Varian Gemini-300 spectrometer or a varian VXR-500 spectrometer. Chemical shifts were reported relative to the residue peaks of the solvent chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). HRMS were obtained at the mass spectrometry facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer. Combustion analysis was carried out in house on a CHNS/O mass spectrometer. All chemicals were obtained from Aldrich Chemical Co. and used as received. *Caution: Trifluoromethanesulfonic acid is a corrosive and hygroscopic liquid that should be handled with care under dry atmosphere.*

General procedure for the preparation of oxazolones (1.14, 2.5, 2.6, 2.7, 2.8). A suspension of N-benzoylated amino acid is taken in dry dichloromethane in a flame dried round bottomed flask. After cooling this solution to 0°C to it is added trifluoroacetic anhydride (1.2 equivalents) drop wise with constant stirring. The reaction is set to stir at room temperature for 12 hours after stirring it at 0°C for half an hour. After approximately 12 hours of stirring the dichloromethane is treated with some ice cold sodium bicarbonate solution and the dichloromethane layer is separated, dried with brine, sodium sulfate and concentrated.

2-phenyl-4H-oxazol-5-one (1.14): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.75 (2H, d, J = 7.0 Hz), 7.39-7.58 (3H, m), 4.09 (2H, s); ^{13}C NMR (75 MHz) ($CDCl_3$): 179.09, 167.95, 131.57, 128.66, 128.33, 127.09, 63.05; IR (cm^{-1}): 1827.0, 1655.1.

4-methyl-2-phenyl-4H-oxazol-5-one (2.5): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.79 (2H, d, J = 6.8 Hz), 7.21-7.52 (3H, m), 4.32 (1H, q, J =8.2 Hz), 1.40 (3H, d, J = 8.2 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$): 178.1, 160.7, 131.8, 128.2, 127.2, 125.2, 60.7, 16.7; IR (cm^{-1}): 1826.8, 1653.2.

4-benzyl-2-phenyl-4H-oxazol-5-one (2.6): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.93 (2H, d, J = 7.6 Hz), 7.45-7.61 (3H, m), 7.12-7.28 (5H, m), 4.74 (1H, m), 3.19-3.47 (2H, m); ^{13}C NMR (125 MHz) ($CDCl_3$): 177.9, 161.2, 135.2, 132.1, 129.6, 128.7, 128.2, 127.9, 127.2, 125.1, 66.1, 38.0; IR (cm^{-1}): 1822.9, 1648.1.

4-isopropyl-2-phenyl-4H-oxazol-5-one (2.7): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.99 (2H, d , J = 7.2 Hz), 7.44-7.55 (3H, m), 4.29 (1H, d, J = 9 Hz), 2.23-2.43 (1H, m), 1.12 (3H, d,

J = 6 Hz), 1.06 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$): 178.0, 162.2, 132..5, 128.1, 127.6, 125.4, 70.1, 18.1, 17.2; IR (cm^{-1}): 1826.0, 1656.9.

2-(4-methoxy-phenyl)-4-methyl-4H-oxazol-5-one (2.8): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.95 (2H, d, J = 7.5 Hz), 6.99 (2H, d, J = 7.5 Hz), 4.43 (1H, q, J = 8.0 Hz), 3.86 (3H, s), 1.58 (3H, d, J = 8.0 Hz); IR (cm^{-1}): 1825.0, 1655.1.

General procedure for the preparation of the oxazol-5-one using EDCI.HCl (2.9, 2.10, 2.11, 2.12). To a solution if the N-benzoylated amino acid in dichloromethane cooled to 0°C is added EDCI.HCl (1 equivalent). The solution is stirred for an hour at 0°C and then for another hour at room temperature. After stirring is complete the dichloromethane solution is treated to ice cold water to remove the EDCI.HCl and the dichloromethane layer is dried with sodium sulfate and concentrated.

2-methyl-4H-oxazol-5-one (2.9): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.06 (2H, s), 2.21 (3H, s); IR (cm^{-1}): 1822.0, 1677.2.

2-benzyl-4H-oxazol-5-one (2.10): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.26-7.40 (5H, m), 4.18 (2H, s), 3.79 (2H, s); ^{13}C NMR (125 MHz) ($CDCl_3$): 180.1, 162.2, 133.4, 129.8, 128.1, 126.2, 61.9, 16.5; IR (cm^{-1}): 1826.8, 1674.4.

2-benzyl-4-methyl-4H-oxazol-5-one (2.11): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.24-7.38 (5H, m), 4.19 (1H, q, J = 8.3 Hz), 3.78 (2H, s), 1.44 (3H, d, J = 8.3 Hz); IR (cm^{-1}) 1823.5, 1677.1.

2,4-dimethyl-4H-oxazol-5-one (2.12): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 4.22 (1H, q, J = 8.6 Hz), 2.23 (3H,s), 1.52 (3H, d, J = 8.6 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$): 180.0, 162.5, 60.1, 15.9, 15.1; IR (cm^{-1}) 1825.0, 1685.8.

General procedure for the preparation of N-benzoylated amino acid using Schotten-Bauman synthesis (2.16, 2.17, 2.18, 2.19, 2.20). To a solution of amino acid in ether, cooled to 0°C in a flame dried round bottomed flask, was added 2N NaOH solution in water. To this is added the benzoyl chloride (1.2 equivalents) drop wise at 0°C with constant stirring. This solution is stirred at 0°C for half an hour and then set to stir at room temperature overnight. After approximately 12 hours of stirring the ether layer is removed and the aqueous layer is acidified to pH 2. The aqueous layer is extracted with ethyl acetate. The ethyl acetate is dried with brine and then with sodium sulfate and concentrated to give the N-benzoylated amino acid.

2-benzoylamino-propionic acid (2.16): ^{1}H NMR (500 MHz) (DMSO) δ 9.90 (1H, bs), 8.59 (1H, d, J = 11 Hz), 7.89 (2H, d, J = 7.2 Hz), 7.26-7.55 (3H, m), 4.41 (1H, m), 1.37 (3H, s); IR (cm^{-1}) 3344.5.9, 1730.0, 1661.1.

2-(4-methoxy-benzoylamino)-propionic acid (2.17): ^{1}H NMR (500MHz) (DMSO) δ 12.46 (1H, bs), 8.42 (1H, d, J = 10.2), 7.82 (2H, d, J = 7.4 Hz), 6.98 (2H, d, J = 7.4 Hz), 4.35-4.41 (1H, m), 3.80 (3H, s), 1.37 (3H, d, J = 8.1 Hz); ^{13}C NMR (125 MHz) (DMSO): 175.1, 166.2, 132.0, 129.9, 126.3, 113.8, 56.0, 49.5, 17.9; IR (cm^{-1}) 3309.9, 1700.9, 1651.1.

2-benzoylamino-3-phenyl-propionic acid (2.18): ^{1}H NMR (500 MHz) (DMSO) δ 8.68 (1H, d, *J* = 10.5 Hz), 7.81 (2H, d, *J* = 7.0 Hz), 7.41-7.52 (3H, m), 7.23-7.39 (5H, m), 4.44-4.60 (1H, m), 2.99-3.21 (2H, m); IR (cm^{-1}) 3292.0, 1716.0, 1668.1.

2-benzoylamino-3-methyl-butyric acid (2.19): ^{1}H NMR (500 MHz) (DMSO) δ 8.38 (2H, d, *J* = 9.2 Hz), 7.85 (2H, d, *J* = 6.8 Hz), 7.24-7.50 (3H, m), 4.22-4.31 (1H, m), 3.32 (1H, bs), 2.03-2.20 (1H, m), 0.89-1.04 (6H, m); IR (cm^{-1}) 3339.9, 1711.8, 1676.3.

benzoylamino-phenyl-acetic acid (2.20): ^{1}H NMR (500 MHz) (DMSO) δ 9.00 (2H, d, *J* = 9.0 Hz), 7.89 (2H, d, *J* = 7.2 Hz), 7.22-7.58 (8H, m), 5.58 (1H, d, *J* = 9.0 Hz), 3.22 (1H, bs); IR (cm^{-1}) 3219.6, 1730.1 1667.9.

Preparation of N-acetylated amino acids (2.25, 2.26, 2.27). A solution of the amino acid ester.HCl in dry dichloromethane is cooled to 0°C and to this is added dry triethyl amine (3 equivalents) drop wise. This is stirred for half an hour at 0°C and then to this is added the acid chloride (1.2 equivalents) drop wise at 0°C. This is stirred overnight. After approximately 12 hours the dichloromethane solution is extracted several times with sodium bicarbonate solution. The dichloromethane layer is then separated dried with brine and then sodium sulfate and concentrated.

The crude product of the above reaction is used in the next step where it is treated with 2N sodium hydroxide and alcohol and stirred at room temperature overnight. After approximately 12 hours the alcohol is removed under vacuum. The mixture is extracted with ether to remove impurities. The aqueous layer is acidified to pH 2 and the acid is extracted in ethyl acetate. The ethyl acetate is dried with brine and sodium sulfate and then concentrated under vacuum.

Phenylacetylamino-acetic acid (2.25): ^{1}H NMR (500 MHz) (DMSO) δ 8.36 (1H, t, J = 9.2 Hz), 7.23-7.40 (5H, m), 3.76 (2H, d, J = 9.2 Hz), 3.56 (1H, s), 3.42 (2H, s); IR (cm^{-1}) 3311.2, 1727.9, 1656.3.

2-phenylacetylamino-propionic acid (2.26): ^{1}H NMR (500 MHz) (DMSO) δ 8.39 (1H, d, J = 9.6 Hz), 7.12-7.39 (5H, m), 4.03-4.11 (1H, m), 3.38 (2H, s), 3.37 (1H, s), 1.21 (3H, d, J = 8.0 Hz); IR (cm^{-1}) 3299.9, 1725.0, 1658.1.

2-acetylamino-propionic acid (2.27): ^{1}H NMR (500 MHz) (DMSO) δ 8.34 (1H, d, J = 8.1 Hz), 4.19-4.24 (1H, m), 3.81 (1H, s), 3.68 (3H, s), 1.32 (3H, d, J = 8.2 Hz).

General procedure for the synthesis of oxazoles: In the general procedure followed for this reaction, the solvent was chosen depending on the R^3 group. Dry benzene (R^3=H) or dry toluene for R^3=CH_3 was used as the solvent. Alternatively, 1,2-dichloroethane was used as solvent with a stoichiometric quantity of the aromatic substrate. A suspension of $AlCl_3$ (3 equivalents) in either benzene or toluene was prepared. To this the oxazol-5-one was added dropwise at 0°C. This solution was stirred at 0°C for half an hour and then at room temperature overnight. After approximately 12 hours of stirring triflic acid (TfOH) (10 equivalents) was added at -78°C. This solution is stirred at -78°C for an hour and the solution is stirred at room temperature for two days. The reaction mixture is treated with an ice-cold water and subsequently washed with sodium bicarbonate. The organic layer is separated and dried over sodium sulfate and concentrated in vacuo. The crude compound was then purified using column chromatography.

2,5-diphenyl-oxazole (1.18): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.06 (2H, d, *J* = 7.4 Hz), 7.66 (2H, d, *J* = 7.6 Hz), 7.36-7.44 (6H, m), 7.28 (1H, t, *J* =7.4 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 160.8, 145.7, 135.9, 129.1, 129.0, 128.7, 128.3, 127.7, 125.4, 126.5, 123.7. MS (EI) m/e 221.0 (100.0) (M^+). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.45; H, 4.98; N, 6.33. Found: C, 81.23; H, 4.41; N, 6.25. IR (cm^{-1}) 2924.46, 1491.16, 1444.87, 1134.29. Melting Point 70 -71°C.

2-benzyl-5-phenyl-oxazole (2.29): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.02 (2H, d, *J* = 7.4 Hz), 7.57 (1H, *J* = 7.2 Hz), 7.47 (2H, t, *J* = 7.2 Hz), 7.34 (2H, t, *J* = 7.0 Hz), 7.26-7.30 (4H, m), 4.30 (2H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 188.9, 136.6, 134.5, 133.1, 129.4, 128.7, 128.6, 128.5, 126.9, 45.4. MS (EI) m/e 235.0 (89.6) (M^+). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.96. Found: C, 81.02; H, 5.58; N, 5.82. IR (cm^{-1}) 2920.61, 1686.30, 1448.80, 1337.23, 1075.23. Melting point 50 -52°C.

2-methyl-5-phenyl-oxazole (2.30): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 7.58 (2H, d, *J* = 7.4 Hz), 7.38 (2H, t, *J* = 7.4 Hz), 7.28 (1H, t, *J* = 7.4 Hz), 7.18 (1H, s), 2.50 (3H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 161.2, 151.3, 129.1, 128.5, 128.3, 124.2, 122.1, 14.3. MS (EI) m/e 159.0 (100.0) (M^+). Anal. Calcd for $C_{10}H_9ON$: C, 75.47; H, 5.66; N, 8.81. Found: C, 71.56; H, 4.02; N, 10.31. IR (cm^{-1}) 2924.90, 1653.52, 1559.26, 1485.45, 1130.73. Melting Point 57 -59°C.

4-methyl-2,5-diphenyl-oxazole (2.31): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.09 (2H, d, *J* = 7.4 Hz), 7.69 (2H, d, *J* = 7.7 Hz), 7.42-7.49 (5H, m), 7.33 (1H, t, *J* = 7.4 Hz), 2.49 (3H,

s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 159.8, 145.6, 133.9, 131.0, 129.3, 128.9, 128.8, 127.7, 127.5, 126.3, 125.4, 33.9. MS (EI) m/e 235.1 (100.0) (M^+). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.95. Found: C, 81.41; H, 5.20; N, 5.95. IR (cm^{-1}) 2930.00, 1597.26, 1485.38, 1448.73, 1075.00. Melting Point 78 -80°C.

4-benzyl-2,5-diphenyl-oxazole (2.32): ^1H NMR (300 MHz) ($CDCl_3$) δ 8.11 (2H, d, J = 7 Hz), 7.66 (2H, d, J = 7.2 Hz), 7.40-7.48 (5H, m), 7.28-7.36 (5H, m), 7.21 (1H, s), 4.21 (2H, s); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 160.1, 146.8, 138.8, 136.0, 132.5, 130.5, 129.1, 129.0, 128.9, 128.7, 128.3, 127.7, 126.7, 126.6, 125.9, 33.4. MS (EI) m/e 310.8 (100.0) (M^+). Anal. Calcd for $C_{22}H_{17}NO$: C, 84.89; H, 5.47; N, 4.50. Found: C, 84.83; H, 5.66; N, 4.20. IR (cm^{-1}) 2924.64, 1599.82, 1493.79, 1447.76, 1069.98, 1026.89. Melting Point 53 -56°C.

4-isopropyl-2,5-diphenyl-oxazole (2.33): ^1H NMR (500 MHz) ($CDCl_3$) δ 8.10 (2H, d, J =7.7 Hz), 7.65 (2H, d, J = 7.6 Hz), 7.39-7.47 (5H, m), 7.32 (1H, t, J = 7.7 Hz), 3.29 (1H, hept, J = 6 Hz), 1.38 (6H, d, J = 6 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 159.7, 144.0, 143.3, 129.9, 129.4, 128.8, 128.6, 127.8, 127.6, 126.3, 125.9, 26.0, 22.0. MS (EI) m/e 263.0 (78.7) (M^+). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.13; H, 6.46; N, 5.32. Found: C, 81.83; H, 6.54; N, 5.10. IR (cm^{-1}) 2959.33, 1607.17, 1485.52, 1444.37, 1113.79, 1052.06. Melting Point 95 -98°C.

2,4,5-triphenyl-oxazole (2.34): ^1H NMR (500 MHz) ($CDCl_3$) δ 8.15 (2H, d, J = 7.2 Hz), 7.72 (2H, d, J = 7.4 Hz), 7.67 (2H, d, J = 7.2 Hz), 7.45-7.51 (3H, m), 7.31-7.42 (6H, m);

^{13}C NMR (125 MHz) ($CDCl_3$) δ 160.1, 145.5, 136.7, 132.5, 130.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.3, 126.5, 126.4. MS (EI) m/e 297.1 (35.3) (M^+). Anal. Calcd for $C_{21}H_{15}NO$: C, 84.85; H, 5.05; N, 4.71. Found: C, 84.35; H, 5.15; N, 4.72. IR (cm^{-1}) 1596.71, 1583.10, 1514.21, 1456.10, 1399.91, 1245.81, 1025.81. Melting Point 112 -113°C.

4-methyl-2-phenyl-5-p-tolyl-oxazole (2.35): ^1H NMR (500 MHz) ($CDCl_3$) δ 8.08 (2H, d, *J* = 7.2 Hz), 7.58 (2H, d, *J* = 7.4 Hz), 7.37-7.42 (3H, m), 7.28 (2H, d, *J* = 7.2 Hz), 2.48 (3H, s), 2.40 (3H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 159.5, 146.0, 137.9, 135.9, 130.5, 129.8, 129.0, 127.8, 126.7, 126.2, 125.5, 21.5, 13.5. MS (EI) m/e 249.1 (100.0) (M^+). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.03; H, 6.02; N, 5.62. Found: C, 81.02; H, 6.07; N, 5.46. IR (cm^{-1}) 2920.97, 1603.96, 1478.32, 1444.83, 1244.72, 1092.74. Melting Point 80 - 82°C.

5-(4-methoxy-phenyl)-4-methyl-2-phenyl-oxazole (2.36): ^1H NMR (500 MHz) ($CDCl_3$) δ 8.05 (2H, d, *J* = 7.2 Hz), 7.59 (2H, d, *J* = 7.4 Hz), 7.46-7.39 (3H, m), 6.98 (2H, d, *J* = 7.4 Hz), 3.83 (3H, s), 2.44 (3H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 159.1, 158.8, 145.4, 131.7, 129.9, 128.7, 127.5, 126.8, 126.0, 121.9, 114.2, 55.3, 13.3. MS (EI) m/e 265.1 (100.0) (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.98; H, 5.66; N, 5.28. Found: C,76.93; H,5.64; N,5.27. IR (cm^{-1}) 1604.98, 1549.04, 1489.24, 1286.68, 1248.10, 1174.80, 1014.69. Melting Point 88 -90°C.

5-(4-methoxy-phenyl)-2-phenyl-oxazole (2.37): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.07 (2H, d, *J* = 7.4 Hz), 7.63 (2H, d, *J* = 7.4 Hz), 7.45-7.44 (3H, m), 7.30 (1H, s), 6.95 (2H, d, *J* = 7.2 Hz), 3.82 (3H, s); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 160.0, 155.8, 130.2, 129.0, 128.8, 127.6, 126.3, 125.8, 120.9, 117.3, 110.9, 55.5. MS (EI) m/e 251.1 (100.0) (M^+). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.38; H, 5.45; N, 5.52. IR (cm^{-1}) 2920.11, 1585.70, 1566.63, 1495.12, 1446.93, 1341.64, 1253.48, 1128.55, 1023.47. Melting Point 118 -120°C.

5-biphenyl-4-yl-2-phenyl-oxazole (2.38): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.12 (2H, d, *J* = 7.4 Hz), 7.78 (2H, d, J = 7.2 Hz), 7.67 (2H, d, *J* = 7.2 Hz), 7.62 (2H, d, J = 7.4), 7.51-7.44 (6H, m), 7.36 (1H, t, J = 7.2); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 161.2, 151.1, 141.2, 140.3, 130.4, 128.9, 128.8, 127.7, 127.6, 127.4, 126.9, 126.8, 126.3, 124.6, 123.5. MS (EI) m/e 297.2 (100.0) (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 84.85; H, 5.05; N,4.71. Found: C, 84.35; H, 4.88; N, 4.44. IR (cm^{-1}) 2919.71, 1652.70, 1558.21, 1540.85, 1477.21, 1409.71, 1139.73, 1060.66. Melting Point 152 -154°C.

5-(4-bromo-phenyl)-2-phenyl-oxazole (2.39): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.07 (2H, m), 7.53 (4H, s), 7.45 (3H, m), 7.41 (1H, s); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 161.3, 150.2, 132.0, 130.4, 128.8, 127.1, 126.8, 126.2, 125.5, 123.9, 122.2. MS (EI) m/e 299.0 (81.5) (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 59.80; H, 3.32; N, 4.65. Found: C, 59.79; H, 3.04; N, 4.14. IR (cm^{-1})3059.49, 2924.46, 1684.07, 543.25, 1479.59, 1448.73, 1136.22, 1074.49. Melting Point 93 -95°C.

5-naphthalen-1-yl-2-phenyl-oxazole (2.41): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.36 (1H, d, *J* = 7.2 H), 8.15 (2H, d, *J* = 7.3 Hz), 7.90 (2H, t, *J* = 7.2 Hz), 7.81 (1H, d, *J* = 7.0 Hz), 7.61-7.47 (7H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 161.5, 150.5, 133.9, 130.4, 130.1, 129.6, 128.8, 128.7, 127.5, 127.1, 126.8, 126.4, 126.3, 126.2, 125.3, 125.2, 124.8. MS (EI) m/e 271.2 (100.0) (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 84.13; H, 4.79; N, 5.17. Found: C, 84.53; H, 4.43; N, 5.56. IR (cm^{-1}) 3055.35, 2923.57, 1658.49, 1589.06, 1481.07, 1448.28, 1133.94, 1072.23, 1024.02. Melting Point 103 -106°C.

5-naphthalen-2-yl-2-phenyl-oxazole (2.42): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 8.19 (1H, s), 8.16 (2H, d, *J* = 7.2 Hz), 7.90-7.88 (2H, m), 7.83 (1H, d, *J* = 7.1 Hz), 7.77 (1H, d, *J* = 7.2 Hz), 7.55 (1H, s), 7.53-7.47 (5H, m); ^{13}C NMR (125 MHz) ($CDCl_3$) δ 161.4, 151.4, 133.4, 133.1, 130.4, 128.8, 128.7, 128.2, 127.9, 127.4, 126.8, 126.5, 126.4, 125.3, 123.9, 122.9, 122.1. MS (EI) m/e 271.2 (100.0) (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 84.13; H, 4.79; N, 5.17. Found: C, 83.42; H, 4.25; N, 5.43. IR (cm^{-1}) 2921.64, 1698.99, 1683.56, 1652.7, 1558.21, 1540.85, 1456.00, 1128.16. Melting Point 98 -100°C.

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