THE CHEMISTRY AND USE OF PYRROLINE RING SYSTEMS IN THE SYNTHESIS OF NATURAL PRODUCTS.

by

Phillip John Persichini III

Report submitted to the Faculty of the Virginia Polytechnic Institute and State University in partial fulfillment for the degree of

MASTERS OF SCIENCE

in

Chemistry

APPROVED:

Tomas Hudlicky, Chairman

James M. Tanko

Joseph S. Merola

date

January, 31 1994

ACKNOWLEDGMENTS

I would sincerely like to thank my research director, Professor Tomas Hudlicky for his patience and guidance above and beyond topics related to chemistry. I would also like to thank the members of my committee whose guidance throughout my less than straightforward path at Virginia Tech was much appreciated. A special thanks goes to Dr. Martin Mandel and Dr. Andrew Poss for aquainting me with the theoretical and practical sides of organic chemistry enabling me to have a unique understanding of the subject which helps me immensely in pursuing me career of teaching organic chemistry. Finally, and most importantly, I would like to thank my wife, Nicole, whose patience, companionship, and understanding make this possible.

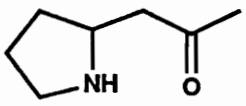
TABLE OF CONTENTS

I. INTRODUCTION

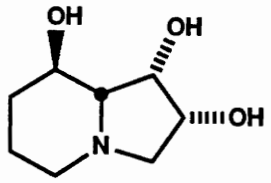
Many natural products possess within their structures pyrrolidine rings of various substitution. Norhygrine (**1**), Swainsonine **2** and (±)-Isorectronecanol **3** are just a few examples of natural products containing the pyrrolidine moiety (Scheme 1).

Most of these types of compounds belong to a class of compounds known as pyrrolizidine and indolizidine alkaloids [2,3]. These systems have been found to possess a wide variety of properties which are of biological importance[4], some of which include:

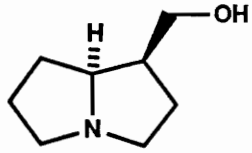
1. Potential treatment of diabetes [5].
2. Potential treatment of viral infections [6].
3. General effect on the cardiopulmonary system [7].



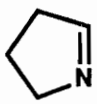
Norhygrine, 1



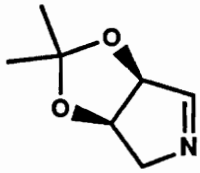
Swainsonine, 2



(±)-Isoretronecanol, 3



1-Pyrroline, 4



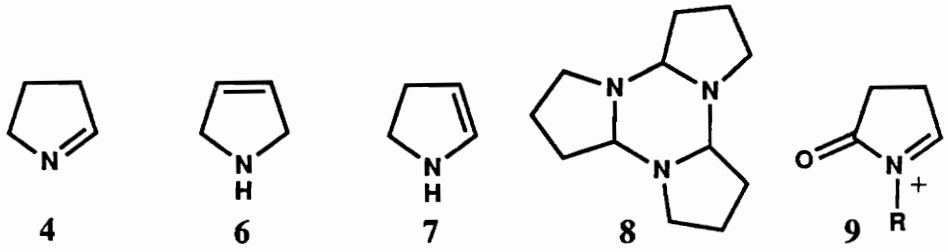
3,4-di-O-isopropylidine-1-pyrroline, 5

Scheme 1.

The most direct method to synthesize these systems involves the use of 1-pyrroline (**4**)[8]. A chiral diol functionality, which is known to enhance biological activity[9], could be incorporated into 3,4-di-*O*-isopropylidine-1-pyrroline **5** whose configuration is present in swainsonine **2**. What follows is a disscussion of methods for the synthesis and use of 1-pyrrolines, including the synthesis of the new 3,4-di-*O*-isopropylidine-1-pyrroline.

II.1. Historical Introduction

The history of pyrroline chemistry[10] began in 1901 when Knorr reported the formation of 3-pyrroline **6** by the chemical reduction of pyrrole with zinc and hydrochloric acid. 1-Pyrroline **4** was not discovered until 1936, when Schopf reported its formation from g-aminobutyraldehyde diethyl acetal upon hydrolysis at pH 5[11],but it was never isolated. It's isolation and characterization was not realized until 1948 when Schopf, utilizing a different synthetic route to 1-pyrroline that involved the N-halogenation of pyrrolidine followed by dehydrohalogenation with alcoholic potassium hydroxide gave 1-pyrroline but it rapidly polymerized to the trimer, tripyrroline **8**[12,13]. Schopf showed that the tripyrroline could be de-polymerized upon heating, with distillation[13] and thus characterized. 2-Pyrroline **7** is the enamine tautomer of the aldimine 1-pyrroline and as such is much less stable[14] (Scheme 2.).



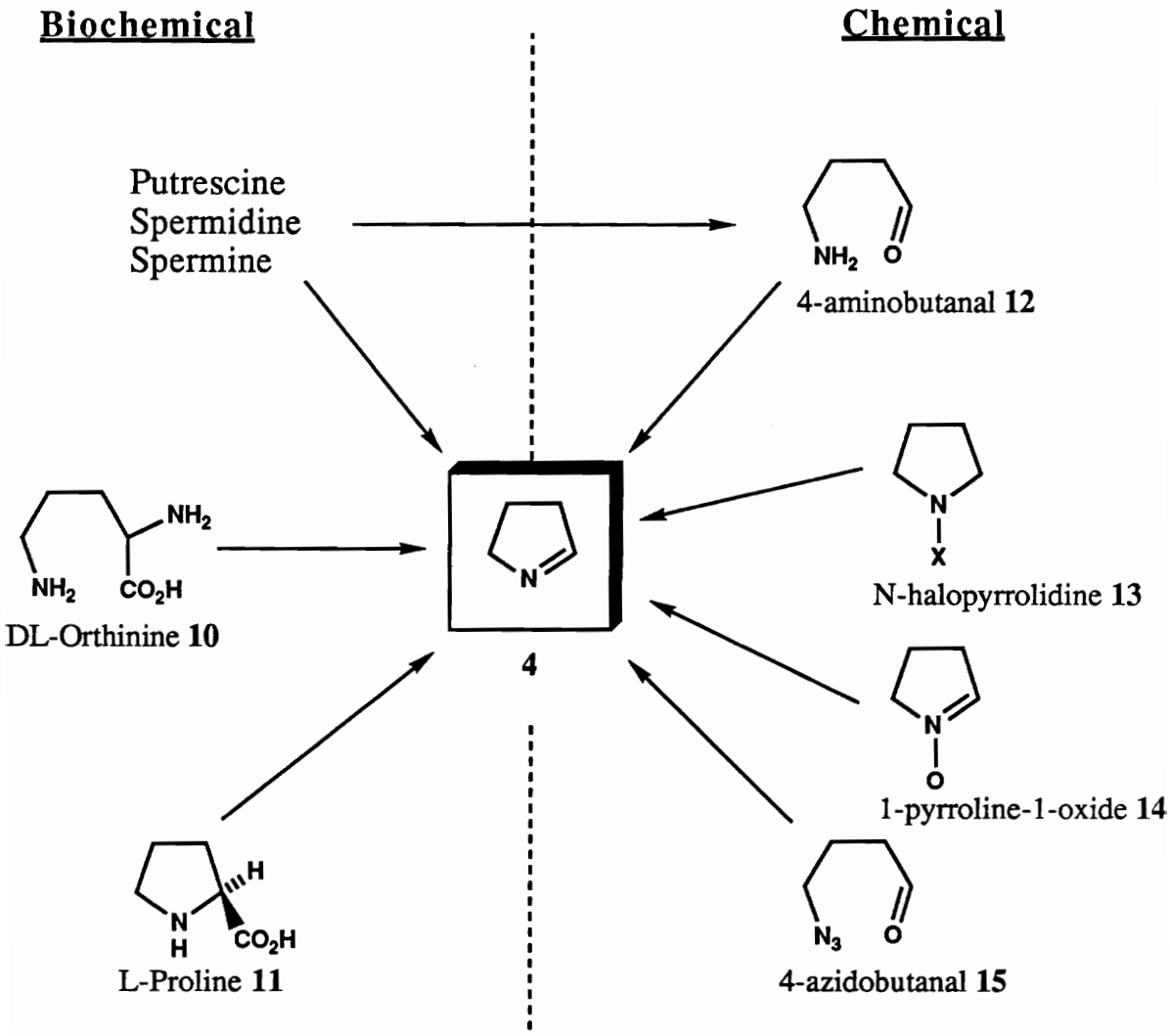
4 **6** **7** **8** **9**

Scheme 2.

To date there have been many different ways to prepare 1-pyrroline. This topic is covered in the next section. A separate section follows, that addresses reactions and reactivity of 1-pyrroline. The last section contains a brief overview of the preparation and chemistry of cyclic acyliminium compounds[15] such as 9.

II.2. Review of Methods for the Synthesis of 1-Pyrroline

The synthesis of 1-Pyrroline can be separated into two general categories, the first being biochemical and the second, chemical (Scheme 3.). These catagories will be disscussed separately along with a disscussion on each of the individual methods.

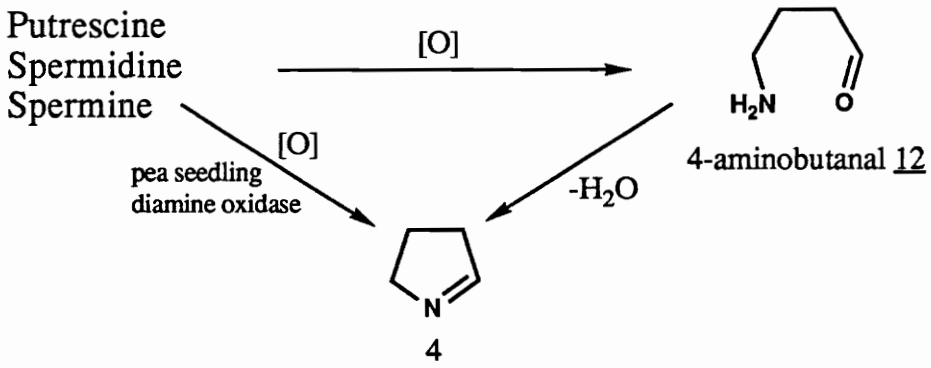


Scheme 3.

II.2.1 Biochemical

The synthesis of 1-pyrroline through biochemical means can be accomplished using two types of compounds. The first involves the biologically abundant amines putrescine, spermidine and spermine, which are believed to be vestigial male sex pheromones for our species[17]. 1-Pyrroline can be obtained by the reaction of these biological amines by oxidation (probably with diamine oxidase)[18] to 4-aminobutanal and then intramolecular condensation of the amine on the aldehyde with the loss of water to give 1-pyrroline.

An applicable laboratory mimic of this process involves the use of 1,4-diaminobutane (putrescine) and its oxidation with pea seedling diamine oxidase[20] and subsequent formation of 1-pyrroline as stated above (Scheme 4.).

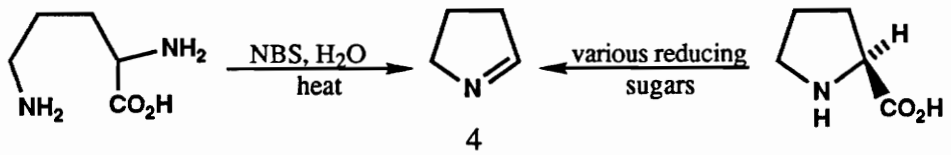


4-aminobutanal 12

4

Scheme 4.

The other types of compounds that are known to produce 1-pyrroline are amino acids. dl-Orthinine is reacted in an aqueous media with N-bromosuccinimde at elevated temperatures to give 1-pyrroline[19]. Another amino acid, L-proline, when heated with various reducing sugars forms 1-pyrroline in low yield (Scheme 5.).



DL-orthinine 10

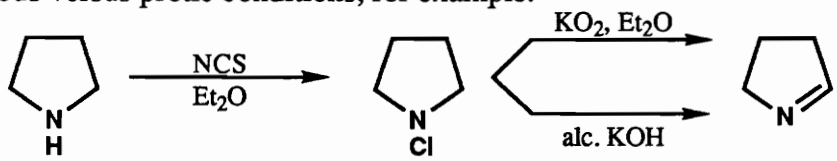
4

L-proline 11

Scheme 5.

II.2.2 Chemical

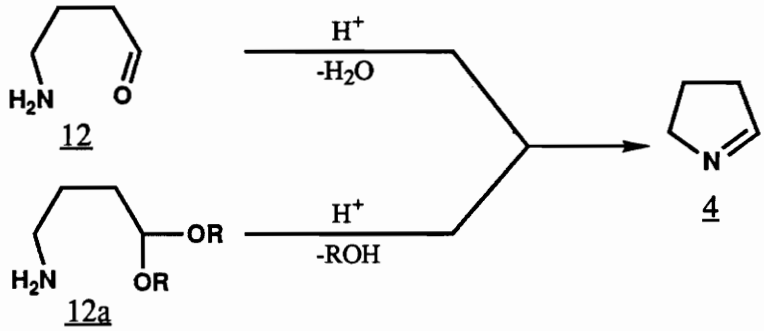
By far, the most widely used methods of preparing 1-pyrroline(s) involves the chemical manipulation of readily available precursors.The first and most popular involves the dehydrohalogenation of N-halopyrrolidines. The N-halopyrrolidines themselves are easily prepared from pyrrolidine **13a** usually by reaction with N-chlorosuccinimide, or hypochlorite. The dehydrohalogenation of the N-halopyrrolidine **13** can take place in two ways. The first involves the exposure to ethanolic potassium hydroxide[13]; the second is a reaction with potassium superoxide[21] (Scheme 6.). The choice of a particular procedure depends on the subsequent reactions to be performed on the 1-pyrroline[21], such as anhydrous versus protic conditions, for example.



13a 13 4

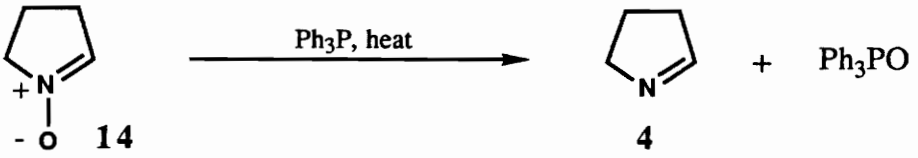
Scheme 6.

The second method involves the acid condensation of 4-aminobutanal **12** or more commomly the protected acetal **12a** form of this compound[8]. This process proceeds with the loss of water (or the corresponding alcohol) from the acetal, to give 1-pyrroline (Scheme 7.). This is a very convienient laboratory method for the preparation of 1-pyrroline, but the cost of the amino acetals is significantly more than that of pyrrolidine.



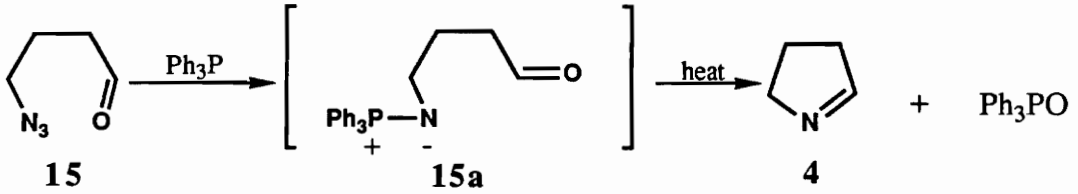
Scheme 7.

The third method, which needs only to be mentioned in passing due to its scarcity of application in the literature, involves the oxygen transfer of 1-pyrroline-1-oxide **14** to triphenylphosphine[16] yielding 1-pyrroline and triphenylphosphine oxide (Scheme 8.).



Scheme 8.

The last and most recent method involves a variation of the Staudinger reaction, intramolecular aza-Wittig reaction[22] (Scheme 9.). This reaction takes place when 4-azido-butyraldehyde **15** is reacted with triphenylphosphine yielding the intermediate salt **15a** which collapses upon heating to form 1-pyrroline.



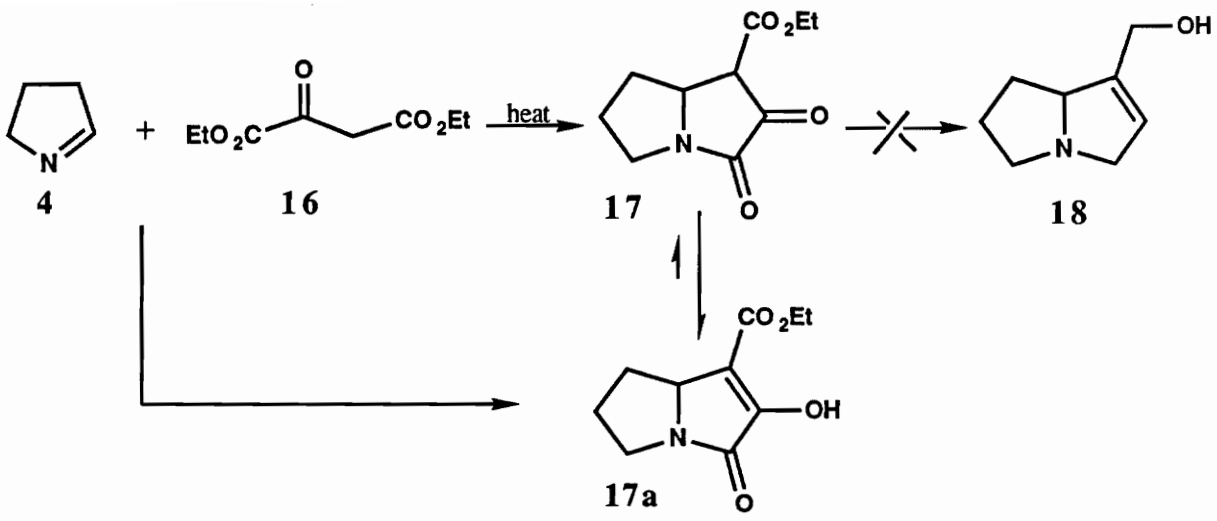
Scheme 9.

II.3. Review of Reactions of 1-Pyrroline

Once the reactive 1-pyrroline has been formed most of the elaborations involving that ring have led to its incorporation into various alkaloid systems. Since the alkaloids have been classical targets in organic synthesis for many years, this overview will limit the discussion to the reactions of 1-pyrroline that have led to different types of alkaloids, employing different types of methods.

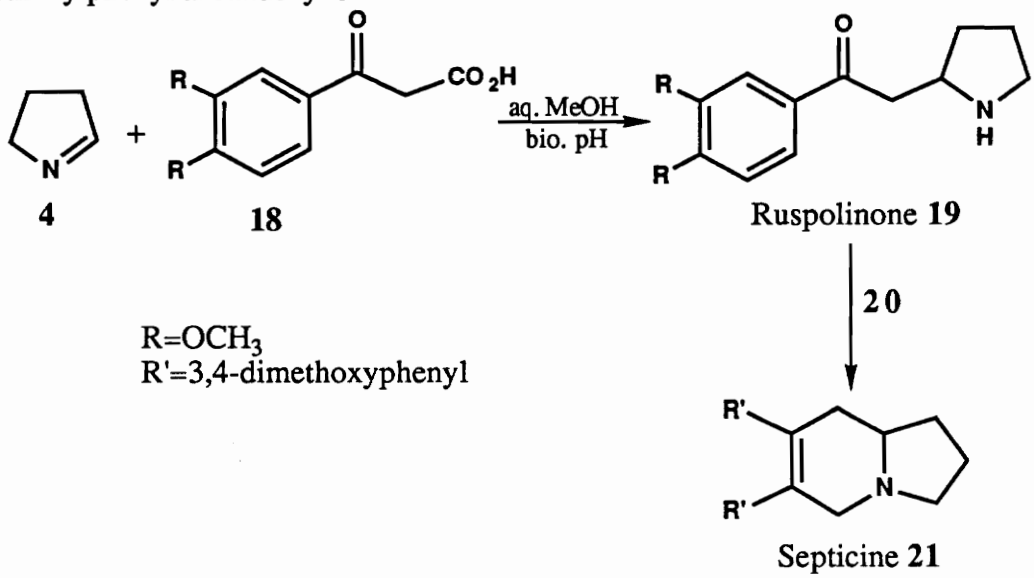
II.3.1 Condensations with enols and/or enol ethers

One of the first uses of 1-pyrroline in the incorporation into pyrrolizidine structure is due to the efforts of Goldschmidt[8]. He condensed 1-pyrroline **4** with ethyl oxosuccinate **16** by refluxing a solution of ether/ethanol and 1-pyrroline (freshly prepared by the dehydrohalogenation of N-chloropyrrolidine **13** using alcoholic potassium hydroxide) with a benzene solution of **16**, to give 1-carboethoxy-2,3-dioxopyrrolizidine **17**. Goldschmidt envisioned that a stepwise reduction and dehydration would produce *dl*-supinidine **18**, but was unsuccessful. Rapoport[23] later showed that the more stable form of **17**, **17a** was formed, and was unable to isolate **17** by equilibration methods (Scheme 10.).



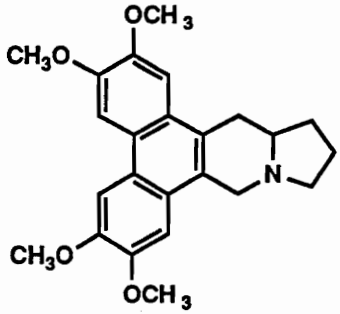
Scheme 10.

Herbert [24] updated this type of condensation method and biogenetically patterned the synthesis of ruspolinone **19** from the reaction of 1-pyrroline **4** with benzoyl acetic acid **18** in aqueous methanol at biological pH (Scheme 11.). With ruspolinone **19** in hand Herbert further elaborated this aklaloid into the septicine alkaloid **21**, by reaction with 3,4-dimethoxy phenyl acetaldehyde **20**.

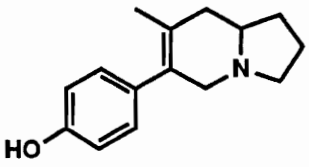


Scheme 11.

By this same condensation methodology, the following alkaloids have been prepared: tylophorine **22** and ipalbidine **23**, (Scheme 12.) along with similar alkaloids differing only in the substitution on the aromatic ring [26,27,28].



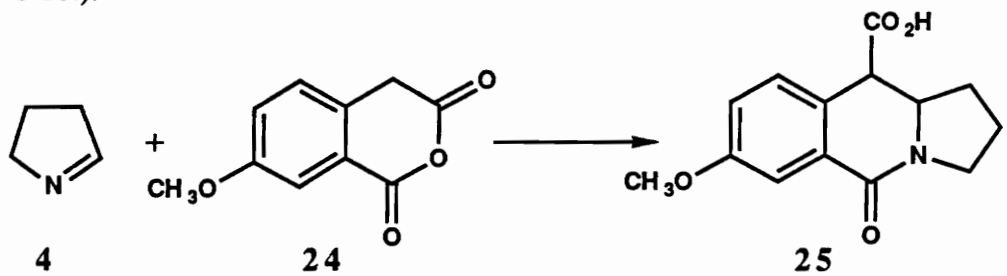
Tylophorine **22**



Ipalbidine **23**

Scheme 12.

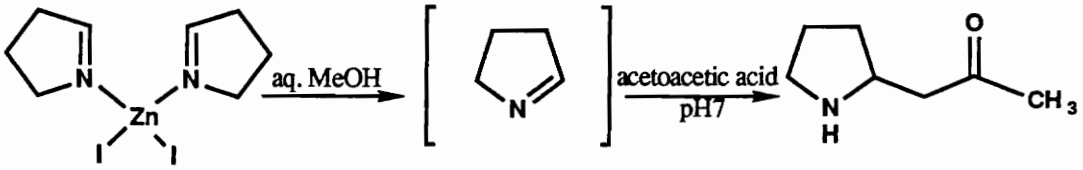
Other natural product have also been synthesized employing this methodology. Smith[25] condensed 7-methoxy-1,3-isochromanedione **24** with 1-pyrroline **4**, (Scheme 13.) to obtain the deazaanthramycin derivative, hexahydropyrrolo[1,2-b]isoquinolone **25**. Rapoport[23] also has elaborated compounds similar to **17a** to B-lactam derivatives (See Scheme 10.).



4 **24** **25**

Scheme 13.

The most recent use of these types of enol condensations with 1-pyrroline involves the use of a stabilized form of 1-pyrroline by Robins[8] . Pyrroline **4** is complexed with zinc iodide to give a compound that can be kept in a bottle without the subsequent trimerization that usually plagues 1-pyrroline. This zinc complex **26** was subjected to the same chemistry previously discussed (See Scheme 11 and references therein). To show its utility norhygrine **27**, and ruspolinone **21** were prepared.



26 **4** Norhygrine **27**

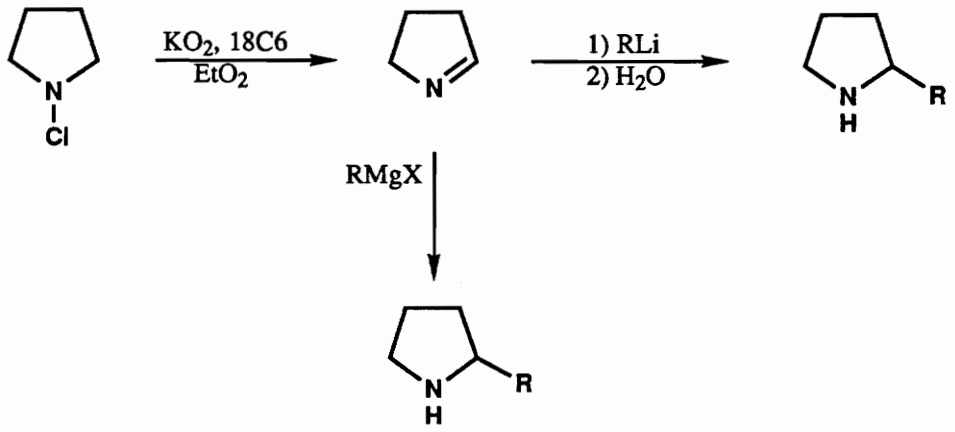
Scheme 14.

The zinc complex itself was prepared in Robins laboratory by the acid catalyzed condensation of 4-aminobutyraldehyde diethyl acetal in a diethyl ether/water mixture. The reaction was basified with potassium carbonate at 5^{o}C, the organic layer was separated, dried (Na_2SO_4), and stirred at 5^{o}C with zinc iodide. The complex **26** percipitated out of solution and collected by filtration.

II.3.2. Addition Reactions of Organometallic Reagents

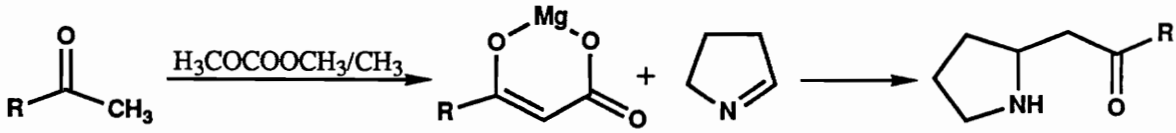
The original use of an organometallic reagent in conjunction with 1-pyrroline dates to 1951 when Maginnity[29] used the Grignard reagent methyl magnesium iodide as an analytical probe for distinguishing between such 1-pyrroline and 2-pyrroline isomers. This analytical method involved the use of a special apparatus named the Zerevitinov[30] apparatus which was designed to measure both the amount of methane generated and the total amount of Grignard reagent consumed in the reaction[31]. Maginnity in his further work[32] attempted to determine the exact nature of the compounds resulting from Grignard reactions that take place with compounds like 1-pyrroline, but he was unsuccessful.

Scully later showed that when he prepared 1-pyrroline via the reaction of potassium superoxide with the N-chloramine precursor in aprotic conditions the subsequent reaction with Grignard reagent was unsuccessful[21]. In a similar manner, he also showed the successful addition of organolithium reagents to cyclic imines such as 1-pyrroline, thus providing a new approach to the regioselective alkylation of pyrrolidine[21] (Scheme 15.).



Scheme 15.

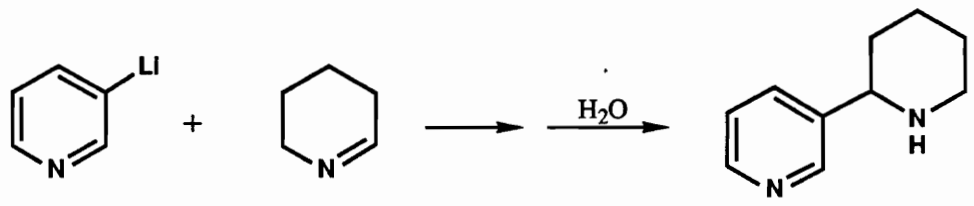
Schopf and coworkers had explored the reaction of B-keto-acids under "physiological" conditions (See disscussion of similar work in Section **II.3.1.**) to establish pathways of plant alkaloid biogenesis[33]. Synthetic application of this reaction, however, was limited because of the low water solubility of many B-keto-acids[34] and the requirement to maintain a pH below 11 to avoid self-condensation of reactants. These limitations were overcome when Grisar, in 1974 developed a general reaction that is based on the addition of internal enolate magnesium salts of B-keto-acids **6** in dimethylformamide. The salts were readily obtained from methyl ketones **5** and magnesium methyl carbonate,[35] reaction with 1-pyrroline[36] (Scheme 17.).



5 **6** Norhygrine **7**

Scheme 17.

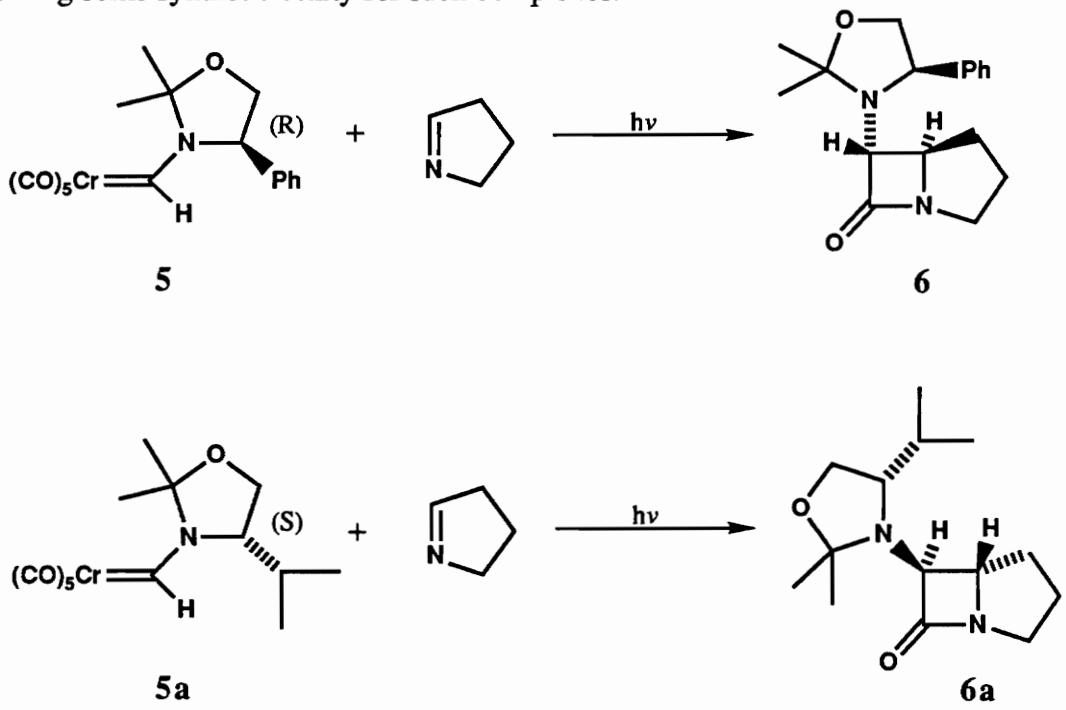
One of the more interesting applications of this reaction involves the synthesis of the tobacco alkaloid *dl*-anabasine **4**[21]. Although it does not employ the use of 1-pyrroline the synthetic utility of this reaction is nicely demonstrated with its six-membered counterpart **3** in reaction with 3-pyridyllithium **2** (Scheme 16.).



2 **3** **4**

Scheme 16.

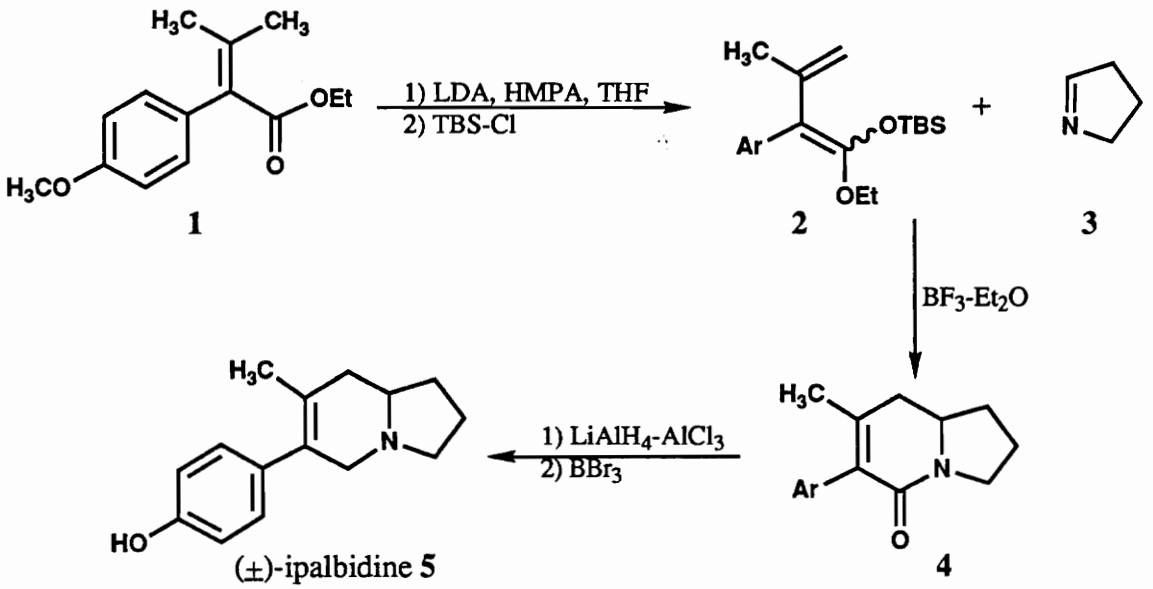
The most recent use of organometallic reagents in the reaction with 1-pyrroline is demonstrated in the work of Hegedus[37,38]. He used optically active chromium complexes utilizing (S)-valine **5a** and (R)-phenyl glycine **5** derived chiral auxillaries and subjected them to photolysis in the presence of 1-pyrroline (Scheme 18.). Optically active B-lactams **6** and **6a** were produced only in their trans form when cyclic imines such as 1-pyrolline were employed. These reactions also proceeded with $\geq 97\%$ diastereomeric excess showing some synthetic utility for such complexes.



Scheme 18.

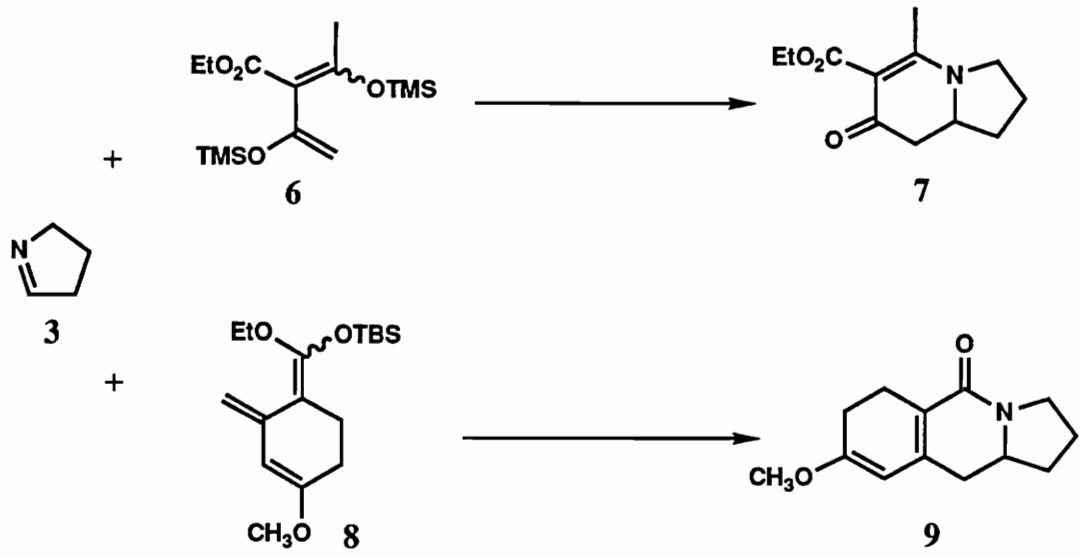
II.3.3. Lewis Acid Activation of 1-Pyrroline

Surpisingly the only example of the use of 1-pyrroline in a Lewis-acid meadiated reaction has been with highly nucleophilic dienes. In 1986 Danishefsky reported the synthesis of (±)-ipalbidine **5** [39] (Scheme 19.) from the reaction of the known a-aryl-B-methylcrotonate derivative **1** with lithium diisopropylamide in THF in the presence of HMPA, followed by the quenching of the resultant ester enolate with t-butyldimethylsilyl chloride affording the silyl ketene acteal **2**. The reaction of this silyl ketene acetal **2** 1-pyrroline **3** in methylene chloride under the influence of BF_3-etherate with yields the lactam **4** and with subsequent reduction using $LiAlH_4$-$AlCl_3$, and demethylation with boron tribromide gives the hexahydroindolizidine (±)-ipalbidine **5** in a 78% yield from the crotonate derivative **1**.



Scheme 19.

Danishefsky has also shown the utility of this reaction with two other similar silyl ketene acetals[40] (Scheme 20.). The use of the so-called "Danishefsky diene" **6** gave rise to the vinylogous lactam **7**, and similarly the reaction of silyl ketene acetal **8** with 1-pyrroline **3** to give lactam **9**.

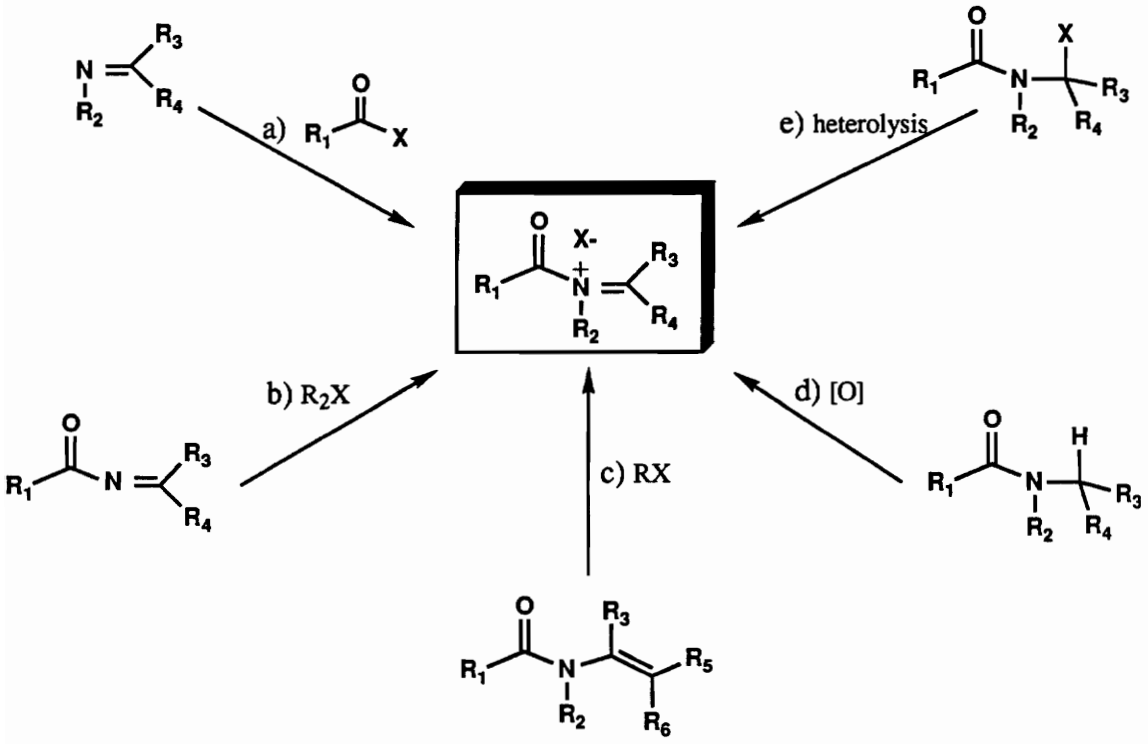


Scheme 20.

II.4. Overview of Pertinent N-Acyliminium Derivative Chemistry

II.4.1. Generation of N-Acyliminium Ions and Synthesis of Their Precusors

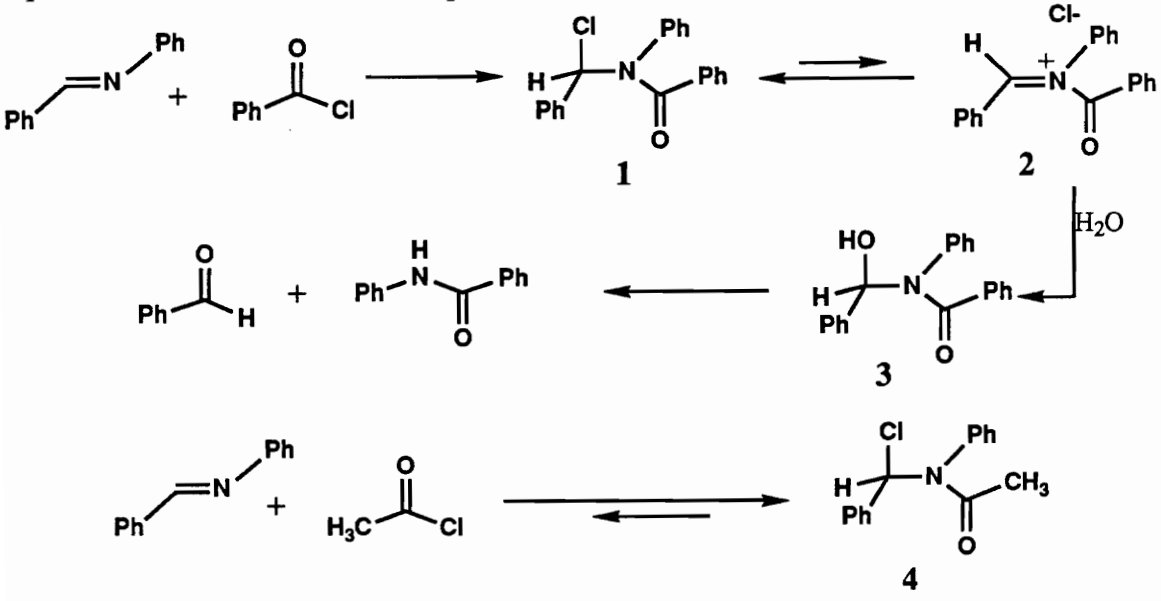
In 1965 Zaugg and Martin provided a detailed account on the generation of N-acyliminium ions and the synthesis of their precursors[41]. In subsequent years some of these methods have been refined and new ones have been added. In this overview an attempt is made to give a brief review of the methods that exist to arrive at N-acyliminium compounds. There are five major synthetic pathways to N-acyliminium ions as shown in Scheme 21. Each will be discussed and, when appropriate, synthesis of precursors and synthetic applications will also be presented.



Scheme 21.

II.4.1a. N-Acylation of Imines

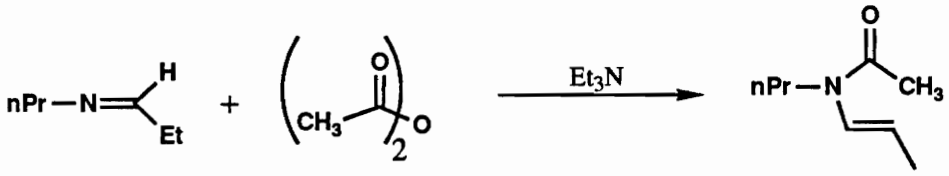
Imines are readily available by the condensation of aldehydes or ketones with primary amines[42]. Their acylation with reactive carboxylic acid derivatives like acid chlorides or anhydrides was first reported in 1914, when James and Judd reacted benzaniline with benzoyl chloride[43]. The crystalline product **2** was readily hydrolized in water to give benzaldehyde and benanilide. The lability of the carbon-chlorine bond is responsible for the formation of shows the N-acyliminium ion in this system. The structure, however, is best represented by the covalent structure **1**. The acylation of imines has been shown to be an equilibrium[44], which shifts to the side of the adduct **1** when the temperature is lowered. Using ^1H NMR it was determined that in the reaction between equimolar amounts of benzaniline and acetyl chloride at 40^oC, 95% of the acetyl chloride had been converted to the adduct **4**. At 65^oC, the corresponding proportion was reduced to 90% (Scheme22.). The position of the equilibrium will naturally be highly dependent on the structure of the imine and the reactive acid derivative, but no systematic study has been reported to date that illustrates this point.



Scheme 22.

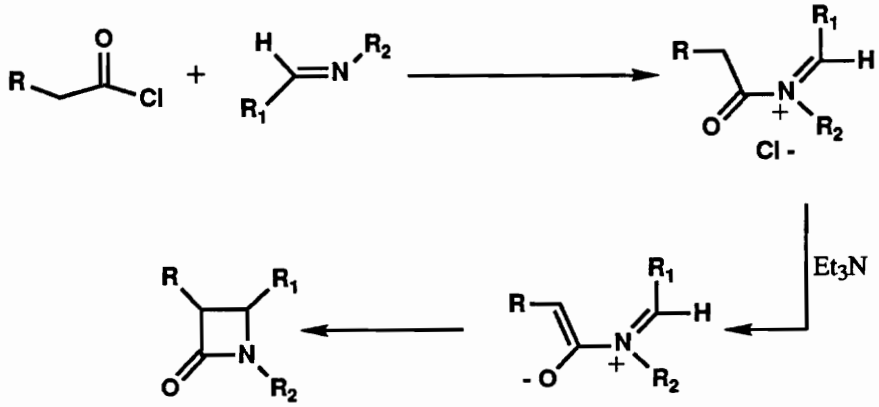
The fate of the adduct, which is highly reactive, but has been isolated in some cases[45], is heavily dependent on the structure of the starting imine. Some of the more important applications are shown below, but further discussion is beyond the scope of this overview.

Enamide formation (Scheme 23.):



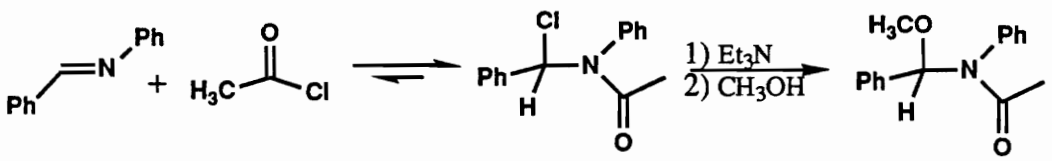
Scheme 23.

Synthesis of B-lactams (Scheme 24.):



Scheme 24.

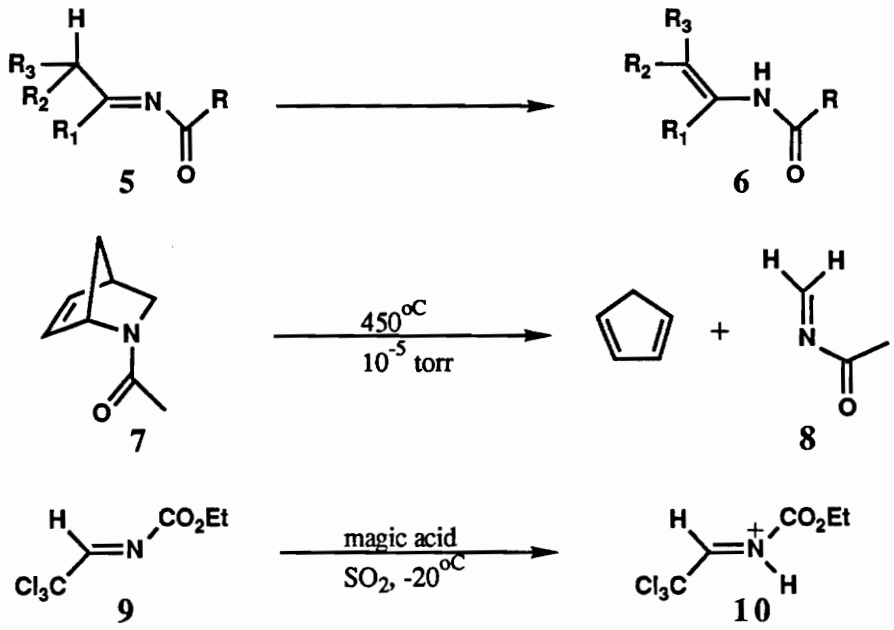
Trapping reactions with carbon and heteroatom nucleophiles (Scheme 25.):



Scheme 25.

II.4.1b. N-Protonation of N-Acylimines

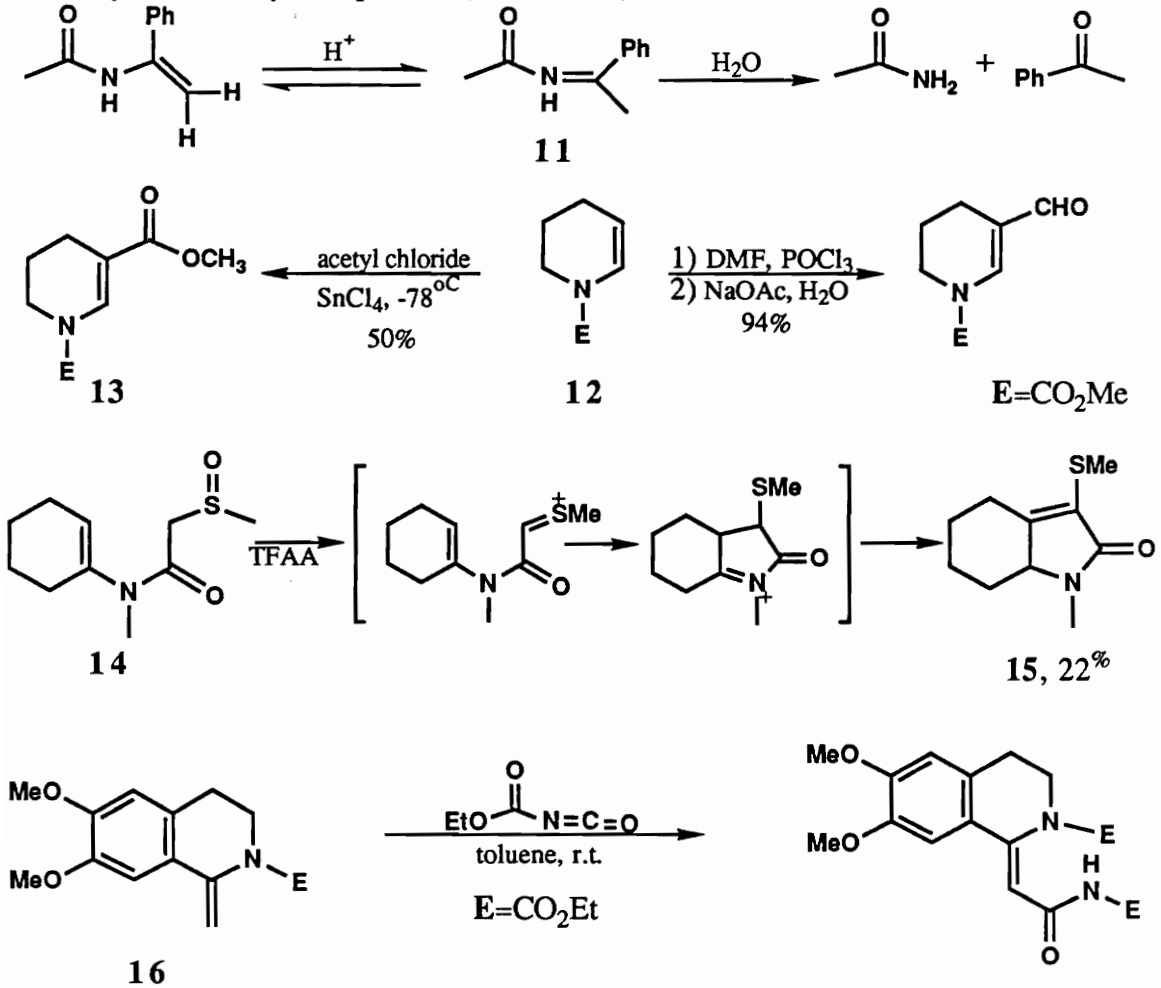
This method for the preparation of N-acyliminium ions is more of a mechanistic than of synthetic interest since N-acylimines **5** themselves are rather unstable. When possible, they tautomerize rapidly into the corresponding enamides **6**. Only those acylimines bearing, on the imino carbon atom, electron withdrawing substituents or tetra substituted groups have been isolated[46,47]. Recently Lasne succeeded in preparing the parent compound **8** via flash vacuum pyrrolysis of **7**. N-Methylene acetamide slowly decomposes in solution even at -100^{o}C while in its pure state polymerization occurs at -150^{o}C. Krow[49] studied the protonation of acylimines **9** with fluorosulfonic acid-antimony pentafluoride and inferred from the ^{1}H NMR spectrum that the N-acyliminium ion **10** form, has the trans configuration (Scheme 26.).



Scheme 26.

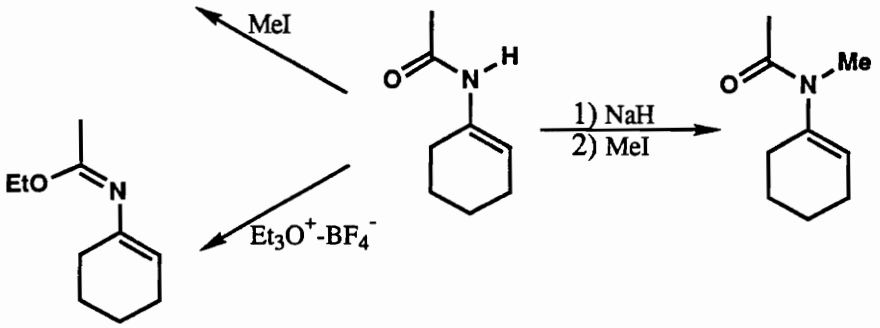
II.4.1c. Electrophilic Additions to Enamides

Enamides are stable compounds under neutral or basic conditions. With Bronsted acids they participate in the rate determining protonation at carbon, which leads to hydrolysis in aqueous medium[50]. The intermediate after protonation is the N-acyliminium ion **11**. Other electrophilic addition reactions to enamides have recently been reported by several groups[51,52,53]. Friedel-Crafts type reaction of **12** with acetyl chloride in the presence of tin tetrachloride affords **13** in excellent yield. Enamide addition to the sulfonium salt obtained from **14** by a Pummerer reaction, gives, after proton loss, and olefin isomerization **15**. Reaction of enecarbamate **16** with ethoxycarbonyl isocyanate smoothly leads to acylated product (Scheme 27.).



Scheme 27.

In all of these reactions, an N-acyliminium ion acts as an intermediate which subsequently losses a proton with formation of a new enamide product. The main reason is that amide protonation and acylation reactions are reversible, which is generally not the case with amide alkylation (Scheme 28.).

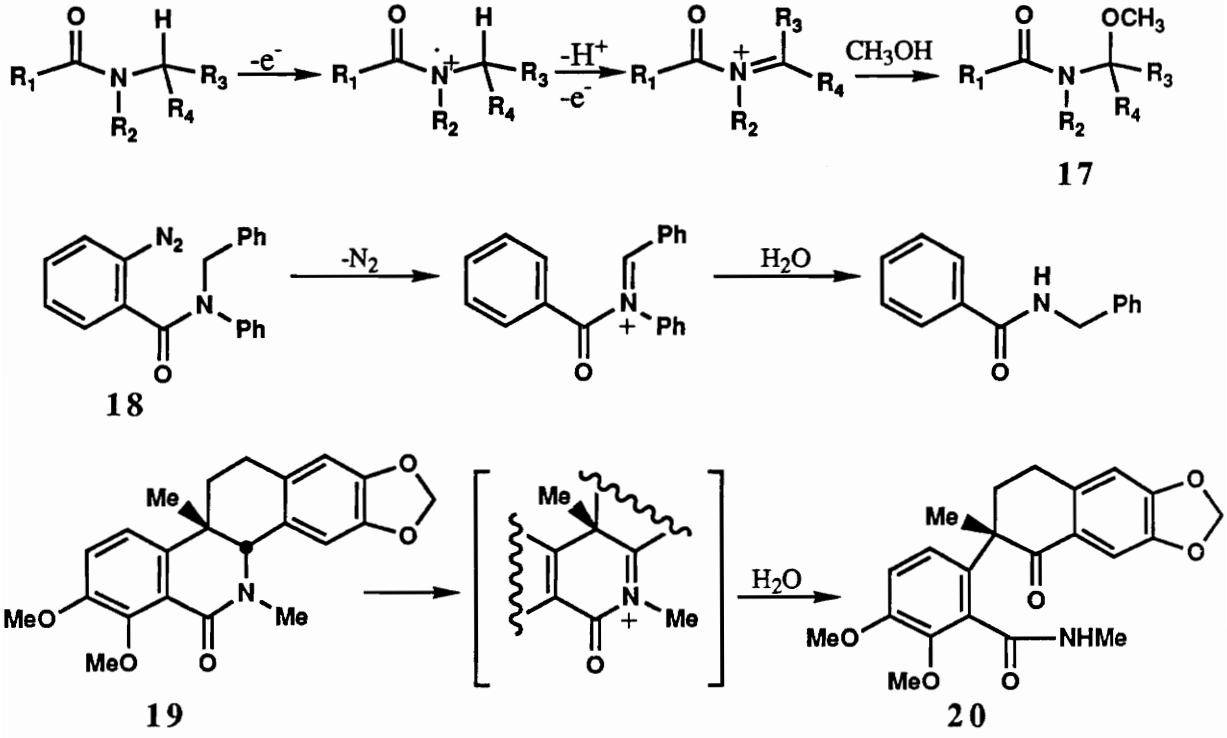


Scheme 28.

II.4.1d. Oxidation of Amides

Removal of a hydride from the a-carbon of an amide formally leads to an N-acyliminium ion. The most common way to effect this transformation is the electrochemical method, pioneered primarily by Shono[54]. The mechanism involves initial removal of an electron from the lone pair on nitrogen followed by a proton and another electron. This electrochemical oxidation is typically done in the presence of a nucleophile, mostly methanol (Scheme 29.). This is done so that the N-acyliminium ion is trapped as soon as it is generated to give a-methoxyamides **17**. There are a few reports of other methods for the generation of N-acyliminium ion from amides by formal hydride abstraction. Thermal decomposition of diazonium ion **18** produces, although not cleanly, benzaldehyde and N-benzylamide following hydrolysis of the N-acyliminium ion [55]. Cyclic amide **19** gives on oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) ketone **20** from hydrolysis.

Mechanism:

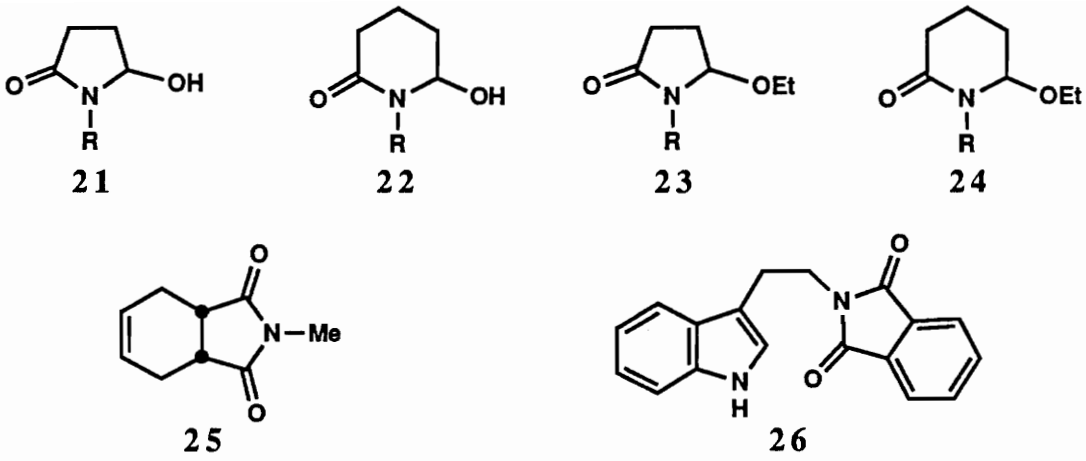


Scheme 29.

II.4.1e. Heterolysis of Amides, Bearing a Leaving Group X on the a-Carbon

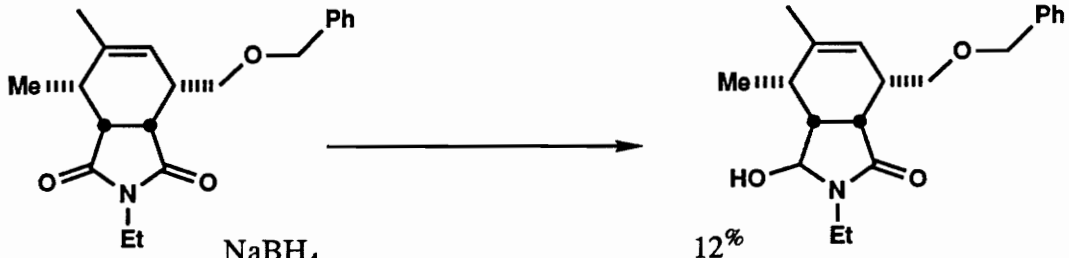
Heterolysis of a-substituted amides is the most often employed method for the generation of synthetically useful N-acyliminium ions. Approximately 90% of the examples contain an oxgen substituent. There are many methods of preparation for these heterolysis precursors . The many types of heterolysis include the addition of oxygen nucleophiles to N-acyliminium ions or N-acyl imines (See Schemes 26, 27 and references cited therein), reaction of primary or secondary amides with aldehydes and ketones[57,58] ,reduction of N-acylimidates[59], Grignard addition to cyclic imides[60], some very elegant work has employed these methods including R.B. Woodward who synthesized isolongistrobine[57] by one of the prementioned methods.

Speckamp and coworkers have made N-acyliminium compounds useful to the synthetic community by refining the partial reduction of cyclic imides[61-63]. They have developed this partial to a high yielding procedure by using excess sodium borohydride (NaBH4) in ethanol. During the reaction a dilute solution of hydrochloric acid in ethanol is slowly added in order to stop the reaction medium from becoming to basic, causing ring opening of the product. Ring opening is furthermore prevented by conducting the reduction of succinimides at temperatures below 5^{o}C and reduction of glutarimides below -10^{o}C. Inthis way hydroxy lactams **21** and **22** (R=H, alkyl and aryl) can be obtained from succinimide and glutarimide, respectively, in excellent yields. The corressponding ethoxy lactams **23** and **24** are isolated, if the reaction medium is made strongly acidic prior to work-up. More complex imides such as **25** and **26** are also reduced in excellent yields to their corressponding hydroxy lactams (Scheme 30.). It has been reported that the addition of acid is not necessary for obtaining a good yield of hydroxy lactams, if the reduction is carried out at -4^{o}C in methanol as the solvent[64].



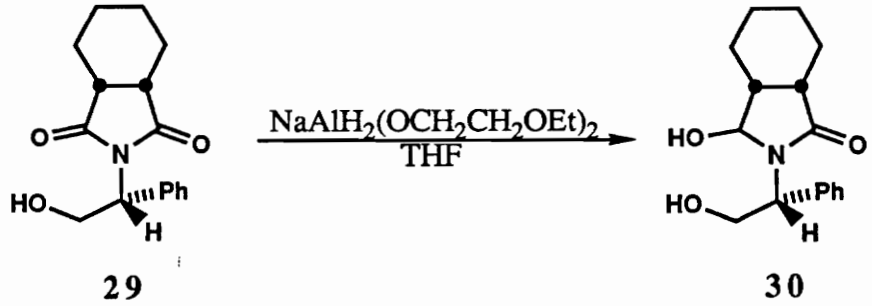
Scheme 30.

Asymmetrically substituted cyclic imides pose the problem of regiochemistry of reduction. In the reaction of geminally disubstituted succinimides it has been found that the carbonyl group ajacent to the quaternary center, the more hindered one, is preferentially reduced[63]. This phenomenon of preferential reduction of the sterically more hindered carbonyl group of succinimides bears a close resemblance to the behaviour of succinic anhydrides toward reducing agents. Various explanations have been forwarded[65] but the matter appears to be complicated and it is unlikely that one will be able to predict the regiochemical outcome of more complex imide systems. As a side note, glutarimides are preferentially reduced at the less hindered carbonyl group[66]. The use of diisobutylaluminium hydride (DIBAH) for the preferential reduction of cyclic imides was first reported by Winterfeldt[67]. The important aspect of its use is the fact that the regiochemical outcome is the opposite. Imide **27** gives 12% of one regioisomer with $NaBH_4$ and 65% using DIBAH (Scheme 31.).



Scheme 31.

A stereochemical interesting reaction is the reduction of imide **29** to **30**[68]. The best steroselectivity is attained by using an aluminium hydride reagent containing two active hydrides. Appearently, the first hydride connects tthe aluminium to the oxygen of the hydroxy group, so the reduction of the carbonyl by the second hydride occurs in an intramolecular fashion enhancing the chance of high asymmetric induction. Sodium borohydride reduction of optically active imides have also been reported by Wakabayashi and Saito[69] (Scheme 32.).



Scheme 32.

VI. REFERENCES

1. Cyclohexadiene *cis*-diols are obtained by the corresponding arenes with whole cells of Pseudomonas putida 39/D (Biotype B organism), as previously described: Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, J.J. *Biochemistry* **1970**, *9*, 1626; Gibson, D.T.; Koch, G.R.; Kallio, R.E. *Biochemistry* **1968**, *7*, 2653. P. putida strain 39/D is obtained after mutagenesis of the organism with nitrosoguanidine. The organism therefore lacks the ability to process aromatic hydrocarbons beyond the first degradative step of the metabolic pathway. Other similar organisms have been prepared by the same procedure (U.S. Patent 4,508,822 and U.S.Patent 4,927,759) and although isolated from different sources, all of them produce *cis*-diols from aromatic compounds.

2. "Naturally Occuring Pyrrolizidine Alkaloids"; Ed. A.F.M. Rizk, CRC Press, Inc., Boca Raton, Fla., U.S.A., 1990.

3. Robins, D.J. *Nat. Pdts. Rep.* **1992**, 313.

4. (a) Hohenschutz, L.D.; Bell, E.A.; Jewess, P.J.; Leworthy, D.P.; Pryce, R.J.; Arnold, E.; Clardy, J. *Phytocemistry* **1981**, *20*, 811. (b) Saul, R.; Chambers, J.P.; Molyneux, R.J.; Elbein, A.D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. (c) Fleet, G.; Fellows, L.E. in "Natural Product Isolation"; G.H. Wagman and R. Cooper, Ed.; Elsevier: Amsterdam, 1988; pp 540.

5. (a) Rhinehart, B.L.; Robinson, K.M.; Payne, A.J.; Wheatly, M.E.; Fisher, J.L.; Liu, P.; Cheng, W. *Life Sci.* **1987**, *41*, 2325. (b) Trugnan, G.; Rousset, M.; Zweibaum, A. *FEBS Lett.* **1986**, *195*, 28.

6. (a) Sunkara, P.S.; Bowlin, T.L.; Liu, P.; Sjoerdersma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206. (b) Nicols, E.J.; Manger, R.; Hakomori, S.; Herscovics, A.; Rohrschneider, L.R. *Molec. Cell. Biol.* **1985**, *5*, 3467.

7. Huxtable, R.J.; Shubat, P.J. *Pharmacol. Ther.*, **1990**, *47*, 371.

8. (a) Robins, D.J.; Baxter, G.; Melville, J.C. *Synlett* **1991**, 359. (b) Goldschmidt, B.M. *J. Org. Chem.* **1962**, *27*, 4057.

9. Cenci di Bello, I.; Fleet, G.; Namgoong, S.K.; Tadano, K. *Biochem. J.* **1989**, *259*, 895.

10. Knorr, L.; Rabbe, P. *Ber.* **1901**, *34*, 3491.

11. Schopf, C.; Oechler, F. *Ann.* **1936**, *1*, 523.

12. Schopf, C.; Arnold, W. *Ann.* **1948**, *1*, 559.

13. Schopf, C.; Arm, H.; Krimm, H. *Chem. Ber.* **1951**, *84*, 690.

14. Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* **1954**, *76*, 5597.

15. Speckamp, N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

16. Bonnet, R.; Agnoli, F. *Can J. Chem.* **1962**, *40*, 181.

17. Amoore, J.; Forrester, L.J.; Buttery, R.G. *J. Chem. Ecology* **1975**, *1*, 299.

18. Tabor, H. *Pharmacol. Rev.* **1964**, *16*, 245.

19. Herbert, R.B.; Jackson, F.B.; Nicolson, I.T.; Cragg, J.E.; Moody, C.J. *J. Chem. Soc.(P1)* **1982**, 2477.

20. Clarke, A.J.; Mann, P.J.G. *Biochem. J.* **1959**, *71*, 596.

21. Scully, F. *J. Org. Chem.* **1980**, *45*, 1515.

22. Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1992**, *48*, 4045.

23. Rapoport, H.; Bender, D.R.; Bjeldanes, L.F.; Knapp, D.R. *J. Org. Chem.* **1975**, *40*, 1264.

24. Herbert, R.; Jackson, F.B.; Nicolson, I.T. *J. Chem. Soc.(Chem. Comm.)* **1976**, 450.

25. Smith, F.T.; DeRuiter, J.; Carter, D.A. *J. Heterocyclic Chem.* **1989**, *26*, 1815.

26. Bhakuni, D.; Mangla, V.K. *Tetrahedron* **1981**, *37*, 401.

27. Herbert, R.; Jackson, F.B.; Nicolson, I.T. *J. Chem. Soc.(P1)* **1984**, 825.

28. Bhakuni, D.; Mangla, V.K. *Ind. J. Chem.* **1980**, *19B*, 748.

29. Maginnity, P.; Cloke, J.B. *J. Am. Chem. Soc.* **1951**, *73*, 49.

30. Zerevitov, D. *Ber.* **1908**, *41*, 2233.

31. Maginnity, P.; Cloke, J.B. *Anal. Chem.* **1948**, *20*, 978.

32. Maginnity, P.; Gair, T.J. *J. Am. Chem. Soc.* **1952**, *74*, 4958.

33. Schopf, C.; Herbert, G.; Rausch, R.; Schroder, G. *Leibigs Ann. Chem.* **1959**, *626*, 123.

34. Wisse, J.H.; Zweers, A.; Jongkind, J.F.; Bont, W.S.; Bloemendal, H. *Rec. Trav. Chim.* **1966**, *85*, 865.

35. Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598.

36. Grisar, J.M.; Claxton, G.P.; Stewart, K.T. *Synthesis* **1974**, 284.

37. Hegadus, L.; Miller, D.B. *J. Org. Chem.* **1989**, *54*, 1241.

38. Hegadus, L.; Imwinkerlried, R.; Alarid-Sargent, M.; Dvork, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.

39. Danishefsky, S.; Vogel, C. *J. Org. Chem.* **1986**, *51*, 3915.

40. Danishefsky, S.; Vogel, C.; Langer, M. *Tetrahedron Lett.* **1985**, *26*, 5983.

41. Zaugg, H.E.; Martin, W. Organic Reactions **1965**, *14*, 52.

42. Campbell, K.; Sommers, A.H.; Campbell, B.K. *J. Am. Chem. Soc.* **1944**, *66*, 82.

43. James, T.; Judd, C. *J. Chem. Soc.* **1914**, *105*, 1427.

44. Bose, A.K.; Spiegelman, G.; Manhas, M.S. *Tetrahedron Lett.* **1971**, 3167.

45. Bohme, R.; Toblonsky, A. *Chem. Ber.* **1963**, *96*, 600.

46. Hall, H.; Miniutti, D.L. *Tetrahedron Lett.* **1984**, *25*, 943.

47. Steglich, W.; Jendrezejweski, S. *Chem. Ber.* **1981**, *114*, 1337.

48. Lasne, M.; Ripoll, J.L.; Thuiller, A. *J. Chem. Res.(S)* **1982**, 214.

49. Krow, G.; Pyun, C.; Marakowski, J. *J. Org. Chem.* **1974**, *34*, 2449.

50. Csizmodia, V.; Tidwell, T.T.; Koshy, K.M.; Lau, K.C.M.; McClelland, R.A.; Nowlan, V.J. *J. Am. Chem. Soc.* **1979**, *101*, 974.

51. Shono, T.; Matumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697.

52. Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209.

53. Lenz, G.; Woo, C.M. *J. Org. Chem.* **1982**, *47*, 3049.

54. Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

55. Cohen, T.; Lipowitz, J. *J. Am. Chem. Soc.* **1964**, *86*, 2514.

56. Onda, M.; Sugama, Y.; Yokoyama, Y.; Tada, F. *Chem. Pharm. Bull.* **1974**, *22*, 2365.

57. Woodward, R.B.; Wuonola, M.A. *Tetrahedron* **1976**, *32*, 1085.

58. Zollar, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 836.

59. Matsumoto, T.; Matsuda, F.; Tomiyoshi, N.; Yanagiya, M. *Tetrahedron Lett.* **1983**, *24*, 1277.

60. Speckamp, W.N.; Dijkink, J. *Heterocycles* **1979**, *12*, 1147.

61. Speckamp, W.N.; Huisman, H.O.; Hubert, J.C.; Steege, W.*Syn. Comm.* **1971**, *1*, 103.

62. Speckamp, W.N.; Hubert, J.C.; Huisman, H.O. *Tetrahedron Lett.* **1972**, 4493.

63. Speckamp, W.N.; Wijnberg, J.B.P.A.; Schoemaker, H.E. *Tetrahedron* **1978**, *34*, 179.

64. Chamberlin, R.; Nguyen, H.D.; Chung, J.Y.L. *J. Org. Chem.* **1984**, *49*, 1682.

65. Rosenfeld, R.; Dunitz, J.D. *Helv. Chim. Acta.* **1978**, *61*, 2176.

66. Tagemann, E. *Helv. Chim. Acta.* **1959**, *37*, 185.

67. Winterfeldt, E.; Benz, G.; Krohn, K.; Mueller, W.; Thielke, D. *Synthesis* **1975**, 617.

68. Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385.

69. Wakabayashi, T.; Saito, M. *Tetrahedron Lett.* **1977**, 93.

VITA :

Phillip John Persichini III was born in Olean, New York on May 5, 1966. He graduated from Bradford Area High School in Bradford, Pennsylvania in 1984, and entered the University of Pittsburgh-Bradford later that year. Phillip graduated with a Bachelor of Science degree in chemistry in 1988. Upon graduation he accepted a job at Allied-Signal's Buffalo Research Laboratory where he remained until the fall of 1990. He continued his study of chemistry under the advisement of Professor Tomas Hudlicky at Virginia Tech in the pursuit of a Master's degree in Organic Chemistry. During this time Phillip was married to Nicole L. Roesch, and he also accepted a faculty position at the instructor level to teach organic chemistry at Radford University.