2007

# Synthetic approach to epibatidine from 1-(phenylsulfonyl)pyrrole

Brandon G. VanNess
*Wright State University*

# SYNTHETIC APPROACH TO EPIBATIDINE FROM

# 1-(PHENYLSULFONYL)PYRROLE

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

By

BRANDON G. VANNESS
B.S., Miami University of Ohio, 2005

2007
Wright State University

WRIGHT STATE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

June 29, 2007

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Brandon G. VanNess ENTITLED Synthetic Approach to Epibatidine from 1-(Phenylsulfonyl)pyrrole BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

Daniel M. Ketcha, Ph.D.
Thesis Director

Kenneth Turnbull, Ph.D.
Department Chair

Committee on
Final Examination

Daniel M. Ketcha, Ph.D.

Eric Fossum, Ph.D.

Kenneth Turnbull, Ph.D

Joseph F. Thomas, Jr., Ph.D.
Dean, School of Graduate Studies

ABSTRACT

Brandon G. VanNess. M.S., Department of Chemistry, Wright State University, 2007. Synthetic Approach to Epibatidine from 1-(Phenylsulfonyl)pyrrole.

The goal of this research was to synthesize the natural product epibatidine, a non-opiate analgesic and nicotinic acetylcholine agonist originally isolated from *Epipedobates tricolor*. A synthetic pathway utilizing a Diels-Alder cycloaddition of a 3-pyridyl substituted pyrrole and tosylacetylene was conceived based upon the original mass spectral fragmentation pathway of epibatidine determined by Daly. Although this pathway had been previously attempted using 1-(triisopropyl)-3-[5-(2-chloropyridyl)]pyrrole in the key Diels-Alder step, the lack of cycloadduct suggested that a pyrrole with a more electron withdrawing protecting group was required for this step. Therefore, synthesis of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole via a palladium catalyzed cross-coupling reaction of 1-(phenylsulfonyl)-3-pyrroline and 2-chloro-5-iodopyridine was set as a synthetic goal and accomplished. The 1-(phenylsulfonyl)-3-pyrroline could be obtained by reduction of 1-(phenylsulfonyl)pyrrole with sodium cyanoborohydride in trifluoroacetic acid.

The key Diels-Alder reaction required further investigation to determine the extent to which 1-(phenylsulfonyl)pyrrole would undergo cycloaddition with dienophiles such as tosylacetylene and dimethyl acetylenedicarboxylate. A solid foundation had been established for this reaction under thermal conditions, but the use of microwave

irradiation to afford the cycloaddition had not been previously investigated. It was found that this reaction occurs readily upon microwave irradiation, although not to the extent that the original thermal reactions did. Since it has always been assumed that strongly electron withdrawing substituents on the pyrrole nitrogen serve to decrease the aromaticity of this heterocycle, an even more electron withdrawing pyrrole, 1-(4-nitrophenylsulfonyl)pyrrole was synthesized and reacted under Diels-Alder conditions with dimethyl acetylenedicarboxylate, although no conclusion could be drawn on which diene is more reactive.

The stumbling block of this research has been the Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole with tosylacetylene. Although a product was isolated from the reaction, it was determined this product was not to be the desired cycloadduct and has remained unknown following limited characterization. The Diels-Alder reaction of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole was attempted with tosylacetylene but the desired cycloadduct could not be found.

TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

LIST OF TABLES

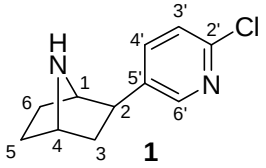
ACKNOWLEDGMENT

I would like to thank my mother, father, sister, and grandmother for supporting me throughout my time at Miami University and Wright State University. Without their continued support, I would not have been able to complete this endeavor.

I would like to thank Dr. Daniel Ketcha for providing much needed guidance and being able to deal with me for the past two years. I would also thank Dr. Eric Fossum and Dr. Kenneth Turnbull for their guidance.

# INTRODUCTION

Epibatidine (**1**), *exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane, was isolated by Daly and coworkers from the skin of the Ecuadorian poison dart frog *Epipedobates tricolor* (of the family Dendrobatidae) in 1992.[1,2] This novel alkaloid is the first natural product shown to possess a 7-azabicyclo[2.2.1]heptane (7-azanorbornane)[3] structure, and also displays a relatively rare 2-chloro-5-pyridyl substituent which is attached to the bicyclic ring in an *exo*-orientation. This molecule was found to be at least 200 times more potent than morphine in bioassays of analgesic-like effects in mice, however its effects were not blocked by the opiate receptor antagonist naloxone. Subsequent studies showed that epibatidine is an extremely potent agonist of nicotinic acetylcholine receptor (nAChR) that has been found to be involved in the mediation of several human disorders such as Alzheimer's and Parkinson's diseases.[4,5] Because of the intriguing biological activity demonstrated by this novel heterocycle, its unique chemical structure, and its scarcity in nature (1 mg isolated from 750 frogs), this molecule has become a synthetic objective of both academic and industrial research groups worldwide.

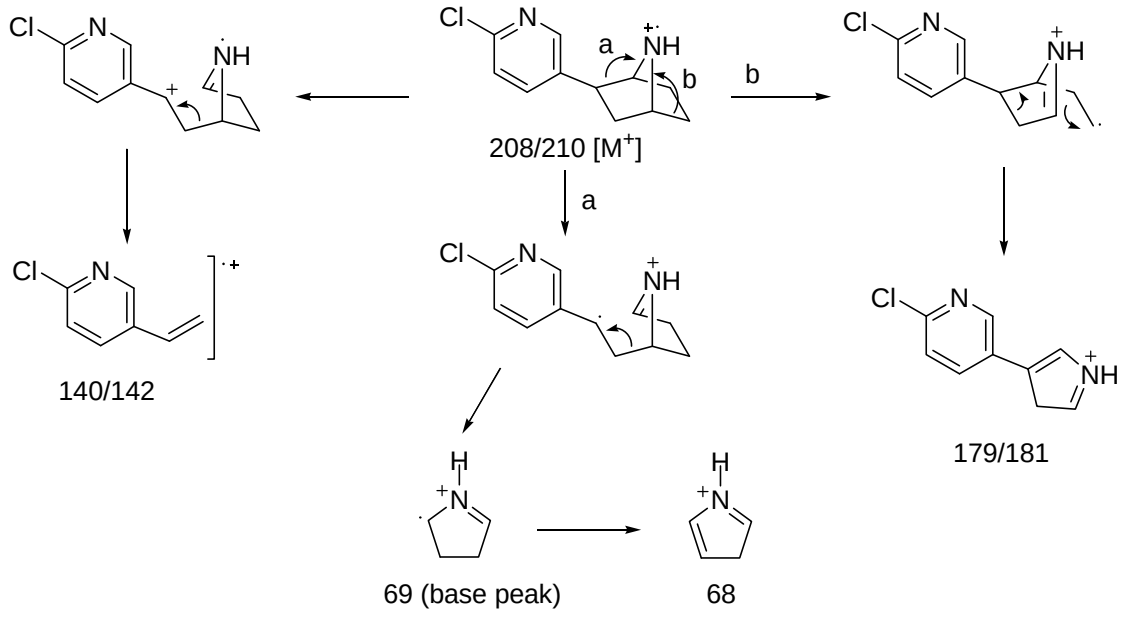



**1**

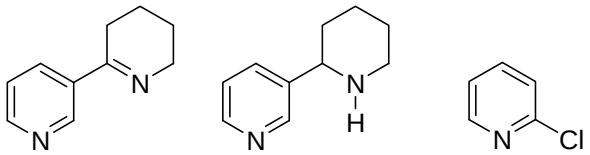
Daly noticed that the material that produced a Straub-tail response when injected into mice was easily isolated by gas chromatography-mass spectrometry and gave a

parent ion peak ($M^+$) (*m/z* 208) and an ($M^+$ +2) peak (*m/z* 210) which were in a 3 : 1 ratio typical of chlorine.[1] The high resolution mass fragmentation pattern determined after careful isolation of this molecule, named epibatidine, gave a parent ion of *m/z* 208.0769 that was assigned to the molecular formula $C_{11}H_3N_2{}^{35}Cl$ (Scheme 1).[1] It was noted by Daly that two additional fragments contained $^{35}Cl$, $C_9H_8N_2Cl^+$ (*m/z* 179.0362, $M^+$ - $C_2H_5$) and $C_7H_7NCl^+$ (*m/z* 140.0263, $M^+$ - 68), but the base peak did not show any chlorine present due to the assignment of $C_4H_7N^+$ to the *m/z* 69.0489 peak.[1] Daly reported that epibatidine was a basic, relatively polar alkaloid with the ability to exchange and acetylate one NH.[1] The UV chromophore was reported to have $\lambda_{max}^{CH_3OH}$ at 217 nm and a broad shoulder at 250-280 nm which suggested a pyridine moiety since 2-chloropyridine gives a $\lambda_{max}^{hexanes}$ at 269 nm.[1] Epibatidine provided a negative Ehrlich test on TLC which indicated the lack of pyrrole or indole structure.[1]

**Scheme 1**



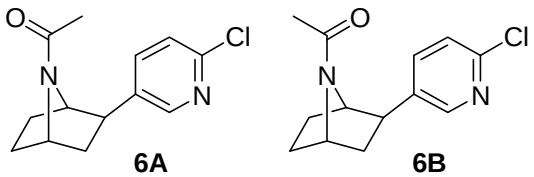
Comparison of Daly's GC-FTIR spectrum for epibatidine showed similar peaks as to those of the tobacco alkaloid anabasine (**3**), 2-(3-pyridyl)piperdine (**4**), and 2-chloropyridine (**5**). The strong IR absorbances around 1450 and 1118 $cm^{-1}$ are similar to those of **4** at 1428 and 1112 $cm^{-1}$ and of **5** at 1423 and 1132 $cm^{-1}$ which suggested the strong possibility of a pyridine moiety.[1] It must be noted that Daly only provided the labeled FTIR spectrum in his original paper and did not provide any tabular data for these peaks, which leads to the absorption at 1450 $cm^{-1}$ to be proximate.




**3** **4** **5**

The original $^1H$ NMR spectrum of epibatidine was tentatively assigned in a mixture of $D_2O$/DCl as: $\delta$ (J in Hz): 1.73-2.10 (m), 2.38 (dd, $J_1 = 9.7$, $J_2 = 13.8$, $H_{3n}$), 3.46 (dd, $J_1 = 6.0$, $J_2 = 10$, $H_{2n}$), 4.28 (t, J = 4.6, $H_4$), 4.23 (dd, $J_1 = 7.0$, $J_2 = 13.9$, $H_{3x}$), 4.9 (d, $H_1$), 7.68 (d, J = 8.8, $H_{5'}$), 8.08 (dd, $J_1 = 2.7$, $J_2 = 8.4$, $H_{4'}$), and 8.41 (d, J = 2.6, $H_{2'}$) where **n** denotes *endo*- and **x** denotes *exo*-position of hydrogen. Acylation of epibatidine was done in order to improve the NMR spectra and resulted in **6A** and **6B**. The $^1H$ NMR signals for **6A**: ($CDCl_3$) $\delta$ (J in Hz): 1.50-1.78 (m, A+B, $H_{5n}$, $H_{6n}$), 1.78-1.92 (m, A+B, overlapping $H_{3x}$ with $H_{5x}$, $H_{6x}$), 1.88 (s, $CH_3CO$), 2.02 (dd, $J_1 = 8.8$, $J_2 = 12.5$, $H_{3n}$), 3.01 (dd, $J_1 = 4.4$, $J_2 = 8.8$, $H_{2n}$), 3.93 (d, J = 4.0, $H_1$), 4.85 (t, $J_1 = J_2 = 4.8$, $H_4$), 7.28 (d, J = 8.4, $H_{5'}$), 7.50 (dd, $J_1 = 2.6$, $J_2 = 8.2$, $H_{4'}$), 8.26 (d, J = 2.6, $H_{2'}$); $^1H$ NMR for **6B**: ($CDCl_3$) $\delta$ (J in Hz): 1.50-1.78 (m, A+B, $H_{5n}$, $H_{6n}$), 1.78-1.92 (m, A+B, overlapping $H_{3x}$ with $H_{5x}$, $H_{6x}$), 2.09 (s, $CH_3CO$), 2.16 (dd, $J_1 = 9.2$, $J_2 = 12.1$, $H_{3n}$), 2.96 (dd, $J_1 = 4.8$, $J_2 = 8.8$, $H_{2n}$), 4.29 (t, J = 4.8, $H_4$), 4.69 (d, J = 4.8, $H_1$), 7.24 (d, J = 8.1, $H_{5'}$), 7.58 (dd, $J_1 = 2.6$, $J_2 = 8.5$,

$H_{4'}$), and 8.20 (d, J = 2.2, $H_{2'}$).[1] The $^1H$ signals from the $\delta$ 7.2 – 8.3 ppm region are assigned to a 6-chloropyridine with substitution at the 3-position since the peaks in this region differ from those of 2-chloro-5-picoline (in $CDCl_3$) by 0.06 ppm while the coupling constants are within a 0.2 Hz difference for the signals.[1] Daly noted that the remaining signals are characteristic of that of a cyclohexane in the boat configuration since coupling of bowsprit hydrogens and adjacent *trans*-axial hydrogens is very small or zero in the boat configuration and no such coupling was found between the hydrogens $H_1$ and $H_2$.[1]




**6A** **6B**

The original isolation of epibatidine was undertaken after a sample of the extracts of *Epipedobates tricolor* were noted to produce a Straub-tail reaction (>45° arch) when injected into mice.[1] Daly noted that morphine required a dose of 10 mg/kg in order to elicit the Straub-tail reaction and could be quenched with 5 mg/kg of naloxone being administered 20 minutes prior to 20 mg/kg of morphine.[1] Epibatidine showed a very different response, only 20 μg/kg was required and only slight quenching occurred with naloxone while the effect lasted from 1 to 2 hours after initial dose.[1] Testing of the analgesic properties of (-)-epibatidine was further explored by the use of 5 μg/kg dose for hot-plate analgesia where a 10 mg/kg dose of morphine was required to delay the mice from sensing the heat of a metal hot plate set to 55-56 °C.[2] The analgesic effects of (-)-epibatidine, but not morphine, were quenched via the administration of the nicotinic antagonist mecamylamine.[6] This started to prove the case for epibatidine's analgesic

effects occurring through a non-opiate pathway. The elucidation of epibatidine as a nicotinic acetylcholine receptor agonist was confirmed by the testing of nicotine binding receptors in which epibatidine was shown to be 20-fold more potent than nicotine at central nicotine binding sites.[6]

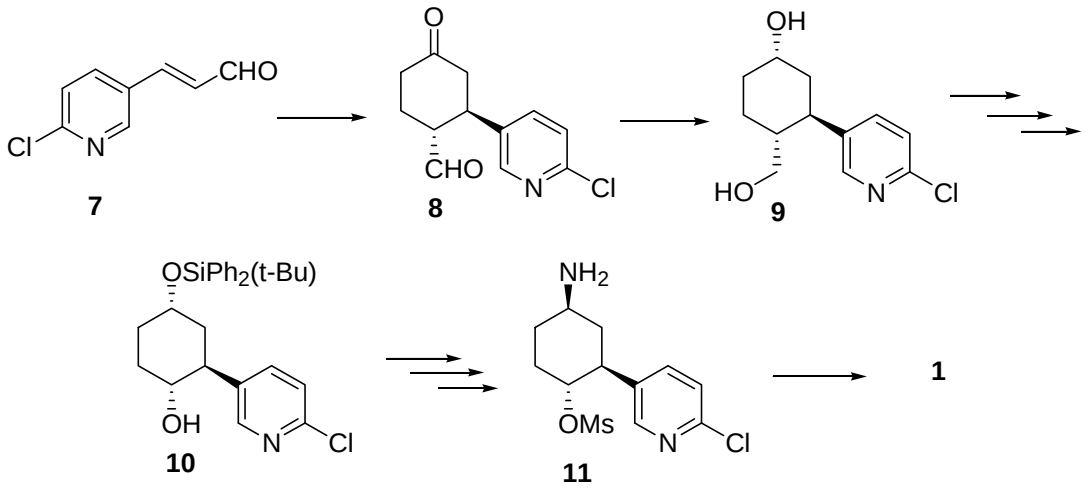
## REPORTED SYNTHESES OF EPIBATIDINE

The synthesis of epibatidine was very important for structure proving purposes immediately following Daly's original publication with many prominent researchers around the world trying various routes towards this medicinally important material.[7] Both racemic and enantioselective syntheses of epibatidine have been devised, wherein construction of the 7-azabicyclo[2.2.1]heptane ring has been effected by one of two ways: either by base-promoted internal nucleophilic displacement reactions of cyclohexylamine derivatives possessing a leaving group at the 4-position,[7] or by the Diels-Alder reaction of N-acylpyrrole substrates with pyridyl-substituted acetylenes.[8]

The first total synthesis of (±)-epibatidine was developed by Broka at Syntex Discovery Research[9] (Scheme 2). Broka started by performing an addition of (triphenylphosporanylidene)acetaldehyde to 6-chloronicotinaldehyde to from the enal **7**. This enal was converted to the single stereoisomer of ketoaldehyde **8** in 75% via a reaction of **7** with 2-(trimethylsilyloxy)-1,3-butadiene and dilute HCl in $H_2O$-THF-MeOH. Reduction of **8** with L-Selectride afforded **9** which required several steps to remove the additional carbon and protect the phenol to provide **10**. Conversion of **10** to **11** was accomplished via benzoylation of the unprotected phenol, deprotection of the silyl group and subsequent introduction of the azido group which was reduced to a primary amine via $SnCl_2$, and subsequent conversion of the benzoyl protection group to a methylsulfonyl (Ms) protecting group which gave **11.** Allowing **11** to react in heated

chloroform for 4 days results in ring formation to produce **1** after exposure to aqueous $NaHCO_3$ and heating for an additional day. The data Broka collected on his synthetic epibatidine was in agreement with Daly's, $^1$H NMR: ($CDCl_3$) $\delta$ (J in Hz): 8.28 (d, J = 2.5, 1H), 7.79 (dd, $J_1$ = 8.3, $J_2$ = 2.5, 1H), 7.25 (d, J = 8.3, 1H), 3.85 (t, J = 3.2, 1H), 3.60 (d, J = 3.0, 1H), 2.80 (dd, $J_1$ = 8.9, $J_2$ = 5.0, 1H), 1.94 (dd, $J_1$ = 12.2, $J_2$ = 9.0, 1H), 1.71-1.50 (m, 5H); $^{13}$C NMR: ($CDCl_3$) $\delta$: 149.0, 148.8, 140.6, 137.7, 124.0, 62.8, 56.6, 44.4, 40.1, 31.2, 29.8; no MS reported.

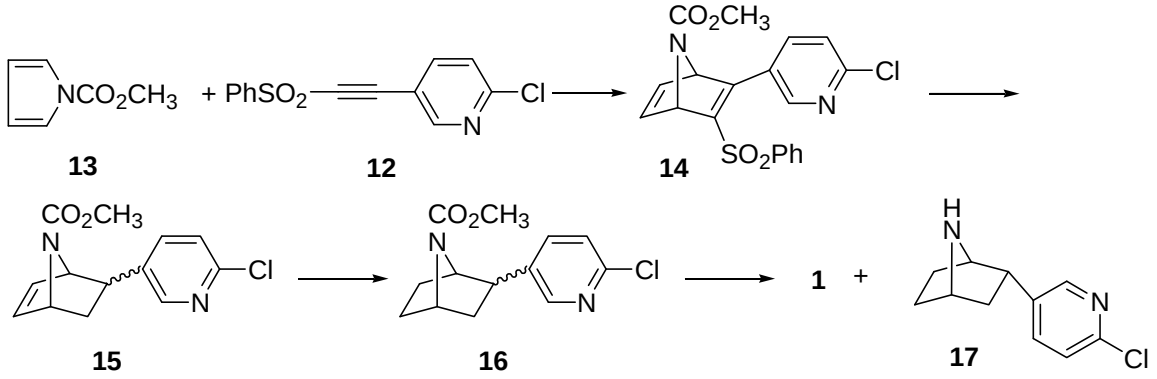
**Scheme 2**




The synthesis of racemic epibatidine via the use of phenylsulfonyl 6-chloro-3-pyridyl acetylene (**12**) as a dienophile for Diels-Alder reactions was first reported by Huang and Shen[8] (Scheme 3). They reacted **12** with an excess of 1-methoxycarbonylpyrrole (**13**) as a solvent and reactant at 80-85 °C for 24 h to get adduct **14** in 50-70%. Adduct **14** was converted to 1-(methoxycarbonyl)dehydroepibatidine (**15**) in a 1 : 2 ratio of *exo* to *endo* isomers via four equivalents of 6% sodium-amalgam in methanol with four equivalents of sodium dihydrosphosphate, where **15** gave mass spectral fragmentation patterns of *m/z* 265 ($M^+$) and 267 ($M^+$ +2). Reductive

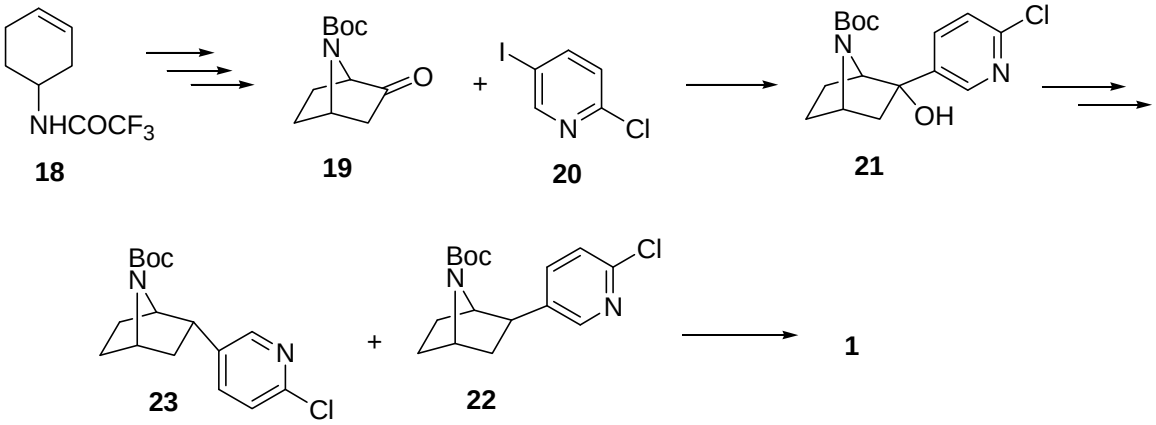
hydrogenation of **15** at atmospheric pressure with 10% Pd/C as catalyst gave **16** in 92% yield as a 1 : 2 mixture of *exo* to *endo* isomers after 5 minutes which exhibited mass fragments of *m/z* 267 ($M^+$), 269 ($M^+$ +2). After a few failed attempts at removing the methoxycarbonyl protecting group, success was found when **16** was deprotected after stirring in a solution of 33% hydrobromic acid in acetic acid at room temperature for 20 h to give rac-epibatidine (25%), rac-*endo*-epibatidine (**17**) (28.4%), and unchanged **16** (20%) which was mainly the *endo*-isomer after column purification. The rac-epibatidine was further resolved to *d* and *l* isomers via di-*p*-toluoyl tartaric acid salts, *ee* >95%. The data provided for rac-epibatidine included $^1$H NMR: (QE-300, $CDCl_3$) $\delta$ (J in Hz): 8.265 (d, J = 2.4, $H_{2'}$), 7.757 (dd, J = 8.1, 2.4, $H_{5'}$), 7.221 (d, J = 8.1, $H_{4'}$), 3.795, 3.560 (t, J = 3.9, br.s. $H_{1,4}$), 2.760 (dd, J = 9.0, 4.8, $H_2$), 1.988 (br.s., $H_7$), 1.904 (dd, J = 12.0, 9.0, $H_{3e}$), 1.50-1.65 (m, 5H, $H_{3a,5,6}$); $^{13}$C NMR (QE-300, $CDCl_3$) $\delta$: 149.409 ($C_{6'}$), 149.237 ($C_{2'}$), 141.441 ($C_{3'}$), 138.105 ($C_{5'}$), 124.359 ($C_{4'}$), 63.209 ($C_1$), 56.882 ($C_4$), 44.952 ($C_2$), 40.752 ($C_3$), 31.784, 30.546 ($C_{5,6}$); MS *m/z* 209 ($M^+$), 211 ($M^+$ +2). The reported data for rac-*endo*-epibatidine included $^1$H NMR: (QE-300, $CDCl_3$) $\delta$ (J in Hz): 8.219 (d, J = 1.8, $H_{2'}$), 7.447 (dd, J = 8.1, 1.8, $H_{5'}$), 7.252 (d, J = 8.1, $H_{4'}$), 3.760 (q, J = 2H, $H_{1,4}$), 3.289 (ddd, J = 12.0, 4.8, 5.7, $H_2$), 2.087 (br, J = $H_7$), 2.120 (tdd, J = 12.3, 4.8, 3.3, $H_{3e}$), 1.488 (dd, J = 12.3, 5.7, $H_{3a}$), 1.55-1.72 (m, 1H), 1.33-1.43 (m, 3H); $^{13}$C NMR: (QE-300, $CDCl_3$) $\delta$: 150.005 ($C_{2'}$), 149.568 ($C_{6'}$), 138.812 ($C_{5'}$), 136.285 ($C_{3'}$), 124.175 ($C_{4'}$), 61.535 ($C_1$), 57.955 ($C_4$), 45.337 ($C_2$), 35.311 ($C_3$), 31.433 ($C_5$), 24.533 ($C_6$); MS *m/z* 209 ($M^+$), 211 ($M^+$ +2). The rac-*endo*-epibatidine is confirmed for *endo* stereochemistry as a result of the extra splitting at 3.289 ppm for $H_2$ since the $H_1$ and $H_2$ protons are splitting. This is in contrast to the *exo*-isomer which follows the Karplus diagram and has no splitting between the $H_1$ and $H_2$ due to the 90 degree angle between these hydrogens.

**Scheme 3**




The route to epibatidine reported by Fletcher[10] (Scheme 4) relied on converting N-trifluoroacetylaminocyclohex-3-ene (**18**) through a series of steps, which included epoxidation, cyclization, and Swern oxidation, to ketone **19**. Once **19** was isolated, it was reacted with 2-chloro-5-iodopyridine (**20**) in the presence of n-butyllithium to afford the coupled alcohol **21**. In order to arrive at **1**, alcohol **21** was dehydrated via conversion of the free alcohol to an *S*-methyl xanthate derivative which underwent thermolysis in refluxing toluene and subsequent hydrogenation with Adams' catalyst to yield a mixture of *exo*- (**22**) and *endo*-N-boc-epibatidine (**23**) which were separated by column chromatography. Fletcher was able to convert the undesired **23** to the desired **22** in high yields via epimerization with potassium *tert*-butoxide in *tert*-butyl alcohol. The deprotection of **22** occurred in high yield with trifluoroacetic acid at room temperature to yield racemic epibatidine **1**. Fletcher reported the NMR analysis of **1** as the hemi-oxalate salt, $^1$H NMR: (360 MHz, $CD_3SOCD_3$) $\delta$ (J in Hz): 8.39 (d, J = 2.5, 1H), 7.86 (dd, J = 8.3, 2.4, 1H), 7.46 (d, J = 8.3, 1H), 4.17 (s, 1H), 4.08 (s, 1H), 3.20 (dd, J = 9.4, 4.8, 1H), 2.18 (dd, J = 12.7, 9.4, 1H), 1.55-1.85 (m, 5H).

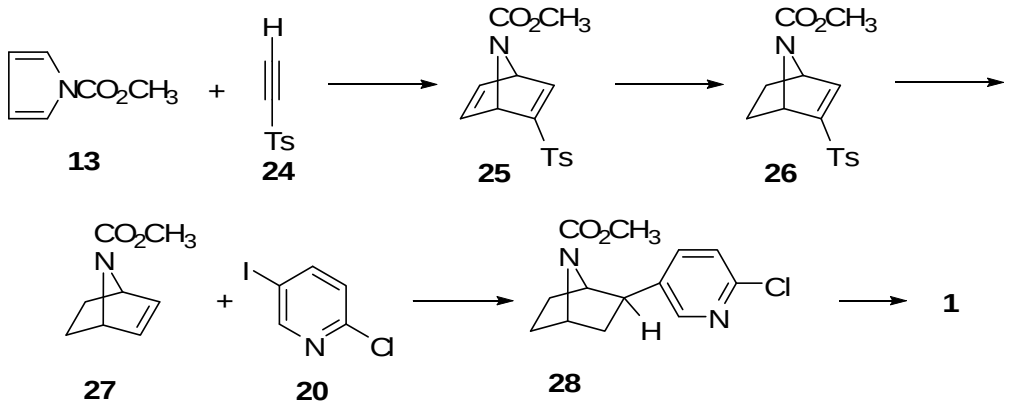
**Scheme 4**




In 1993, Clayton and Regan were the fourth group to report a synthetic route to epibatidine that relied on a Diels-Alder cycloaddition followed by a reductive palladium cross-coupling reaction[11] (Scheme 5). Clayton started by performing the Diels-Alder cycloaddition of 1-methoxycarbonylpyrrole (**13**) with *para*-toluenesulphonylacetylene (**24**) at 80-85 °C for 24 h to give the bicyclic adduct **25** in 36%.[11] The use of selective catalytic hydrogenation of **25** resulted in reduction of the more electron rich alkene to give **26** in 99% which was then subjected to a solution of 6% sodium amalgam in methanol-THF to remove the *para*-tosyl group which gave **27**. The palladium catalyzed cross-coupling of **27** with 2-chloro-5-iodopyridine (**20**) required 8 mole percent bis(triphenylphosphine)palladium(II) acetate (generated *in situ* from palladium acetate and triphenylphosphine), DMF, piperidine, and formic acid at 70 °C for 6.5 h to yield **28** stereoselectively as the *exo*-isomer in 35%. Finally, **28** was allowed to stir in a solution of hydrobromic acid and acetic acid at room temperature for 22 h to yield (-)-epibatidine in 74%. Clayton provided the $^1$H NMR of **26**: (200 MHz, $CDCl_3$) $\delta$ (J in Hz): 8.22 (d, J = 2.5, 1H), 7.60 (dd, $J_1$ = 8.2, $J_2$ = 2.5, 1H), 7.23 (d, J = 8.2, 1H), 4.44 (br t, 1H), 4.20 (br s, 1H,), 3.67 (s, 3H), 2.89 (dd, $J_1$ = 9.1, $J_2$ = 5.0, 1H), 2.03 (dd, $J_1$ = 12.0, $J_2$ = 8.5, 1H), 1.7-1.9 (m, 3H), 1.5-1.65 (m, 2H); and the $^1$H NMR of (-)-epibatidine: (200 MHz, $CDCl_3$) $\delta$

(J in Hz): 8.27 (d, J = 2.6, 1H), 7.76 (dd, $J_1$ = 8.4, $J_2$ = 2.5, 1H), 7.24 (d, J = 8.4, 1H), 3.84 (t, J = 3.5, 1H), 3.60 (br s, 1H), 2.79 (dd, $J_1$ = 8.8, $J_2$ = 5.3, 1H), 1.94 (dd, $J_1$ = 12.2, $J_2$ = 9.1, 1H), 1.72-1.50 (m, 5H). Clayton reasoned that the lack of splitting between the $H_1$ and $H_2$ in the $^1$H NMR was the result of a dihedral angle of 90° which would be consistent with the *exo*-isomer.[11]

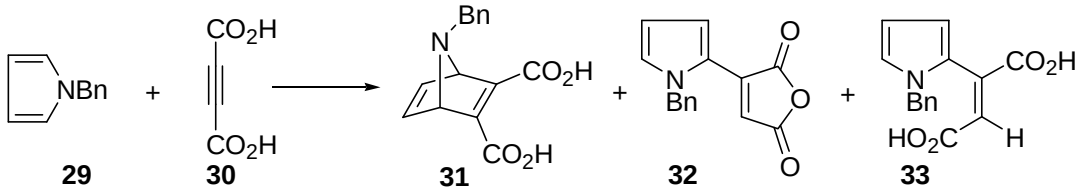
**Scheme 5**



## AN OVERVIEW OF DIELS-ALDER REACTIONS INVOLVING PYRROLE

The ability to utilize pyrrole as a diene in Diels-Alder cycloadditions has been relatively unsuccessful since pyrrole, unlike furan, undergoes substitutive processes leading to α-substituted pyrroles[12] and dihydroindoles.[13] The first example of a pyrrole partaking in a normal Diels-Alder addition involved the reaction of N-benzylpyrrole (**29**) and acetylenedicarboxylic acid (**30**) in refluxing ether for 24 hr[14] (Scheme 6). This reaction resulted in three products, the desired cycloadduct 7-benzyl-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid (**31**), and two Michael-type addition products at the 2-position of the pyrrole: N-benzylpyrrole—maleic anhydride (**32**) and N-benzylpyrrole-α-fumaric acid (**33**). It is interesting to note that **31** (also known as a 7-azanorbornadiene) precipitated out of solution upon reaction and was easily collected via filtration, **32** was isolated as crystals after cooling the filtrate, and **33** was isolated from concentration of the mother liquors.[14] While there is no specific explanation for the formation of **32**, it can be speculated that it is due to dehydration of a *cis*-isomer of **33** since acidification of **32** resulted in a diacid with a different melting point than **33**. This reaction shows the complex nature of the Diels-Alder reaction upon pyrroles due to competition with Michael-additions that is atypical of other dienes.

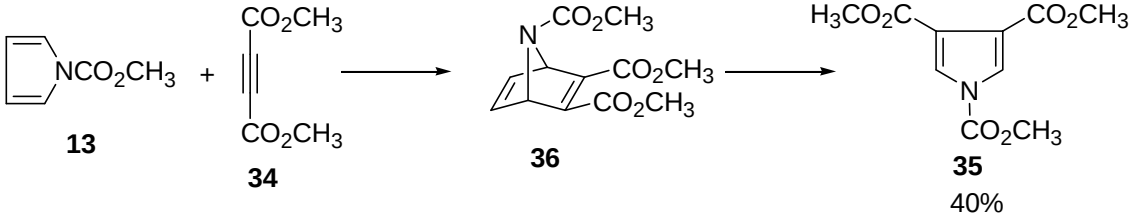
**Scheme 6**




**29** **30** **31** **32** **33**

In hopes to increase the ability of pyrroles to behave as better dienes, research began to revolve around the use of more electron-withdrawing N-protecting groups in an effort to reduce the aromatic character of the pyrrole ring. The use of **13** as the primary N-substituted pyrrole diene originated with Acheson and Vernon when they reacted **13** with dimethyl acetylenedicarboxylate (**34**) to produce acetylene and trimethyl pyrrole-1,3,4-tricarboxylate (**35**) from the retro-Diels-Alder reaction of the desired trimethyl 7-azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylate (**36**)[15,16] (Scheme 7).

**Scheme 7**

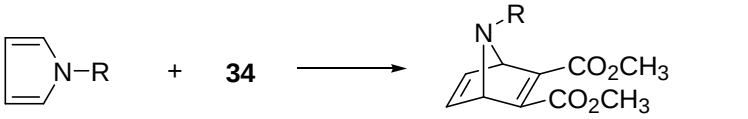



**13** **34** **36** **35**
40%

There are other electron-withdrawn substituted pyrroles that can be used successfully for Diels-Alder reactions and two such dienes have been reported by Prinzbach and coworkers: 1-(*p*-toluenesulfonyl)pyrrole (**37**) and 1-acetylpyrrole (**38**)[17] (Scheme 8). The heating of **37** or **38** with an excess of **34** resulted in the preparation of the two 7-azanorbornadiene derivatives (**39** and **40**, respectively) in isolated yields of only 30-40%. The low yields are due to the high reaction temperatures (105-142 °C), the reversible nature of the reactions, and the retro-Diels-Alder processes that can occur. Prinzbach reported the $^1$H NMR of **39** as $^1$H NMR ($CDCl_3$) $\delta$ (J in Hz): 2.41 (d, J = 8.0,

2H), 2.74 (d, 2H); 2.96 (t, J = 1.5, 2H); 4.58 (t, J = 1.5, 2H), 6.38 (s, 6H), 7.59 (s, 3H); and the $^1$H NMR of **40** as $^1$H NMR ($CDCl_3$) $\delta$ (J in Hz): 2.77 (m, 2H); 4.21 (m, 1H), 4.36 (m, 1H); 6.19 (s, 6H); 8.07 (s, 3H).

**Scheme 8**

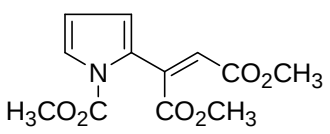



**37** R = $SO_2$-$C_6H_4$-*p*-$CH_3$
**38** R = $COCH_3$

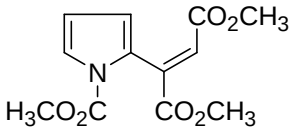
**39** R = $SO_2$-$C_6H_4$-*p*-$CH_3$
**40** R = $COCH_3$

The uncatalyzed Diels-Alder reaction of pyrroles tends to afford lower than expected yields which decreases the attractiveness of this reaction. Efforts were undertaken to develop methods that could increase the Diels-Alder cycloadduct yields and limit the amount of side products formed by the use of Lewis acid catalysts.[18-20] The use of the Lewis acid aluminum chloride ($AlCl_3$) as a catalyst was demonstrated by Bansal.[18] Not only did the use of $AlCl_3$ allow for lower reaction temperatures for the reaction of **13** with **34**, but a notable yield increase of the 7-azanorbornadiene cycloadduct **36** occurred; up to 93% yield with the use of a 5 : 1 ratio of $AlCl_3$ to **13** with no Michael adduct isolated.[18] Unfortunately, at lower ratios of $AlCl_3$, the yields of **36** decreased as the formation of both *cis*- and *trans*- dimethyl 2-(1-(methoxycarbonyl)-1H-pyrrol-2-yl)fumarate (**41** and **42**, respectively) increased. A 1 : 1 ratio of $AlCl_3$ to **13** at 40 °C for 30 min resulted in the isolation of **36** in 54%, **41** in 30%, and **42** in 4% while a 3 : 1 ratio of $AlCl_3$ to **13** at 40 °C for 1 h resulted in the isolation of **36** in 76% and **42** in 19%, thus requiring careful attention to the amount of catalyst used. Bansal reported the $^1$H NMR spectral data of **36** as (60 MHz, $CDCl_3$) $\delta$: 2.83 (m, 2H, olefinic), 4.48 (m, 2H, bridgehead), 6.18 (s, 6H, carbomethoxy), and 6.35 (s, 3H, N-carbomethoxy). Bansal was

also able to confirm the isolation of **36** by heating at 170 °C to induce retro Diels-Alder reaction to produce **35**.[18]

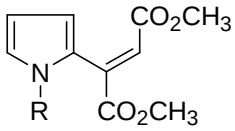



**41**



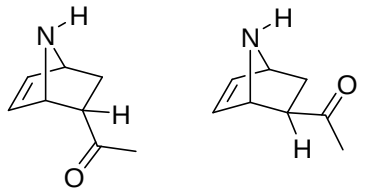

**42**

When Donnini repeated Bansal's work by reacting 1-(*p*-toluenesulfonyl)pyrrole (**37**) and 1-acetylpyrrole (**38**) with dimethyl acetylenedicarboxylate (**34**), he noted different product yields when performing the reaction of **37** with **34** under the same ratio of aluminum chloride catalyst that Bansal used.[19] Donnini was able to obtain a 65% yield of the desired Diels-Alder cycloadduct **40** with a 5 : 1 ratio of $AlCl_3$ and **38**, but the Michael product **43** was produced in a 10% yield while the same conditions with **37** resulted in isolation of **39** in 60% and the Michael product **44** in 40%.[19] When using a 3 : 1 ratio of $AlCl_3$ to **37**, the cycloaddition resulted mainly in the isolation of the Michael product **44** while a 7 : 1 ratio of $AlCl_3$ to **37** was sufficient to produce equal amounts of the cycloadduct **39** and the Michael product **44**.[19] The reported $^1$H NMR spectral data of **39** in ($CDCl_3$) $\delta$: 1.95 (s, 3H), 3.84 (s, 6H), 5.55 (m, 1H), 5.72 (m, 1H), 7.10 (m, 2H); and **43** in ($CDCl_3$) $\delta$ (J in Hz): 2.48 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 6.27 (s, 1H), 6.32 (s, 1H), 6.93 (s, 1H), 7.28 (t, J = 2.5, 1H).[19]



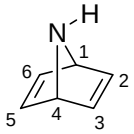

**43** R = $COCH_3$
**44** R = $SO_2$-$C_6H_4$-*p*-$CH_3$

It was shown by McCabe's group that pyrrole itself could undergo cycloaddition with methyl vinyl ketone by the use of the catalyst $Cr^{3+}$-exchanged Tonsil 13 clay. McCabe's work showed that pyrrole reacted to produce a mixture of *endo* : *exo* (4.0 : 1) cycloadducts (**45** and **46**, respectively) in 35% yield after 20 min at 25 °C while the same reaction showed no product formation after two days in the absence of catalyst.[20] McCabe reasoned that this result may arise from the ability of the secondary amine product to coordinate with the clay catalyst and remain in the active site or ligate to the metal more effectively than the aromatic pyrrole nitrogen.[20]




**45** **46**

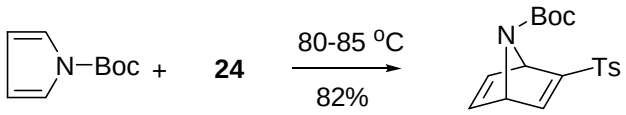
Other attempts at using uncatalyzed reactions of N-substituted pyrroles have focused on different dienophiles, in which two such cases have led to epibatidine.[8,11] The use of **24** as a dienophile was first reported by Vogel and coworkers in which **13** underwent reaction to yield **25** in 60% after heating at 80-85 °C for 24 h.[21] It is interesting to note that Vogel converted **25** to 7-azabicyclo[2.2.1]hepta-2,5-diene (**47**) via a series of deprotection steps and reported the $^{1}$H NMR of **47** as (90 MHz, $CDCl_3$) $\delta$ (J in Hz): 2.63 (s, 1H, N-*H*), 4.73 (br. s, 2H, bridgehead), and 7.06 (br. s, 4H, olef. *H*); and the $^{13}$C NMR of **47** as (90 MHz, $CDCl_3$) $\delta$: 145.57 ($C_{2,3,5,6}$) and 66.28 ($C_{1,4}$).[21]




**47**

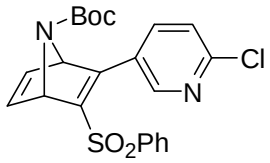
Muchowski found that one set of optimal conditions to effect the cycloaddition was to heat a 2:1 molar ratio of the N-(*tert*-butyloxycarbonyl)pyrrole (**48**) and **24** without solvent at 80-85 $^{o}$C for 48 hrs.[22] Removal of the excess pyrrole derivative (recoverable) by column chromatography on silica gel gave the cycloadduct **49** in 82% yield (Scheme 9). The reported $^{13}$C NMR of **49** is (300 MHz, $CD_3SOCD_3$) δ: 158.25, 153.12, 144.72, 141.72 (2C), 135.64, 130.13 (2C), 127.57 (2C), 80.46, 67.86, 66.49, 27.54 (3C), and 20.98.[22]

**Scheme 9**




**48** **49**

As mentioned above, the use of phenylsulfonyl 6-chloro-3-pyridyl acetylene (**12**) in a Diels-Alder reaction with **13** was reported by Shen in his synthetic route to epibatidine.[8] Carroll applied similar conditions but utilized five equivalents of **48** to react with **12** to obtain the cycloadduct **50** in 78% yield.[23]



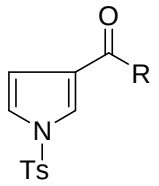

**50**

## VARIOUS ROUTES TO AFFORD 3-ARYL PYRROLES

There are a variety of ways in which to synthesize 3-substituted pyrroles, especially 3-aryl pyrroles. The Friedel-Crafts acylation reaction[24] and the halogen metal exchange reaction[25] are ways in which N-substituted pyrroles can be efficiently substituted at the 3-position, but both of these reactions are not suited for aryl substitution. A convenient route to 3-aryl pyrroles is the palladium catalyzed cross-coupling reaction of 3-halopyrroles, pyrrole-3-boronic acids, and 3-pyrrolines,[26-29] in which the latter requires an oxidation in order to afford a stabile 3-aryl pyrrole (*vide infra*). There are a variety of different conditions (e.g., catalyst, ligand, base, solvent, temperatures, etc.) that have been shown to work in the palladium cross-coupling reactions of 3-halogenated pyrroles, pyrrole-3-boronic acids, and 3-pyrrolines, but none of these routes have shown a clear cut, high yield synthesis of 3-aryl pyrrolines and 3-aryl pyrroles in which the production of byproducts and complicated precursor synthesis were left to a minimum. A final option would be to perform *de novo* synthesis of the pyrrole ring[30] by establishing substitution during the ring construction process.

The Friedel-Crafts reaction is a simple route to 3-substituted pyrroles once nitrogen protection has occurred. Usually the acylation of N-substituted pyrroles requires three molar equivalents of desired anhydride and six molar equivalents of aluminum chloride. This route easily converts 1-(*p*-toluenesulfonyl)pyrrole (**37**) to 3-acetyl-1-tosylpyrrole (**51A**) in quantitative yields when using acetic anhydride.[24] Similar

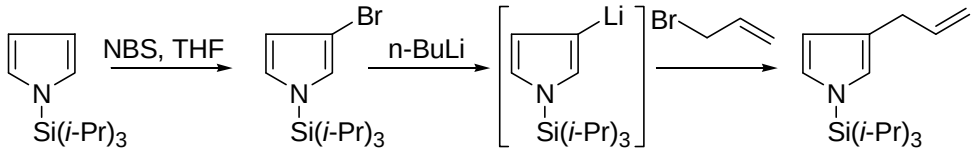
results were reported when using propionic anhydride (**51B**, 84%), phenylacetyl chloride (**51C**, 80%), and isobutyryl chloride (**51D**, 94%).[24] Reductions, Grignard reactions, and Wittig reactions can result in additional functionality of the molecule, although there is no direct route to 3-aryl pyrroles via these routes.




**51A**, R = $CH_3$
**51B**, R = $CH_2CH_3$
**51C**, R = $C_6H_5$
**51D**, R = $CH_2CH(CH_3)_2$

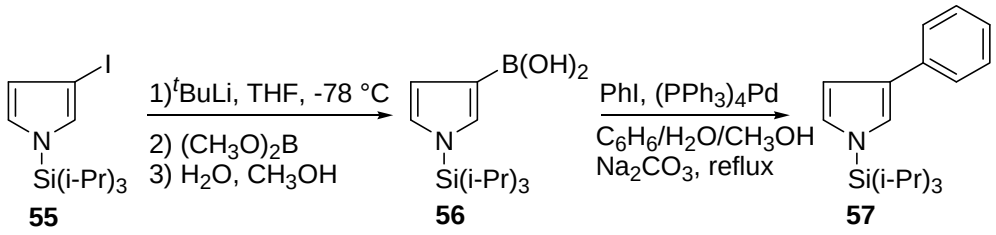
Another route to 3-substituted pyrroles is via the use of the halogen-metal exchange on 3-substituted pyrroles, usually involving bromine substitutents. The requirement of an already 3-substituted pyrrole is easily accomplished by the bromination of 1-(triisopropylsilyl)pyrrole (**52**) with NBS in THF at -78 °C to produce 3-bromo-1-(triisopropylsilyl)pyrrole (**53**) in a 90% yield[25] (Scheme 9). The slow introduction of n-butyllithium to **53** removes the bromine to afford the corresponding lithio species which undergoes reaction with electrophiles such as allyl bromide producing 3-allyl-1-(triisopropylsilyl)pyrrole (**54**) in 80% yield. Other electrophiles can be used and yields vary from 69% for benzyl chloride to quantitative for $D_2O$.[25]

**Scheme 9**



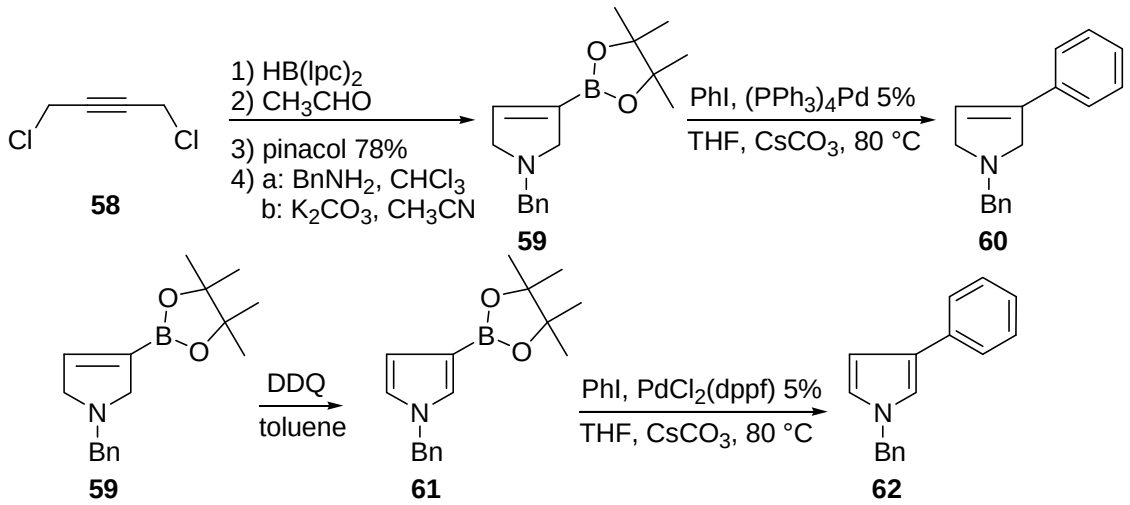
The use of palladium as catalyst in the cross-coupling of 3-halopyrroles, pyrrole-3-boronic acids, and 3-pyrrolines has been investigated numerous times.[26-29] Muchowski[26] has been able to prepare a number of different phenyl boronic acids and react them with 1-(triisopropylsilyl)-3-iodopyrrole (**55**) to afford modest yields (20-35%) of the corresponding 3-aryl pyrroles. The preparation of **55** was achieved by the reaction of N-iodosuccinimide with 1-(triisopropylsilyl)pyrrole. The lack of commercially available boronic acid inputs as well as the inconvenience of preparing a large number of aryl boronic acids at that time led Muchowski to prepare 1-(triisopropylsilyl)pyrrole-3-boronic acid (**56**) in which **55** was reacted with *tert*-butyllithium in THF at -78 °C, then trimethylborate, followed by hydrolysis[27] (Scheme 11). The cross-coupling reactions of **56** with aryl halides was performed using tetrakis(triphenylphosphine)palladium(0) as a catalyst in typical Suzuki[31] cross-coupling reactions. As an example, iodobenzene was reacted with **56** to produce 1-(triisopropylsilyl)-3-phenylpyrrole (**57**) in 96% yield after reacting with 5 mole percent catalyst in refluxing benzene/water/methanol mixture for 16 h. Unfortunately, Muchowski's route requires two steps after synthesis of the N-protected pyrrole (i.e., halogenation, boronation) before the cross coupling reaction may begin and, coupled with the expense of N-iodosuccinimide, limit the cost effectiveness of this reaction.

**Scheme 10**



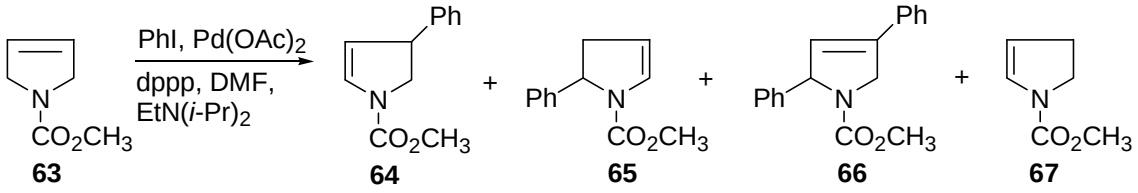
An adaptation of Muchowski's work was done by Carboni[27] with the use of the boronic esters of pyrrolines. Carboni's work required a four step pyrroline ring formation from 1,4-dichlorobut-2-yne (**58**) using diisopinocampheylborane for hydroboration, acetaldehyde for dealkylation, pinacol for ester exchange, and finally benzylamine for ring closure to give the 3-pyrroline boronic ester **59**. From here, **59** underwent facile coupling with iodobenzene utilizing 5 mole percent tetrakis(triphenylphosphine)palladium(0) catalyst and CsF as base in refluxing THF allowing isolation of the resulting 1-benzyl-3-phenylpyrroline (**60**) in 80% yield[27] (Scheme 11). Following the oxidation of **59** with DDQ to procure the pyrrole boronic ester **61**, the coupling reaction of **61** with iodobenzene required the use of 5 mole percent dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) in the presence of cesium carbonate in THF at 80 °C to produce the desired 1-benzyl-3-phenylpyrrole (**62**) in 74% yield.[27] Although **60** and **62** are isolated in high yields, the synthetic steps required to procure the boronic esters by *de novo* ring construction are daunting.

**Scheme 11**



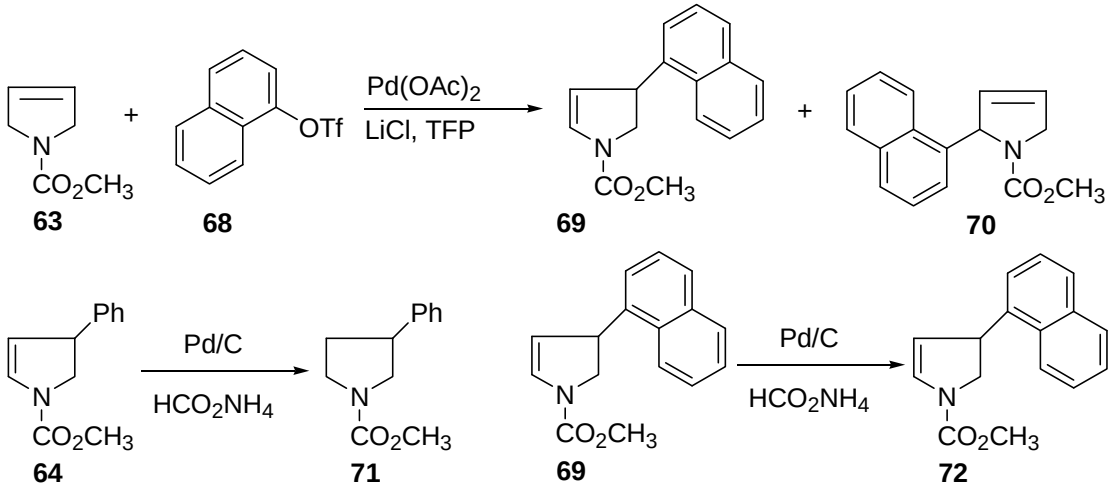
A less tedious route suggested by Hallberg[28] focused on reacting 1-methoxy-carbonyl-3-pyrroline (**63**) with iodobenzene in the presence of palladium catalyst. The initial reaction required palladium(II) acetate and 1,3-bis-[diphenylphosphino]propane as a phosphine ligand in the presence of the base N,N-diisopropylethylamine in DMF at 100 °C. The desired cross-coupling product, namely 1-(methoxycarbonyl)-3-phenyl-2-pyrroline (**64**) was isolated, along with 1-(methoxycarbonyl)-2-phenyl-4-pyrroline (**65**), 1-(methoxycarbonyl)-2,4-diphenyl-3-pyrroline (**66**) and 1-(methoxycarbonyl)-2-pyrroline (**67**) in greater than 10% yields (Scheme 12). The main drawback to this reaction is formation of three byproducts since palladium catalyzed coupling and π-bond isomerization are competing reactions. The isomerization of **63** results in **67** which can also undergo coupling with iodobenzene to form **65**, thereby giving mixtures of **64** and **65** which are not easily separable via standard chromatography techniques.[28] Noting work by Overman[32] in which silver additives were used to control double bond migration in intramolecular Heck-reactions, Hallberg was able to eliminate formation of byproducts **65** and **67** by using silver carbonate as base and P(*o*-tol)$_3$ as ligand in the reaction. Unfortunately, silver carbonate could not limit formation of the di-addition product **66** which required a large excess (10 : 1) of **63** to iodobenzene in order to reduce formation of **66** to 10-20% which was easily separated from **63** by column chromatography.[28]

**Scheme 12**



Hallberg was able to show similar results when using 1-naphthyltriflate (**68**) but this reaction required use of lithium chloride and tri[2-furyl]phosphine (TFP) as binding ligand to afford high ratios of the coupling products **69** and **70** (98 : 2)[28] (Scheme 13). The problem with the single addition products **64** and **69** are that they tend to decompose slowly in air so that long term storage and characterization of these unstable compounds required hydrogenation to their respective 1-methoxycarbonyl-3-arylpyrrolidines **71** and **72** via Pd/C and ammonium formate[28] (Scheme 13). Another option that could be used to prevent decomposition of **64** and **69** is to oxidize them to their respective 3-aryl-1-(methoxycarbonyl)pyrroles, although this was not reported by Hallberg.

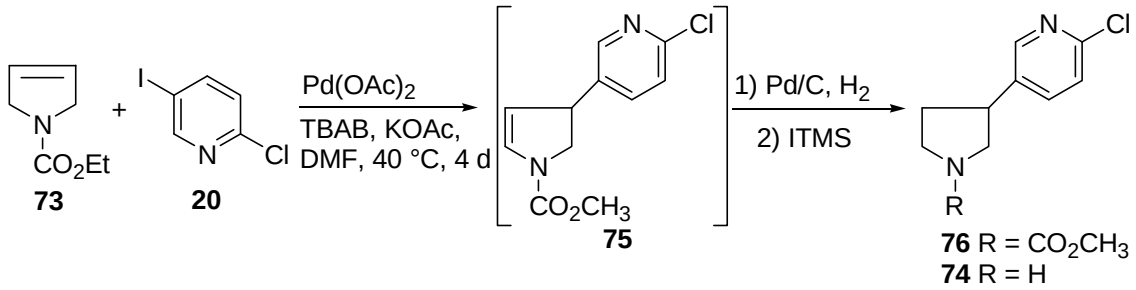
**Scheme 13**




While Hallberg's examples show the effectiveness of using palladium catalyzed cross-coupling reactions on 3-pyrrolines to afford 3-arylpyrrolidines after hydrogenation, the coupling of 2-chloro-5-iodopyridine (**20**) to 1-(ethoxycarbonyl)-3-pyrroline (**73**) was demonstrated by Bai, which just happened to be published in the same issue of the *Journal of Organic Chemistry*. In this work, Bai sought to synthesize an analogue of epibatidine (desethyleneepibatidine, **74**) by removing the bicyclic portion of the

epibatidine[29] (Scheme 14). The palladium catalyzed coupling of **73** and **20** required palladium(II) acetate, tetrabutylammonium bromide, potassium acetate, and DMF (40 °C for 4 d) to afford the coupling product **75** which was immediately hydrogenated with Pd/C and $H_2$ to produce the more stabile 1-(ethoxycarbonyl)-3-[5-(2-chloropyridyl)]pyrrolidine (**76**) in 62% overall yield.[29] Deprotection of **76** with iodotrimethylsilane gave **74**. The hot plate assay experiment for **74** showed no activity when mice were injected with doses up to 4 mg/kg. Bai did report NMR's for **76** and **74** as follows: $^1$H NMR for **76**: (400 MHz, $CDCl_3$) $\delta$ (J in Hz): 8.25 (d, J = 2.4, 1H), 7.49 (dd, J = 8.2, 2.4, 1H), 7.24 (d, J = 8.2, 1H), 4.13 (q, J = 6.9, 2H), 4.84 (m, 1H), 3.63 (m, 1H), 3.25-3.47 (m, 2H), 2.30 (br s, 1H), 1.95 (m, 1H); $^1$H NMR for **74**: (400 MHz, $CDCl_3$) $\delta$ (J in Hz): 8.22 (d, J = 2.4, 1H), 7.52 (dd, J = 8.4, 2.4, 1H), 7.23 (d, J = 8.4, 1H), 5.70 (br s, 1H), 2.83-3.39 (m, 5H), 2.25 (m, 1H), 1.80 (m, 1H); $^{13}$C NMR for **74**: (400 MHz, $CDCl_3$) $\delta$: 149.5, 148.6, 137.6, 137.3, 124.1, 53.6, 46.5, 41.8, 34.0. This route could also utilize an oxidative step immediately following the palladium-coupling reaction to give a stabilized 3-aryl-1-(ethoxycarbonyl)pyrrole instead of the pyrrolidine **76**, but this was not reported by Bai.

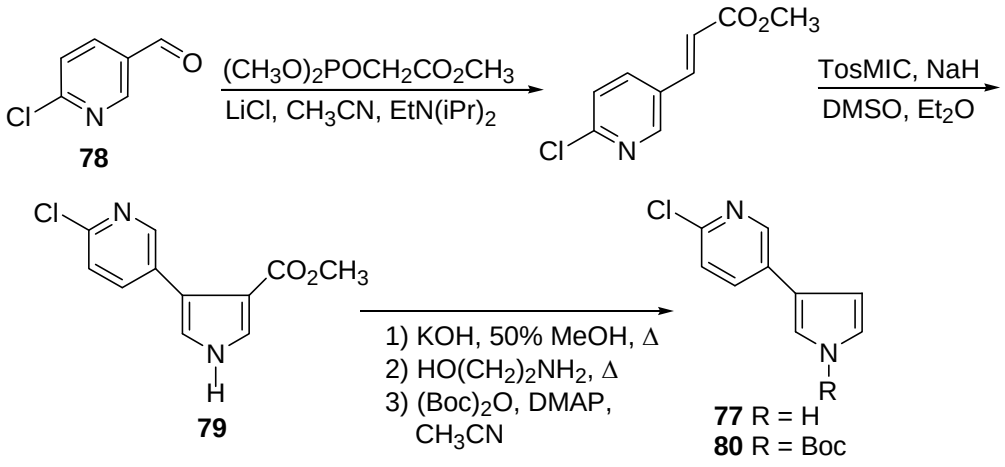
**Scheme 14**




One of the ways to place an aryl substitutent at the 3-position of the pyrrole ring is to follow Trudell's synthesis of 3-aryl pyrroles from the aryl aldehydes. The most

relevant example to our work is the formation of 3-[5-(2-chloropyridyl)]pyrrole (**77**) via the starting material 6-chloronicotinaldehyde (**78**)[30] (Scheme 15). The aldehyde is converted to a 3-arylacrylate ester using a Masamune-Rousch olefination reaction, followed by the van Leusen procedure using toluenesulphonylmethyl isocyanide (TosMIC) to produce the 4-[5-(2-chloropyridyl)]-3-(methoxycarbonyl)pyrrole (**79**) which underwent ester hydrolysis and decarboxylation to give **77**. From that point, **77** could be protected as the 1-(*tert*-butoxycarbonyl)-3-[5-(2-chloropyridyl)]pyrrole (**80**) for long term handling.[30] Although this route does give the necessary substitution at the 3-position of pyrroles, it is long and labor intensive. The NMR spectra for **77** and **80** were reported as follows: $^{1}$H NMR for **77** ($CD_3COCD_3$) $\delta$ (J in Hz): 10.42 (br s, 1H), 8.60 (s, 1H), 7.92 (d, J = 8.2, 1H), 7.35 (d, J = 6.6, 1H), 7.31 (s, 1H), 6.91 (s, 1H), 6.55 (s, 1H); $^{13}$C NMR for **77** ($CD_3COCD_3$) $\delta$: 147.6, 146.5, 135.6, 132.5, 124.7, 120.5, 120.1, 116.7, 106.4; $^{1}$H NMR for **80** ($CD_3COCD_3$) $\delta$ (J in Hz): 8.69 (d, J = 2.4, 1H), 8.06-8.03 (m, 1H), 7.81 (s, 1H), 7.44 (d, J = 2.5, 1H), 7.36 (d, J = 2.1, 1H), 6.75 (s, 1H), 1.64 (s, 9H); $^{13}$C NMR for **80** ($CD_3COCD_3$) $\delta$: 149.4, 149.1, 147.3, 136.5, 130.3, 129.9, 123.9, 122.3, 117.8, 110.6, 84.9, 28.0.[30]

**Scheme 15**

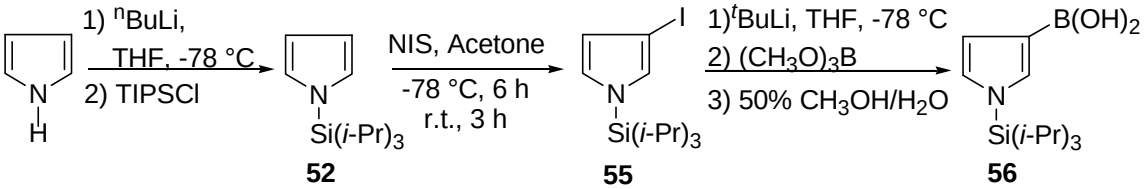


The last two examples by Bai and Trudell show that there are two possible routes that could be used to synthesize a 3-[5-(2-chloropyridyl)]pyrrole for use as a diene in Diels-Alder cycloadditions. Modification of either route is needed in order to afford a diene. Bai's route would require oxidation instead of reduction of the coupled product **75** to afford a diene. Trudells' ring synthesis is complex and requires a substantial amount of steps in order to make the final product, and therefore is not likely the most efficient route to a 3-aryl pyrrole. Between Hallberg's and Bai's work with the palladium catalyzed cross-coupling of 3-pyrrolines, it is not clear which set of reaction conditions will afford the highest yields of a 3-[5-(2-chloropyridyl)]pyrrole and therefore further investigation of Hallberg's and Bai's conditions is required. Although it has been shown that the initial coupling product can undergo reduction, it remains unclear whether or not oxidation will be possible. Intense research is needed if a Diels-Alder reaction can be used to synthesis epibatidine by the route suggested by Daly's mass spectral fragmentation sequence.

## WORK PREVIOUSLY COMPLETE BY THE KETCHA LABORATORY

Work previously accomplished in this laboratory by Tuerdi[33] focused on the synthesis of 3-aryl pyrroles via the Muchowski[27] boronic acid route. Tuerdi protected pyrrole by abstracting the *N*-proton with *n*-butyllithium in dry THF at -78 °C followed by quenching with triisopropylsilyl chloride which, after distillation, afforded to 1-(triisopropylsilyl)pyrrole (**52**) in 98% yield (Scheme 16). From this point, **52** was subjected to iodination via N-iodosuccinimide at -78 °C in acetone to yield 1-(triisopropylsilyl)-3-iodopyrrole (**55**) in 66% yield after column chromatography with hexanes.[33] Halogen metal exchange upon **55** with *n*-butlylithium and subsequent addition of freshly distilled trimethylborate and quenching with 50% methanol in water gave impure 1-(triisopropylsilyl)pyrrole-3-boronic acid (**56**) in 52% yield after workup and recrystallization since boronic acid could not be removed from **56**.[33]

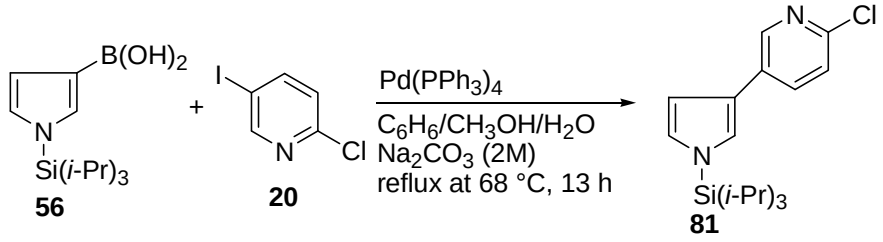
**Scheme 16**




The Suzuki-coupling of **56** with 2-chloro-5-iodopyridine (**20**) with tetrakis(triphenylphosphine)palladium(0) as catalyst gave 1-(triisopropylsilyl)-3-[5-(2-chloropyridyl)]pyrrole (**81**) in 45% yield as a yellow solid (Scheme 17).[33] The $^1$H NMR of **81**: (300 MHz, $CDCl_3$) $\delta$ (J in Hz): 8.55 (d, J = 2.36, 1H), 7.74 (dd, J = 2.46, 8.34, 1H),

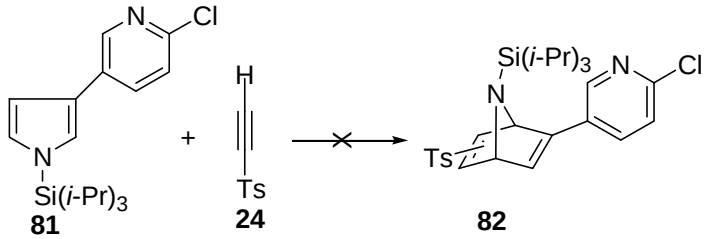
7.25 (d, J = 8.29, 1H), 7.07 (s, 1H), 6.83 (t, J = 2.25, 1H), 6.58 (t, J = 1.06, 1H), 1.47 (sept., J = 7.66, 3H), 1.13 (d, J = 7.35, 18H); $^{13}$C NMR of **81**: (300 MHz, $CDCl_3$) $\delta$: 147.6, 146.2, 135.0, 130.9, 126.0, 123.9, 122.2, 121.2, 108.5, 17.7, 11.6.[33]

**Scheme 17**




The Diels-Alder cycloaddition of **81** with tosylacetylene (**24**) did not yield the desired cycloadduct **82** after heating neat at 85 °C under an argon atmosphere[33] (Scheme 18). Tuerdi believed this was due to the electron rich nature of the pyrrole ring and therefore attempted to convert the triisopropylsilyl protecting group to a more electron withdrawing group.[33]

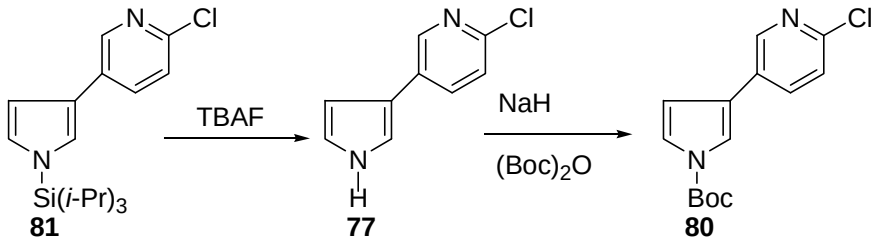
**Scheme 18**




To that end, Tuerdi deprotected **81** with tetrabutylamonium fluoride (TBAF) to isolate 3-[5-(2-chloropyridyl)]pyrrole (**77**) and subsequently utilized NaH and di-*tert*-butyl dicarbonate to produce 1-(*tert*-butoxycarbonyl)-3-[5-(2-chloropyridyl)]pyrrole (**80**) in 95% yield[33] (Scheme 19). Tuerdi reported the NMR data for this conversion as follows: the $^1$H NMR of **77** by Tuerdi: (300 MHz, $CD_3COCD_3$) $\delta$ (J in Hz): 10.40 (1H,

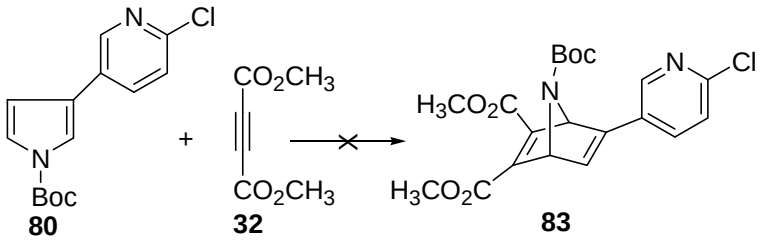
N-H), 8.61 (d, J = 2.4, 1H), 7.93 (dd, J = 2.6, 8.2, 1H), 7.35 (m, 2H), 6.91 (q, J = 2.4), 6.56 (q, J = 2.1, 1H); $^{13}$C NMR of **77** by Tuerdi: (300 MHz, $CD_3COCD_3$) $\delta$: 147.7, 146.6, 135.7, 132.6, 124.7, 120.5, 120.2, 116.7, 106.4; the $^{1}$H NMR of **80** by Tuerdi: (300 MHz, $CDCl_3$) $\delta$ (J in Hz): 8.55 (d, J = 2.3, 1H), 7.75 (dd, J = 2.4, 8.4, 1H), 7.54 (t, J = 1.6, 1H), 7.32-7.29 (m, 2H), 6.50 (dd, J = 1.7, 3.0, 1H), 1.63 (t, J = 20.9, 9H); the $^{13}$C NMR of **80** by Tuerdi: (300 MHz, $CDCl_3$) $\delta$: 149.0, 148.3, 146.4, 135.3, 129.2, 124.1, 123.0, 121.5, 116.5, 84.4, 27.9.[33]

**Scheme 19**




Upon heating of **80** with **24** under neat conditions at 85 °C, there were no signs of the desired Diels-Alder cycloadduct **83**, only decomposition products could be found[33] (Scheme 20). From this point, **80** was reacted with dimethyl acetylenedicarboxylate (**34**) which resulted in the isolation of decomposition products only.[33] These unfortunate results put this synthetic route to epibatidine at a standstill until further investigation of the reactivity of N-substituted pyrroles in Diels-Alder reactions could be completed.

**Scheme 20**



Model studies of the Diels-Alder cycloaddition were carried out by Tuerdi with the simpler substrates, 1-(triisopropylsilyl)pyrrole (**52**) and 1-(phenylsulfonyl)pyrrole (**84**). Even though the Diels-Alder reactions of 1-(trimethylsilyl)pyrrole with highly reactive dienophiles like benzyne and benzyne derivatives were reported to be successful,[34] there were no reports at that time if acetylenic derivatives with electron withdrawing groups could be employed as dienophiles for these pyrroles. Therefore, an investigation of the Diels-Alder reaction of 1-(triisopropylsilyl)pyrrole (**52**) with dimethyl acetylenedicarboxylate (**32**) and tosylacetylene (**24**) was initiated. However, decomposition occurred when a mixture of **52** and **24** was heated at 58 °C; additionally, when the same reagents were stirred in 5.0 M $LiClO_4$-$Et_2O$ solution at room temperature or reflux, no reaction occurred.[33] Tuerdi attempted to perform an $AlCl_3$ catalyzed Diels-Alder reaction between **52** and **32**, but this also led to decomposition at room temperature; and no reaction took place when stirred in 5.0 M $LiClO_4$-$Et_2O$ solution.[33]

In an effort to determine if a more electron withdrawing protecting group could afford the Diels-Alder reaction, 1-(phenylsulfonyl)pyrrole (**84**) and tosylacetylene (**24**) were heated in toluene at 91 °C. The expected cycloadduct **85** from this reaction was not found, only decomposition of the starting materials occurred.[33] When this reaction was repeated in refluxing benzene at 75 °C for 24 hours no reaction took place.[33] However, Tuerdi noted that a new product, postulated as being **85** but not isolated, was formed (by TLC) when the reaction time in refluxing benzene was extended to five days[33] (Scheme 21). Additionally, heating **84** (5 equiv) with **24** (1 equiv) also gave the same product (by TLC) again only in trace amounts.[33] It should also be noted that the 5 M $LiClO_4$-$Et_2O$ solution or $Fe^{3+}$-montmorillonite catalyst did not effect the reaction at all[33] (Table I).

**Scheme 21**

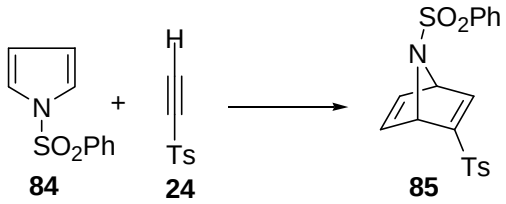


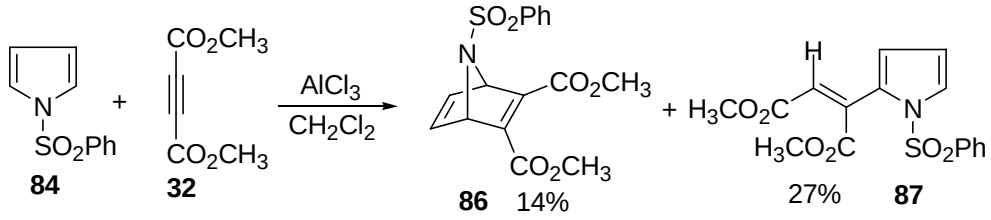

**Table I. Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole with tosylacetylene**

| Entry | Mol ratio (**84**:**32**)[a] | Solvent | Temp (°C) | Time (h) | Product (**85**) |
|---|---|---|---|---|---|
| 1 | 2:1 | Toluene | 91 | 16 | decomp. |
| 2 | 1:1 | Benzene | 75 | 24 | no rxn |
| 3 | 1:1 | Benzene | 75 | 120 | trace rxn |
| 4 | 2:1 | $LiClO_4$-$Et_2O$ | 25 | 96 | no rxn |
| 5 | 5:1 | None | 83 | 12 | trace rxn |

a. reactions completed without catalyst

From this point, Tuerdi attempted to repeat the conditions employed by Bansal[18] by utilizing the Lewis acid ($AlCl_3$) catalyst for the reaction of **84** with dimethyl acetylenedicarboxylate (**32**). The resulting cycloadduct 1-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptadiene-2,3,-dicarboxylate **(86)** was isolated in 14% yield while the Michael adduct **87** was isolated in 27% yield[33] (Scheme 22). This is in contrast to Bansal's isolation of cycloadduct **36** in 93%, thus suggesting that Lewis acid catalysts may not be suitable or equally effective for every 1-(phenylsulfonyl)pyrrole.

**Scheme 22**




Therefore, the cycloaddition of **84** with **32** was attempted under neat conditions without catalyst by Tuerdi using the same 1 : 5 ratio of **84** to **32**.[33] Tuerdi was able to obtain the cycloadduct **86** in 18% yield. Unlike the $AlCl_3$ catalyzed reaction, the neat

reaction did not produce the Michael adduct **87**.[33] Tuerdi noticed that after a certain time the reaction stops without going to completion, and extending the reaction time after this point did not appear to decrease the amount of remaining **84**. However, when two equiv of **84** were heated with one equiv of **32** for 24 hours at 90-95 °C, the yield of the Diels-Alder adduct **86** increased to 45% from the 18% observed when DMAD was in excess.[33] Moreover, when the ratio of **84** to **32** was increased to 4 : 1, the cycloadduct **86** was isolated in a remarkable 85% yield based on the amount of unreacted **84** recovered (Table II).[33] However, when the ratio was decreased to 0.1, no product was isolated under identical reaction conditions (entry 4).[33]

**Table II. Thermal Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole with dimethyl acetylenedicarboxylate.**

| entry | Mol ratio (**84**:**32**) | Temp (°C) | Time (h) | Yield (**86**) |
|---|---|---|---|---|
| 1 | 0.2 | 63 | 36 | 18 % |
| 2 | 0.2 | 100-155 | 18 | 0 |
| 3 | 1.8 | 100 | 24 | 45 % |
| 4 | 0.1 | 95 | 24 | 0 |
| 5 | 4.0 | 95 | 24 | 85 % |

Tuerdi also investigated the Diels-Alder reaction of **84** with methyl vinyl ketone using Lewis acid ($AlCl_3$) and cation exchanged clay catalysts ($Fe^{3+}$-mont. K-10), but decomposition occurred in both cases.[33] It is from this point in which this thesis continues to explore the ability of 1-(phenylsulfonyl)pyrrole to react under Diels-Alder conditions and the synthesis of epibatidine resumes.

## RESULTS AND DISCUSSIONS

The synthetic route chosen for the synthesis of epibatidine (**1**) requires a Diels-Alder cycloaddition of a suitable 3-aryl substituted pyrrole with the dienophile tosylacetylene (**24**). The questions raised about the reactivity of 1-(phenylsulfonyl)pyrrole (**84**) in Diels-Alder reactions with **24** and dimethyl acetylenedicarboxylate (**32**) in Tuerdi's thesis became the starting point of this endeavor towards epibatidine. But first, like any synthetic journeys, large quantities of the necessary starting materials had to be synthesized.

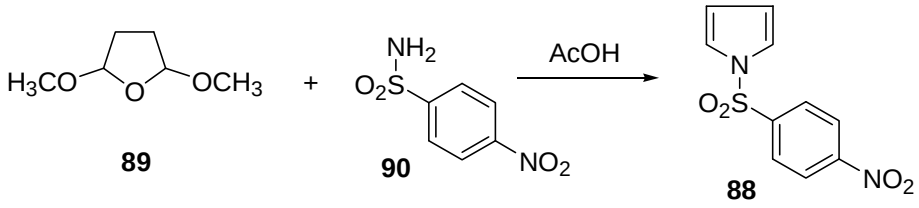
Typically, 1-(phenylsulfonyl)pyrrole (**84**) is synthesized by stirring a mixture of pyrrole and benzenesulfonyl chloride with the phase transfer catalyst tetrabutylammonium hydrogensulfate in a solution of 50/50 methylene chloride and 10% sodium hydroxide overnight. The isolation of **84** is usually straightforward, the spent phase transfer catalyst is filtered off, organic and aqueous solvents are separated, and the aqueous solvent is washed with methylene chloride. Then the combined organic layers are washed with saturated sodium bicarbonate, with distilled water, and finally with brine before drying over anhydrous sodium sulfate. The solvent is reduced *in vacuo* to yield a solid which is usually recrystallized from methanol to give **84** as an off white product. Unfortunately this procedure never worked properly and resulted in a dark brown solid that was only soluble in large quantities of acetone. Attempts to recrystallize this solid in methanol proved unsuccessful due to its low solubility. Purification of the brown solid

by column chromatography was unsuccessful due to the inability to dissolve appreciable quantities of the brown solid in methylene chloride or ethyl acetate so that it could be added to a pre-packed column.

Therefore, it was deemed important to find another route to 1-(phenylsulfonyl)pyrrole (**84**). After reading Gültekin's report[35] on the synthesis and proposed use of 1-(4-nitrobenzenesulfonyl)pyrrole (**88**) in Diels-Alder reactions (Gültekin did not report any Diels-Alder reactions with **88**)[35], it was noted that **84** and **88** could be made from the reaction of 2,5-dimethoxytetrahydrofuran (**89**) with a corresponding primary arylsulfonamide in refluxing acetic acid. In order to repeat Gültekin's synthesis of **88**,[35] it was necessary to acquire 4-nitrophenylsulfonamide (**90**). Although commercially available, it was decided to purchase 4-nitrophenylsulfonyl chloride in case Gültekin's route failed so that the 4-nitrophenylsulfonyl chloride could be used just like phenylsulfonyl chloride in the previously attempted synthetic route to **84**. The conversion of 4-nitrobenzenesulfonyl chloride to 4-nitrophenylsulfonamide (**90**) was accomplished by addition of aqueous ammonia, which gave **90** in 88% yields.

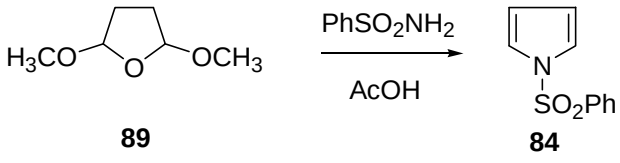
A large scale reaction for the synthesis of 1-(4-nitrobenzenesulfonyl)pyrrole (**88**) was accomplished by reacting a 3-fold excess of 2,5-dimethoxytetrahydrofuran (**89**) to 4-nitrobenzenesulfonamide (**90**) in acetic acid (Scheme 23). The reaction was heated at reflux for 4 h, allowed to cool to room temperature, and then the mixture was poured into ice cold water. A precipitate formed and was collected via vacuum filtration, then recrystallized from methanol to give **88** in a 36% yield. A 3-fold excess of **89** was used to ensure that the primary amine **90** would be consumed in the reaction and also because any unreacted **89** was easily separated due to its greater solubility in water.

**Scheme 23**



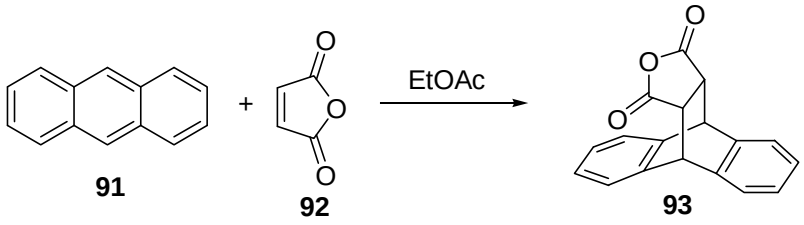

Noting the low yield of this reaction, the procedure was modified for use in the commercial monomode microwave reactor. A microwave vial was loaded with **89**, benzenesulfonamide, and glacial acetic acid and heated in the microwave for 10 min at 170 °C (Scheme 24). When using the previously mentioned work-up, 1-(phenylsulfonyl)pyrrole (**84**) was isolated in 81% yield (based on limiting reagent) after recrystallization. While the use of microwave irradiation can afford **84** in high yields and a shorter reaction time, the microwave vial has inherent quantity limitations and cannot be scaled safely above a total of 1 g of starting materials. Therefore, in order to synthesize large quantities of **84**, it would be necessary to perform this previously described thermal reaction.[35] Thankfully, large quantities of **84** had been previously synthesized in this laboratory and were used for further reactions, but since 1-(4-nitrophenylsulfonyl)pyrrole (**88**) had not been previously synthesized in this laboratory, it was necessary to repeat the large scale synthesis a few times since the microwave conditions were not reasonable for such quantities.

**Scheme 24**



With these necessary starting materials in hand, it was decided to determine if it was possible to perform a known Diels-Alder reaction. The Diels-Alder cycloaddition of anthracene (**91**) and maleic anhydride (**92**) to form the cycloaddition product 9,10,11,15-tetrahydro-9,10[3',4']-furanoanthracene-12,14-dione (**93**) was chosen to be repeated since it involved materials readily available in the lab and was a reaction that had been reported numerous times[36] (Scheme 25). Also, the current Diels-Alder cycloaddition reaction undertaken by the undergraduate organic labs was the reaction of furan with maleic anhydride in diethyl ether which was allowed to react at room temperature for a week. Therefore, the reaction of **91** with **92** was investigated as a way to permit the undergraduate organic lab students to perform a Diels-Alder cycloaddition during the lab period with a simple work-up.

**Scheme 25**




**91** **92** **93**

Initially, three samples of 1 : 2 ratios of anthracene (**91**) to maleic anhydride (**92**) were refluxed in toluene, 1,4-dioxane, and ethyl acetate to determine if the reaction could be accomplished by the organic lab students during the time frame of the lab. After 4 h, only partial conversion of starting materials occurred in all three solvents (by TLC), and it was noted that the ethyl acetate reaction required a total of 8 h to reach completion. After reducing the solvent volume *in vacuo* and adding hexanes, the cycloadduct **93** fell out of ethyl acetate solution and was isolated in 98% yield by vacuum filtration. This reaction under reflux proved to be far too long to be performed in the two hour time

frame for the undergraduate organic lab, and therefore microwave heating was investigated as a faster method of cycloaddition.

A series of reactions of the 1 : 2 ratio of anthracene and maleic anhydride in ethyl acetate were performed in order to determine which temperature would be best to complete the reaction in only 5 min of heating in a commercial monomode microwave reactor using a sealed vial. The two reactions undertaken at 150 °C resulted in 49% and 59% conversion, respectively, and the temperature was increased to 170 °C and resulted in an initial yield for cycloadduct **93** of 32% which was increased to 93% after four additional reactions under the same time and temperature conditions. The key to increasing the yield of the reaction was to cool the microwave vial in an ice bath and then pour the contents into 35 mL of ice cold hexanes, followed by continued cooling in an ice bath until precipitation ceased and then using a Hirsch funnel for vacuum filtration.

Although these results are very helpful in proving that a Diels-Alder cycloaddition can be undertaken in the undergraduate organic teaching lab with the use of a commercially available microwave reactor, the tedious workup conditions may prove too daunting for the organic teaching lab. Another key factor is the total microwave reaction time. Although the reaction requires 5 min of heating, each sample run would require between 8 to 12 min to heat to temperature, react at temperature, and then cool down. This doubling of the reaction time may not be convenient if the only microwave available is a one vial reactor since a large section (18 pairs of students) could take up to 3 h to run every microwave sample.

Focus now returned to completing Tuerdi's investigation of the reactivity of 1-(phenylsulfonyl)pyrrole (**84**) with the acetylenic dienophiles **24** and **32**. Repetition of the

thermal reaction of a 4 : 1 ratio of **84** to dimethyl acetylenedicarboxylate (**32**) neat at 95 °C, proved to be a dismal failure with the cycloadduct **86** being isolated in 1.5% (21% based on recovered **84**), not the 85% (based on recovered **84**) noted by Tuerdi.[33] Repeated attempts of this Diels-Alder reaction using Tuerdi's thermal conditions could not afford yields (based on recovered **84**) of the cycloadduct **86** that Tuerdi noticed.

Noting the success of the anthracene and maleic anhydride reactions in the microwave, an attempt to perform the Diels-Alder cycloaddition of 1-(phenylsulfonyl)pyrrole (**84**) with dimethyl acetylenedicarboxylate (**32**) in a commercial monomode microwave reactor was made. Multiple reactions were tried using various solvents (toluene, acetonitrile, nitromethane, but not ethyl acetate), temperatures, and reactions times and most yielded only trace amounts of cycloadduct **86** (by TLC). The best amount of cycloadduct **86** noted (by TLC) occurred when the reaction was performed at 140 °C and 30 min. Failure seemed to follow this Diels-Alder reaction through every attempt at isolating large quantities of the desired cycloadduct.

Recalling the original microwave assisted organic synthesis reactions performed by Gedye[37] and Giguere[36d], an old domestic microwave was setup in an available hood. The 700 Watt multimode microwave oven was used to perform a series of solventless cycloadditions by reacting 1-(phenylsulfonyl)pyrrole (**84**) with dimethyl acetylenedicarboxylate (**32**) using silica gel as a medium. After dissolving **84** and **32** in a minimal amount of methylene chloride in an Erlenmeyer flask, silica gel was added and the slurry was uniformly mixed and placed under vacuum for 2 h or until a dry, fine powder was observed at the bottom of the flask. Different ratios of **84** to **32** were heated at different times and power levels and all reactions had a 50 mL beaker placed over the

neck of the Erlenmeyer flask to keep splatter to a minimum inside the microwave (Table III). After separating the reacted material from the silica gel and performing flash chromatography, the best choice of conditions was found to correspond to a ratio of 1 : 4 of **84** to **32**, a time of 2 min, and full power to afford 26.6% isolated yield of **86** and a yield of 72% of **86** based on recovered **84** which was close to Tuerdi's 85% yield. There were no traces (by TLC) of residual **32** after the reaction reached completion, which is strange since Tuerdi noted that a 4:1 ratio of **84** to **32** was required to use up all of the dienophile.[33]

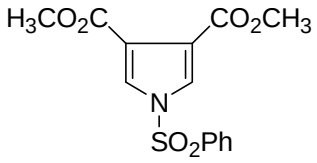
**Table III. Mulitmode microwave Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole and dimethyl acetylenedicarboxylate**

| Trial | mol ratio (**84** : **32**) | Time (min) | Power (%) | Isolated Yield | Yield[a] |
|---|---|---|---|---|---|
| 1 | 1 : 1 | 2 | 100 | 10.5 % | 33.2 % |
| 2 | 1 : 1 | 5 | 50 | 9.6 % | 36.1 % |
| 3 | 1 : 2 | 2 | 100 | 20.1 % | --- |
| 4 | 1 : 4 | 2 | 100 | 26.6 % | 72.9 % |
| 5 | 1 : 4 | 10 | 20 | 20.0 % | --- |

a. yields based on actual diene reacted

Something interesting to note was the formation of another product, the retro Diels-Alder adduct dimethyl 1-(phenylsulfonyl)pyrrole-3,4-dicarboxylate (**94**). This retro product could be isolated from the reaction of a 1 : 4 ratio of **84** to **32** at 2 min at full power as a by-product of the reaction (12.2% isolated, 33.4% based on recovered **84**) but the preferred method was to react a 1 : 4 ratio of **84** to **32** for 10 min at full power since these conditions resulted in only trace amounts of cycloadduct **86** and proved to be easier for isolation **94** from the residual starting materials, although lower yields (2.1%) were noticed. Unfortunately, the Michael-adduct **87** that Tuerdi had noticed was never isolated from any of these reactions. There was also a drawback to the use of the solventless

conditions, separating the products and residual starting materials from the silica gel required copious amounts of methanol and evaporation before flash chromatography could be performed. At one time it was suggested to add the silica gel from the reaction vessel directly to the top of a pre-packed column, but this separation only seemed to increase subsequent overlaps in collection fractions.




**94**

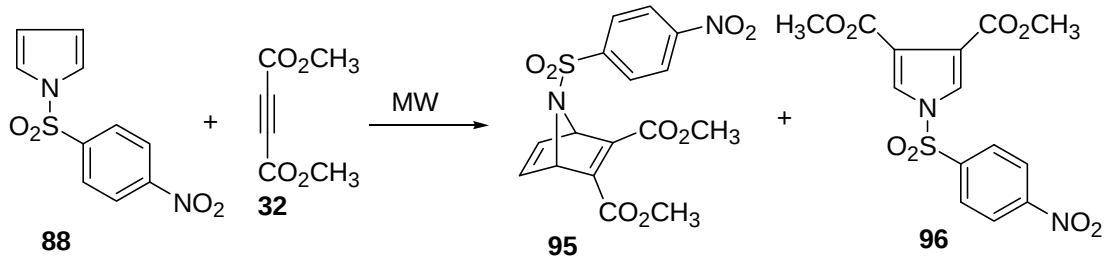
In the hopes of limiting the formation of the retro Diels-Alder product **94** and noting the success of the anthracene and maleic anhydride reactions, a return to the monomode microwave for the cycloaddition of 1-(phenylsulfonyl)pyrrole (**84**) with dimethyl acetylenedicarboxylate (**32**) was in order. This time, the reaction was tried using the 1 : 4 ratio of **84** to **32** neat for 20 min at 140 °C. The cycloadduct **86** was easily isolated in 23.4% yield (23.8% yield based on recovered **84**) along with only trace amounts of retro product **94** after pouring the contents of the microwave vial directly onto a pre-packed flash chromatography column for purification.

This reaction was also attempted at higher temperatures and shorter times to investigate if a yield increase could occur. Using ethyl acetate as solvent in the same ratios previously used, a vial was heated at 170 °C for 10 min and only 13.5% of cycloadduct **86** could be isolated, retro Diels-Alder **94** was not specifically isolated in this reaction, although it was present by TLC. A polar protic solvent, methanol, was also tried but initial pressure readings resulted in the reaction being lowered to 160 °C and run

for 20 min to yield **86** in 12%, again **94** was not isolated but was noted by TLC. It should be noted that, as compared to the multimode reactions, there was residual **32** along with **84** after the reaction was completed.

With a good understanding of the reactivity of 1-(phenylsulfonyl)pyrrole (**84**) with dimethyl acetylenedicarboxylate (**32**), focus turned to the reactivity of 1-(4-nitrophenylsulfonyl)pyrrole (**88**) with **32** and to investigate if the cycloadduct **95** and retro Diels-Alder adduct **96** could be isolated (Scheme 26). The neat monomode reaction was chosen as the main point of comparison since this allowed shorter reaction times and simple flash chromatography purification with little workup. Initial attempts to perform the reaction of a 1 : 4 ratio of **88** and **32** neat at 140 °C for upwards of 30 min under microwave irradiation gave little to no trace of the desired products. Seeing a new roadblock, it was finally determined that heating a 1 : 4 ratio of **88** and **32** for 170 °C for 10 min could yield products via TLC and resulted in the isolation of two products. The cycloadduct 1-(4-nitrophenylsulfonyl)-7-azabicyclo[2.2.1]heptadiene-2,3,-dicarboxylate (**95**) was isolated in a yield of 16.8% (33.6% based on recovered **88**) while the retro Diels-Alder product dimethyl 1-(4-nitrophenylsulfonyl)pyrrole-3,4-dicarboxylate (**96**) was recovered in a yield of 7.3% (13.6% based on recovered **88**). The reaction is therefore successful, 1-(4-nitrophenylsulfonyl)pyrrole (**88**) can undergo Diels-Alder cycloaddition with an acetylenic dienophile (**32**) but the conditions are not optimized.

**Scheme 26**



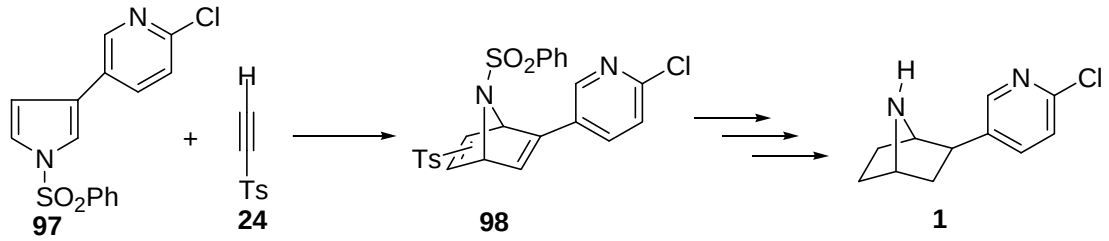

In order to determine if 1-(4-nitrophenylsulfonyl)pyrrole (**88**) gave the same reactivity as that of 1-(phenylsulfonyl)pyrrole (**84**), it became important to find a set of reaction conditions to best compare the yields of cycloadducts. Due to the determination that **88** did not react with **32** in noticeable yields at 140 °C under neat conditions, and instead of repeating the cycloaddition of **84** and **32** neat at 170 °C, the solvent ethyl acetate was chosen to perform the reaction of **88** and **32** at 170 °C for 10 min. Once a reaction of a 1 : 4 ratio of **88** to **32** was completed at 170 °C for 10 min in ethyl acetate, the cycloadduct **95** was isolated in only a 3.1% yield while retro Diels-Alder product **96** was isolated in a 8.0% yield. When compared to the reaction of **84** and **32** under the same conditions, there is a marked decrease in desired cycloadduct formation at this temperature and time for **88**. This is in contrast to the literature that has suggested that when the electron withdrawing ability of the N-subsitutent for pyrrole is increased, greater yields for cycloadducts should be noted.[15,16,35] The lower yields of the cycloadduct in experiments with **88** may be based on the purification techniques utilized (flash chromatography) or may be a result of the temperature used, so future investigation of the reactivity of **88** as compared to **84** is needed.

It should be noted that the retro Diels-Alder cycloadduct **96** could be isolated in higher quantities (although lower yields) by the solventless multimode reaction of a 1 : 4

ratio of **88** and **32** on silica gel for 5 min at full power (700 Watts). Although only a yield of 1.26% pure **96** could be isolated, the material was of enough quantity to allow for combustion analysis, NMR, and GC/MS. This was the only multimode reaction of **88** attempted and the cycloadduct **95** was not noticed (by TLC).

Now that it has been determined that a microwave Diels-Alder cycloaddition can occur between 1-(phenylsulfonyl)pyrrole (**84**) and dimethyl acetylenedicarboxylate (**32**), the focus of the research now turned back to the synthesis of epibatidine (**1**). The plan was to synthesize 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole (**97**) and react it with tosylacetylene (**24**) to form the epibatidine bicylic precursor (**98**) that should undergo a series of reactions similar to Clayton's route[11] to epibatidine, thus constituting a formal total synthesis of this natural product (Scheme 27). This plan required synthesis of the dienophile **24** and the diene **97** with a subsequent Diels-Alder reaction of the two molecules. Since the reactivity of **97** was not known, nor was it known if **97** could even be synthesized, a model Diels-Alder study of 1-(phenylsulfonyl)pyrrole (**84**) with **24** would be required.

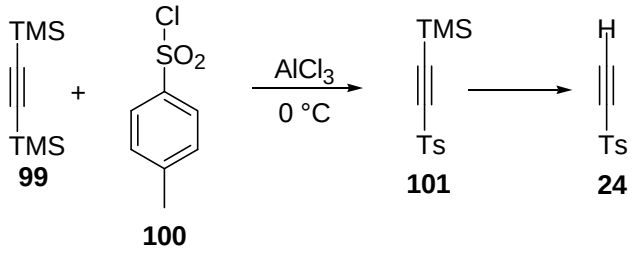
**Scheme 27**




The synthesis of tosylacetylene (**24**) has been reported in the literature by Paquette[38] and Trudell[39] by a two step process that starts with the reaction of bis(trimethylsilyl)acetylene (**99**) with *p*-toluenesulfonyl chloride (**100**) in the presence of

the Lewis acid aluminum chloride in an inert atmostphere (Scheme 28). The product of this reaction, *p*-tolyl-2-(trimethylsilyl)ethynyl sulfone (**101**), is then converted to tosylacetylene (**24**) by removal of the trimethylsilyl protecting group by either adding a buffer solution of 6.2 x $10^{-3}$ M potassium bicarbonate and 6.2 x $10^{-3}$ M potassium carbonate to the crude **101** with additional workup[38] or passing the crude **101** through a well packed silica gel column using the eluent 90 : 10, hexanes : ethyl acetate.[39]

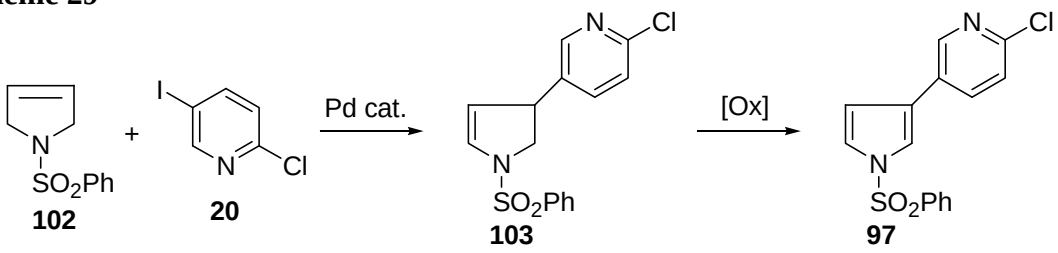
**Scheme 28**




At first, this reaction appeared to be straightforward, but problems quickly arose. The addition of a solution of 1 equivalent of **99** in methylene chloride to a solution of 1.12 equivalents of **100** and 1.12 equivalents of $AlCl_3$ in methylene chloride (both solutions under inert atmospheres at 0 °C) was allowed to stir overnight at room temperature to afford **101** in 93.4% yields after workup. It is here that the deprotection does not occur as described in the literature. The use of Paquette's method[38] with a freshly prepared buffer solution and subsequent workup resulted in incomplete conversion of **101** to **24** (by TLC). Trudell's flash chromatography method[39] is able to effect the deprotection, but requires multiple well-packed silica gel columns to perform the deprotection. It required an average of three to four flash columns to effect the conversion of **101** to **24** in order to obtain substantial quantities of **24** in high purity.

The time consuming nature of performing multiple columns in order to purify and procure the large quantities of tosylacetylene (**24**) necessary for subsequent Diels-Alder reactions led to performing work towards the synthesis of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole (**97**). There are three possible routes that could be used to synthesize **97**. The first route would be a Suzuki palladium catalyzed cross coupling of a pyrrole-3-boronic acid with 2-chloro-5-iodopyridine (**20**) which has already been done by Tuerdi[33] but is unrealistic due to the number of steps. The second possibility is to utilize Trudell's route to 1-(*tert*-butoxycarbonyl)-3-[5-(2-chloropyridyl)]pyrrole (**80**) via ring synthesis[30] but the lack of any experience using TosMIC ruled out this route to **97**. The final possible route to **97** is an adaptation of the palladium catalyzed cross-coupling reaction of a N-protected 3-pyrroline with **20** as previously shown by Hallberg[28] and Bai.[29] It was decided that the coupling of 1-(phenylsulfonyl)-3-pyrroline (**102**) with **20** to afford 1-(phenylsulfonyl)-4-[5-(2-chloropyridyl)]-2-pyrroline (**103**) could be accomplished and subsequent oxidation could afford **97** (Scheme 29), although it was unclear if the oxidative step would be successful. Therefore, it was essential to produce copious quantities of **102** and **20** in order to investigate the possible conditions for the palladium catalyzed cross-coupling reaction.

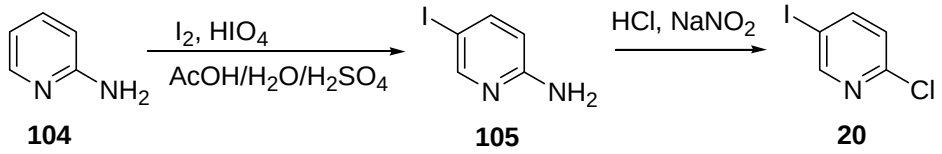
**Scheme 29**



The synthesis of 2-chloro-5-iodopyridine (**20**) was accomplished via the conversion of 2-aminopyridine (**104**) to 2-amino-5-iodopyridine (**105**) and subsequent conversion of **105** to the 2-chloro derivate **20** (Scheme 30). Taking a page from Tuerdi's thesis, the iodination of **104** was accomplished with modification of the procedures reported by Hama.[40a] A mixture of **104** (5 equiv.), periodic acid dihydrate (1 equiv.), and iodine (2 equiv.) was heated in a mixture of acetic acid/water/sulfuric acid (300:60:9) at 75-80 °C overnight to give two isomers, **105** and 2-amino-3-iodopyridine. After quenching with aqueous dilute sodium thiosulfate to remove unreacted iodine, Hama's procedure calls for extraction with ether and then washing the extract with aqueous dilute NaOH, drying with anhydrous potassium carbonate, and reducing the ether *in vacuo*.[40a] It was here that Tuerdi noted that the undesired 2-amino-3-iodopyridine had a greater solubility in ether than did the desired **105** isomer.[33] Following Tuerdi's observation, extraction of the aqueous layer with ether took place making sure that small volumes of ether were used in order to limit extraction of excessive amounts of the **105** isomer. It was also found that by taking samples of the aqueous layer after each ether extraction and performing TLC analysis in methylene chloride, the removal of the undesired 2-chloro-3-iodopyridine could be monitored while limiting the loss of **20**. Once the extraction was complete, addition of 10% aqueous NaOH to the aqueous layer caused precipitation of the 5-iodo isomer **105** which was then collected via vacuum filtration. Recrystallization of the crude **105** in methanol gave pure off-white crystals in 37.2% yield. The yield can be increased by subjecting the ether extract to flash chromatography, but this was not done. The conversion of **105** to **20** was straightforward and occurred by dissolving **105** in cold HCl and slowly adding $NaNO_2$. The mixture was allowed to stir until it reached

room temperature, at which time it was neutralized by aqueous 50% NaOH and the precipitate collected and recrystallized from methanol to give pure **20** in a 40.9% yield.

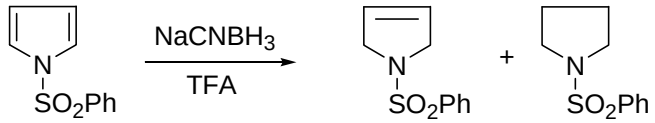
**Scheme 30**




**104** **105** **20**

With one of the necessary cross-coupling reagents in hand, the synthesis of the other began. A report by Ketcha showed that 1-(phenylsulfonyl)pyrrole (**84**) underwent reduction to 1-(phenylsulfonyl)-3-pyrroline (**102**) by use of $NaCNBH_3$ and trifluoroacetic acid (TFA)[41] (Scheme 31). This reaction was undertaken initially on the 0.5 g scale as reported by Ketcha.[41] When confidence in the reduction reaction had been built, the synthesis of **102** was scaled up to the reduction of 3 g quantities of **84** at a time. Ketcha had warned that a fire could be generated if $NaCNBH_3$ was added too quickly to the solution,[41] and this had yet to be observed in the reactions performed. But, upon further scale-up, a fire did occur and resulted in all subsequent reactions not exceeding a 5 g scale. The reduction of **84** not only resulted in **102**, but **102** was further reduced to 1-(phenylsulfonyl)pyrrolidine (**106**) which had the same retention factor as **102** by TLC. The ratio of **102** to **106** was determined by GC/MS to be 10 : 1.

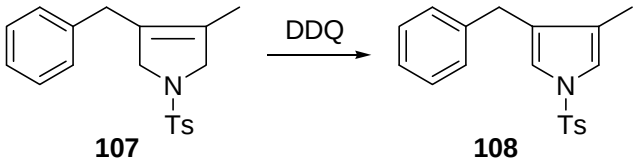
**Scheme 31**




**84** **102** **106**

Although the reduction of **84** to **102** could be afforded, it remained unclear whether or not **102** could be oxidized. It was essential to determine the conditions necessary to afford oxidation of **102**, because if this could not be done, the oxidation of the product from the palladium catalyzed cross-coupling reaction may prove impossible. A review of literature found two possible conditions that could afford this oxidation; the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with heating to convert both 3-pyrroline and 2-pyrroline to pyrroles[42] or the use of manganese oxide on silica under multimode microwave heating to afford the oxidation of tetra-substituted pyrrolidines to pyrroles.[43] An example stood out, the use of DDQ to afford the oxidation of 1-(*p*-toluenesulfonyl)-3-benzyl-4-methyl-3-pyrroline (**107**) to its subsequent pyrrole (**108**) since this example had a similar N-substituted electron withdrawing group and two electron donating groups[42c] (Scheme 32). An oxidation of **102** to **84** with a 1.5 molar equivalent of DDQ under monomode microwave irradiation (5 min, 180 °C) was performed as a test and proved to be successful, this reaction was able to yield **84** in 81.3%.

**Scheme 32**

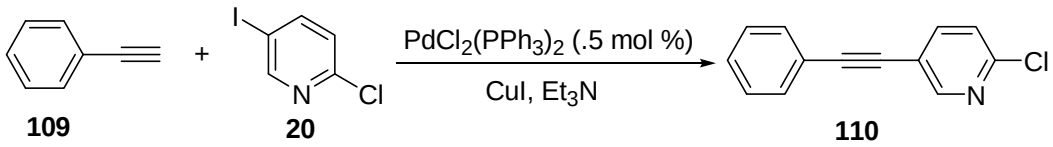



**107** **108**

Now that both required cross-coupling reagents were available, the opportunity to perform a test of the palladium catalyzed cross-coupling reaction was undertaken. The reaction of phenylacetylene (**109**) and 2-chloro-5-iodopyridine (**20**) under Sonogashira conditions[44] to afford 2-chloro-5-(phenylethynyl)pyridine (**109**) was done in order to

confirm that coupling would occur at the iodo position of **20** (Scheme 33). A round bottom flask was loaded with a 1 : 1 ratio of **109** to **20**, 0.5 mole % $PdCl_2(PPh_3)_2$, 2 mole percent copper(I)-iodide (CuI), and triethylamine ($Et_3N$) as solvent and placed in an ice bath. After stirring at room temperature for 18 h, the solvent was reduced *in vacuo* and the contents poured into ice water that afforded a precipitate that, once recrystallized, proved to be pure **110** (71.3% yield). It should be noted that the melting point for the recrystallized **110** was 76-78 °C, while the literature[42g] melting point was 68-69 °C, and repeated recrystallizations of **110** did not result in melting points lower than 76-78 °C. Also, the $^1H$ NMR, $^{13}C$ NMR, and MS of recrystallized **110** were all in agreement with the literature values.[42g]

**Scheme 33**




**109** **20** **110**

Investigation of the palladium catalyzed cross-coupling between a 1 : 1 ratio of 1-(phenylsulfonyl)-3-pyrroline (**102**) and 2-chloro-5-iodopyridine (**20**) took place under three conditions, Sonogashira,[44] Bai,[29] and Hallberg[28] as set forth in Table IV. The Sonogashira conditions (entry 1) afforded no products after being stirred at room temperature for 7 days. This was an expected result since the Sonogashira reaction works best with arylacetylenes.[44] The reaction under Bai's conditions[29] (entry 2) did not afford any coupling products (by GC/MS and TLC) after reacting for 7 days at 40 °C. Success was found from the coupling reaction that utilized Hallberg's conditions[28] (entry 3). The reaction was checked after 24 h (by TLC and GC/MS) and afforded a new spot (by TLC)

and showed one additional GC peak (since both starting materials were still present after reaction) that had an *m/z* of 320 ($M^+$).

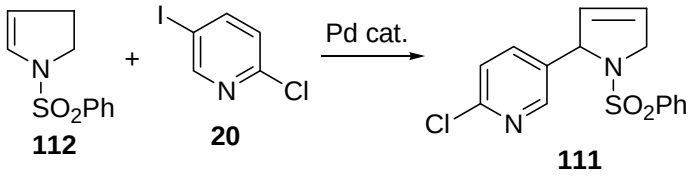
**Table IV. Reaction conditions for Pd catalyzed cross-coupling of 1-(phenylsulfonyl)-3-pyrroline with 2-chloro-5-iodopyridine**

| Condition | Pd cat. (mol %) | Co-reagent(s) | Solvent | Temp (°C) | Time |
|---|---|---|---|---|---|
| Sonogashira | $PdCl_2(PPh_3)_2$ (0.5) | CuI (2 mol %) | $Et_3N$ | 0 – 23 | 7 d |
| Bai | $Pd(OAc)_2$ (0.5) | TBAB, KOAc | DMF | 40 | 7 d |
| Hallberg | $Pd(OAc)_2$ (0.5) | $PPh_3$, $Ag_2CO_3$ | DMF | 100 | 24 h |

This peak isolated from the Hallberg conditions with an *m/z* 320 ($M^+$) was believed to be the coupling product 1-(phenylsulfonyl)-4-[5-(2-chloropyridyl)]-2-pyrroline (**103**), although it could have been 1-(phenylsulfonyl)-2-[5-(2-chloropyridyl)]-3-pyrroline (**111**). The isomer **111** would have arrived from the cross-coupling of 1-(phenylsulfonyl)-2-pyrroline (**112**) which would have been generated from isomerization of **102** with heat (Scheme 34). When Hallberg[28] reported his work using 1-(methoxycarbonyl)-3-pyrroline (**63**), he utilized $Ag_2CO_3$ as a base to eliminate isomerization to 1-(methoxycarbonyl)-2-pyrroline (**67**) upon heating, therefore it was assumed that $Ag_2CO_3$ would have the same effect on the 1-(phenysulfonyl)-3-pyrroline (**102**) and limit its isomerization upon heating. The only way to confirm the identity of the *m/z* 320 ($M^+$) product as either **103** or **111** would have been to compare the $^1H$ NMR proton splitting patterns of the pyrroline rings. The splitting pattern of **103** should give a two hydrogen doublet at 3.37 ppm ($C_5$), a one hydrogen double triplet at 3.69 ppm ($C_4$), a one hydrogen double doublet at 4.49 ppm ($C_3$), and a one hydrogen double at 5.77 ppm ($C_2$); the splitting pattern for **111** should give a two hydrogen doublet at 3.78 ppm ($C_5$), a one hydrogen double triplet at 5.75 ppm ($C_4$), a one hydrogen double doublet at 5.75 ppm ($C_3$), and a one hydrogen doublet at 4.59 ppm ($C_2$). These splitting patterns could not be

used to confirm the identity of the product because it could not be isolated from the reaction mixture, the product decomposed before purification by flash chromatography could occur.

**Scheme 34**




Large scale reactions under the Hallberg[28] conditions tended to result in limited amounts of the putative coupling product **103** with starting materials being recovered. Therefore, the reaction was performed under microwave heating using 1.0 mole percent $Pd(OAc)_2$ and 0.7 mole percent $Ag_2CO_3$ at 180 °C for 25 min to afford better conversion of starting materials to product. The lack of the $PPh_3$ ligand, which was done by accident, did not seem to have an effect on the reaction. Although oxidation of **103** to **97**, along with **102** to **84**, was subsequently performed with DDQ via a monomode microwave reactor, this microwave reaction proved to be dangerous without purification of the coupling products. High differential pressures were generated during the DDQ oxidation reactions (15-20 bar) and many vials required manual release of the pressure (by inserting a needle to pierce the septum in the cap of the microwave vial) after cooling to 40 °C would not reduce the differential pressure below 4 bar. Although it is typical for the pressure to increase in a monomode microwave with heating as the solvent begins to boil, this pressure tends to reduce with cooling. In this case, the increase in pressure may be the result of $CO_2$ gas being evolved when DDQ is in the presence of $Pd(OAc)_2$ and

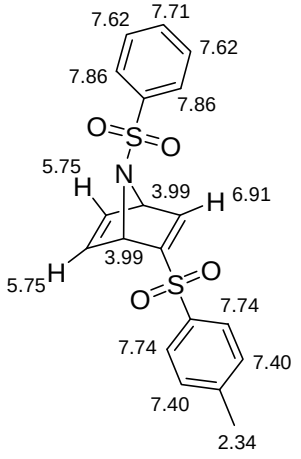
$Ag_2CO_3$ since this gas production was not noticed in the oxidation of **102** to **84** with DDQ under microwave heating or during the coupling reactions.

Therefore, to avoid blowing up the microwave reactor, thermal heating of the crude coupling reaction mixtures with 1.5 molar equivalents of DDQ at 100 °C was utilized. One advantage to the thermal reaction was the isolation of unreacted **102** (which was not oxidized to **84**, and no **84** could be found via GC/MS or TLC analysis) after the reaction mixture was heated for 7 days, although it should be noted that this was not confirmed by repeating the oxidation of **102** with DDQ under thermal conditions. Purification of the oxidized product by flash chromatography yielded 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole (**97**) in 1.08%. The low yield of the reaction requires further optimization of the reaction conditions.

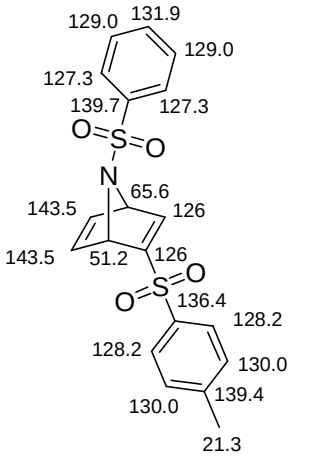
Now that the desired diene, **97**, had been isolated in small quantities, the final steps began to present problems. A model Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole (**84**) with tosylacetylene (**24**) to form the bicylic product **85** was performed at 140 °C for 20 min in the monomode microwave. A new UV active chromophore of lower $R_f$ than the starting materials was noted by TLC (eluent methylene chloride) and this chromophore was then isolated by column chromatography with great care. When analysis of this material was performed, the $^1H$ NMR ($CDCl_3$) lacked bridging hydrogens at 3.99 ppm nor did the vinyl hydrogens show up at 5.75 ppm (as predicted by NMR prediction software) but a multiplet showed up at 2.41-2.45 ppm that is similar to the 2.48 ppm of the toluene $CH_3$ peak from tosylacetylene (**24**). The $^{13}C$ NMR ($CDCl_3$) spectrum showed a peak at 20.7 ppm that is similar to the 21.8 ppm peak for the toluene $CH_3$ peak from tosylacetylene (**24**), but lacked peaks for the bridging

carbons (65.6 and 51.2 ppm as predicted by NMR prediction software). A GC/MS sample of this product showed only solvent contaminants. The combustion analysis for this material returned %C as 59.57%, %H as 4.45%, and %N as 0.39%, therefore the lack of any nitrogen atoms rules out this product as being the cycloadduct **85**. It is unclear what this material is since high resolution MS was not performed and without percent sulfur or percent oxygen analysis, this particular molecule remains unknown. There were no other UV active chromophores that could be isolated readily from the Diels-Alder reaction of **84** and **24**.

$^{1}$H NMR predictions for **85**




$^{13}$C NMR predictions for **85**




Once it was realized that the desired cycloadduct **85** from the Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole (**84**) and tosylacetylene (**24**) could not be isolated, this cycloaddition route for epibatidine (**1**) synthesis proved to be unrealistic. An attempt was made to react 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole (**97**) with **24** neat at 140 °C for 20 min in the hopes that **97** may undergo the desired Diels-Alder cycloaddition. All hopes of isolating the desired epibatidine precursor were quenched when only the

starting materials were noted by TLC and no other UV active chromophores were present.

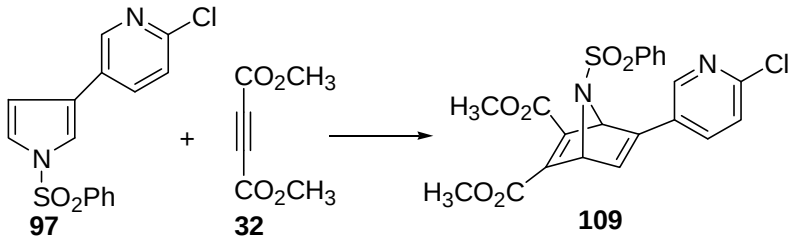
The proposed synthetic route to epibatidine (**1**) from 1-(phenylsulfonyl)pyrrole (**84**) has not been a complete failure. A better understanding of the Diels-Alder reactivity of **84** with dimethyl acetylenedicarboxylate (**32**) has been accomplished, along with isolation and characterization of the retro Diels-Alder product **94** from this reaction. The Diels-Alder reaction of 1-(4-nitrophenylsulfonyl)pyrrole (**88**) with **32** has been accomplished and both the cycloadduct **95** and retro product **96** were isolated and characterized. The synthesis of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole (**97**) through the palladium catalyzed cross-coupling reaction of 1-(phenylsulfonyl)-3-pyrroline (**102**) and 2-chloro-5-iodopyridine (**20**) and subsequent oxidation with DDQ was successful, although room for optimization still exists. It is the Diels-Alder reaction of **84** or **97** with tosylacetylene (**24**) that has not occurred and has resulted in more questions about the byproducts of the reaction than there are answers.

## FUTURE WORK

There are unresolved issues that need to be addressed before this synthetic route to epibatidine (**1**) can be scrapped. The first issue is a full characterization of the unknown product from the Diels-Alder cycloaddition of 1-(phenylsulfonyl)pyrrole (**84**) with tosylacetylene (**24**). One option would be to determine the exact mass of the unknown material through high resolution mass spectrometry. Another option would be to determine the mass fragmentation pattern and parent ion of this unknown product via LC/MS. It may be possible to find cycloadduct **85** if a crude reaction sample is run on a LC/MS.

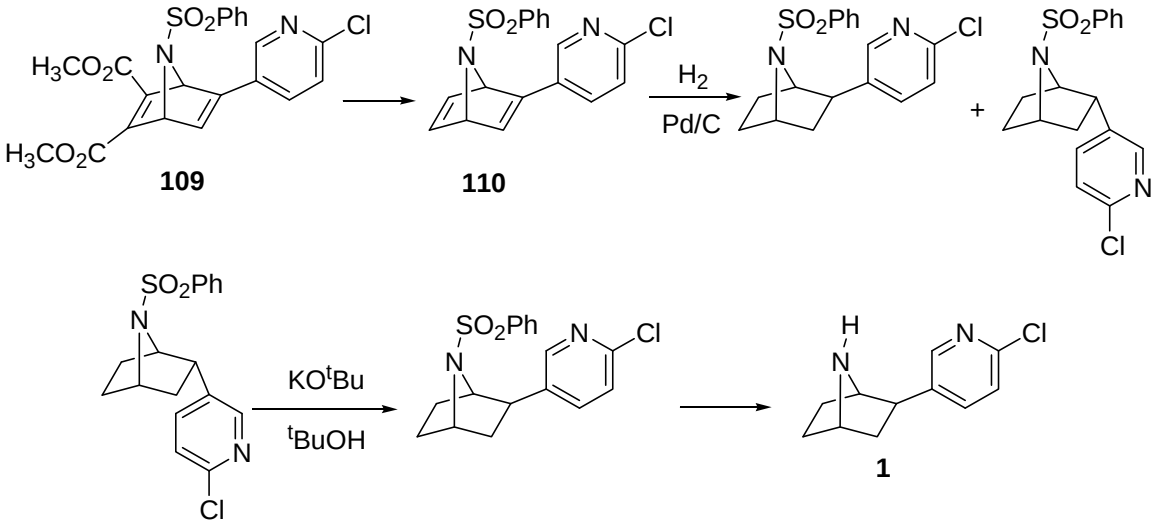
The second unresolved issue is that of the reactivity of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole (**97**) towards cycloaddition reactions. Recalling the success of the Diels-Alder cycloaddition of **84** with dimethyl acetylenedicarboxylate (**32**), it may be possible to perform this same reaction by substituting **97** for **84** (Scheme 33). If this reaction proves successful, the cycloadduct **109** could be used as the bicyclic precursor to epibatidine (**1**).

**Scheme 33**



The conversion of cycloadduct **109** to epibatidine would first require conversion of the methyl carboxylate groups to carboxylic acids and subsequent decarboxylation which should result in **110** (Scheme 34). Hydrogenation of **110** should yield two products, *endo*- and *exo*-N-(phenylsulfonyl)epibatidine which should be separable by flash chromatography. It should be possible to epimerize the *endo*-isomer to the *exo*-isomer with potassium *tert*-butoxide in *tert*-butyl alcohol as Fletcher[10] reported in his route to epibatidine. The final step would be deprotection of the *exo*-N-(phenylsulfonyl)epibatidine.

**Scheme 34**




The final issue to be resolved would be optimization of the palladium coupling and oxidation reactions for the synthesis of **97**. A simple solution may be an increase in the amount of $Pd(OAc)_2$ catalyst used from 1.0 mole percent to 1.5 mole percent. Another option may be to either utilize AgOAc instead of $Ag_2CO_3$ as base, or use a larger molar equivalence of the $Ag_2CO_3$. There is the possibility that this reaction is already at a maximum yield, although that is difficult to believe.

## EXPERIMENTAL

Melting points were determined via the use of open capillaries with an Electrothermal melting point apparatus and are reported uncorrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN. The $^{1}H$ and $^{13}C$ NMR data were obtained on a Bruker Avance 300 MHz NMR in $CDCl_3$ solution unless otherwise indicated. The chemical shifts are reported in δ (ppm) downfield from tetramethylsilane as an internal standard; coupling constants (J) are in Hz. The following abbreviations are used to describe peak patterns where appropriate: s, singlet; d, doublet, dd, double doublet; t, triplet; q, quartet; dt, double triplet; m, multiplet. An HP 6890 GC/MS was used to obtain GC/MS spectra and mass fragments are reported as mass per charge, *m/z*. Flash column and thin layer chromatography (TLC) were performed on silica gel with indicated solvent systems. All glassware and syringes were oven-dried for the reactions which require anhydrous conditions.

The multimode microwave used for solventless reactions on silica gel was a GE JES638WF 700 Watt domestic microwave with a turntable with time and power controls. The monomode microwaves consisted of two, a Biotage Creator 300 Watt system and a Biotage Initiator 400 Watt system. Both Biotage microwaves were capable of providing control over time, temperature, maximum pressure, and power wattage output. All reactions run in the monomode microwaves were run under fixed hold time conditions so that the timer countdown started after reacting reaction temperature, and the solvent

absorption level was set to normal for low polarity solvents, high for alcohols, and very high for anhydrous N,N-dimethylformamide (DMF) due to the varying ability of each solvent to convert electromagnetic radiation to heat.

**1-(Phenylsulfonyl)pyrrole** (**84**)

To a 2-5 mL microwave vial was combined benzenesulfonamide (0.3220 g, 2.048 mmol) with 2,5-dimethoxytetrahydrofuran (780 μL, 0.796 g, 6.02 mmol) in and glacial acetic acid (4 mL) with a stir bar. The vial was capped, placed into a Biotage Creator microwave, and heated at 170 °C for 10 min under fixed hold time conditions with a pre-stirring of 10 sec. The vial was allowed to cool to room temperature, opened and poured into ice cold $H_2O$ (25 mL) and the solid was collected via vacuum filtration. Recrystallization from methanol gave pure **84** (0.3459 g, 81.48%) with m.p. 86-87 °C; lit. m.p.[35c] 87-88 °C; MS (*m/z*): 210 ($M^+$ +3), 209 ($M^+$ +2), 208 ($M^+$ +1), 207 ($M^+$), 143, 141, 125, 115, 104, 97, 89, 83, 77 (100%), 66, 51, 45, 39, 28; $^1$H NMR: ($CDCl_3$) $\delta$: 7.76 (d, J = 7.5, 2H), 7.49 (t, J = 7.3, 1H) 7.39 (m, 2H), 7.08 (t, J = 2.0, 2H), 6.21 (t, J = 2.0, 2H); and $^{13}$C NMR: ($CDCl_3$) $\delta$: 139.1, 133.8, 139.4, 126.7, 120.8, 113.7.

**4-Nitrobenzenesulfonamide** (**90**)

To an ice cold solution of aqueous ammonia (6 mL) was slowly added a solution of 4-nitrobenzenesulfonyl chloride (5.1840 g, 23.39 mmol) in methylene chloride (25 mL) with stirring. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2x 15 mL). The combined organic layer was washed with distilled $H_2O$ (2x 25 mL), brine (1x 25 mL), dried ($Na_2SO_4$), and the solvent was removed *in*

*vacuo*. Recrystallization in methanol gave pure **90** (4.2013 g, 88.34%): m.p. 176-177 °C; lit. m.p.[35b] 179-181 °C; MS (*m/z*) 204 ($M^+$ +2), 203 ($M^+$ +1), 202 ($M^+$, 100%), 186, 172, 156, 138, 122, 108, 92, 80, 75, 64, 50, 39, 30; $^1$H NMR ($CD_3SOCD_3$) $\delta$: 8.41 (d, J = 8.9, 2H), 8.08 (d, J = 8.9, 2H), 7.76 (s, 2H); $^{13}$C NMR ($CD_3SOCD_3$) $\delta$: 149.4, 149.1, 127.2, 124.4.

**1-(4-Nitrophenylsulfonyl)pyrrole** (**89**)

To a 250 mL round bottom flask was added 4-nitrobenzenesulfonamide (4.3059 g, 21.29 mmol), 2,5-dimethoxytetrahydrofuran (16.6 mL, 16.9 g, 128 mmol), and AcOH (50 mL). The mixture was refluxed with stirring for 4 h. The reaction was cooled to room temperature, poured into ice cold $H_2O$ (100 mL), and the precipitate was collected via vacuum filtration. Recrystallization in methanol gave pure **89** (1.9096 g, 35.56%): m.p. 139-141 °C, lit. m.p.[35a] 415 K [141.85 °C]; MS (*m/z*): 256 ($M^+$ +4), 255 ($M^+$ +3), 254 ($M^+$ +2), 253 ($M^+$ +1), 252 ($M^+$, 100%), 236, 222, 206, 190, 186, 170, 158, 154, 142, 120, 122, 115, 111, 106, 102, 96, 92, 88, 82, 76, 70, 66, 62, 55, 50, 45, 39, 32, 28; $^1$H NMR ($CDCl_3$) $\delta$: 8.34 (d, J = 7.9, 2H), 8.03 (d, J = 8.32, 2H), 7.17 (s, 2H), 6.36 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$: 150.6, 144.3, 128.1, 124.7, 121.0, 144.9.

**9,10,11,15-Tetrahydro-9,10[3',4']-furanoanthracene-12,14-dione** (**93**) **via thermal conditions**

To a 250 mL round bottom flask was added anthracene (1.7811 g, 10 mmol), maleic anhydride (1.9746 g, 20 mmol), and ethyl acetate (100 mL) with a stir bar. A reflux condenser was attached and the system was heated to reflux for 8 hr. The system was

allowed to cool to room temperature, hexanes (75 mL) were added to precipitate the adduct. Vacuum filtration yielded pure **93** (2.7255 g, 98.7%): m.p. 266-268 °C, lit. m.p.[36c] 262-263 °C; MS (m/z): 278 ($M^+$ +2), 277 ($M^+$ +1), 276 ($M^+$), 231, 207, 202, 198, 189, 178 (100%), 163, 151, 139, 133, 126, 122, 111, 101, 94, 89, 82, 76, 67, 63, 54, 50, 44, 39, 28; $^1$H NMR ($CDCl_3$) $\delta$: 7.38 (dd, $J_1$ = 5.3, $J_2$ = 3.2, 2H), 7.33 (dd, $J_1$ = 5.4, $J_2$ = 3.2, 2H), 7.23-7.17 (m, 4H), 4.82 (s, 2H), 3.51 (dd, $J_1$ = 2.3, $J_2$ = 1.7, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$: 170.5, 140.6, 138.1, 127.8, 127.2, 125.2, 124.4, 40.0, 45.4.

**9,10,11,15-Tetrahydro-9,10[3',4']-furanoanthracene-12,14-dione (93) via microwave conditions**

To a 2-5 mL microwave vial, was combined anthracene (0.3567 g, 2 mmol) and maleic anhydride (0.3930 g, 4 mmol) with a stir bar and ethyl acetate (5 mL). The vial was capped, placed into a Biotage Creator microwave, and heated at 170 °C for 5 min using fixed hold time and normal absorption. The vial was removed and cooled in an ice bath, de-capped, and poured into a 150 mL beaker. Hexanes were added until precipitation stopped. The precipitate was collect on a vacuum filter to yield pure **93** (0.5127 g, 92.7%): m.p. 265-267 °C.

**1-(Phenylsulfonyl)-7-azabicyclo[2.2.1]heptadiene-2,3-dicarboxylate (86) via thermal conditions**

To a dry 50 mL three-neck round bottom was added 1-(phenylsulfonyl)pyrrole (5.8636 g, 28.29 mmol) and dimethyl acetylenedicarboxylate (1.0363 g, 7.292 mmol) and the mixture was heated neat under nitrogen at 95 °C in an oil bath for 24 h. After cooling,

purification was achieved via column chromatography (90 : 10 hexanes : ethyl acetate, then 70 : 30 hexanes : ethyl acetate) and resulted in isolation of pure **86** (0.1473 g, 1.490%); 21.43% based on 5.4559 g 1-(phenylsulfonyl)pyrrole recovered): m.p. 114-115 °C; lit. m.p.[33] 115-116 °C; $^{1}$H NMR ($CDCl_3$) $\delta$: 7.71 (dd, $J_1$ = 6.9, $J_2$ = 1.5, 2H), 7.58-7.47 (m, 3H), 7.05 (t, J = 1.6, 2H), 5.45 (t, J = 1.6, 2H), 3.73 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$: 162.3, 151.4, 143.1, 137.8, 133.1, 129.2, 128.2, 70.0, 52.2.

**1-(Phenylsulfonyl)-7-azabicyclo[2.2.1]heptadiene-2,3-dicarboxylate (86) via multimode microwave**

To a dry 125 mL Erlenmeyer flask was added 1-(phenylsulfonyl)pyrrole (0.2086 g, 1.006 mmol), dimethyl acetylenedicarboxylate (491.3 μL, 0.5684 g, 4.000 mmol), and silica gel (0.5 g). The reactants were dissolved in a minimal amount of methylene chloride, stirred, and the solvent was allowed to evaporate in a fume hood. The flask was placed in a multimode microwave, covered with a 50 mL beaker, and heated for 2 min at full power. The Erlenmeyer flask was removed from the microwave and let cool to room temperature. The silica gel was washed with methylene chloride (3x 25 mL), the organic layers were combined and the solvent reduced *in vacuo*. Purification via flash chromatography (80 : 20 hexanes : ethyl acetate, then 65 : 35 hexanes : ethyl acetate) resulted in pure **86** (0.0937 g, 26.6% isolated; 72.9% based on 0.1323 g of 1-(phenylsulfonyl)pyrrole recovered).

**1-(Phenylsulfonyl)-7-azabicyclo[2.2.1]heptadiene-2,3-dicarboxylate (86) via monomode microwave**

To a 2-5 mL microwave vial was combined 1-(phenylsulfonyl)pyrrole (1.5255 g, 7.3607 mmol) and dimethyl acetylenedicarboxylate (3.6 mL, 4.16 g, 29.3 mmol) with a stir bar. The vial was capped and heated in a Biotage Creator at 140 °C for 20 min with normal absorption. The vial was removed, allowed to cool, and the solvent was reduced *in vacuo*. Purification via flash chromatography (80 : 20 hexanes : ethyl acetate, then 65 : 35 hexanes : ethyl acetate) gave **86** (0.5218 g, 20.29% isolated; 20.69% based on 0.0284 g of 1-(phenylsulfonyl)pyrrole recovered).

**Dimethyl 1-(phenylsulfonyl)pyrrole-3,4-dicarboxylate (94)**

To a 125 mL Erlenmeyer flask was dissolved 1-(phenylsulfonyl)pyrrole (1.0350 g, 4.994 mmol) and dimethyl acetylenedicarboxylate (2.55 mL, 2.95 g, 20.7 mmol) in a minimal amount of methylene chloride. To this was added silica gel (0.5 g) and solvent was removed by vacuum. The flask was placed into the domestic microwave and irradiated at full power (700 W) for 5 min. The flask was removed and allowed to cool; then the silica gel was washed with ethyl acetate and methanol to separate the organic products. The solvent was reduced in vacuo and purified by flash chromatography (85 : 15 hexanes : ethyl acetate, then 75 : 25 hexanes : ethyl acetate) to yield pure **94** (0.0338 g, 2.09%): m.p. = 90-93 °C; MS (*m/z*): 327 ($M^+$ +4), 326 ($M^+$ +3), 325 ($M^+$ +2), 324 ($M^+$ +1), 323 ($M^+$), 292, 261, 233, 228, 212, 207, 198, 185, 169, 156, 151, 141, 136, 130, 125, 120, 115, 108, 102, 97, 92, 82, 77 (100%), 65, 59, 51, 42, 37, 28; $^1$H NMR ($CDCl_3$) $\delta$: 7.87 (d, J = 7.2, 2H), 7.59 – 7.65 (m, 3H), 7.50 (t, J = 8.1, 2H), 3.75 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$: 162.6,

137.5, 135.1, 130.0, 127.5, 125.8, 119.6, 52.0. Anal. Calcd for $C_{14}H_{13}NO_6S$: C, 52.01; H, 4.05; N, 4.33; Found: C, 51.81; H, 3.98; N, 4.29.

**1-(4-Nitrophenylsulfonyl)-7-azabicyclo[2.2.1]heptadiene-2,3-dicarboxylate** (**95**)

To a 2-5 mL microwave vial was combined 1-(4-nitrophenylsulfonyl)pyrrole (1.2663 g, 5.020 mmol) and dimethyl acetylenedicarboxylate (2.466 mL, 2.853 g, 20.08 mmol) with a stir bar. The vial was capped and heated in a Biotage Creator at 170 °C for 10 min with normal absorption. The vial was removed, allowed to cool, and the solvent was reduced *in vacuo*. Purification via flash chromatography (80 : 20 hexanes : ethyl acetate, then 65 : 35 hexanes : ethyl acetate) gave pure **95** (0.3335 g, 16.85% isolated; 33.59% based on 0.6313 g 1-(4-nitrophenylsulfonyl)pyrrole recovered): m.p. 147-149 °C; $^1$H NMR ($CDCl_3$) $\delta$: 8.24 (dt, $J_1$ = 8.69, $J_2$ = 1.82, 2H), 7.84 (dt, $J_1$ = 8.69, $J_2$ = 1.82, 2H), 7.04 (t, J = 1.62, 2H), 5.42 (t, J = 1.82, 2H), 3.65 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$: 161.2, 150.3, 149.5, 142.8, 142.3, 128.6, 123.5, 69.0, 51.3; Anal. Calcd for $C_{16}H_{14}N_2O_8S$: C, 48.73; H, 3.58; N, 7.10; Found: C, 48.79; H, 3.63; N, 7.02.

**Dimethyl 1-(4-nitrophenylsulfonyl)pyrrole-3,4-dicarboxylate** (**96**)

To a 125 mL Erlenmeyer flask was dissolved 1-(4-nitrobenzenesulfonyl)pyrrole (1.2765 g, 5.060 mmol) and dimethyl acetylenedicarboxylate (2.55 mL, 2.95 g, 20.7 mmol) in a minimal amount of methylene chloride. To this was added silica gel (0.5 g) and solvent was removed by vacuum. The flask was placed into the domestic microwave and irradiated at full power (700 W) for 5 min. The flask was removed and allowed to cool; then the silica gel was washed with ethyl acetate and methanol to separate the organic

products. The solvent was reduced in vacuo and purified by flash chromatography (85 : 15 hexanes : ethyl acetate, then 75 : 25 hexanes : ethyl acetate) to yield pure **96** (0.0234 g, 1.26%): m.p. 117-119 °C; MS (*m/z*): 371 ($M^+$ +3), 370 ($M^+$ +2), 369 ($M^+$ +1), 368 ($M^+$), 350, 337 (100%), 327, 319, 307, 291, 281, 273, 253, 227, 207, 197, 186, 180, 168, 158, 152, 140, 122, 113, 104, 92, 84, 76, 65, 59, 50, 39, 28; $^1$H NMR ($CDCl_3$) $\delta$: 8.41 (d, J = 8.9, 2H), 8.14 (d, J = 9.0, 2H), 7.67 (s, 2H), 3.84 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$: 162.2, 151.3, 142.8, 128.9, 125.7, 125.1, 120.6, 52.1; Anal. Calcd for $C_{14}H_{12}N_2O_8S$: C, 45.65; H, 3.28; N, 7.61; Found: C, 45.66; H, 3.26; N, 7.52.

**Ethynyl p-tolyl sulfone (tosylacetylene)** (**24**)

Step 1: To an oven dried 100 mL Erlenmeyer flask cooled under nitrogen was added methylene chloride (25 mL) to powdered aluminum chloride (4.3394 g, 32.544 mmol). To this was slowly added *p*-toluenesulfonyl chloride (6.1591 g, 32.306 mmol) and the mixture allowed to stir at room temperature for 30 min. Step 2: To an oven dried 250 mL three-neck round bottom flask cooled under nitrogen was added methylene chloride (30 mL) and the vessel was cooled in an ice bath to 0 °C. Then, bis(trimethylsilyl)acetylene (5.0562 g, 29.673 mmol) was added and stirred under nitrogen. Step 3: A 125 mL addition funnel was attached to the round bottom flask to which the contents of the Erlenmeyer flask was added after passing through a plug of glass wool. Slowly, the contents of the addition funnel were added dropwise over 30 min. The addition funnel was rinsed with methylene chloride (10 mL), the three-neck round bottom flask was capped and purged with nitrogen, and the reaction was allowed to stir overnight. The reaction was quenched by pouring into a 1 : 1 solution of 1M HCl (50 mL) and crushed

ice (50 g). The organic layer was separated and the aqueous layer was washed with methylene chloride (2x 25 mL). The combined organic layers were washed with $H_2O$ (2x 25 mL), brine (25 mL), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to yield *p*-tolyl-2-(trimethylsilyl)ethynyl sulfone (6.9976 g, 93.43%) which was passed through well packed flash chromatography columns (90 : 10 hexanes : ethyl acetate) to deprotect. This column purification required four flash columns to eventually produce pure **24** (3.9044 g, 73.01%): m.p. 71-73 °C; lit. m.p.[38] 74-75 °C; MS (*m/z*): 183 ($M^+$ +3), 182 ($M^+$ +2), 181 ($M^+$ +1), 180 ($M^+$, 100%), 155, 147, 139, 134, 131, 124, 121, 115, 111, 107, 103, 95, 91, 86, 80, 77, 74, 69, 65, 62, 57, 51, 48, 45, 39, 32, 28, 25; $^1$H NMR ($CDCl_3$) $\delta$: 7.89 (dt, $J_1$ = 8.5, $J_2$ = 1.8, 2H), 7.40 (d, J = 8.0, 2H), 3.49 (s, 1H), 2.48 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 146.0, 137.9, 130.1, 127.7, 81.2, 80.4, 21.8.

**2-Amino-5-iodopyridine** (**105**)

To a 1 L Erlenmeyer flask was combined 2-aminopyridine (53.2658 g, 0.5659 mol), iodic acid (19.6560 g, 0.0862 mol), and iodine (60.1888 g, 0.2371 mol) in a solution of $HOAc/H_2O/H_2SO_4$ (300 : 62.5 : 10, 372.5 mL) and heated to 80 °C with stirring overnight. The mixture was cooled to room temperature, poured into 5% sodium thiosulfate (300 mL) and extracted with ethyl ether (4x 80 mL). To the aqueous layer in an ice bath was slowly added 20% NaOH until neutralization was complete. The resulting precipitate was recrystallized from methanol to give pure **105** (46.3533 g, 37.23%): m.p. 125-126 °C, lit. m.p.[40b] 126-128 °C; MS (*m/z*): 221 ($M^+$ +1), 220 ($M^+$, 100%), 203, 193, 177, 165, 152, 139, 127, 110, 93, 76, 66, 60, 50, 39, 28; $^1$H NMR ($CDCl_3$) $\delta$: 8.05 (d, J =

2.2, 1H), 7.59 (dd, J = 6.5, 2.3, 1H), 6.36 (d, J = 8.8, 1H), 6.14 (br s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$: 158.7, 152.9, 144.2, 110.8, 75.5.

**2-Chloro-5-iodopyridine** (**20**)

To a 125 mL Erlenmeyer flask containing 2-amino-5-iodopyridine (2.0026 g, 9.1023 mmol) was added HCl (25 mL) until the sample was dissolved and then the mixture was cooled in an ice bath to 0 °C. Slowly, $NaNO_2$ (1.0506 g, 15.226 mmol) was added in increments after which the reaction was allowed to warm to room temperature. The mixture was then neutralized with 50% NaOH, cooled, and the precipitate collected. Recrystallization from methanol gave pure **20** (0.8906 g, 40.86%): m.p. 96-97 °C, lit. m.p.[40c] 96 °C; MS (*m/z*): 243 ($M^+$ +4), 242 ($M^+$ +3), 241 ($M^+$ +2), 240 ($M^+$ +1), 239 ($M^+$, 100%), 210, 204, 199, 190, 186, 177, 164, 152, 139, 127, 119, 112, 106, 102, 85, 76, 72, 62, 50, 44, 38, 32, 28; $^1$H NMR ($CD_3SOCD_3$) $\delta$: 8.68 (d, J = 2.4, 1H), 8.22 (dd, J = 5.9, 2.4, 1H), 7.40 (d, J = 8.35, 1H); $^{13}$C NMR ($CD_3SOCD_3$) $\delta$: 155.5, 149.8, 147.6, 126.3, 92.7.

**1-(Phenylsulfonyl)-3-pyrroline** (**102**)

To magnetically stirred trifluoroacetic acid (10 mL) in a 125 mL Erlenmeyer flask in an ice bath was slowly added $NaCNBH_3$ (0.45 g, 7.25 mmol) in small portions. The resulting mixture was stirred for an additional 30 min, and then 1-(phenylsulfonyl)pyrrole (0.5080 g, 2.45 mmol) was added slowly as a solid. After 1 h, additional $NaCNBH_3$ (0.45 g, 7.25 mmol) was added. The mixture was stirred overnight, quenched with water, and extracted with methylene chloride (3x 50 mL). The combined organic layers were washed

with sat. $NaHCO_3$ (3x 30 mL), water (2x 20 mL), brine (1x 20 mL), and dried ($Na_2SO_4$). Solvent was evaporated *in vacuo*, purification by recrystallization from methanol to give pure **102** (0.4645 g, 90.6%): m.p. 118-120 °C, lit. m.p.[41] 120-121 °C; MS (*m/z*): 211 ($M^+$ +2), 210 ($M^+$ +1), 209 ($M^+$), 208 ($M^+$ -1), 207 ($M^+$ -2), 144, 141, 130, 125, 118, 115, 109, 104, 98, 94, 91, 82, 77 (100%), 74, 68, 64, 61, 57, 51, 45, 41, 37, 32, 28; $^1$H NMR ($CD_3SOCD_3$) $\delta$: 7.84 (d, J = 6.9, 2H), 7.66 (m, 3H), 5.69 (s, 2H), 4.03 (s, 4H); $^{13}$C NMR ($CD_3SOCD_3$) $\delta$: 136.3, 133.0, 129.4, 127.2, 125.5, 54.8.

**Oxidation of 1-(phenylsulfonyl)-3-pyrroline (102) to 1-(phenylsulfonyl)pyrrole (84)**

To a monomode microwave vial was added 1-(phenylsulfonyl)-3-pyrroline (0.2115 g, 1.011 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.3457 g, 1.523 mmol) in toluene (5 mL) and the vial was heated at 180 °C for 5 min. After cooling, the contents were purified by flash column (50 : 50 hexanes : methylene chloride) to give pure **84** (0.1703 g, 81.30%): m.p. 86-87 °C, MS (*m/z*) 210 ($M^+$ +3), 209 ($M^+$ +2), 208 ($M^+$ +1), 207 ($M^+$), 147, 141, 125, 115, 104, 97, 89, 83, 77 (100%), 66, 51, 45, 39, 28.

**2-Chloro-5-(phenylethynyl)pyridine (110)**

To an oven dried 125 mL flat-bottom flask was added a solution of 2-chloro-5-iodopyridine (4.8011 g, 20 mmol) and phenylacetylene (2.05 g, 1.90 mL, 20 mmol) in triethylamine (40 mL) and the mixture was allowed to stir in an ice bath at 0 °C. To this solution was added copper-I-iodide (0.07 g, 0.4 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.1 g, 0.1 mmol). The solution was allowed to warm to room temperature and stirred for 18 h. The solvent was reduced *in*

*vacuo* and then the contents were poured into ice cold $H_2O$ (30 mL) and the precipitate was collected via vacuum filtration. Recrystallization via methanol gave **110** (3.0544 g, 71.3%): m.p. 76-78 °C, lit m.p.[42g] 68-69 °C; MS (*m/z*): 216 ($M^+$ +3), 215 ($M^+$ +2), 214 ($M^+$ +1), 213 ($M^+$), 212 ($M^+$ -1), 207, 177, 151, 126, 111, 107, 99, 93, 87, 75, 63, 51, 44, 40 (100%), 32, 28; $^1$H NMR ($CDCl_3$) $\delta$: 8.53 (d, J = 1.9, 1H), 7.74 (dd, J = 5.9, 2.4, 1H), 7.55-7.52 (m, 2H), 7.39-7.35 (m, 3H), 7.36 (t, J = 2.04, 1H), 7.31 (d, J = 8.3, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$: 152.0, 150.4, 140.9, 131.7, 129.1, 128.5, 123.9, 122.2, 119.4, 93.8, 84.7.

**1-(Phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole** (**97**)

Through a series of nine microwave vials was reacted 1-(phenylsulfonyl)-3-pyrroline (3.5804 g, 17.11 mmol), 2-chloro-5-iodopyridine (5.4997 g, 22.97 mmol), palladium(II) acetate (0.4196 g, 1.869 mmol), and silver carbonate (3.3525 g, 12.16 mmol) in DMF (5 mL per vial) at 180 °C for 25 min per each microwave vial. After cooling, the insoluble material was separated via vacuum filtration and all contents were poured into a 250 mL round bottom flask to which was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (5.0407 g, 22.21 mmol) and allowed to stir at 100 °C for 7 days. Once the solution was cool, it was extracted with a 1 : 1 ratio of ethyl acetate : $H_2O$ (250 mL), the organic layer separated and aqueous layer was extracted thrice with ethyl acetate (50 mL). The organic layers were combined and washed thrice with saturated $NaHCO_3$ (3x 50 mL), brine (50 mL), and dried ($MgSO_4$). Once the solvent was reduced in vacuo, purification by flash chromatography (50 : 50 hexanes : methylene chloride, then 25 : 75 hexanes : methylene chloride) yielded pure **97** (0.0590 g, 1.08%; 1.18% based on 0.2939 g of **97** recovered): m.p. 108-110 °C; MS (*m/z*): 322 ($M^+$ +4), 321 ($M^+$ +3), 320 ($M^+$ +2), 319 ($M^+$ +1), 318

($M^+$, 100%), 281, 254, 218, 207, 190, 177, 165, 150, 141, 123, 115, 110, 102, 97, 88, 77, 63, 51, 44, 39, 28; $^1$H NMR ($CDCl_3$) $\delta$: 8.41 (d, J = 2.4, 1H), 7.84 (d, J = 7.4, 2H), 7.62 (dd, $J_1$ = 8.3, $J_2$ = 2.5, 1H), 7.55 (t, J = 2.2, 2H), 7.48-7.43 (m, 2H), 7.38 (dd, $J_1$ = 2.5, $J_2$ = 1.8, 1H), 7.21 (d, J = 8.3, 1H), 7.18 (dd, $J_1$ = 3.3, $J_2$ = 2.4, 1H), 6.50 (dd, $J_1$ = 3.4, $J_2$ = 1.7, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$: 149.7, 146.6, 138.6, 135.6, 134.3, 129.6, 128.4, 127.0, 125.0, 124.3, 122.3, 117.0, 111.7; Anal. Calcd for $C_{15}H_{11}ClN_2O_2S$: C, 56.52; H, 3.48; N, 8.79; Found: C, 55.66; H, 3.79; N, 8.80.

**Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole with tosyl acetylene**

To a microwave vial was combined 1-(phenylsulfonyl)pyrrole (0.9039 g, 4.361 mmol) with tosyl acetylene (1.5556 g, 8.632 mmol) and ethyl acetate (5 mL). The vial was heated for 15 min at 140 °C in the monomode microwave. After cooling, column chromatography (90 : 10 hexanes : ethyl acetate, then 80 : 20 hexanes : ethyl acetate) afforded an unknown product (0.0507 g): m.p. sublimes ~ 125 °C; $^1$H NMR ($CDCl_3$) $\delta$: 8.63 (s, 3H), 7.80 (d, J = 8.2, 5H), 7.69 (d, J = 8.2, 6H), 7.67 (d, J = 8.2, 7H), 7.35 (d, J = 8.6, 11H), 7.32 (d, J = 8.23, 11H), 7.00 (d, J = 11.8, 2H), 6.57 (d, J = 11.8, 2H), 2.45-2.41 (m, 30H); $^{13}$C NMR ($CDCl_3$) $\delta$: 144.7, 142.4, 135.0, 130.7, 129.8, 129.5, 129.2, 128.5, 124.9, 127.5, 127.2, 20.7; Elem. anal. found: C, 59.57; H, 4.45; N, 0.39.

## REFERENCES


1. Spande, T.F.; Garraffo, H.M.; Edwards, M.W.; Yeh, H.J.C.; Pannell, L.; Daly, J.W. "Epibatidine: a novel (chloropyridyl)azabicycloheptane with potent analgesic activity from an Ecuadoran poison frog" *J. Am. Chem. Soc.* **1992**, *114*, 3475-3478.
2. Daly, J.W.; Garraffo, H..; Spande, T.F.; Decker, M.W.; Sullivan, J.P.; Williams, M. "Alkaloids from frog skin: the discovery of epibatidine and the potential for developing novel non-opioid analgesics" *Nat. Prod. Rep*. **2000**, *17*, 131-135.
3. Chen, Z.; Trudell, M.L. "Chemistry of 7-azabicyclo[2.2.1]heptadienes, 7-azabicyclo[2.2.1]hept-2-enes, and 7-azabicyclo[2.2.1]heptanes" *Chem. Rev*. **1996**, *96*, 1179-1193.
4. a) Li, T.; Qian, C.; Eckman, J.; Huang, D.F.; Shen, T.Y. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2759. b) Qian, C.; Li, T.; Shen, T.Y.; Libertine-Garaham, L.; Eckman, J.; Biftu, T.; Ip, S. "Epibatidine is a nicotinic analgesic" *Eur. J. Pharmacol.* **1993**, *250*, R13-R14. c) Badio, B.; Shi, D.; Garraffo, M.; Daly, J.W. "Antinociceptive effects of the alkaloid epibatidine: further studies on involvement of nicotinic receptors" *Drug Dev. Res*. **1995**, *36*, 46-59.
5. Holladay, M.W.; Dart, M.J.; Lynch, J.K. "Neuronal nicotinic acetylcholine receptors as targets for drug discovery" *J. Med. Chem*. **1997**, *40*, 4169-4194.

6. Badio, B.; Daly, J.W. "Epibatidine, a potent analgetic and nicotinic agonist." *Mol. Pharmacol.* **1994**, *45*, 563-569.

7. a) Olivo, H.F.; Hemenway, M.S. "Recent synthesis of epibatidine, a review" *Org. Prep. Proced. Int.* **2002**, *34*, 1-25. b) Fletcher, S.R.; Baker, R.; Chambers, M.S.; Hobbs, S.C.; Mitchell, P.J. "The synthesis of (+)- and (-)-epibatidine" *J. Chem. Soc., Chem. Commun*, **1993**, 1216-1218. c) Fletcher, S.R.; Baker, R.; Chambers, M.S.; Herbert, R.H.; Hobbs, S.C.; Thomas, S.R.; Verrier, H.M.; Watt, A.P.; Ball, R.G. "Total synthesis and determination of the absolute configuration of epibatidine" *J. Org. Chem.* **1994**, *59*, 1771-1778. d) Sestanji, K.; Melenski, E.; Jirkovsky, I. "Synthesis of epibatidine" *Tetrahedron Lett*. **1994**, *35*, 5417-5420. e) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G.; Romagnoli, R.; Zanirato, V, "Total synthesis of (±)-epibatidine" *Tetrahedron Lett.* **1994**, *35*, 9297-9300. f) Trost, B.M.; Cook, G.R. "An asymmetric synthesis of (-)-epibatidine" *Tetrahedron Lett*. **1996**, *37*, 7485-7488. g) Olivo, H.F.; Hemenway, M.S. "Total synthesis of (±)-epibatidine using a biocatalytic approach" *J. Org. Chem*. **1999**, *64*, 8968-8969. h) Corey, E.J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D.C.; Sarshar, S. "Stereocontrolled total synthesis of (+)- and (-)-epibatidine" *J. Org. Chem*. **1993**, *58*, 5600-5602.

8. a) Huang, D.F.; Shen, T.Y. "A versatile total synthesis of epibatidine and analogs" *Tetrahedron Lett*. **1993**, *34*, 4477-4480. b) Kotian, P.L.; Carroll, F.I. "Synthesis of (+) and (-) epibatidine" *Synth. Commun*. **1995**, *25*, 63-71.

9. Broka, C.A. "Total synthesis of epibatidine" *Tetrahedron Lett*. **1993**, *34*, 3251-3254.

10. Fletcher, S.R.; Baker, R.; Chambers, M.S.; Hobbs, S.C.; Mitchell, P.J. "The synthesis of (+)- and (-)-epibatidine" *J. Chem. Soc. Chem. Commun.*, **1993**, 1216-1218.

11. Clayton, S.C.; Regan, A.C. "Total synthesis of (±)-epibatidine" *Tetrahedron Lett.* **1993**, 34, 7493-7496.

12. Diels, O; Alder, K. *Ann. Chem.* **1932**, *498*, 1.

13. Diels, O.; Alder, K. "Synthesen in der hydroaromatischen reihe" *Justus Liebigs Ann. Chem*. **1931**, *490*, 267-276.

14. a) Mandell, L.; Blanchard, W.A. "The reaction of N-benzylpyrrole with acetylenedicarboxylic acid. A Diels-Alder addition to a pyrrole" *J. Am. Chem. Soc.* **1957**, *79*, 6198-6201. b) Mandell, L.; Piper, J.U.; Pesterfield, C.E. "Diels-Alder addition to pyrroles" *J. Org. Chem*. **1963**, *28*, 574-575. c) Marchand, A.P.; Allen, R.W. "Synthesis of 7-azanorbornene and N-methyl-7-azanorbornene" *J. Org. Chem*. **1975**, *40*, 2551-2552.

15. a) Acheson, R.M.; Vernon, J.M. "Addition reactions of heterocyclic compounds. Part VIII. Methyl pyrrole-1-carboxylate and dimethyl acetylenedicarboxylate" *J. Chem. Soc.* **1961**, 457-459. b) Acheson, R.M.; Vernon, J.M. "Addition reactions of heterocyclic compounds. Part XII. Pyrroles and acetylene derivatives" *J. Chem. Soc.* **1963**, 1008-1011.

16. Gabel, N.W. "Diels-Alder reactions of 1-carbomethoxypyrroles and dimethyl acetylenedicarboxylate" *J. Org. Chem*. **1962**, *27*, 301-303.

17. a) Kitzing, R.; Fuchs, R.; Joyeux, M.; Prinzbach, H. "Aza-7-norbornadienes" *Helv. Chim. Acta* **1968**, *51*, 888-895. b) Prinzbach, H.; Fuchs, R.; Kitzing, R.

"Synthesis and pyrolysis of 3-azaquadricyclane derivatives. A new azepine synthesis" *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 67-68.

18. a) Bansal, R.C.; McCulloch, A.W.; McInnes, A.G. "Influence of Lewis acids on the Diels-Alder reaction. Part I. An improved synthesis of 7-azanorbornadiene, 3-azaquadricyclane, and azepine derivatives" *Can. J. Chem.* **1969**, *47*, 2391-2394. b) Bansal, R.C.; McCulloch, A.W.; McInnes, A.G. "Influence of Lewis acids on the Diels-Alder reaction. III. Rearrangement of dimethyl N-carbomethoxy-7-azabicyclo[2.2.1]2,5-heptadiene-2,3-dicarboxylate adducts to dimethyl N-carbomethoxy-3-aminophthalates" *Can. J. Chem.* **1970**, *48*, 1472-1474.

19. Donnini, G.P.; Just, G. "Diels-Alder reactions of pyrroles as an entry to substituted 3-oxatropanes and tetrasubstituted pyrrolidines" *J. Heterocyclic Chem.*, **1977**, *14*, 1423-1425.

20. Adams, J. M.; Dyer, S.; Martin, K.; Matear, W. A.; McCabe, R. W. "Diels-Alder Reactions Catalysed by Cation-exchanged Clay Minerals." *J. Chem. Soc. Perkin Trans*. **1994**, 761-765.

21. a) Altenbach, H.-J.; Blech, B.; Marco, J.A.; Vogel, E. "7-Azanorbornadiene" *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 778. b) Altenbach, H. J.; Constant, D.; Martin, H.-D.; Mayer, B.; Müller, M.; Vogel, E. "Synthesis and photoelectron spectra of 7-azanorbornadiene and related compounds: An analysis with fragment orbitals" *Chem. Ber.* **1991**, *124*, 791-801.

22. a) Leung-Toung, R.; Liu, Y.; Muchowski, J.M.; Wu, Y.-L. "Synthesis of conduramines from N-tert-butoxycarbonylpyrrole" *J. Org. Chem*. **1998**, *63*, 3235-3250. b) Leung-Toung, R.; Liu, Y.; Muchowski, J.M.; Wu, Y.-L. *Tetrahedron Lett*. **1994**, *35*, 1639-1642.

23. a) Huang, D.F.; Shen, T.Y. “A versatile total synthesis of epibatidine and analogs” *Tetrahedron Lett*. **1993**, *34*, 4477-4480. b) Kotian, P.L.; Carroll, F.I. “Synthesis of (+) and (-) epibatidine” *Synth. Commun*. **1995**, *25*, 63-71.

24. Settambolo, R.; Lazzaroni, R.; Messeri, T.; Mazzetti, M.; Salvadori, P. ”Synthesis of 3-vinylpyrrole” *J. Org. Chem*. **1993**, *58*, 1899-1902.

25. Kozikowski, A.P.; Cheng, X-M. “A synthesis of 3-substituted pyrroles through the halogen-metal exchange reaction of 3-bromo-1-(triisopropylsilyl)pyrrole” *J. Org. Chem.* **1984**, *49*, 3239-3240.

26. Alvarez, A.; Guzmán, A.; Ruiz, A.; Velarde, E.; Muchowski, J.M. “Synthesis of 3-arylpyrroles and 3-pyrrolylacetylenes by palladium-catalyzed coupling reactions” *J. Org. Chem.* **1992**, *57*, 1653-1656.

27. Hercouet, A.; Neu, A.; Peyronel, J-F.; Carboni, B. “Suzuki coupling reactions in heterocyclic chemistry: synthesis of 3-substituted pyrrolines and pyrroles” *Synlett*, **2002**, *5*, 829-831.

28. Sonesson, C.; Larhed, M.; Nyqvist, C.; Hallberg, A. “Regiochemical control and suppression of double bond isomerizatiion in the heck arylation of 1-(methoxycarbonyl)-2,5-dihyropyrrole” *J. Org. Chem.* **1996**, *61*, 4756-4763.

29. Bai, D.; Xu, R.; Chu, G.; Zhu, X. “Synthesis of (±)-epibatidine and its analogues” *J. Org. Chem*. **1996**, *61*, 4600-4606.

30. Pavri, N.P.; Trudell, M.L. ”An efficient method for the synthesis of 3-arylpyrroles” *J. Org. Chem*. **1997**, *62*, 2649-2651.

31. Miyaura, N.; Yanagi, T.; Suzuki, A. “The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases” *Synth. Commun*. **1981**, *11*, 513.

32. a) Abelman, M.M.; Oh, T.; Overman, L.E. "Intramolecular alkene arylations for rapid assembly of polycyclic systems containing quaternary centers. A new synthesis of spirooxindoles and other fused and bridged ring systems" *J. Org. Chem.* **1987**, *52*, 4130. b) Abelman, M.M.; Overman, L.E. "Palladium-catalyzed polyene cyclizations of dienyl aryl iodides" *J. Am. Chem. Soc*. **1988**, *110*, 2328.

33. Tuerdi, H. M.S. Thesis, Wright State University, Dayton, OH, 1996.

34. a) Anderson, P. S.; Christy, M. E; Engelhardt, E. L.; Lundell, G. F.; Ponticello, G. S. *J. Heterocyclic Chem.* **1977**, *14*, 213-217. b) Anderson, P. S.; Christy, M. E.; Lundell, G. F.; Ponticello, G. S. *Tetrahedron Lett*. **1975**, *30*, 2553-2556.

35. a) Gültekin, Z.; Frey, W.; Hökelek, T. "N-(p-Nitrophenylsulfonyl)-1H-pyrrole" *Acta Crystal. Sec. E.* **2004**, *E60*, o2488-o2490. b) Mahalingam, A.K.; Wu, X.; Wan, Y.; Alterman, M. "Scandium triflate as an efficient and recyclable catalyst for the deprotection of tert-butyl aryl sulfonamides" *Synth. Commun.* **2005**, *35*, 417-425. c) Zelikin, A.; Shastri, V.R.; Langer, R. "Facile synthesis of 3-alkylpyrroles" *J. Org. Chem.* **1999**, *64*, 3379-3380.

36. For a discussion on the Diels-Alder reaction of anthracene and maleic anhydride: a) Bachmann, W.E.; Kloetzel, M.C. "The reaction between maleic anhydride and polycyclic hydrocarbons" *J. Am. Chem. Soc.* **1938**, *60*, 381-482. b) Yates, P.; Eaton, P. "Acceleration of the Diels-Alder reaction by aluminum chloride" *J. Am. Chem. Soc.* **1960**, *82*, 4436-4437. c) Olah, G.A.; Meidar, D.; Fung, A.P. "Synthetic methods and reactions; 59. Catalysis of Diels-Alder reactions by Nafion-H per fluorinated resin sulfonic acid" *Synthesis* **1979**, *4*, 270-1. d) Giguere, R.; Bray, T.L.; Duncan, S.M.; Majetich, G. "Application of commercial microwave ovens to organic synthesis" *Tetrahedron Lett.* **1986**, *27***,** 4945-4948. e)

Bose, A.K.; Manhas, M.S.; Ghosh, M.; Shah, M.; Raju, V.S.; Bari, S.S.; Newaz, S.N.; Banik, B.K.; Chaudhary, A.G.; Barakat,K.J. "Microwave-induced organic reaction enhancement chemistry. 2. Simplified techniques" *J. Org. Chem.* **1991**, *56*, 6968-6970. f) Jones, S.; Wilson, I. "Synthesis of substituted 3-furan-2-(5*H*)-ones via an anthracene Diels-Alder sequence" *Tetrahedron Lett.* **2006**, *47*, 4377-4380.

37. Gedye, R.; Smith, F; Westaway, K.; Ali, H.; Baldisera, L; Laberge, L.; Rousell, J. "The use of microwave ovens for rapid organic synthesis" *Tetrahedron Lett.* **1986**, *27*, 279-282.

38. Waykole, L.; Paquette, L.A. "Ethynyl *p*-tolyl sulfone (benzene, 1-(ethynylsulfonyl)-4-methyl-1)" *Org. Synth.* **1989**, *67*, 149-56.

39. Chen, Z.; Trudell, M.L. "A simplified method for the preparation of ethynyl p-tolyl sulfone and ethynyl phenyl sulfone" *Synth. Commun*. **1994**, *24*, 3149-3155.

40. a) Hama, Y.; Nobuhara, Y.; Aso, Y.; Otsubo, T.; Ogura, F. "Preparation and properties of pyridine-analogue of TCNQ dianion salt" *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1683-1686. b) Bochis, R.J.; Dybas, R.A.; Eskola, P.; Kulsa, P.; Linn, B.O.; Lusi, A.; Meitzner, E.P.; Milkowski, J.; Mrozik, H.; Olen, L.E.; Peterson, L.H.; Tolman, R.L.; Wagner, A.F.; Waksmunski, F.S. "Methyl 6-(phenylsulfinyl)imidazo[1,2-a]pyridine-2-carbamate, a potent, new anthelmintic" *J. Med. Chem.* **1978**, *21*, 235-237. c) Bouillon, A.; Lancelot, J-C; Collot, V.; Bovy, P.; Rault, S. "Synthesis of novel halopyridinylboronic acids and esters. Part 1: 6-halopyridin-3-yl-boronic acids and esters" *Tetrahedron*, **2002**, *58*, 2885. d) Giantsidis, J.; Galeriu, C.; Landee, C.P.; Turnbull, M.M. "Transition metal halide salts of 2-amino-5-substituted-pyridines: Synthesis, crystal structure and magnetic

properties of two polymorphs of $(5\text{-IAP})_2CuCl_4$ [5-IAP=2-amino-5-iodopyridinium]" *J. Coord. Chem.* **2002**, *55*, 795-803.

41. Ketcha, D.M.; Carpenter, K.P.; Zhou, Q. "Reduction of N-(phenylsulfonyl)pyrroles with sodium cyanoborohydride in trifluoroacetic acid" *J. Org. Chem.* **1991**, *56*, 1318-1320.

42. a) Doyle, M.P.; Yan, M.; Hu, W.; Gronenberg, L.S. "Highly selective catalyst-directed pathways to dihydropyrroles from vinyldiazoacetates and imines" *J. Am. Chem. Soc.* **2003**, *125*, 4692-4693. b) Ohri, R.V.; Radosevich, A.T.; Hrovat, K.J.; Music, C.; Huang, D.; Holman, T.R.; Toste, F.D. "A Re(V)-catalyzed C-N bond-forming route to human lipoxygenase inhibitors" *Org. Lett.* **2005**, *7*, 2501-2504. c) Gowrisankar, S.; Lee, K.Y.; Kim, J.N. "Synthesis of 3,4-disubstituted 2,5-dihyrofurans starting from the Baylis-Hillman adduct via consecutive radical cyclization, haloactonization, and decarboxylate strategy" *Tetrahedron Letts.* **2005**, *46*, 4859-4863. d) Aggarwal, V.K.; Charmand, J.P.H.; Fuentes, D.; Harvey, J.N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J-L; Winn, C.L. "Highly enantioselective synthesis of glycidic amindes using camphor-derived sulfonium salts. Mechanism and applications in synthesis" *J. Am. Chem. Soc.* **2006**, *128*, 2105-2114. e) Padwa, A.; Norman, B.H. "A [4 + 1] annulation approach to nitrogen heterocycles using 2,3-bis(phenylsulfonyl)-1,3-buatdiene and primary amines" *J. Org. Chem.* **1990**, *55*, 4801-4807.

43. Oussaid, B.; Garrigues, B.; Souflaoui, M. "Nouvelle méthode de synthèse de pyrroles sous micro-ondes" *Can. J. Chem.* **1994**, *72*, 2483-2485.

44. For a review of the Sonogashira reaction, consider the following: a) Doucet, H.; Hierso, J.C. "Palladium-based catalytic systems for the synthesis of conjugated

enynes by Sonogashira reactions and related alkynylations" *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871. b) Mio, M.J.; Kopel, L.C.; Braun, J.B.; Gadzikwa, T.L.; Hull, K.L.; Brisbois, R.G.; Markworth, C.J., Grieco, P.A. "One-Pot Synthesis of Symmetrical and Unsymmetrical Bisarylethynes by a Modification of the Sonogashira Coupling Reaction" *Org. Lett.* **2002**, *4*, 3199-3202. c) Bhattacharya, S.; Sengupta, S. "Palladium catalyzed alkynylation of aryl halides (Sonogashira reaction) in water" *Tetrahedron Lett.* **2004**, *45*, 8733-8736. d) Park, S.; Kim, M.; Koo, D.H.; Chang, S. "Use of ruthernium/alumina as a convenient catalyst for copper-free Sonogashira coupling reactions" *Adv. Synth. Catal.* **2004**, *346*, 1638-1640. e) Wang, M.; Li, P.; Wang, L. "Microwave irradiated solventless Sonogashira reaction on nickel(0) powder doped $KF/Al_2O_3$" *Synth. Commun.* **2004**, *34*, 2803-2812. f) Melucci, M.; Barbarella, G.; Zambianchi, M.; Di Pietro, P.; Bongini, A. "Solution-phase microwave-assisted synthesis of unsubstituted and modified α-quinque- and sexithiophenes" *J. Org. Chem.* **2004**, *69*, 4821-4828. g) Dawood, K.M.; Solodenko, W.; Kirschning, A. "Microwave-accelerated Mizoroki-heck and Sonogashira cross-coupling reactions in water using a heterogeneous palladium(II)-precatalyst" *ARKIVOC* (Gainesville, FL, U.S.), **2007**, *5*, 104-124.