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The synthesis of novel nitrogen containing heterocycles

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The Synthesis of Novel Nitrogen Containing Heterocycles

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By

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THESIS CERTIFICATION

I, Arife Yazici, hereby declare that all material in this thesis, submitted in partial fulfillment of the requirements of the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

Arife YAZICI

Date:

To my husband and son.

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PUBLICATIONS ARISING FROM THIS THESIS

1. Nalivela Kumara Swamy, Arife Yazici and Stephen G. Pyne. "Copper Mediated Cyclization-Halogenation and Cyclization-Cyanation Reactions of β-Hydroxyalkynes and *ortho*-Alkynyl Phenols and Anilines" *Journal of Organic Chemistry* **2010**, submitted.

2. Jury, Jasmine C.; Swamy, Nalivela K.; Yazici, Arife; Willis, Anthony C.; Pyne, Stephen G. "Metal-Catalyzed Cycloisomaerization Reactions of *cis*-4-Hydroxy-5-alkynylpyrrolidinones and *cis*-Hydroxy-6-alkynylpiperidinones : Synthesis of Furo[3,2-*b*]pyrroles and Furo[3,2-*b*]pyridines" *Journal of Organic Chemistry* **2009**, *74*, 5523-5527.

3. Yazici, Arife; Pyne, Stephen G. "Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part 1)" *Synthesis* **2009**, 339-368.

4. Yazici, Arife; Pyne, Stephen G. "Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part 2)" *Synthesis* **2009**, 513-541.

5. Pyne, Stephen G.; Au, Christopher W. G.; Davis, Andrew S.; Morgan, Ian R.; Ritthiwigrom, Thunwadee; Yazici, Arife. "Exploiting the borono-Mannich reaction in bioactive alkaloid synthesis" *Pure and Applied Chemistry* **2008**, *80*, 751-762.

6. Morgan, Ian R.; Yazici, Arife; Pyne, Stephen G. "Diastereoselective Ritter Reactions of Chiral Cyclic *N*-Acyliminium Ions: Synthesis of Pyrido- and Pyrrolo[2,3-*d*]oxazoles and 4-Hydroxy-5-*N*-acylaminopyrrolidines and 5-Hydroxy-6-*N*-acylaminopiperidines" *Journal of Organic Chemistry* **2008**, *73*, 2943-2946.

7. Morgan, Ian R.; Yazici, Arife; Pyne, Stephen G. "Diastereoselective borono-Mannich reactions on cyclic *N*-acyliminium ions" *Tetrahedron* **2008**, *64*, 1409-1419.

ABSTRACT

This thesis reports on the development of new methods for the synthesis of functionalized pyrrolidines. These compounds are of important since they are the common ring structure that forms the bicyclic, heterocyclic core structure of the pyrrolizidine, indolizidine and *Stemona* alkaloids.

In Chapter 2 we report our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones from the borono-Mannich reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with boronic acids in the presence of $BF_3.Et_2O$. The 4,5-dihydroxypyrrolidin-2-one gave in two cases 4,5-*cis* adducts with very high *cis* selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave 4,5-*trans* adducts with good *trans* selectivity and in good to moderate yields. Unfortunately the desired dienyl 4,5-*cis* adduct, required for the synthesis of the *Stemona* alkaloids, could only be obtained in the low yield of 33%. A RCM reaction of this compound gave the desired pyrrolo[1,2-*a*]azepine in 72% yield.

In Chapter 2 we also report the formation of a novel, Ritter reaction product, a pyrrolo[3,2-*b*]oxazole as an unwanted side product in the borono-Mannich reaction when acetonitrile was used as a solvent.

In Chapter 3 we describe an efficient synthesis of pyrrolo[3,2-*b*]oxazoles from the Ritter reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with nitriles in the presence of $BF_3.Et_2O$. When 4-benzyloxy-5-hydroxypyrrolidin-2-one was used as the substrate the corresponding pyrrolo[3,2-*b*]oxazoles were formed along with the corresponding *N*-benzyl amides, which were formed from the Ritter reactions of benzyl cation and the nitrile. The isolation of these amide compounds were consistent with our proposed reaction mechanism. Two of the pyrrolo[3,2-*d*]oxazole compounds were hydrolyzed to novel 5-acylaminopyrrolidinones.

In Chapter 4 we report the metal-catalyzed cycloisomerization reactions of 3-hydroxy-2-alkynylpyrrolidine which was obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine and potassium phenylethynyltrifluoroborate. The cycloisomerization reaction of this pyrrolidine afforded a 2,5-disubstituted furan when Ag(I), Au(I) or Pd(II)/Cu(I) were used as a catalyst. While 3-halo-2,5-disubstituted furans were synthesized from the corresponding CuCl or CuBr

mediated reactions. Novel 3-iodo, 3-phenyl and 3-cyano susbstituted furo[3,2-*b*]pyrroles were synthesized from the reactions of the 3-hydroxy-2-alkynylpyrrolidine with CuI, CuCN and PhI/$Pd(dba)_2$, respectively.

In Chapter 5 a novel method for the synthesis of 3-cyanoindoles is reported. This method showed good tolerance to electron-donating and electron withdrawing substituents on the starting *ortho*-alkynylaniline and allowed 3-cyanoindoles to be obtained in a single step. While the method of Wang provides 3-bromo and 3-chloro indoles in one step from *ortho*-alkynylanilines this method has not been extended to make 3-cyanoindoles. Future studies could involve the examination of Wang`s conditions using $CuCN/O_2$ instead of $CuBr_2$ or $CuCl_2$ to prepare 3-cyanoindoles.

ABBREVIATIONS

$[\alpha]_D$	Specific Rotation
Ac	Acetyl
Ac_2O	Acetic anhydride
amu	Atomic mass unit
ArC	Aromatic carbon
ArCH	Aromatic methine
Bu	Butyl
Bn	Benzyl
br. s	Broad singlet
CAN	Cerium ammonium nitrate
Cbz	Benzyloxycarbonyl
C_6D_6	Deuterated benzene
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CH_3NO_2	Nitromethane
COSY	Correlation spectroscopy
d	Day
d	Doublet (NMR)
δ	Chemical shift
dd	Doublet of doublets (NMR)
DCE	1,2-Dichloroethane
DEPT	Distortionless enhancement by polarization transfer
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
de	Diastereomeric excess
dr	Diastereomeric ratio
ee	Enantiomeric excess
EE	Ethoxyethyl
eq	Molar equivalents
Et_2O	Diethylether

EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour
HMBC	Heteronuclear multiple bond correlation
HREIMS	High resolution electron impact mass spectrometry
HRESIMS	High resolution electrospray ionization mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IR	Infrared spectroscopy
J	Coupling constant (NMR)
Lit.	Literature
LREIMS	Low resolution electron impact mass spectrometry
LRESIMS	Low resolution electrospray ionization mass spectrometry
m	Multiplet (NMR)
MeOH	Methanol
min	Minutes
MOM	Methoxymethyl
Mp	Melting point
NIS	*N*-Iodosuccinimide
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser enhancement spectroscopy
ϕ	Dihedral angle
Ph	Phenyl
PMB	*p*-Methoxybenzyl
ppm	Parts per million (NMR)
q	Quartet (NMR)
RCM	Ring closing metathesis
R_f	Retardation factor
rt	Room temperature
s	Singlet (NMR)
sat.	Saturated
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl

td	Triplet of doublets
t	Triplet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-Tetramethylethylenediamine
TMS	Tetramethylsilane

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