



Development and exploration of nitrogen heterocycle methodologies : experimental and theoretical investigations

by Thomas Nicholas Jones

A dissertation submitted in the partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

Montana State University

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Abstract:

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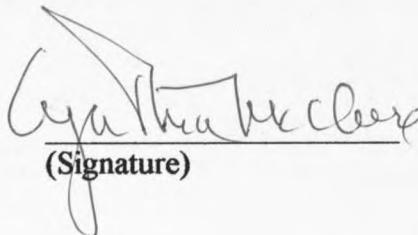
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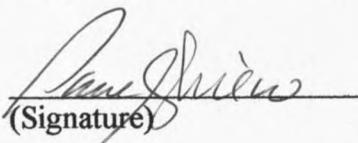
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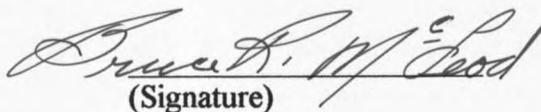
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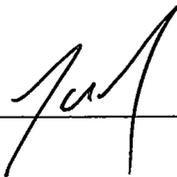

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LIST OF ABBREVIATIONS

ADPM	Aza-di- π -methane
B3LYP	Becke 3-parameter exchange and Lee-Yang-Parr correlation
BS1	6-31G*
BS2	6-311G**
BS3	6-311G**
CAN	Ceric ammonium nitrate
CAS-SCF	Complete Active Space – Self Consistent Field
CNDO/S	Complete Neglect of Differential Overlap with Spectroscopic extension
Δ SCF	Difference between two Self Consistent Field optimized states
DFT	Density Functional Theory
DPM	Di- π -methane
ED ₅₀	Effective Dosage
FVP	Flash Vacuum Pyrolysis
HF	Hartree-Fock
HOMO	Highest Occupied Molecular Orbital
h ν	light
I1	Intermediate 1
I1co	Intermediate 1co
I1cc	Intermediate 1cc
I2	Intermediate 2
I3	intermediate-3

INDO-MO	Intermediate Neglect of Differential Overlap – Molecular Orbitals
ISC	Intersystem Crossing
KTPBH	Potassium tert-isopropoxyborohydride
KVP	Keto Vinyl Phosphonate
LUMO	Lowest Unoccupied Molecular Orbital
MC-SCF	Multi Configuration - Self Consistent Field
MO	Molecular Orbital
MP	Moller Plessett perturbative methods
NPA	Natural Population Analysis
ODPM	Oxa-di- π -methane
P	Product
PES	Potential Energy Surface
PMP	4-Methoxyphenyl
QCISD	Quadratic Configuration Interaction of Singles and Doubles
S ₀	Singlet ground state
S ₁	First excited singlet state
sens	Triplet sensitizer
SM	Starting Material
SOMO	Singly Occupied Molecular Orbital
SPE	Single Point Energy
TD-DFT	Time Dependant – Density Functional Theory
TIPS	Triisopropylsilyl

- TS0 Transition State between I1 (exo) and I1 (endo)
- TS1 Transition State between I1 and I2
- TS2 Transition State between I2 and I3

ABSTRACT

The first room temperature stable 4-ethoxy-2,3-dihydropyridines derived from 2,3-dihydropyridones were prepared. Additionally, 2,3-dihydropyridinium salts derived from N-substituted-2,3-dihydropyrid-4-ones have also been prepared. These compounds were screened under a variety of different Diels-Alder conditions and found to be unreactive.

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CHAPTER 1

INTRODUCTION

The development and exploration of synthetic methodologies are central to organic chemistry. Often chemists are faced with unexpected or undesirable results. Understanding and possibly utilizing these results can lead to new and interesting chemistries.

The objectives of this work are three fold: (1) development of methodology to access new 2,3-dihydropyridines such as 4-ethoxy-2,3-dihydropyridine, **1**, (Figure 1); (2) understanding the role of C3-substituents in the oxa-di- π -methane photoisomerization (Scheme 1); and (3) development of methodology toward the preparation of bisphosphonomethyl-pyrimidinediones **2** (Figure 1). Herein these methodologies will be explored, and new insights into their chemistries will be presented.

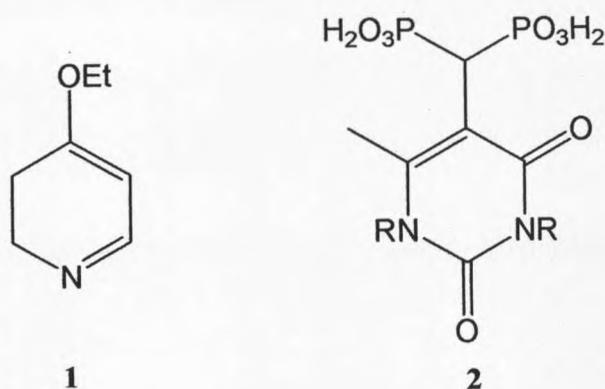
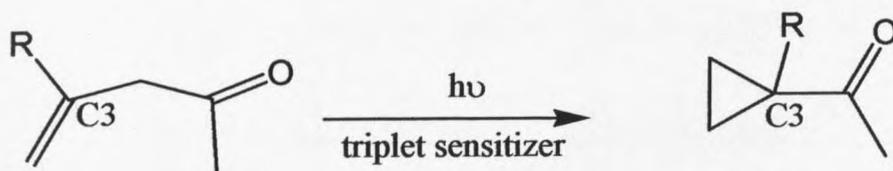


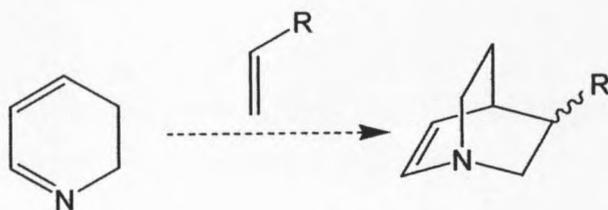
Figure 1



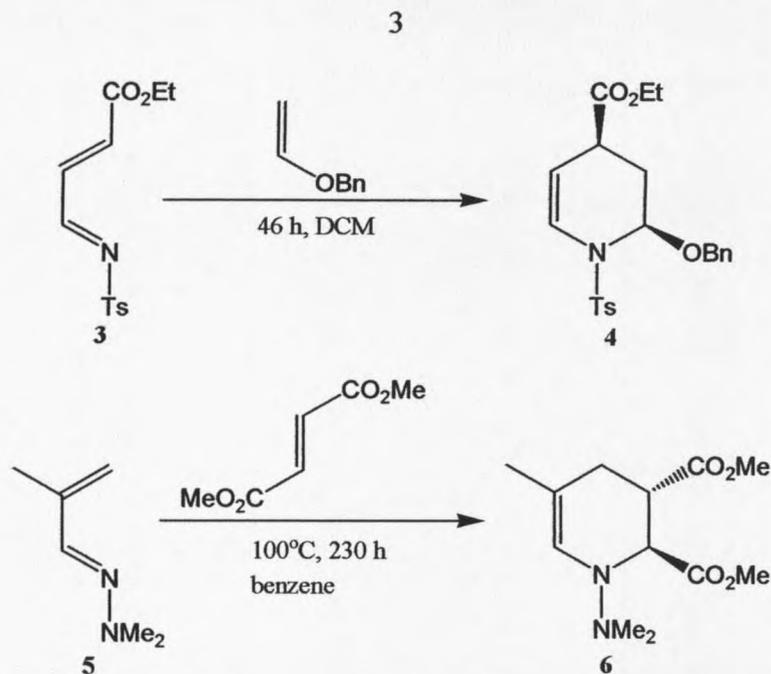
Scheme 1

2,3-Dihydropyridines

The aza-Diels-Alder reaction has the potential to be a very powerful method for the preparation of interesting nitrogen heterocyclic molecules. However, there is a large void in this area, as there are no examples of 2,3-dihydropyridines being utilized in the aza-Diels-Alder reaction (Scheme 2). This has made the synthetic preparation of quinuclidines significantly more complex than if an aza-Diels-Alder reaction could be used to assemble the quinuclidine core. The preparation of new 2,3-dihydropyridines and their attempted use in aza-Diels-Alder reactions is described in Chapter 2. Currently nearly all examples of 1-azadienes which undergo aza-Diels-Alder reactions are limited to acyclic unsaturated imines, two of which are shown in Scheme 3.^{1,2} Two cases exist where the aza-dienes are cyclic, but are part of fused aromatic systems.^{3,4} This will be discussed further in Chapter 2.



Scheme 2



C3-Substituent Effects on the Oxa-Di- π -Methane Photoisomerization

The oxa-di- π -methane (ODPM) photoisomerization has proven to be a useful synthetic transformation.⁵ Syntheses of several natural products have been realized using the ODPM photoisomerization.⁶ Examples of these include Modhephene,⁷ (-)-Coriolin,⁸ and (-)-Silphiperfol-6-en-5-one⁹ (Figure 2). Recently, the use of basic nitrogen containing substrates have been reported to react under ODPM conditions to produce the desired tricyclic compounds **7** and **8** (Scheme 4).^{10,11,12} However, the reaction conditions did not prove to be general, and the conversion of imidate **9** to the desired photoproduct **10** was not observed (Scheme 4).¹¹ One other example of a failed ODPM photoisomerization where the C3-substituent was an electron donating alkoxy group has been found.^{5d} The role of the C3-substituent on the ODPM photoisomerization is explored in Chapter 3.

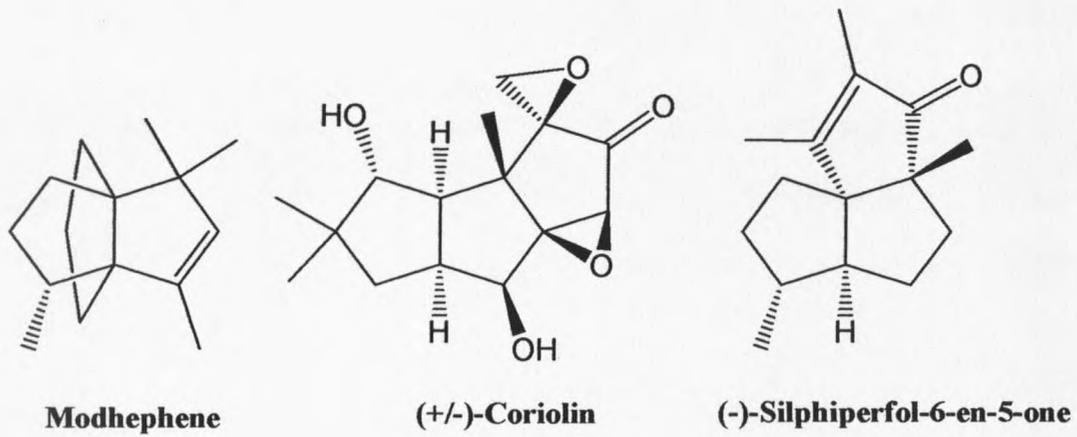
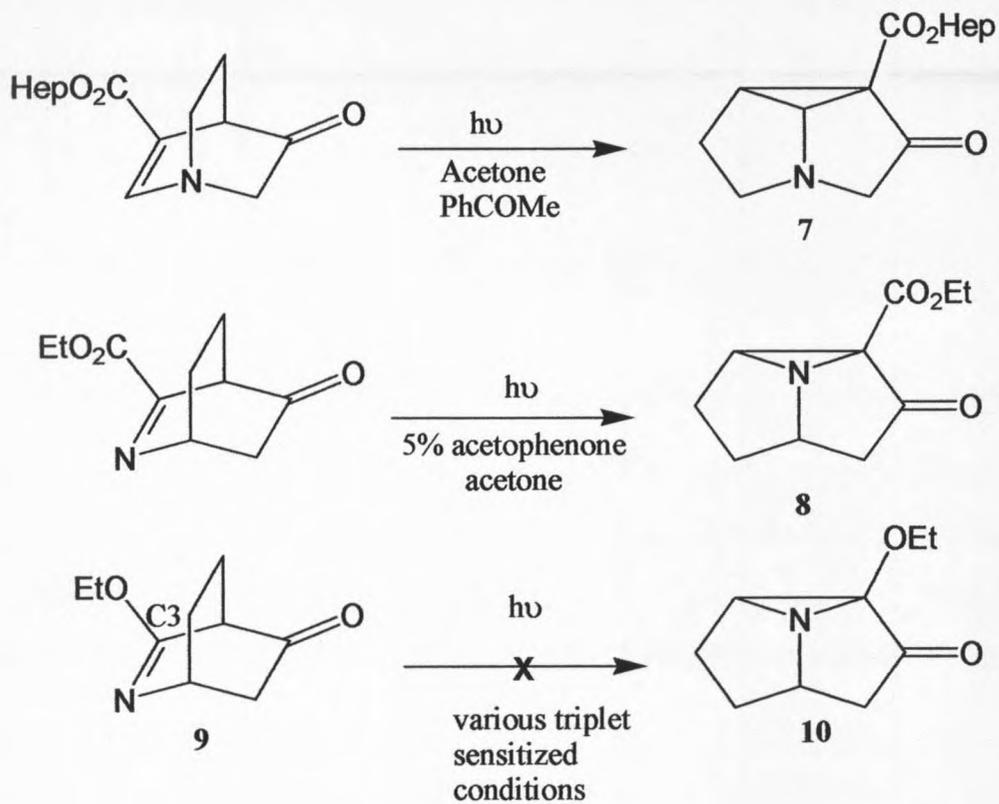


Figure 2



Scheme 4

