Synthesis of Aziridines and Secondary Amides Using Aminating Reagents and Their Biological Evaluation

Abstract of Thesis

Submitted to

Babasaheb Bhimrao Ambedkar University

(A Central University) Lucknow

For The Degree

Of

Doctor of Philosophy

In

Chemistry

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(M. Sc.)

Enrolment Number: 629/19

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2022

ABSTRACT

The thesis entitled **"Synthesis of Aziridines and Secondary Amides Using Aminating Reagents and Their Biological Evaluation"** is divided into five chapters and describes the preparation of valuable aziridines and secondary amides *via N*-insertion process using *O*-(sulfonyl)hydroxylamine derivatives as nitrogen source. Nitrogen containing heteroatomic compounds are the most abundant in nature due to their widespread occurrence and association in almost every physiological process of plants and animals. In these molecules, N-atom acts as a basic functional group and also can be a part of the complex heterocyclic system. *N*-containing heteroatomic compounds play a significant active role in various therapeutic applications. Owing to this, the C-N bond formation is essential in synthetic organic and medicinal chemistry. Among these nitrogen containing heteroatomic molecules, aziridines and secondary amides are highly desirable because they are present in natural, semi-synthetic, and synthetic bioactive compounds and they are also used as important synthetic intermediates.

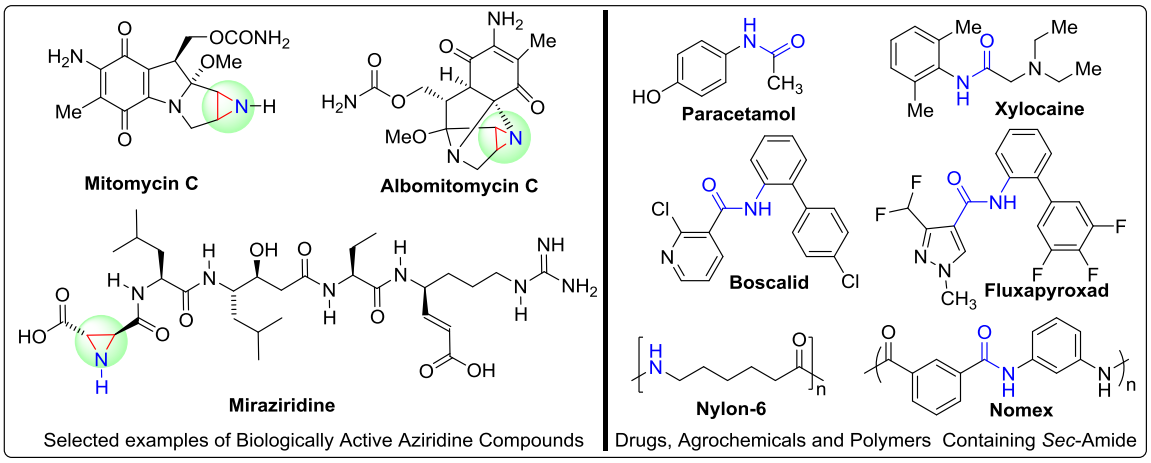
There are numerous methods available in the literature for the synthesis of aziridines and secondary amides however still some limitations are associated with these methods such as the use of expensive/toxic transition metals, requirement of additives, use of stoichiometric coupling reagents, poor yields, narrow substrate scopes, and typical reaction procedures. In this context, we have developed highly efficient, one-pot, atom-economical, mild, and operationally simple methods for the synthesis of *N*-H and *N*-Me aziridines from olefins and secondary amides directly from ketones *via* Beckmann rearrangement using *O*-substituted hydroxylamine derived reagents as a nitrogen source. These methods are discussed in different chapters of this thesis.

Chapter 1

General Introduction

Chapter 1 describes a brief discussion about the importance of *N*-containing heteroatomic compounds and the various approaches to achieve them. Among the numerous *N*-heteroatomic compounds, aziridines and secondary amides show their importance in

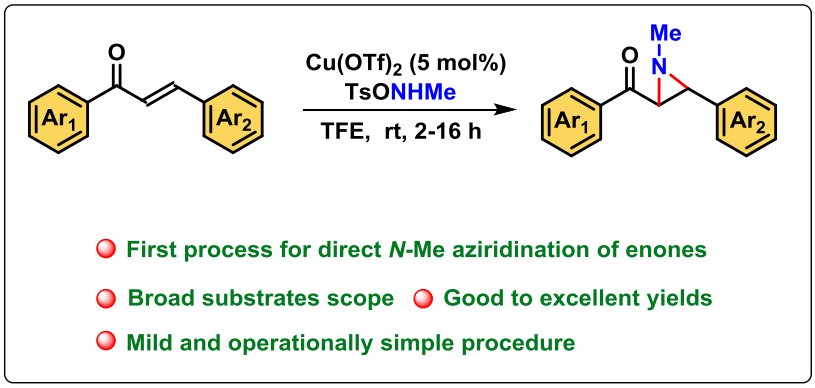
different therapeutic areas. The synthetic methodologies and biological importance of aziridines and secondary amides are summarized in different sections. In the final section of this chapter, the various applications of *O*-substituted hydroxylamine reagents are briefly discussed.



Chapter 2

Cu(II)-Catalyzed N-Me Aziridination of Enones Using N-methyl-O-tosylhydroxylamine as Aminating Reagent

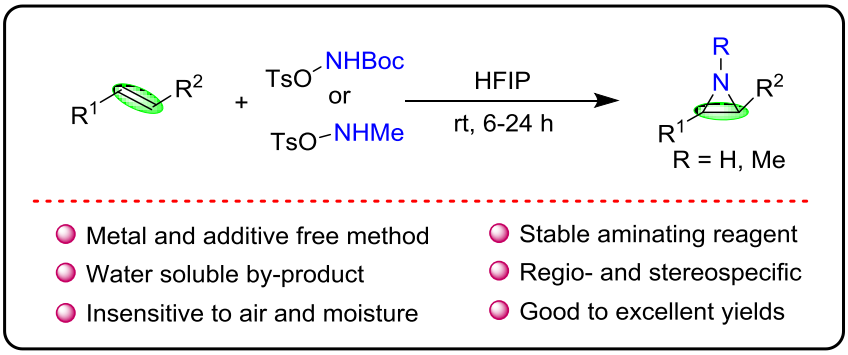
Chapter 2 describes the first and direct *N*-Me aziridination of enones using TsONHMe (*N*-methyl-*O*-tosylhydroxylamine) as a nitrogen source and $Cu(OTf)_2$ as a catalyst in TFE solvent. This mild, one-pot and operationally simple aziridination process provides a wide range of *N*-Me aziridines in good to excellent yields and diastereoselectivity. The reaction is supposed to proceed *via* Aza-MIRC (Aza-Michael Initiated Ring Closer) pathway.



Chapter 3

Metal and Additive Free N-H/N-Me aziridination of olefins Using O-(sulfonyl)hydroxylamine as Aminating Reagent

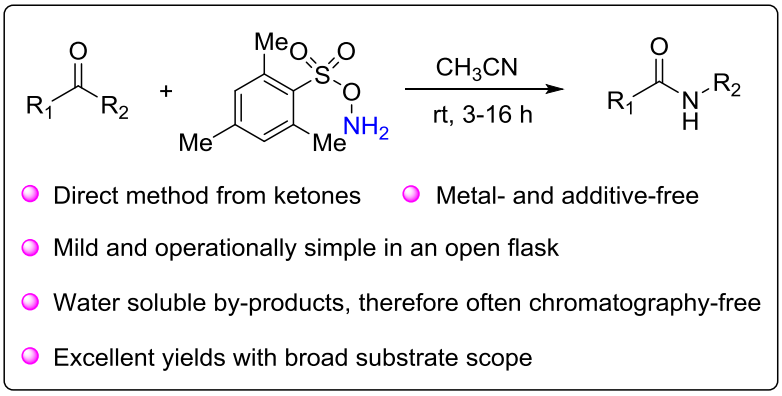
The third chapter describes the synthesis of metal and additive free direct *N*-H and *N*-Me aziridines from olefins. Synthesis of unactivated aziridines from olefins is less explored and the majority of reported protocols involve transition metal catalyzed reactions. Owing to the benefits of metal-free synthetic process we have developed a metal and additive-free synthetic method for the preparation of *N*-H/*N*-Me aziridines from olefins using TsONHBoc or TsONHMe as a nitrogen surrogate. This one-pot, mild and stereospecific method delivers the respective aziridines in good to excellent yields.



Chapter 4

Direct Synthesis of Secondary Amides from Ketones through Beckmann Rearrangement using O-(Mesitylsulfonyl)hydroxylamine

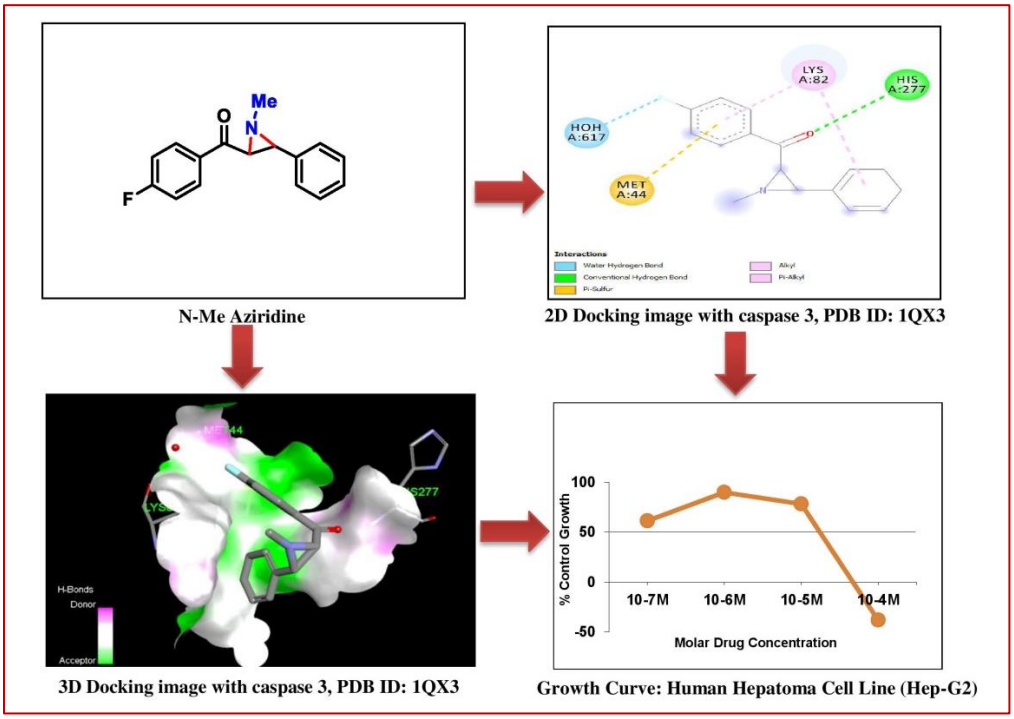
In this chapter, we have described a highly efficient, metal-free direct method for the synthesis of secondary amides and lactams from ketones using *O*-(Mesitylsulfonyl)hydroxylamine (MSH) as an aminating reagent. Various ketones were easily transformed into corresponding secondary amides under this mild reaction condition with high yields, and various functional groups were well tolerated. The products were usually isolated with an easy aqueous work-up in high purity without column chromatography.



Chapter 5

Biological Studies of N-Me Aziridines

In this chapter, Biological studies of structurally varied enone aziridines are discussed. Molecular Docking studies were performed to understand the anticancer mechanistic aspects by using the molecular target of apoptotic proteins caspase 3 (PDB ID: 1QX3) and caspase 9 (PDB ID: 2AR9) to screen most active compounds. The best screened compounds were taken against the human hepatoma cancer cell line (Hep-G2 cell). *N*-Me Aziridines having Me, NO_2, and F-group at the *p*-position of the phenyl ring showed good potency (GI50 < 10 μg/mL).



LIST OF PUBLICATIONS

1. *Cu $(OTf)_2$-Catalyzed Beckmann Rearrangement of Ketones Using Hydroxylamine-O-sulfonic Acid (HOSA)*
   Sailu Munnuri, Saumya Verma, **Dinesh Chandra**, R. R. Anugu, John R Falck, Jawahar L Jat
   Synthesis **2019**, *51*, 3709-3714

2. *Zinc(II)-Catalyzed Synthesis of Secondary Amides from Ketones via Beckmann Rearrangement Using Hydroxylamine-O-sulfonic Acid in Aqueous Media*.
   Saumya Verma, Puneet Kumar, Anil K. Khatana, **Dinesh Chandra**, Ajay K. Yadav, Bhoopendra Tiwari, Jawahar L. Jat
   Synthesis **2020**, *52*, 3272-3276.

3. *Direct Synthesis of Secondary Amides from Ketones through Beckmann Rearrangement using O-(mesitylsulfonyl)hydroxylamine*.
   Dinesh Chandra, Saumya Verma, Chandra Bhan Pandey, Ajay K. Yadav, Puneet Kumar, Bhoopendra Tiwari, Jawahar L. Jat
   Tetrahedron Lett. **2020**, *61*, 151822.

4. *Fe(II)-Catalyzed Synthesis of Unactivated Aziridines (N-H/N-Me) from Olefins Using O-Arylsulfonyl Hydroxylamines.*
   Dinesh Chandra, Ajay K. Yadav, Vikram Singh, Bhoopendra Tiwari, Jawahar L. Jat
   ChemistrySelect **2021**, *6*, 10524-10526.

5. *Direct N-Me Aziridination of Enones.*
   Jawahar L. Jat, Ajay K. Yadav, Chandra Bhan Pandey, **Dinesh Chandra**, Bhoopendra Tiwari
   J. Org. Chem. **2022**, *87*, 3751–3757

6. *A Synthetic Overview of Enones Aziridination*
   Dinesh Chandra, Puneet Kumar, Ajay K. Yadav, Ganesh Kumar, and Jawahar L. Jat
   ChemistrySelect 2022, *7*, e202200267; doi: 10.1002/slct.202200267

7. *Metal and Additive-Free Intermolecular Aziridination of Olefins Using N-Boc-O-Tosylhydroxylamine*
   Jawahar. L. Jat, **Dinesh Chandra**, Puneet Kumar, Vikram Singh, Bhoopendra Tiwari
   Synthesis, **2022**, *54*, 4513-4520.

8. *Metal-Free Direct Transformation of Aryl Boronic Acid to Primary Amines*
   Puneet Kumar, Saumya Verma, Komal Rathi, **Dinesh Chandra**, Ved Prakash Verma, Jawahar L. Jat
   Eur. J. Org. Chem., 2022, e202200508; doi: 10.1002/ejoc.202200508

9. *Metal-free Synthesis of Secondary Amides using N-Boc-O-tosylhydroxylamine as Nitrogen Source via Beckmann Rearrangement*
Jawahar L Jat, Puneet Kumar, Saumya Verma, **Dinesh Chandra**, Vikram Singh, Bhoopendra Tiwari
New J. Chem., **2022**, *46*, 14782-14785.