# *N*-H/*N*-Me Aziridination Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents and Their Computational Studies

**Abstract of Thesis**

***Submitted to***

**Babasaheb Bhimrao Ambedkar University**
**(A Central University)**
**Lucknow**

**For The Degree**

*Of*

**Doctor of Philosophy**

*In*

**Applied Chemistry**


***Submitted By***

**Ajay Kumar Yadav**
**(M. Phil, CSIR-UGC NET)**
**Enrolment Number: 952/17**

***Under the Supervision of***

**Dr. Jawahar Lal Jat**
**Assistant Professor**
**Department of Applied Chemistry**
**School for Physical Sciences**
**Babasaheb Bhimrao Ambedkar University**
**(A Central University)**
**Vidya Vihar, Raebareli Road, Lucknow-226025, Uttar Pradesh (India)**


**December, 2021**

# Abstract

The thesis entitled "***N*-H/*N*-Me Aziridination Using *O*-(Sulfonyl)hydroxylamines as Aminating Agents and Their Computational Studies**" consists of five chapters. Aziridines are highly interesting molecules, present in numerous bio-active natural, semi-synthetic and synthetic products. They exhibit various important transformation reactions *via* ring-opening, rearrangement and ring-expansion and they also display several biological activities such as anticancer, antimicrobial, antifungal, antimalarial and antiviral etc. Consequently, the synthesis of aziridines has been the focus of intense research over the last two decades. However, the majority of the developed protocols were devoted to the synthesis of protected aziridines (*N*-Ts, acyl, Ns etc.) only, as the removal of the protective groups from nitrogen is difficult because of the unwanted opening of the strain aziridine ring. Indeed, synthesis of unprotected (*N*-H/N-Me) aziridines would alleviate the aforesaid issue. However, practical and direct syntheses of unprotected aziridines from olefins are very limited. The development of powerful nitrogen transfer reagents such as *O*-(Sulfonyl)hydroxylamine derivatives have played an important role in the placement of nitrogen into a variety of useful molecules. Recently, they have been used in C-H amination, Beckmann and aziridination reaction etc. Some special features of *O*-(Sulfonyl)hydroxylamine reagent, such as benign nature to generate water-soluble by-product, lower cost, operative under mild reaction conditions, commercially available, ease of synthesis and non-toxicity etc., made them very popular among the scientific community for further exploration. In this context, we have developed the highly efficient, one-pot, atom-economical, environmentally benign, mild and operationally simple methods for the synthesis of *N*-H and *N*-Me aziridines from olefins using *O*-(sulfonyl)hydroxylamines as the aminating agents. In addition, we have also developed the first *N*-Me aziridination of Enones.

**Chapter 1**: **A General Overview on Aziridines and *O*-(Sulfonyl)hydroxylamines: Introduction and Motivation of Present Work**

This chapter starts with a brief introduction to the origin, structure, properties, reactivity and general reactions of aziridine synthesis. The synthetic and biological application of aziridines is summarized in Figure A. The importance and reactivity of *O*-(sulfonyl)hydroxylamines reagents have been briefly described in this chapter. The

experimental investigations and findings are described in the subsequent chapters (Chapters 2 to 5). Each chapter is individually discussed, and distributed in introduction, literature review, results and discussions, experimental section, and references.

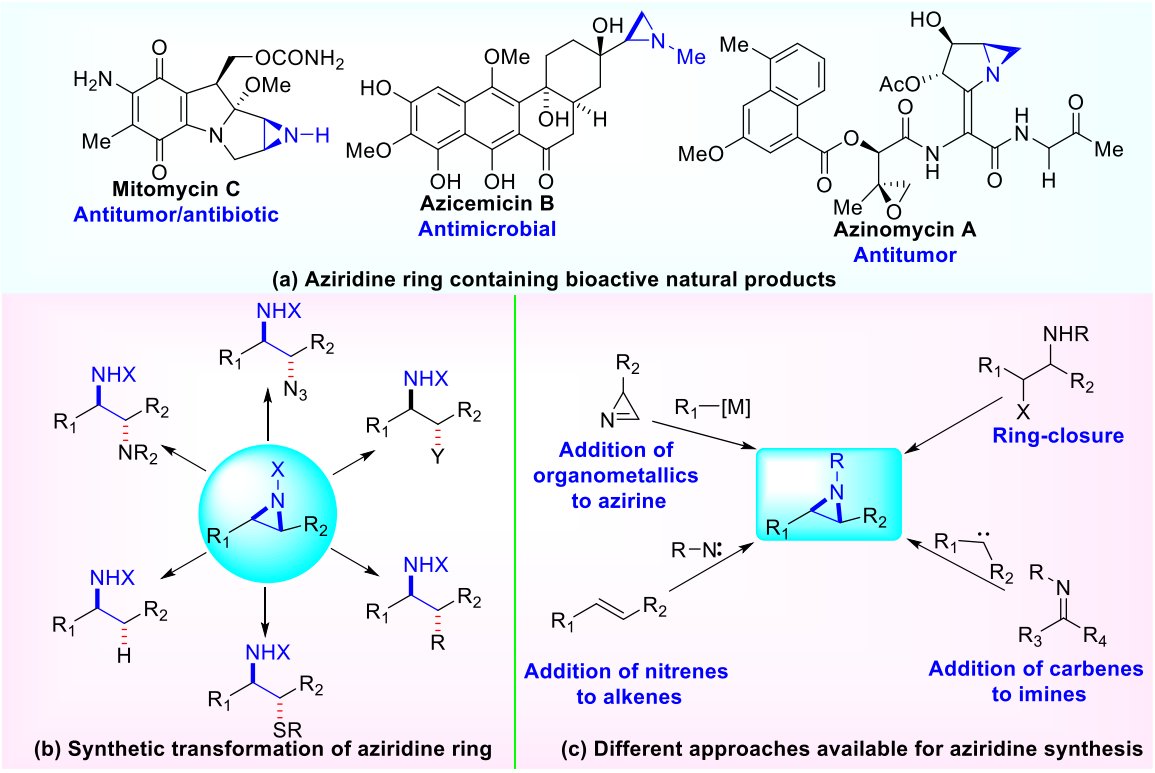
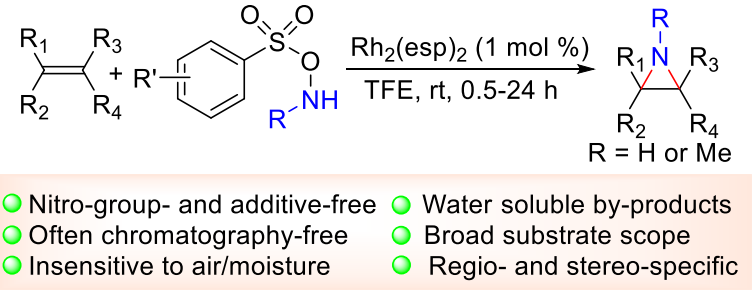



**Figure A**. General applications and synthesis of aziridines

## Chapter 2: Rh(II)-Catalyzed Direct *N*-H/*N*-Me Aziridination of Unactivated Olefins Using *O*-(Sulfonyl)hydroxylamines

This chapter describes the development of Rh(II)-catalyzed synthesis of *N*-H/*N*-Me aziridines from olefins using *O*-(sulfonyl)hydroxylamines as the aminating agent (Scheme A).

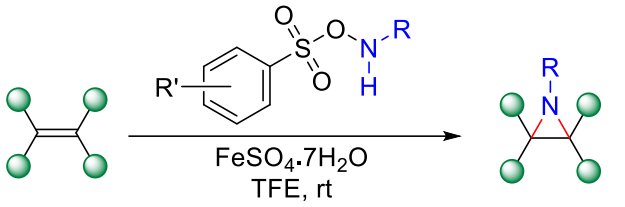



**Scheme A**. Rh(II)-catalyzed synthesis of *N*-H/*N*-Me aziridines from olefins

This one-pot, mild, simple, practical and stereospecific method afforded varieties of aziridines in good to excellent yields. Most of the products could be isolated in high purity without column chromatography, just after aqueous workup.

**Chapter 3**: **Fe(II)-Catalyzed Unactivated (*N*-H/*N*-Me) Aziridination of Olefins using O-Arylsulfonyl Hydroxylamines as Nitrogen Source**

This chapter describes the information about Fe(II)-catalyzed synthesis of *N*-H and *N*-Me aziridines from alkenes using *O*-arylsulfonyl hydroxylamines (Scheme B). This stereospecific, one-pot, economical aziridination could be conducted under the mild and operationally simple condition to provide the unprotected aziridines in excellent yields within a short period of time.



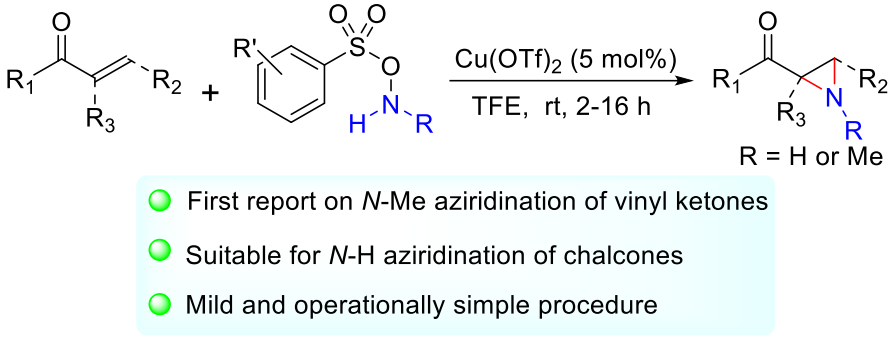

R = H or Me; R' = 2,4,6-trimethyl or *p*-Methyl

- Iron metal catalyzed
- Shorter reaction time
- Easily removable by-product
- Regio, stereo and chemoselective
- Insensitive to air/moisture

**Scheme B**. Fe(II)-catalyzed synthesis of unactivated aziridines from olefins

**Chapter 4**: **Cu(II)-Catalyzed Direct and Stereospecific *N*-H and *N*-Me Aziridination of Enones**

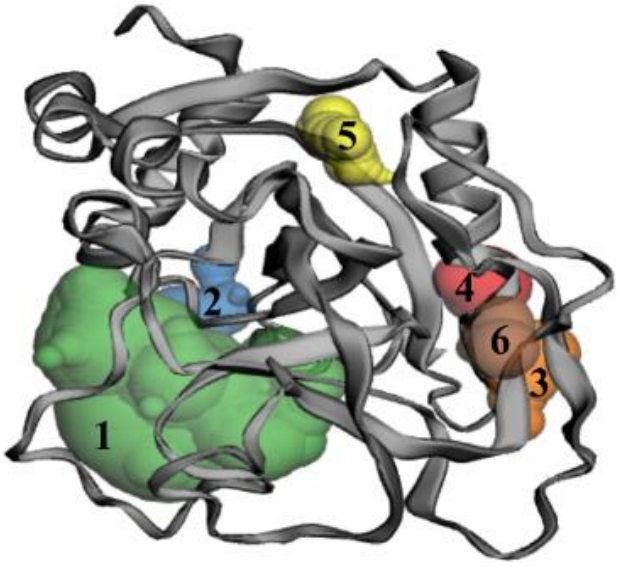
This chapter describes the $Cu(OTf)_2$ catalyzed first and direct *N*-Me aziridination of vinyl ketones employing *N*-methyl-*O*-tosylhydroxylamine as the aminating agent. Under this reaction condition, *N*-H aziridination of chalcones could also be achieved by using *O*-(mesitylenesulfonyl)hydroxylamine (Scheme C). This one-pot, open-flask, stereospecific, and practical method afforded a broad range of *N*-H/*N*-Me aziridines in good to excellent yields.




**Scheme C**. Cu(II)-catalyzed synthesis of *N*-H/*N*-Me aziridines from enones

**Chapter 5**: **Evaluation of anticancer activity of *N*-H/*N*-Me Aziridine derivatives as a potential poly (ADP-ribose) polymerase 1 inhibitor**

Poly [ADP-Ribose] polymerase 1 (PARP1) has recently been thought to be one of the potentially successful targets against cancer, specifically for ovarian and BRCA mutated breast cancers. Here, unprotected (*N*-H/*N*-Me) aziridine derivatives were recognized as potential anticancer compounds targeting the apoptotic pathway using a combined molecular descriptors (MDs) computation, prediction of activity spectra for substances (PASS), adsorption, distribution, metabolism, excretion and toxicity (ADMET) evaluation, Brain Or Intestinal Estimated (BOILED-Egg), Bioactivity score (BAS), docking-based virtual screening (DBVS), integral docking and molecular dynamics (MD) simulation. Twenty one *N*-H/*N*-Me aziridine derivatives were screened to identify molecular binding to the PARP1 binding pocket followed by docking and MD simulation. Compound 3a has a good binding profile along with all the targets but potentially can interact better with the PARP1 as observed by the molecular docking evaluations (Figure B).



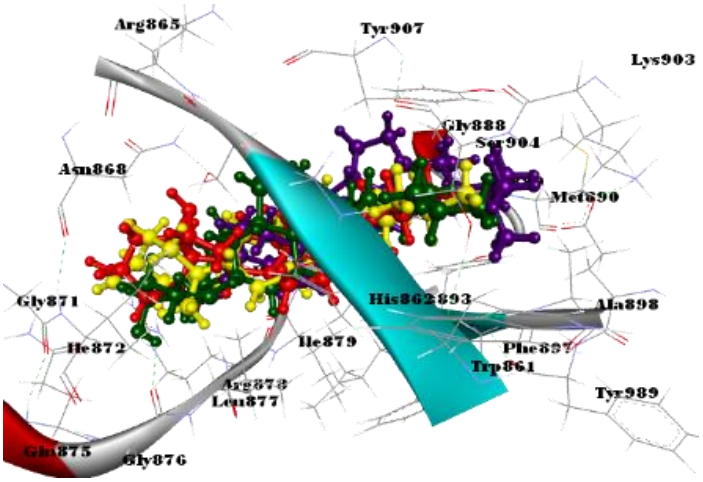



**Figure B**. Computational study of aziridine derivatives against anticancer activity

The docking complexes of the lead compound 3a with the target PARP1 were found stable during molecular dynamics simulations as represented by the obtained parameters including radius of gyration (Rg) and root mean square deviation (RMSD). Compound 3a yielded good binding free energy using the analysis of molecular mechanics generalized born surface area (MM-GBSA) and molecular mechanics Poisson–Boltzmann surface area (MMPBSA). Therefore, the finding of the studies unravels the possible compounds 3a as lead anticancer candidate against selected PARP1.