Abstract

The content of this thesis has been divided into five chapters based on the results of experiment work performed during the complete course of the research period. The chapter **1** of the thesis presents an introduction to nitrogen and sulfur heterocyclic compounds, their biological significance and the literature method for their synthesis. Chapter **2** describes a method for the diastereoselective synthesis of substituted tetrahydro-thiophenes and -thiopyrans *via* thia-Prins cyclization reaction. Chapter **3** deals with the diastereoselective synthesis of substituted morpholines from *N*-tethered alkenols and its application in total synthesis of (±)-chelonin A. In chapter **4**, $FeCl_3$-mediated carbenium-ion induced intramolecular cyclization of *N*-tethered alkyne-benzyl alkanols is described. Chapter **5** presents the synthesis of tetrahydroisoquinolines from *N*-tethered aryl-benzyl alkanols mediated by $BF_3{\cdot}OEt_2$.

Chapter 1: Introduction to Nitrogen and Sulfur Heterocyclic Compounds

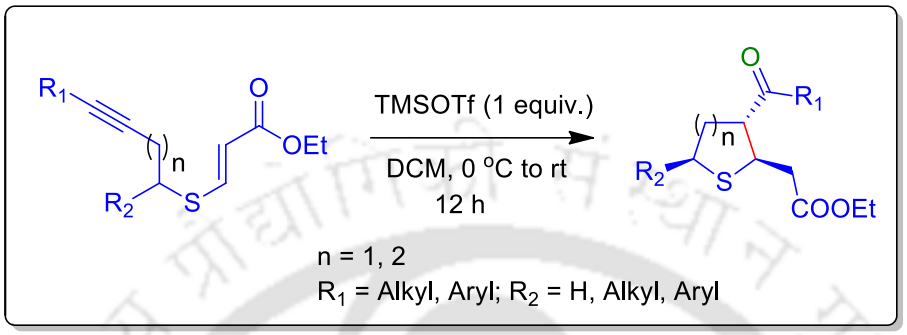
Saturated five- and six-membered nitrogen and sulfur heterocyclic compounds are the core structural component found in a broad array of natural products, bioactive compounds and important synthetic intermediates. The wide range of biological activities and the synthetic usefulness give nitrogen and sulfur heterocyclic compounds a privileged role in organic chemistry.

To build these classes of heterocycles, many strategies have been developed over the years. The most widely used methods are the 1,*n*-enyne rearrangement, ring-closing metathesis, cascade reactions, Prins cyclization reactions, transition metal salts catalyzed cyclization reactions and nucleophilic substitution reactions of activated alcohols etc. Among these methods stated, introductory chapter mainly discusses Prins cyclization, aza-Prins cyclization, thia-Prins cyclization and nucleophilic substitution reactions of activated alcohols in detail for the construction of these heterocycles.

Chapter 2: Diastereoselective Synthesis of Substituted Tetrahydro-thiophenes and -thiopyrans *via* Thia-Prins Cyclization Reaction

Prins cyclization is a powerful strategy for the synthesis of five- and six-membered oxygen heterocycles. Although the Prins cyclization is familiar in organic synthesis, its

analogue thia-Prins cyclization is less familiar. Analogous to Prins cyclization reaction, thia-Prins cyclization leads to five- and six-membered tetrahydrothiophenes and tetrahydrothiopyrans. In this chapter, we described an efficient method for the synthesis of tetrahydro-thiophenes and -thiopyrans from thioacrylates *via* intramolecular thia-Prins cyclization (*Scheme 1*).



Scheme 1

The reaction is highly diastereoselective and the stereochemistry of the trisubstituted tetrahydrothiophenes was characterized by 2-D nuclear Overhauser effect spectroscopy (NOESY). It showed a clear characteristic nOe correlations between the hydrogens C-2H and C-5H and the absence of nOe between C-3H and C-5H, which clearly indicates that the substituents at 2,5 positions are *cis* to each other and the benzoyl substituent at C-3 is *trans* to other two substituents. It was further confirmed by X-ray crystallographic analysis (Figure 1).

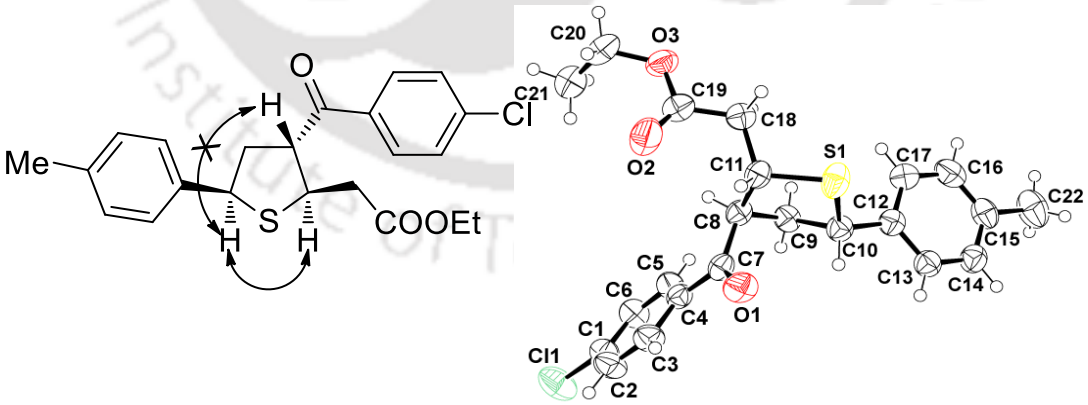


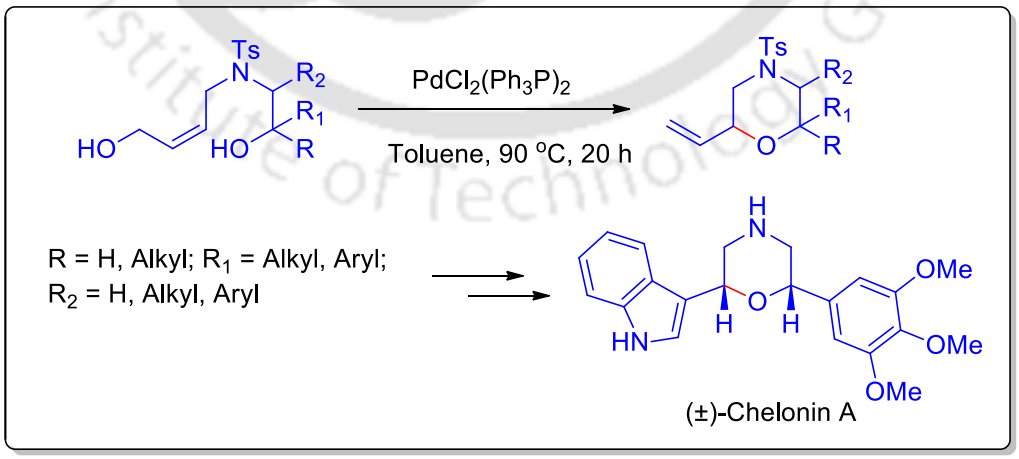
Figure 1. *nOe and ORTEP diagram of ethyl 2-((2R*,3R*,5R*)-3-(4-chlorobenzoyl)-5-(p-tolyl)tetrahydrothiophen-2-yl)acetate*

Similarly, the stereochemistry of 2,3,6-trisubstituted tetrahydrothiopyrans was confirmed by NOE spectroscopy of ethyl 2-((2*R**,3*R**,6*R**)-3-benzoyl-6-phenyltetrahydro-2*H*-thiopyran-2-yl)acetate, which indicates that the substituents at 2,6 positions are *cis* to each other and the benzoyl substituent at C-3 is *trans* to the other two substituents.

In conclusion, an efficient and highly diastereoselective method for the synthesis of di- and tri-substituted tetrahydro-thiophenes and -thiopyrans in good yields has been developed from thioacrylates *via* intramolecular thia-Prins cyclization reaction.

Chapter 3: Diastereoselective Synthesis of Substituted Morpholines from *N*-Tethered Alkenols: Total Synthesis of (±)-Chelonin A

Morpholine derivatives are widely distributed in many naturally occurring and biologically active molecules. In particular, 2,6-disubstituted and 2,5-disubstituted morpholine derivatives are important pharmacophores in medicinal chemistry. For example, the natural product chelonin A, which was isolated from the marine sponge *Chelonaplysilla* sp. have been reported to exhibit antimicrobial activity against *Bacillus subtilis* and *in-vivo* antiinflammatory activity in the mouse. In this chapter, we discuss an efficient method for the diastereoselective synthesis of 2,6-disubstituted and 2,5-disubstituted morpholines using intramolecular C-O bond formation of *N*-tethered diols consisting of alkanol and alkenol catalyzed by palladium(II) chloride. This methodology was further utilized for the total synthesis of (±)-chelonin A, starting from *N*-tethered diol in 5 steps with an overall 26% yields (*Scheme 2*).



Scheme 2

The reaction is highly diastereoselective with predominant formation of *cis* isomers for both 2,6-disubstituted and 2,5-disubstituted morpholines. The relative stereochemistry of 2,6-disubstituted morpholines was determined by 2-D nuclear Overhauser enhancement spectroscopy (NOESY) and X-ray crystallographic analysis of (2*R**,6*S**)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine (Figure 2). Similarly, the relative stereochemistry of the 2,5-disubstituted morpholines was determined by X-ray crystallographic analysis of compound (*2S**,*5S**)-5-Benzyl-4-tosyl-2-vinylmorpholine (Figure 2).

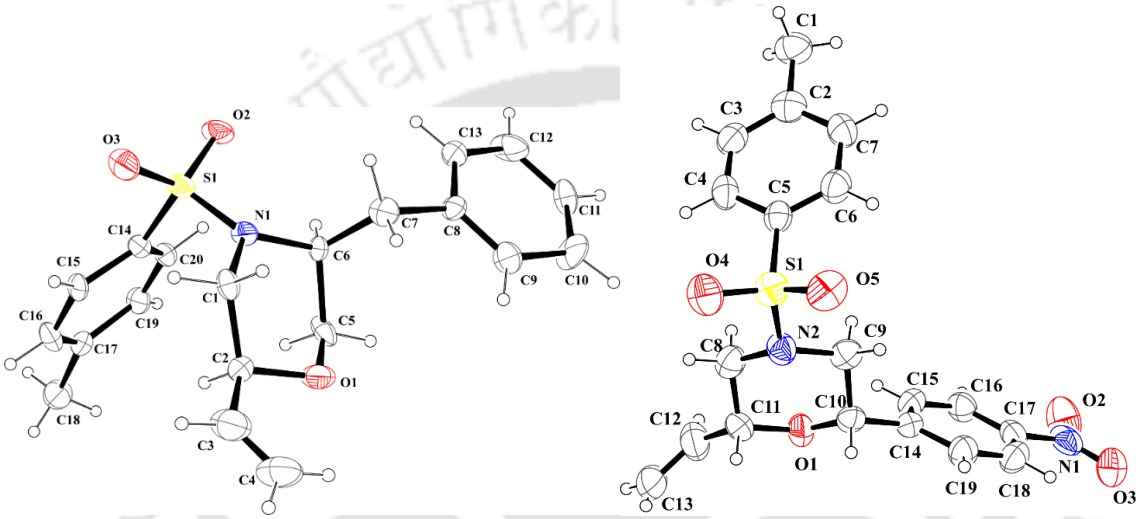


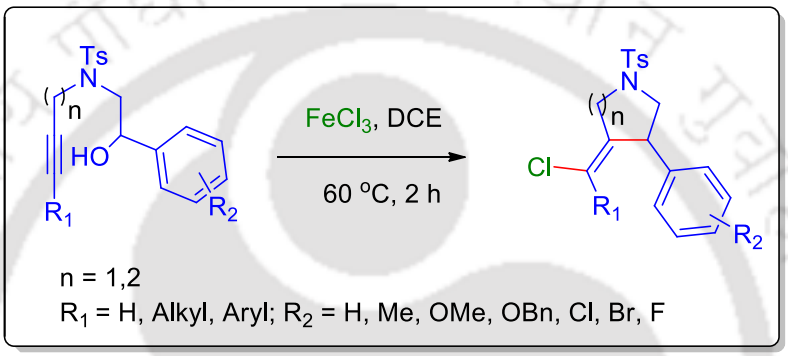
Figure 2. *ORTEP diagram of (2S*,5S*)-5-Benzyl-4-tosyl-2-vinylmorpholine and (2R*,6S*)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine*

In conclusion, we developed an efficient method for the synthesis of substituted morpholines *via* palladium(II) catalysed intramolecular cyclization reaction of *N*-tethered diols in good yields. The major advantage of this reaction is that it regioselectively generates a vinyl group at position 2 of the morpholine ring, which can be used for the synthesis of natural product (±)-chelonin A.

Chapter 4: $FeCl_3$-Mediated Carbenium Ion Induced Intramolecular Cyclization of *N*-Tethered Alkyne-Benzyl Alkanols

Nucleophilic substitution of alcohols *via* a formal dehydration process is an important strategy for the organic chemists to access wide variety of functionalised derivatives. Direct nucleophilic substitution of an alcohol is not possible as hydroxide is a poor leaving group and therefore activation is usually required. However, π-activated

alcohols, such as allylic, benzylic and propargylic alcohols can be activated towards nucleophilic attack by the use of Lewis and Brønsted acids. In this chapter, we present a methodology for the synthesis of pyrrolidines and piperidines derivatives from *N*-tethered alkyne-benzyl alkanols *via* ferric chloride ($FeCl_3$) mediated intramolecular carbenium-ion induced cyclization reaction (*Scheme 3*). In this reaction, ferric chloride acts as a Lewis acid to remove hydroxyl group of benzyl alkanol to afford benzyl carbenium ion followed by nucleophilic attack by alkyne and simultaneous *anti*-addition of chloride ion across the alkyne to form pyrrolidine and piperidine derivatives with exocyclic chloro-alkylidene and -arylidene moiety.



Scheme 3

The reaction is highly *Z* selective for pyrrolidines and *E* selective for piperidines. The addition reaction to the triple bond proceeds with *anti*-mode in preference to *syn*-mode in both the cases. Therefore, the *E*/*Z* selectivity is just a consequence of the IUPAC nomenclature. The stereochemistry of the pyrrolidine products was confirmed by X-ray crystallographic analysis of (*Z*)-3-(Chloro(phenyl)methylene)-4-(2-chlorophenyl)-1-tosylpyrrolidine (Figure 3).

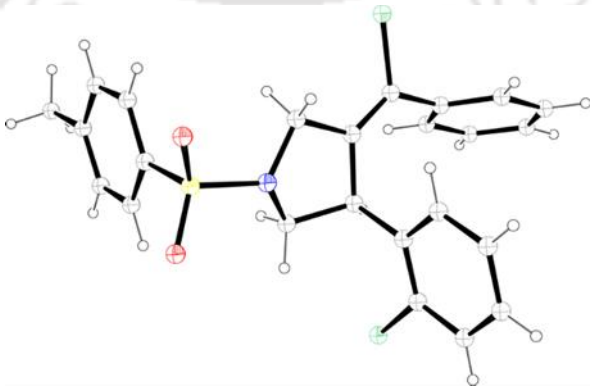
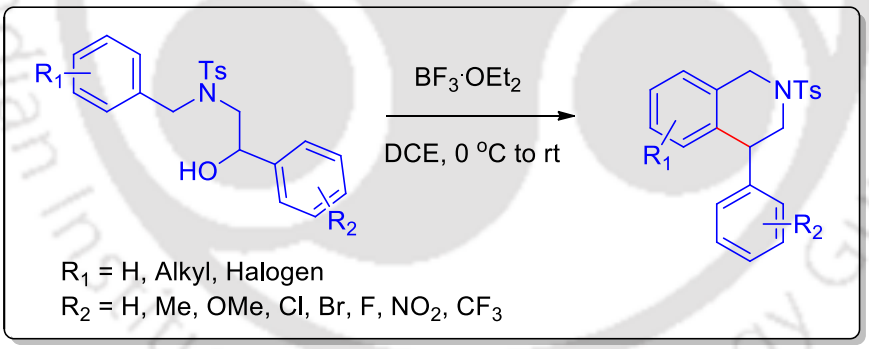


Figure 3. *ORTEP diagram of (Z)-3-(Chloro(phenyl)methylene)-4-(2-chlorophenyl)-1-tosylpyrrolidine*

In conclusion, we have developed an efficient method for the synthesis of substituted pyrrolidine and piperidine derivatives with exocyclic chloro-alkylidene and -arylidene moiety in good yields. The reaction is *Z* selective for pyrrolidines and *E* selective for piperidines. One of the important aspects of the reaction is the dual role exhibited by ferric chloride as Lewis acid as well as chloride nucleophile.

Chapter 5: Synthesis of Tetrahydroisoquinolines from *N*-Tethered Aryl-Benzyl Alkanols mediated by $BF_3{\cdot}OEt_2$

The Friedel-Crafts reaction is one of the most powerful methods to synthesize aromatic compounds and has been widely used in various industrial processes. Carbocation generated from the treatment of π-activated alcohols with Lewis and Brønsted acids may be used as electrophilic alkyl equivalents in Friedel-Crafts alkylation reactions. In this chapter, we discuss a general methodology for the synthesis of 4-aryl-tetrahydroisoquinolines from *N*-tethered aryl-benzyl alkanols mediated by boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in good to excellent yields (*Scheme 4*). In the process, benzylic alcohol is used as an electrophilic alkyl equivalent in presence of Lewis acid $BF_3{\cdot}OEt_2$ for the intramolecular Friedel-Crafts alkylation reactions.



Scheme 4

In conclusion, we have developed an alternate, efficient methodology for the synthesis of 4-aryl-tetrahydroisoquinoline derivatives in good to excellent yields. The reaction is very mild and can be carried out by inexpensive and commercially available $BF_3{\cdot}Et_2O$ as Lewis acid.