ABSTRACT OF THE THESIS ENTITLED

BASE-MEDIATED REGIO- AND STEREOSELECTIVE INTERMOLECULAR HYDROAMINATION OF ALKYNES

SUBMITTED BY
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ABSTRACT

Abstract of the thesis entitled “Base-Mediated Regio- And Stereoselective Intermolecular Hydroamination of Alkynes” to be submitted by Ms. Megha Joshi, Department of Chemistry, University of Delhi for the award of Doctor of Philosophy.

The thesis is divided into four chapters:

CHAPTER 1. Hydroamination: A general introduction

CHAPTER 2. Base-mediated hydroamination of internal alkynes

PART A. Addition of N-heterocycles onto Symmetrical Internal alkynes

PART B. Addition of N-heterocycles onto Unsymmetrical Internal alkynes

CHAPTER 3. Base-catalyzed hydroamination of terminal alkynes

CHAPTER 4. Preferential addition of N-heterocycles onto halo-arylalkynes over N-arylation

The chapter wise content is described briefly in the following pages:

CHAPTER 1: Hydroamination: A general introduction

Hydroamination of alkenes, alkynes, and related unsaturated substrates represents an attractive strategy for the preparation of nitrogen heterocycles, enamines and imines. Enamines occupy a prominent place in organic synthesis, and variety of methods has been reported in the literature for their synthesis. Intermolecular addition of alkynes to primary and secondary amines have been well studied, however, addition of N-heterocycles on internal alkynes remain elusive.
A notable work was reported by Knochel in 1999 for the addition of heterocyclic amines to phenylacetylene using CsOH.H₂O in NMP (Scheme 1).

**Scheme 1.**

Later Kondo reported the addition of O- and N-nucleophiles to alkynes using phosphazene base t-Bu-P₄. Moreover, only one example of the addition of pyrrole on diphenylacetylene was reported using t-Bu-P₄ with poor stereoselectivity (Scheme 2).

**Scheme 2.** Phosphazene-catalyzed nucleophilic addition onto phenyl- or diphenylacetylene

In this regard, stereo- and regioselective addition of N-heterocycles on alkynes is important and challenging. In our recent report on copper-catalyzed tandem synthesis of indolo- and pyrrolo[2,1-α]isoquinolines, the reaction was proposed to undergo via formation of a hydroaminated intermediate H (Scheme 3).
Scheme 3. Copper catalyzed tandem synthesis of indolo- and pyrrolo[2,1-α] isoquinolines

With these successful reports on the synthesis of biologically important molecules via hydroamination and strong demand for the development of general, flexible, and regioselective methodologies motivated us to explore the addition of heterocyclic amines onto alkynes. The full details of our study on the base-mediated regio- and stereoselective hydroamination of terminal and internal alkynes confirms the mechanistic pathway of tandem synthesis of [2,1-α]isoquinolines.

CHAPTER 2: Base-mediated hydroamination of internal alkynes

The second chapter is hydroamination of internal alkynes and it is divided into part A and part B (Scheme 4). Part A of second chapter shows the addition of various N-heterocycles onto symmetrical internal alkynes. This part also consists of optimization of reaction conditions by varying bases, solvents and temperatures. The regio- and stereoselective addition of N-heterocycles to alkynes using KOH was done and the formation of (Z)-isomers and their conversion to (E)-products were found to be dependent upon time as well as the choice of base. The stereochemistry of the products was established by X-ray crystallographic studies and NOESY data.

Scheme 4. Hydroamination of internal alkynes
Part B of the chapter includes the extension of the methodology for the hydroamination of unsymmetrical internal alkynes. Selective attack of N-heterocycles on a more electrophilic alkynyl carbon was supported by DFT calculations, and intramolecular cyclization of ortho-haloalkynes in indolo-[2,1-α] isoquinolines.

**CHAPTER 3: Base-catalyzed hydroamination of terminal alkynes**

In the third chapter, the scope of the utility of base KOH have been extended to the regio- and stereoselective addition of heterocycles onto variety of terminal alkynes, which furnished diversely substituted styryl enamines (Scheme 1.24).\(^{14}\)

**Scheme 5. Hydroamination of terminal alkynes**

\[ R^2NH + \equiv R^3 \xrightarrow{\text{KOH, DMSO}} R^2N\equiv R^3 \]

This chapter also includes the hydroamination of 1,3- and 1,4-diethynylbenzenes selectively at one alkynyl carbon and chemoselective addition of N-heterocycles onto various alkynes in the presence of KOH only (Scheme 6).

**Scheme 6. Hydroamination of dialkynes**

**CHAPTER 4: Preferential addition of N-heterocycles onto haloarylalkynes over N-arylation**
The fourth chapter describes the preferential addition of \( N \)-heterocycles onto haloarylalkyne over \( N \)-arylation under catalytic conditions (Scheme 7).

**Scheme 7.** Preferential addition of \( N \)-heterocycles onto haloarylalkynes over \( N \)-arylation

For the first time, a reaction of various \( N \)-heterocycles and halo-substituted arylalkynes was performed, and it was observed that under catalytic conditions also, hydroamination is preferred over amination of aryl halide. The results of this study suggested that the mechanism of the copper-catalyzed tandem synthesis of indolo- and pyrrolo[2,1-\( \alpha \)]isoquinolines proceeds via generation of intermediate Q through hydroamination followed by oxidative addition to the key intermediate R and not vice versa (Scheme 8).

**Scheme 8.** Proposed mechanism for the synthesis of [2,1-\( \alpha \)]isoquinolines
In summary, we have described a versatile and efficient regio- and stereoselective synthetic method to produce a broad range of functionalized vinyl- and styryl enamines which are useful and versatile synthetic intermediates for the synthesis of biologically active compounds (Scheme 9).

**Scheme 9:** Base mediated hydroamination of alkynes

This metal and ligand free methodology utilizes a simple and economical base KOH and Cs$_2$CO$_3$ for the addition of N-heterocycles not only onto terminal and internal alkynes but also for 1,3- and 1,4-dialkynes. Addition of heterocyclic nucleophile onto alkynones has also been reported under mild conditions. Selective attack of N-heterocycles on more electrophilic alkynyl carbon was supported by DFT calculations and stereochemistry of the products was established by X-ray crystallographic studies and intramolecular cyclization of ortho-haloalkynes in to indolo-[2,1-α]isoquinolines.

Current work also supports and confirms the mechanistic pathway for the copper-catalyzed tandem synthesis of indolo- and pyrrolo[2,1-α]isoquinolines via formation of Z-stereoisomer by hydroamination of ortho-haloarylalkyne followed by oxidative addition in the presence of metal and ligand.
LIST OF PUBLICATIONS

The thesis is based on the following papers.

