ABSTRACT

The thesis entitled “SYNTHESIS OF NOVEL BIOLOGICALLY ACTIVE HETEROCYCLIC COMPOUNDS” is divided into six chapters. Chapter 1 deals with general survey of literature on the importance of heterocyclic compounds and application of green chemistry catalysts for the preparation of heterocyclic compounds. The chapters 2 deal with different approaches for the preparation of achiral bisimines and its preparation through iron (III) Chloride an eco friendly catalyst. The chapter 3 deals with application of achiral bisimines cobalt complex to enhance the enantiomeric ratio of a key intermediate used in well known drug called rivastigmine. The chapter 4 deals with the application of zeolites for the construction of 4-Alkynyl substituted thiazoles. Whereas the chapter 5 deals with the proline mediated application of 4-Alkynyl substituted thiazoles by Sonogashira coupling with decreased homocoupled products. The chapter 6 deals with summary and conclusion.

Chapter (I): Introduction to green chemistry catalysts

This chapter presents an overview of introduction and literature survey on the preparation and application of achiral Bis-Imines and 4-substituted thiazoles. In addition to this a general literature survey on green chemistry catalyst and its application on heterocyclic compounds.

Since 1991 onwards different types of green chemistry catalyst have been explored for example. a) Achiral bisimines transition metal complex, b) Zeolites c) Rhodium metal complexes d) proline and e) Enzymes. These catalysts found many applications in organic synthesis for eg a) Aldol reaction b) Micheal reaction c) Nazarov cyclization d) Ring opening reactions e) Epoxidation reactions f) potential drug intermediates.
In conclusion the green catalysts have found a key role in organic synthesis. New and interesting achievement in the catalysis chemistry can be expected in near future.

Chapter (II): Iron (III) chloride mediated preparation of achiral bisimines. A new approach for the preparation of achiral bisimines:

Chapter 2 describes the formation of carbon-nitrogen bonds via an iron (III) chloride reaction between aldehydes and ethylenediamine. This methodology mentions use of environment friendly catalyst system for the preparation of achiral bisimines with various substituents. The reactions proceed well to afford a variety of $N^1,N^2$-bis(aryl)ethane-1,2-diamine and $N^1,N^2$-bis(heteroaryl)ethane-1,2-diamine in good yields. The process opens an easy way to access for the preparation of achiral bisimines in which a novel heteroaryl compound is also reported.

\[
\begin{align*}
\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2 + \text{ArCHO} & \xrightarrow{\text{FeCl}_3, \text{rt, MeOH}} \text{ArHC}=\text{NCH}_2\text{CH}_2\text{N}^\equiv\text{CHAr} \\
\text{(1)} & & \text{(2)} & & \text{(3)}
\end{align*}
\]

Scheme 2.1: The iron (III) chloride mediated reaction with protic solvent.

While a number of methods are known to prepare Schiff bases by reacting an amine with a carbonyl compound most of these processes generally require longer reaction time under refluxing conditions. Moreover, in our hand the reaction of 1, 2-amine with aromatic aldehyde under these reaction conditions provided a mixture of mono and bis-Schiff bases. Therefore the ongoing research required an efficient and direct method to prepare our desired bis-imines.

Accordingly, we have developed a new and milder method for this purpose that involved the use of anhydrous Lewis acid as a catalyst. Thus a variety of bis-imines 3 were prepared by reacting ethane-1, 2-diamine 1 with a number of aromatic
aldehydes (2) in the presence of anhydrous ferric chloride (Scheme 2). The results of this study are summarized in Table 1.

Both aryl and heteroaryl aldehydes reacted well with the diamine affording the desired products in good to excellent yields. Aldehydes containing electron donating (e.g. methoxy, hydroxyl, fluoro and bromo) or withdrawing groups (e.g. nitro) were found to be equally effective in terms of product yields.

Table 1.1 Schiff base formation induced by iron chloride.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product\textsuperscript{b}</th>
<th>Yield\textsuperscript{c}</th>
<th>Reaction Time(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{O}^\text{H})=2\text{a}</td>
<td>(\text{O}^\text{N}\text{N}^\text{O})=3\text{a}</td>
<td>90</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>(\text{O}^\text{N})=2\text{b}</td>
<td>(\text{O}^\text{N}\text{N}^\text{O})=3\text{b}</td>
<td>90</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>(\text{O}^\text{H})=2\text{c}</td>
<td>(\text{O}^\text{N}\text{N}^\text{O})=3\text{c}</td>
<td>88</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>(\text{O}^\text{H})=2\text{d}</td>
<td>(\text{F}^\text{N}\text{N}^\text{O})=3\text{d}</td>
<td>80</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>(\text{O}^\text{H})=2\text{e}</td>
<td>(\text{O}^\text{H}\text{N}^\text{O})=3\text{e}</td>
<td>80</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>(\text{O}^\text{H})=2\text{f}</td>
<td>(\text{O}^\text{H}\text{N}^\text{O})=3\text{f}</td>
<td>88</td>
<td>0.5</td>
</tr>
</tbody>
</table>
All the reactions were carried out using aryl aldehyde 2 (11.0 mmol), ethane-1,2-diamine (5.0 mmol) and FeCl₃ (0.1 mmol) in methanol (40 mL) at room temperature.

Identified by ¹H NMR, IR, MS. Isolated yield. Methanol was used as solvent.

Chapter (III): Synthesis of rivastigmine using bis ((1H-imidazol-2-yl) methylene) ethane-1,2-diamine as ligand through CALB mediated enzyme: A novel approach.

In Chapter 3, we apply the method developed for the synthesis of achiral bisimines and apply it towards synthesis of 3-((R)-1-acetoxyethyl) phenyl ethylmethylcarbamate a key intermediate for well known drug called Rivastigmine.

We performed screening of above prepared achiral bisimines transition metal complex as ligands for the enantiomeric enrichment of key intermediate.

\[ M = \text{Co,Cu} \]

Achiral bis-imines cobalt complex as ligand
The protocol mentions the new approach for the preparation enantiomerically pure secondary alcohols using bis ((1H-imidazol-2-yl) methylene) ethane-1, 2-Diamine as ligand by lipase-catalyzed kinetic resolution and application of the above intermediate for the preparation of well known drug called rivastigmine in simple four steps a concise route compared to earlier approach.

**Scheme 3.1**

![Scheme 3.1](image)

**Scheme 3.1:** Synthetic protocol to access the both enantiomers of 3- (1hydroxyethyl) Phenyl ethyl (methyl) carbamate

Among acyl donors vinyl acetate was the best acyl donor (*E*=>200). 48% conversion in 10.5 h with 5 mg mL\(^{-1}\) CAL-B with respect to product. Screening of concentration effects on the acylation of *rac-4* with vinyl acetate and CAL-B proved that the acylation can be performed in a solvent-free system, where the acyl donor was used just in slight excess over the reactive alcohol enantiomer in the resolution mixture.

**Application of above intermediate in preparation of Rivastigmine**

Finally, application of this methodology was demonstrated in preparing the well-known drug rivastigmine which has been used to treat mild to moderate dementia associated with Alzheimer’s and Parkinson’s disease. Thus the enantiopure acetate (*R*)-5 was treated with excess of dimethylamine in toluene to afford the desired (*S*)-8 [(*S*-rivastigmine] in 60% yield (final step, Scheme 5).
Notably, the earlier method for the synthesis of (S)-8 involved asymmetric reduction of the ketone 6 to give the alcohol with the required chirality followed by mesylation and subsequent treatment with dimethylamine. We have developed a novel – lipase based method for acetylation of benzylic secondary alcohol with high enantioselectivity and yield.

Chapter (IV): Zeolite mediated construction of Thiazole moiety.

In this section, we have demonstrated that H-Beta catalyst can be used as an efficient catalyst system for acylation of bis trimethylacetylenes with choro acetyl chloride. The reactions proceed well to afford a mono acylated silyl compound followed by treatment with thioacetamide resulted in 4-(trimethylsilyl ethynyl)-substituted-1, 3-thiazole in good yields. As the fourth position on thiazole is not reactive, this methodology is a general and economical process, opens an easy way to access 4- alkynyl substituted thiazoles. The use of homogeneous Lewis acid catalysts is recognised with a number of disadvantages. Among them the major drawback of these catalysts is they are not regenerable and are used in reactions in more than stoichiometric amounts.

We are first to report the H-Beta catalyst -mediated synthesis of alkynyl substituted thiazoles in dichloromethane, in good yields (scheme 4.1)
Scheme 4.1: The zeolite H-Beta catalyst-mediated construction of 1,3-thiazole ring.

Yet, to my knowledge, there is not any existing report that investigated the catalytic effect of H-Beta catalyst on acylation reactions of for the construction of thiazole moiety, though it is known that the type and amount of metal cation on zeolite may influence the strength and distribution of acid sites. In literature, a few studies or can say no reports are there for the preparation of thiazole framework from H-Beta catalyst.

Chapter (V): proline mediated application of 4-Alkyny substituted thiazoles in Sonogashira coupling.

Proline is the only natural amino acid with secondary amine functionality and thus has a higher pKa value and enhanced nucleophilicity relative to other amino acids and also proline can be regarded as a bifunctional catalyst for the activation of metal catalyst.

When a mixture of aryl and heteroaryl iodides 6a and an 4-alkynyl compound 5 was heated in the presence of palladium catalyst, copper iodide, proline and a base in dimethylformamide, 4-alkynyl thiazole aryl derivatives 7a were obtained in good to excellent yields (60-90%) according to the following scheme-5.1. Among all the ligands screened, the use of proline L3 was found to be the most effective in terms of product yield with less homocoupled product. The maximum yield was achieved by using 5 mol% of L3 and K₂CO₃ as a base and the reaction was completed.
within 5 h. The use of other inorganic/organic bases such as NaOH and DBU was examined and was found to be less effective.

![Chemical Structures]

*Fig-1 N,O Ligands as potential source for Sonogashira coupling.*

This methodology is an improvement of the previously reported methods for the formation of these bonds. The reactions proceed well to afford a variety of 4-alkynyl thiazole aryl derivatives in good yields. This is a general and economical process and opens an easy way to access alkynyl substituted aryl and heteroaryl derivatives.

**Scheme 5.1**

![Reaction Scheme](https://example.com/reaction_scheme.png)

**Scheme 5.1:** L-Proline ligand mediated modified Sonogashira coupling

Since the effective development methods for the functionalization of sulphur containing heterocycles represents a major synthetic challenge towards the synthesis of biologically important heterocycles the present process would find wide usage. Although various methods are known for the synthesis of thiazole containing structures are not common in the literature.
Thus we report, a very convenient and general method for the preparation of 4-alkynyl thiazole aryl derivatives 7 in good yields.

Table 5.1. Pd-Cu mediated coupling reaction of 2-methyl-4-(trimethylsilyl ethynyl)-thiazole (5) with aryl and heteroaryl halides (6) in the presence of L-proline$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product$^c$</th>
<th>Yield$^b$</th>
<th>Reaction Time(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>7a</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>7b</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>7c</td>
<td>85</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td>7d</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
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<td>9</td>
<td>6i</td>
<td>7i</td>
<td>60</td>
<td>5</td>
</tr>
</tbody>
</table>
All the reactions were carried out by using 5 (5.11 mmol, 1.0 equiv), 6a (5.63 mmol, 1.1 equiv), 0.01 eq PdCl₂(PPh₃)₂ (0.042 mmol), L-proline (0.51 mmol, 0.1 eq), Cu-salt (0.25 mmol, 0.05 eq), base (6.24 mmol, 1.25 equiv), water (0.10 mL to 0.15 mL) and a solvent (2.5 mL).

Identified by ¹H NMR, IR, and MS.

Isolated yields

A variety of (hetero) aryl iodides and bromides possessing carbonyl, hydroxyl, ester, and alkoxyester or ether substituent were employed to give the coupled products in good yields.