Synopsis

The thesis entitled “Design and Development of Synthetic Methods using Metal-mediated and Metal-free Redox Reactions: Novel C-H Activations, Reductions and Oxidative Transformations” is presented in 4 chapters

Chapter 1; Iodine catalyzed amination of benzoxazoles: efficient metal free route to 2-aminobenzoxazoles under mild conditions.

The Chapter 1 of this thesis describes iodine catalyzed C-H activation of benzoxazole with primary and secondary amines to form oxidative aminated products. Selective C-H oxidation is a frontline area of modern chemical research as it offers the opportunities to new avenues and more direct synthetic strategies for the synthesis of complex organic molecules. In this context, transition metals such as palladium copper, nickel etc, are used extensively for the functional group directed C-H activation, and thus provides new, rapid, low-cost, and environmentally benign protocols for the construction of new chemical bonds. During the past two decades iodine and hypervalent iodine have been focus of great attention as they provide mild, chemoselective and environmentally benign strategies in contrast to toxic metal oxidants. In this chapter, a facile metal-free route of oxidative amination of benzoxazole with secondary or primary amines in the presence of catalytic amount of iodine (5 mol%) in aq tert-butyl hydroperoxide (1equiv) and AcOH (1.1 equiv) at ambient temperature, under the solvent-free reaction condition is presented. This user-friendly method to form C-N bonds produces tert-butanol and water as the by-products, which are environmentally benign. A wide range of benzoxazole derivatives containing electron-donating and electron-withdrawing groups were coupled with both primary and secondary amines (Scheme 1).

Scheme 1.

\[
\begin{align*}
\text{R-} & \text{N} \quad \text{H} \quad \text{NH2} \quad \text{N} \quad \text{H} \quad \text{NH2}
\end{align*}
\]

Application of this methodology is demonstrated by synthesizing therapeutically active benzoxazoles by reacting 5-chloro-7-methylbenzoxazole with \(N\)-methylpiperazine and \(N\)-ethylhomopiperazine to obtain corresponding \(N\)-aminatedbenzoxazoles, which exhibit antidiarrhetic activity (Scheme 2).4

Scheme 2

\[
\text{R} = \text{-CH}_3, \text{Cl, Ph, NO}_2
\]

Chapter 2: NIS catalyzed reactions. amidation of acetophenones and oxidative amination of propiophenones

Chapter 2 is divided in to 2 parts. Part 1 describes the synthesis of \(\alpha\)-ketoamides by using acetophenone and secondary amine in the presence of \(N\)-iodosuccinamide and TBHP in acetonitrile at room temperature, whereas Part 2 reveals the synthesis of 2-aminoketones by reacting aryl alkyl ketones and suitable secondary amine in the presence of NIS and TBHP.

Part 1: Oxidative amidation, synthesis of \(\alpha\)-ketoamide:

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Alpha α-ketoamides are important intermediates in organic synthesis that are present in a variety of natural products, and pharmaceutically active compounds. Herein, a mild and efficient conversion of acetophenones to α-ketoamide is documented by using aq.TBHP and N-iodosuccinamide (NIS) as a catalyst, at ambient temperature. This amidation reaction was found to be versatile as several acetophenone derivatives containing electron-withdrawing and electron-donating substituents underwent a facile amidation. It was also found that acetyl derivatives of heterocyclic compounds could be easily converted to their corresponding ketoamides (few examples are shown in Scheme 3).\(^5\)

**Scheme 3**

\[
\begin{align*}
\text{O} & \quad \text{NIS 30 mol}\% \\
\text{Ac} & \quad \text{Aq. TBHP (3 equiv)} \\
\text{CH}_2\text{CN, RT, 12h} & \quad \text{N} \\
\end{align*}
\]

**Part 2: Oxidative amination of propiophenones**

Part 2 of Chapter 2 narrates a novel amination of propiophenone and its derivatives catalysed by NIS in the presence of TBHP to furnish their corresponding 2-aminoketone derivatives (Scheme 4). These derivatives are ubiquitous scaffolds that are present in a wide variety of therapeutic agents. Some of these compounds are used in the treatment of depression, smoking cessation, as monoamine uptake inhibitors, rugs for cancer. They are photoinitiators, precursors to β-aminoalcohols, such as pseudoephedrine analogues. 2-Aminoacetophenone analogues are also important intermediates for the formation of several heterocyclic compounds and are active moieties in several important drugs such as ifenprodil,

bupropion, amfepramone and different derivatives as potential pharmacotherapies for cocaine addiction.⁵

**Scheme 4.**

![Chemical structures and reactions](image)

**Chapter 3: Efficient oxidation of primary azides to nitriles**

This Chapter is divided into 2 parts, which presents the oxidation of primary azides to their corresponding nitriles.

**Part 1: An Efficient oxidation of primary azides catalyzed by copper iodide: a convenient method for the synthesis of nitriles**

In Part 1, an efficient oxidation of primary azides catalyzed by copper iodide to their corresponding nitriles is reported. Herein, the oxidation of primary azide to nitrile is performed using catalytic amount of copper iodide, and aq TBHP in water at 100 °C. This methodology is compatible with a wide range of primary benzylic azides that contain electron-donating and electron-withdrawing functional groups. The oxidation was found to be
selective and a number of oxidizable functional groups were well-tolerated during the reaction conditions (few examples are shown in Scheme 5).  

**Scheme 5**

Furthermore, oxidation of secondary azides furnished the corresponding ketones in excellent yields (Scheme 6).  

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Part 2: A Non-metal catalysed oxidation of primary azides to nitriles at ambient temperature

In the Part 2 of Chapter 3, a non-metal catalysed oxidation of primary azides to nitriles at ambient temperature is reported. This part reveals the oxidation of primary azides to nitriles by employing catalytic amounts of KI (25 mol%), DABCO (25 mol%) and aq. TBHP (3 equiv., 70% solution in water). This reaction provides a good selectivity, as double and triple bonds were not oxidized under the reaction conditions. Additionally, chemoselective oxidation of benzylic azides against aliphatic azides increases the potential application of the present method (Scheme 7).

Scheme 7

Chapter 4: Chemoselective reduction of olefins

Part 1: Iron chloride catalysed aerobic reduction of olefins using aqueous hydrazine at ambient temperature

Chapter 4 describes the reduction olefins and acetylenes, which is presented in two Parts. Part 1 documents utility of hydrazine (1.5 equiv) for the chemoselective reduction of nonpolarised carbon-carbon bond using iron catalysts. In this part, a chemoselective reduction of alkenes and alkynes in the presence of a variety of reducible functional groups is demonstrated (Scheme 8). The highlight of the present method is that the reduction proceeds well at room temperature and requires only 1.5 equiv of hydrazine hydrate. The olefin reduction by hydrazine depends upon the controlled release of diimide during the reduction.

Generally, metal catalyzed reduction of olefins employ a large excess of hydrazine (10-20 equiv), which might be attributed to uncontrolled release of diimide during the reduction.\(^8\)

**Scheme 8**

![Scheme 8](image)

**Part 2: Guanidine catalyzed aerobic reduction: a selective aerobic hydrogenation of olefins using aqueous hydrazine**

In Chapter 4, part 2, organocatalytic generation of diimide and its utility to reduce the double bonds is presented. Generation of diimide \textit{in situ} by using organo catalysts and its use for the reduction of carbon-carbon double bond is one of the interesting topics in organic chemistry. It has been shown in this part of the thesis that the reduction of olefin at room temperature can be efficiently performed by using 10 mol\% of guanidine nitrate, 2 equiv of aqueous hydrazine in oxygen atmosphere. This method tolerates a variety of reducible functional groups such as nitro, azido, and bromo and protective groups such as methyl ethers, benzyl ethers, and Cbz groups. It is also shown that terminal olefin can be selectively reduced in the presence of internal olefin (Scheme 9). Unlike other methods that employ diimide strategy, the present method is shown to be efficient in reducing substrates those contain internal double bonds such as cinnamyl alcohol and its derivatives.\(^9\)


Scheme 9

1. Reaction of benzaldehyde with guanidine nitrate in the presence of O₂, EtOH, 100 °C:

   \[
   \text{Benzaldehyde} + \text{Guanidine nitrate, (10 mol%), O}_2, \text{EtOH, 100 °C} \rightarrow \text{Product}
   \]

2. Reaction of benzoic acid with guanidine nitrate in the presence of O₂, EtOH, 50 °C:

   \[
   \text{Benzoic acid} + \text{Guanidine nitrate, (10 mol%), O}_2, \text{EtOH, 50 °C} \rightarrow \text{Product}
   \]