OXIDATIVE TRANSFORMATIONS AND CYCLIZATIONS MEDIATED BY HALOGEN DERIVATIVES

This thesis deals with the catalytic oxidative transformations of various functional groups and oxidative cyclization leading to heterocycles mediated by halogen based reagents. Chapter I deals with the importance of halogens in organic reactions, emphasizing more on their use for oxidative transformations. Further this chapter focuses on the properties and applications of iodine based reagents for various organic transformations. Emphasis on catalytic oxidation over stoichiometric oxidation was presented. Chapter II deals with the catalytic oxidative amidation of aldehydes and alcohols with primary amines and primary amine hydrochlorides using KI-TBHP catalytic system, without the use of any additives and base. In chapter III, the same KI-TBHP catalytic system was used for the oxidative transformation of alcohols, aldehydes and amines into nitriles. Chapter IV deals with the selective oxidation of aromatic amines to nitro derivatives and oxidation of benzylic C-H bonds of alkylarenes into their corresponding carbonyl compounds. Chapter V deals with the formation of heterocycles viz., 2-quinazolines, benzoxazines and oxazolines using cyclizations and oxidative dehydrogenation protocols using KI-TBHP and NaOCl.

Chapter I. Introduction

This chapter describes the physical and chemical properties of halogens emphasizing more on the oxidizing properties of halogens. It includes the oxidation of various organic functional groups using iodine based reagents in stoichiometric amounts. Need for catalytic oxidation using iodine and related reagents was emphasized. The development of environmentally cleaner catalytic oxidative
methodologies is highlighted in this chapter. The use of TBHP and NaOCl as terminal oxidant for various oxidations was described.

**Chapter II. Oxidative Amidation of Aldehydes and Alcohols with Primary amines catalyzed by KI-TBHP**

Simple and convenient methods for the construction of amide (-CONH-) units are highly desirable in synthetic organic chemistry. These motifs play a significant role in pharmaceuticals, natural products and polymers.

Conventional methods for the synthesis of amides involve reactions between carboxylic acids or their activated analogues like acyl chlorides, anhydrides, azides or active esters with amines. An alternative approach, which is quite attractive from the economical and green chemistry point of view, is the oxidative amidation of aldehydes. Few reports adopting the above strategy have appeared in the literature which employs a transition metal catalyst in combination with an oxidant.

The above mentioned reactions either require an expensive transition metal catalyst, ligand and the presence of base or other additives for good yields. Considering both economic and environmental point of view, a new strategy which uses cheaper reagents yet producing desirable yields should be ideal for oxidative amidation. In those aspects, halogens which are economically cheaper and “green” reagents attain a significant position. Several reports appeared recently on the use of iodine for various organic transformations.

In this chapter, a simple and mild procedure for the oxidative coupling of aldehydes, alcohols with primary amines catalyzed by KI and TBHP as an external oxidant to afford amides is described.
Abstract

Scheme 1

Oxidative amidation of a series of structurally and electronically diverse aldehydes and alcohols with different amines to afford amides was described. To widen the scope of oxidative amidation, the present system is extended to chiral aminoacid derivatives, which yielded chiral amides in excellent enantioselectivities. These chiral amides are important intermediates in pharmaceuticals and synthetic organic chemistry.

The advantages of present catalytic system over the earlier reports are:

- This methodology does not require any base or additives.
- It does not require any expensive metals or ligands for construction of important amide linkage.
- Important chiral amides are prepared with high enantioselectivity.
- Formation of amides from alcohols, which is difficult to some extent, was also achieved.
- The reaction was performed with a cheaper and “green” reagent to produce moderate to good yield of the desired products.
Chapter III. Catalytic Oxidative Conversion of Alcohols, Aldehydes and Amines into Nitriles using KI/I$_2$–TBHP system

Nitriles are useful functional groups in synthetic organic chemistry as they are most important precursors for esters, amides, carboxylic acids, amines, and nitrogen-containing heterocycles like oxazoles and imidazoles. Moreover, nitriles can be transformed into heterocyclic compounds of significant biological importance.

The most common and well-known procedure for the preparation of nitriles is the nucleophilic displacement of substrates with suitable leaving groups such as halogen compounds, aryl sulfonates, alcohols, esters, ethers, nitro or amino compounds and diazonium salts with inorganic cyanide ions. The other alternative procedures are dehydration of amides and aldoximes, conversion of alcohols, aldehydes and carboxylic acids to nitriles using various reagents or direct conversion of amines.

The conventional methods and several of these reported procedures often require hazardous reagents, severe reaction conditions, expensive catalysts and additives. To overcome some of these economical and environmental related problems, catalytic methods involving the direct conversion of aldehydes and alcohols to nitriles using commercially available aq.ammonia or direct conversion of primary amines to nitriles via dehydrogenation could be a viable alternative and clean route.

The direct conversion of alcohols, aldehydes and primary amines selectively to their corresponding nitriles using catalytic amount of KI or iodine in combination with TBHP as an external oxidant has been carried out and the results are presented in this chapter.
The present catalytic system was initially tested for the conversion of alcohols to nitriles. The electron donating alcohols were smoothly converted into the nitriles in good yields compared to their electron withdrawing counterparts.

The catalytic system was further examined for the direct conversion of aldehydes to nitriles. The conversion was good irrespective of the electronic nature of the aldehydes. Moreover, these reactions were found to be faster than alcohols. The catalytic studies were also studied for the direct conversion of primary amines to nitriles. Moderate yields were obtained for both electron rich and electron deficient systems. Since the aromatic nitriles are very useful products, the feasibility of the present catalytic system on multi-gram scale was examined for the synthesis of 4-methoxy-benzonitrile.

The advantages of present catalytic system are:

- It avoids the use of expensive metal catalysts and hypervalent iodine reagents.
- Application of single catalytic system to prepare nitriles from different functional groups.
Abstract

➢ The present catalytic system devoid of transition metals also provides an easy scale-up and separation protocol.

Chapter IV. Selective Oxidation of Aromatic Amines to Nitro derivatives and Benzylic Oxidation using KI-TBHP Catalytic System

This chapter is divided into two sections.

Section I. Selective Oxidation of Aromatic Amines to Nitro Derivatives using Potassium Iodide - tert-Butyl Hydroperoxide Catalytic System.

The oxidation of amines is a fundamental reaction for the synthesis of O-containing amine derivatives such as hydroxylamine, nitroso-, nitro-, oxime and azoxy compounds. Nitro compounds are useful in pharmaceuticals.

Classical methods for the preparation of nitroarenes involve direct nitration of the aromatic ring under harsh reaction conditions or through nitration of anionic intermediates originating from alkyl halides, alkenes or ketones. Indirect methods, such as oxidation of aromatic primary amines to nitroarenes, provide an alternative route. Several stoichiometric oxidants such as peracetic acid, MnO₂, Pb(OAc)₄, Hg(OAc)₂ and dioxirane, or various transition metal in combination with peroxides like H₂O₂ and TBHP are reported for the oxidation of aromatic amines and related compounds to nitroarenes.

There are no reports on the direct oxidation of aromatic primary amines to the corresponding nitroarenes using iodine or hypervalent iodine reagents. A mild and selective oxidation of aromatic amines to their corresponding nitro derivatives using potassium iodide as catalyst and TBHP as the external oxidant was presented in this section.
Abstract

\[
\begin{align*}
\text{AtNH}_2 & \xrightarrow{\text{KI, TBHP}} \text{CH}_2\text{CN, 80 °C} \quad \text{ArNO}_2 + \text{H}_2\text{O} \\
& \quad \text{up to 98%}
\end{align*}
\]

Scheme 3

Aromatic amines having electron-donating groups are smoothly converted to their corresponding nitro compounds in good yields. Aromatic amines with electron-withdrawing groups gave lower conversions, however increasing the catalyst loading to 20 mol% led to an improvement in the product formation. In all the cases, nitro derivatives are found to be the sole products. This methodology has been applied to heterocyclic compounds taking 3-aminoquinoline as an example.

Section II. Mild and Efficient Benzylic Oxidation Catalyzed by KI and aqueous tert-Butyl Hydroperoxide

Oxidation of benzylic C-H bonds of alkylarenes into their corresponding carbonyl compounds is one of the most significant transformations for large production of specialty chemicals. Classical methods involve stoichiometric quantities of metal oxidants such as potassium permanganate or potassium dichromate. In order to overcome some of the difficulties associated with stoichiometric oxidants, several catalytic methods are reported over the last few years, especially using oxidants such as alkyl peroxides, TBHP or \(\text{H}_2\text{O}_2\) in combination with variety of transition metals. In parallel, several reports appeared using iron catalysts famously known as Gif oxygenation systems. Recently hypervalent reagents were also employed for this transformation.

However, most of the above procedures have limitations such as usage of toxic metals, low yields of the desired products and poor substrate scope. The reaction conditions are generally harsh and the use of excess amount of base and oxidant leads to
large amount of waste. In case of hypervalent iodine reagents, the main drawback is the use of reagents in more than stoichiometric amounts which is expensive and also the use of an additive.

In this chapter, a relatively mild, selective and catalytic benzylic C-H oxidation using potassium iodide as a catalyst in conjunction with TBHP as an external oxidant at room temperature has been described.

![Scheme 4](image)

**Scheme 4**

The general applicability of this method was evaluated for structurally diverse alkylarenes under optimized reaction conditions using KI as catalyst. The reaction proceeds smoothly producing the required carbonyl compounds in high yields. In case of heterocyclic systems, instead of benzylic oxidation, the reaction proceeds to aromatization of the heterocyclic ring. An attempt has been made to perform one-pot amidation and benzylic oxidation on 1,2,3,4-tetrahydro isoquinoline to give 2-benzoyl-3,4-dihydroisoquinolin-1(2H)-one.

![Scheme 5](image)

**Scheme 5**

Compared to the earlier established methods, the present catalytic system is highly selective towards the carbonyl derivatives and the reaction conditions were milder.
Chapter V.

Synthesis of 2-Oxazolines, 2-Substituted Quinazolines and Benzoxazines via Oxidative Dehydrogenation.

This chapter is divided into two sections.

Section I. Synthesis of 2-oxazolines by oxidative coupling of aldehydes with amino alcohols catalysed by KI-TBHP

Construction of nitrogen containing five-member heterocycles is an important synthetic strategy in organic chemistry, due to their wide range of applicability in synthesis of various biologically active compounds and their scope as chiral ligands in asymmetric catalysis. Oxazoline derivatives exhibit several pharmaceutical activities such as antidiabetic, antihypertensive, antidepressive, anticancer, anti HIV-1, antitumor and antialzheimer activities. Numerous methods for the construction of 2-oxazolines have been reported, from carboxylic acids, esters, nitriles, aldehydes, hydroxyamides and olefins.

Oxidative methods for the formation of heterocycles are quite attractive and several methods were already reported for the formation of benzoazoles, benzimidazoles, imidazolines from aldehydes. However, synthesis of oxazolines by an oxidative strategy from the aldehydes was little explored.

In this chapter, KI in combination with tert- butyl hydroperoxide as the oxidant has been used as the catalytic system for the oxidative cyclization of aldehydes with β-amino alcohols to yield oxazolines.
The general applicability of this reaction was evaluated with diverse aldehydes and amino alcohols. Product yield depends on the nature of amino alcohols and electronic nature of the aldehydes. This oxidative cyclization strategy was applied to the synthesis of optically active 2-oxazolines, which are very useful chiral auxiliaries and as chiral ligands. Products were obtained with moderate to good yields and good enantioselectivity.

Section II. One-pot synthesis of 2-Substituted Quinazolines and Oxazines via Oxidative Dehydrogenation using NaOCl

Quinazolines are important class of compounds frequently found in alkaloids and in many bioactive compounds. Quinazoline ring structure is an essential component in few anticancer drugs like Iressa and Tomudex. Thus a method to develop the quinazoline ring becomes an important strategy due to its various biological importance.

Most of the reported methods for the synthesis of 2-substituted quinazolines involve multi-step synthesis, expensive reagents, starting materials that need prior synthesis of amidines and guanidines, limited substrate scope and difficult work-up procedure for the separation of the desired product. In these aspects, direct coupling of aldehyde with amine followed by dehydrogenation proves to be an easy route for the synthesis of 2-substituted quinazolines and oxazines.
Abstract

In this section, a simple two step strategy was followed for the synthesis of quinazolines and oxazine derivatives, where initial coupling of aldehyde and amine led to the formation of 1,2,3,4-tetrahydroquinazolines and further treatment of the resulting cyclic product with sodium hypochlorite (bleach) led to the desired product in good yields.

The general applicability of the method for the synthesis of quinazolines was evaluated with structurally diverse aldehydes and 2-amino benzylamine derivatives. Irrespective of the electronic nature of the aldehydes used, the yields are moderate to excellent in most cases. In case of aliphatic aldehydes, the yields are moderate due to the inherent difficulty in activating an aliphatic aldehyde compared to aromatic ones.

Scheme 7

The same strategy was applied for the synthesis of oxazines. Instead of 2-amino benzylamine, 2-aminobenzyl alcohol was used as the coupling partner for aldehydes. Moderate to good yields were observed with different aldehydes. There were no appreciable changes with the variation of electronic nature of aldehydes.

Scheme 8
The advantages of the present method are:

- Simple and convenient method for the synthesis of 2-substituted quinazolines and oxazines has been developed.
- This method does not require any catalyst and uses simple and commercially available oxidant for the construction of heterocycles.
- Separation of the intermediate 1,2,3,4-tetrahydroquinazolines was avoided.
- Final separation of product was easily accomplished without any difficulty.