ABSTRACT
DESIGN AND DEVELOPMENT OF SUPPORTED ZIRCONIA CATALYSTS FOR SELECTIVE ORGANIC TRANSFORMATIONS

The thesis, which begins with an introduction (Chapter 1), followed by 4 chapters is outlined here.

Organization of the thesis

The thesis mainly deals with the design and development of supported zirconia catalysts for selective organic transformations particularly C-C bond formations and rearrangement reactions. One of the most fascinating aspects of heterogeneous catalysis is that it is largely an empirical science. In developing large-scale processes, it is extremely important to heterogenize homogeneous catalyst systems, because heterogeneous catalytic systems have many advantages over homogeneous counterparts in liquid-phase reactions, including easy removal of catalysts from reaction mixtures and recycling/reuse of catalysts. Metals and their oxides dominate the vast panorama of heterogeneous catalysis. Precious metals including Pt, Pd, Rh, Ru and Ni
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are employed in various catalytic processes such as naphtha reforming, abatement of automobile emissions, hydrogenation of CO and fats. The metals are employed in the form of finely dispersed particles on high surface area, porous, thermally stable metal oxides, zeolites or carbon supports in order to expose large fraction of metal atoms to reactant molecules. Chapter I highlight the importance of heterogeneous catalysis and discuss various options for the synthesis of heterogeneous catalysts. The need and development of cleaner and greener alternative technologies using truly heterogeneous catalytic system in the synthesis of pharmaceuticals and fine chemicals is also described. Chapter II describes the Bamberger rearrangement of phenylhydroxylamine using sulphated zirconia catalysts. Chapter III deals with the aldol reaction of various isatins with cyclic and acyclic ketones containing α-hydrogen in presence of KOH supported zirconia catalyst. Chapter IV deals with the one pot synthesis of p-aminophenol from nitrobenzene using platinum supported zirconia and sulphated zirconia catalysts. Chapter V deals with the nitroaldol reaction of isatin with KOH supported zirconia catalyst.

Chapter I: Introduction

This chapter describes the various catalyst / process options available for an industrial chemist to effect different organic transformations. It includes a brief introduction of homogeneous, heterogeneous catalysis and basic concepts commonly encountered in catalysis such as selectivity, turnover number, atom economy etc. This chapter also describes the structure, properties and applications of zirconia and supported zirconia catalysts and their importance in organic transformation. The need for the design and development of environmentally cleaner catalytic methodologies using supported solid catalysts is also presented in this chapter.
Chapter-II: Bamberger rearrangement of phenylhydroxylamine on various solid acid catalysts

Chapter II describes the Bamberger rearrangement of N-phenylhydroxylamine to yield p-aminophenol. This chapter also describes the synthesis and characterization of sulphated zirconia catalysts.

In the recent times, inorganic solid acid-catalyzed organic transformations are gaining much attention due to the proven advantage of heterogeneous catalysts, like simplified product isolation. Over the past few years, the preparation and characterization of zirconia based solid acid catalysts have been receiving much attention, among other solid acids such as zeolite, clays, heteropolyacids and ion exchange resins, due to their superior catalytic activity. Many large volume of applications based on sulfated zirconia are reported in the literature, especially in the petroleum industry for alkylations, isomerization and cracking reactions and in organic transformations. The catalytic performance of sulfated zirconia is significantly dependent on preparation methods and on the activation procedures before the reaction. A variety of synthesis methods have been developed in the last two decades. These methods mainly differ on zirconia precursor, sulfation agent, calcination procedure and also activation conditions.

Acid catalyzed rearrangement reactions are broad class of organic reactions where the carbon skeleton of a molecule is rearranged to give structural isomer of the original molecule. In presence of acids, N-phenylhydroxylamines undergo rearrangement to give p-aminophenols. This is called as Bamberger rearrangement. In 1894, Bamberger reported that phenylhydroxylamine readily rearranges to p-aminophenol in sulfuric acid solution. The reaction has since been employed as a convenient method to synthesize para-substituted anilines. Bamberger rearrangement comes under nucleophilic aromatic substitution reaction.
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water is the nucleophile. p-Aminophenol is an important intermediate for the preparation of dyestuffs, pharmaceutically active compounds and plant protection agents. In this regard, Bamberger rearrangement of N-phenylhydroxylamine using various solid acid catalysts has been described (Scheme 1).

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\begin{align*}
\text{NHOH} & \quad \xrightarrow{\text{sulphated zirconia}} \quad \text{NH}_2 \\
\begin{array}{c}
\text{80°C, water, 1hr}
\end{array}
\end{align*}
\]

Scheme 1. Bamberger rearrangement of N-phenylhydroxylamine to p-aminophenol catalyzed by sulphated zirconia.

Advantages

Compatible acidic sites present in sulphated zirconia give rise to Bamberger rearrangement of N-phenylhydroxylamine to p-aminophenol in excellent yields in shorter times, which is superior than the methodologies described earlier. a) high catalytic activity under mild liquid phase conditions, b) easy separation of the catalyst by simple filtration, c) use of non-toxic and inexpensive materials, d) recycling of the catalyst, and e) zero emission of pollutants. The present catalytic system is thus a potential alternative to homogeneous catalytic systems.

Chapter III: A Versatile Methodology for the Synthesis of 3-substituted-3-hydroxyindolin-2-ones via Aldol Condensation of Isatins

The present chapter describes the synthesis of 3-substituted-3-hydroxyindolin-2-ones by using KOH/supported zirconia via aldol condensation. The direct aldol reaction is a very important carbon-carbon bond formation reaction in organic synthesis with
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numerous applications in industry and in laboratory and is classically catalyzed by both Lewis acids and bases. The aldol products, β-hydroxy carbonyl compounds can be readily converted into 1,3-syn and anti-diols and amino alcohols, which are the building blocks in many natural products such as antibiotics, pheromones and in many biologically active compounds. The main limitations in the current processes are the use of stoichiometric amount of base to substrate, longer reaction times, lower yields, and generate large quantities of salts by neutralizing bases or vice-versa, which renders the process incompatible to the environment and uneconomical. 3-Substituted-3-hydroxyindolin-2-ones have received much attention from organic and medicinal chemists because of their key structural functionalities in natural products and drug candidate’s important molecules in the field of medicinal chemistry since their biological activities may be derived from the substituted group at C-3 position. One of the most straightforward approaches to 3-substituted-3-hydroxyindolin-2-ones is obviously a nucleophilic addition of appropriate nucleophiles to isatins. Aldol reaction is one of the most powerful C-C bond forming reactions, where a nucleophile generated by a base is added to aldehydes or ketones. Based on this background, it is reasonable to consider that the aldol reaction of isatin with methyl ketones is an efficient approach for the synthesis of 3-substituted-3-hydroxyindolin-2-ones. In this regard the use of KOH/ZrO₂ for aldol reaction of isatins with ketones to afford the aldol adducts in moderate to good yields with high selectivity under mild conditions is described (Scheme 2).
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Scheme 2. Synthesis of 3-substituted-3-hydroxyindolin-2-ones via aldol condensation of isatin derivatives.

High lights of the present catalytic system

This heterogeneous KOH/ZrO₂ catalyst will be a practical alternative to soluble bases for the direct aldol reactions of isatins in view of the following advantages, a) truly heterogeneous b) high catalytic activity under very mild reaction conditions, c) easy separation of the catalyst by simple centrifugation or filtration and d) the catalyst is easy to handle and reusable for several cycles without loss of activity. The present method is simple and clean over the existing procedures.

Chapter IV: One Pot Synthesis of p-Aminophenol from Nitrobenzene

The present chapter describes the one pot synthesis of p-aminophenol from nitrobenzene using Pt on various supports and sulphated zirconia.

The environmentally benign catalytic processes have replaced several vast generating conventional counterparts. The reduction of organic compounds via catalytic hydrogenation is one of those. The reduction of organic compounds is a key step in the synthesis of several chemicals, pharmaceuticals etc. Conventionally, the reduction has been carried out using stoichiometric amounts of reducing agents such as sodium borohydride, lithium aluminiumhydride, hydrazine hydrate and metal-acid. The major disadvantages of these conventional reduction processes are: (a) use of stoichiometric
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amounts of reducing agents posing serious waste disposal problems due to generation of large quantities of undesired inorganic salts, (b) difficulties in the separation of products from the reaction mixture and its effect on reducing the product yield, (c) non-reusability of reagents, and (d) corrosion problems. Replacement of conventional reduction methods by the catalytic hydrogenation is perhaps one of the most significant achievements of modern catalysis. Based on this, hydrogenation and Bamberger rearrangement of nitrobenzene to p-aminophenol is described using Pt/ZrO₂ and sulphated zirconia as catalyst (Scheme 3)

\[
\text{NO}_2 \quad \xrightarrow{\text{hydrogenation}} \quad \text{NHOH} \quad \xrightarrow{\text{bamberger rearrangement}} \quad \text{NH}_2 \\
\text{NH}_2 \quad \xrightarrow{\text{hydrogenation}} \quad \text{OH}
\]

Scheme 3. One pot synthesis of p-aminophenol from nitrobenzene.

Chapter V: Synthesis of 3-nitroalkyl-3-hydroxy-indolin-2-ones via Henry reaction of isatin derivatives

Oxindoles containing a quaternary benzylic center constitute a common structural motif in many natural products and biologically active compounds. Among them, oxindoles with heteroatoms at the stereogenic center are a useful class of compounds in the field of medicinal chemistry. Owing to the significance of this structural
motif, the development of a catalytic synthetic method for these compounds is highly valuable. Several examples of transition-metal-catalysed preparation of 3-hydroxyoxindoles have been reported.

The Henry or nitroaldol reaction is easily recognizable as one of the classical name reactions in organic synthesis. A coupling reaction between a carbonyl compound and an alkynitro compound bearing α-hydrogens, enables the formation of a carbon-carbon bond with the generation of a new difunctional group, namely the β-nitroalcohol function.

The design and development of environment-friendly solid base catalysts to replace soluble bases for C–C bond formation in organic transformations widely employed in the bulk and fine chemical industries in order to achieve atomic selectivity of the desired product and reduce the salts formed as a result of neutralization of soluble bases is of intense research activity. 2-Nitroalkanols, the products of the Henry reaction, are ubiquitous materials extensively used in many important syntheses.

The present chapter describes the synthesis of 3-nitroalkyl-3-hydroxy-indolin-2-ones via Henry reaction of isatin derivatives using KOH/ZrO₂ as heterogeneous base (Scheme 4).