

General Introduction

Green chemistry is a philosophy of chemical research and engineering that encourages the design of products and processes to minimize the use and generation of hazardous substances. Green catalysis is a subchapter of green chemistry but probably the most important one. Greener and environmentally sound synthetic protocols and reaction conditions have played pivotal roles in recent years toward the goal of switching to increasingly efficient and benign processes that avoid the use of volatile organic solvents, toxic reagents, hazardous and/or harsh reaction conditions, as well as challenging and time-consuming wasteful separations. So, a rapidly growing interest has been observed among the chemists to achieve the biologically important organic compounds in more efficient, sustainable and environmentally friendly ways.¹⁻⁶

Catalysis is becoming a strategic field of science because it represents a new way to meet the challenges of energy and sustainability. These challenges are becoming the main concerns of the global vision of societal challenges and world economy. The concept of green chemistry, which makes catalysis science even more creative, has become an integral part of sustainability.⁷

Conventional catalysts can be divided into homogeneous and heterogeneous, the former holding advantages such as good activity and selectivity, and accessible to mechanistic studies for catalyst optimization. However, the difficulties in separating homogeneous catalysts from reaction medium restrict their applications in industry, especially in the drug and pharmaceutical industry where the metal contamination of products in case of metal-catalyzed synthesis is very common.⁸ To address the separation problems in homogeneous catalysis, chemists and engineers have investigated a wide range of strategies resulting in the use of heterogeneous catalytic systems which appeared to be the best logical solution.⁹ Conventionally, heterogeneous catalysis is favored over homogeneous catalysis for a large number of applications in both fundamental research and industrial applications due to its ease of handling, simple workup, and reusability. Despite their synthetic simplicity, heterogeneous catalysts are typically less effective than their homogeneous counterparts.¹⁰

Therefore, we need a catalyst system that not only shows high activity and selectivity (like a homogeneous system) but also possesses the ease of catalyst separation and recovery (like a heterogeneous system). These goals can be achieved by nanocatalysis. Nanocatalysts bridge the gap between homogeneous and heterogeneous catalysis, preserving the desirable

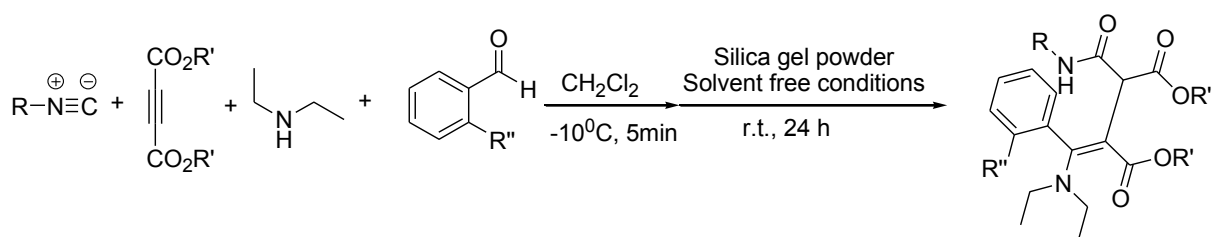
attributes of both systems. As semi heterogeneous catalysts, nanocatalysts with a large surface-to-volume ratio are attractive alternatives to conventional catalysts. Substantial enhancements in catalytic activity, selectivity, and stability are realized by tailoring their size, shape, composition, and electronic structure.¹¹⁻¹⁴ Nanocatalysts are isolated and recovered through filtration or centrifugation methods, whereas the inconvenience and inefficiency of these tedious methods caused by the nano size of the catalyst particles (as it blocks the pores and valves of the filter papers) hamper the sustainability and economics of the nano catalytic strategy.^{7,15}

To overcome this issue, the use of magnetic nano-supports has emerged as one of the best solutions since their insoluble and paramagnetic nature enables easy and efficient separation of the catalysts from the reaction mixture with an external magnet. In addition, controlling of their properties such as size, shape, morphology, and disparity which can mimic the nature, makes it possible for scientists to carefully design the materials that are specifically needed for a particular application.¹⁶

As a society we are increasingly aware of the environmental impact of human activity, and consequently of the need to develop cleaner and more energy-efficient technologies. It has long been recognised that the large-scale use of volatile organic solvents has important implications for environmental contamination.^{17,18} Approaches to solve the problems caused by organic solvents include the use of more benign solvents (especially water and supercritical CO₂), or solvents with negligible vapour pressures (ionic liquids).¹⁸ It has also been said that ‘the best solvent is no solvent’.¹⁸ Despite the power of this statement, the use and understanding of solvent-free synthesis, especially where solid starting materials are concerned, has remained undeveloped in comparison to solvent mediated methods. In the present thesis, the candidate takes the challenge of synthesising some biologically important compounds either in presence of environmentally benevolent solvent, water or under solvent-free conditions to make the methodologies ‘benign by design’.

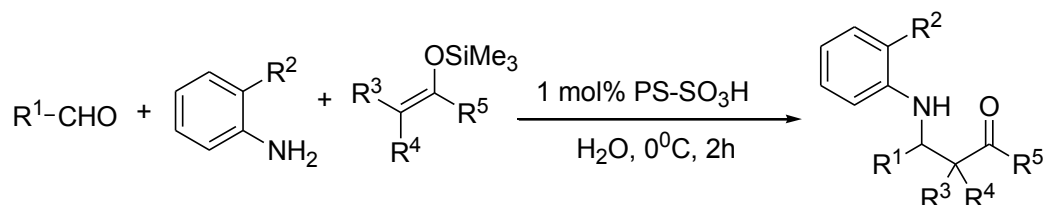
A short review of previous works:

Ramazani and co-workers developed a methodology where the 1:1 intermediate, generated by the addition of an isocyanide to a dialkyl acetylenedicarboxylate was trapped by another iminium ion intermediate, derived from the reaction between an aromatic aldehyde and diethylamine. The reactions were completed in the presence of silica gel powder under solvent-free conditions at ambient temperature to produce dialkyl 2-[(alkylamino)carbonyl]-3-[(Z)-1-(diethylamino)-1-arylmethylidene]succinates (Scheme 1).¹⁹



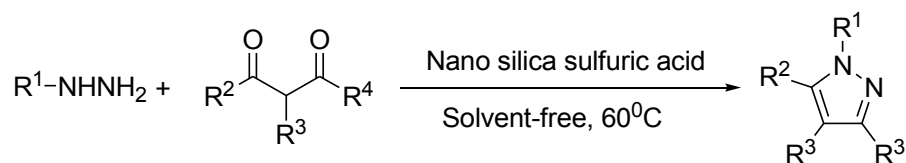
Scheme 1: Synthesis of dialkyl 2-[(alkylamino)carbonyl]-3-[(Z)-1-(diethylamino)-1-arylmethylidene]succinates.

Kobayashi and co-workers demonstrated three-component Mannich-type reactions of various aldehydes, *o*-substituted aromatic amines and silicon enolates (1: 1: 1.5) efficiently catalyzed by hydrophobic polystyrene-supported sulfonic acid (PS-SO₃H) in water medium at 0°C temperature for 2 h (Scheme 2).²⁰



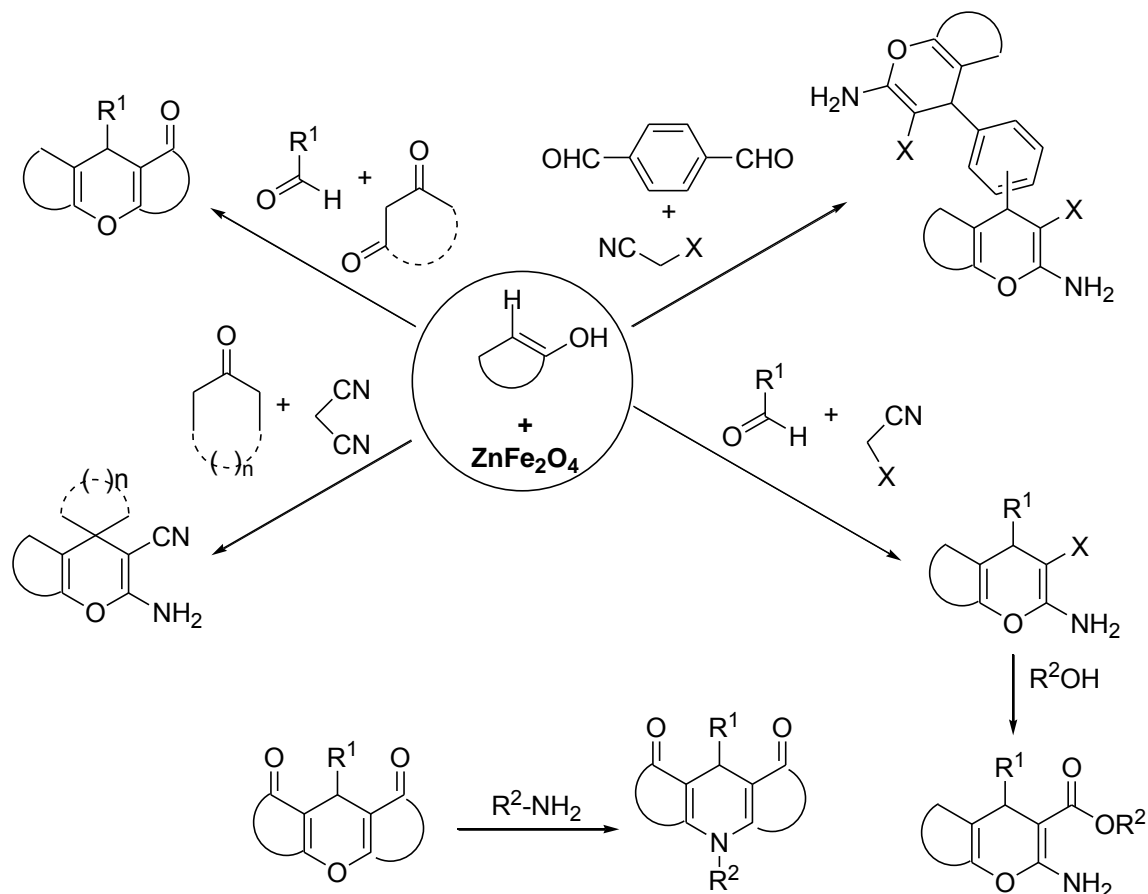
Scheme 2: PS-SO₃H-catalyzed Mannich-type reactions in water using silicon enolates as nucleophiles.

Amrollahi *et al.* developed a methodology for the preparation of pyrazole derivatives by condensing 1,3-diketones and substituted hydrazines in the presence of nano-silica sulfuric acid at 60 °C (Scheme 3).²¹



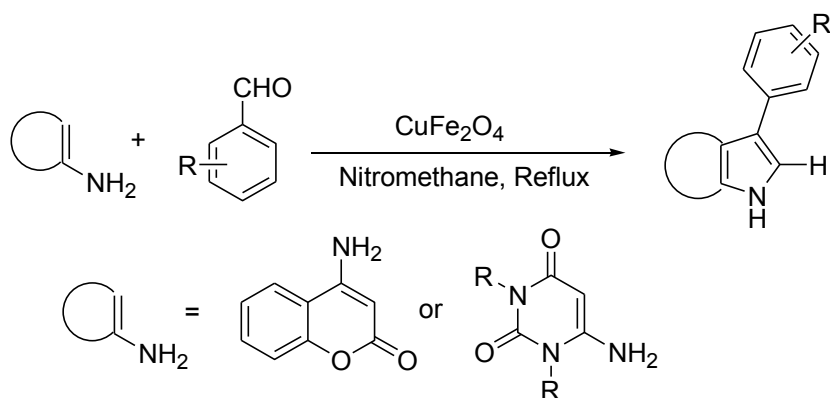
Scheme 3: Condensation of 1,3-diketones and hydrazines in presence of nano-silica sulfuric acid under solvent-free conditions.

Mukhopadhyay *et al.* reported ZnFe_2O_4 nanopowder catalysed one-pot, three-component synthesis of *4H*-pyrans in water and put forward an application of *4H*-pyrans for synthesis of 1,4-DHPs. This was the first attempt towards the synthesis of *4H*-pyran-3-carboxylate from *4H*-pyran-3-carboxamide. (Scheme 4).²²



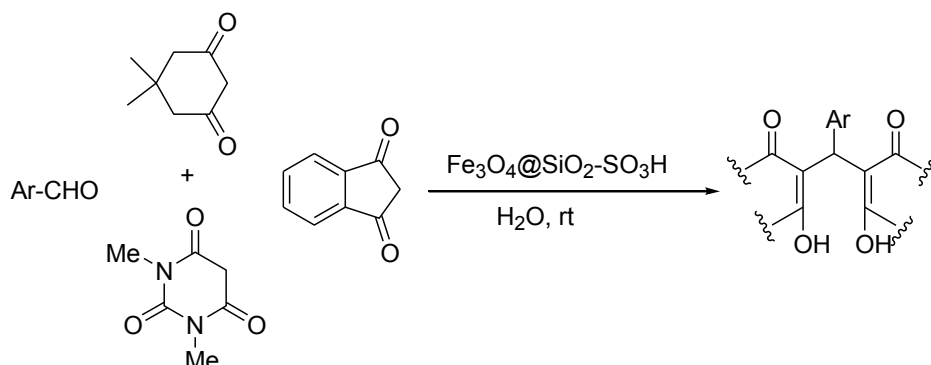
Scheme 4: ZnFe_2O_4 nanopowder catalysed synthesis of *4H*-pyrans.

Das and co workers demonstrated a diversity-oriented synthesis (DOS) of highly substituted coumarin and uracil fused pyrrole derivatives by CuFe_2O_4 catalyzed one-pot three-component domino coupling of 6-aminouracil/4-aminocoumarin, aldehydes and nitromethane (Scheme 5).²³



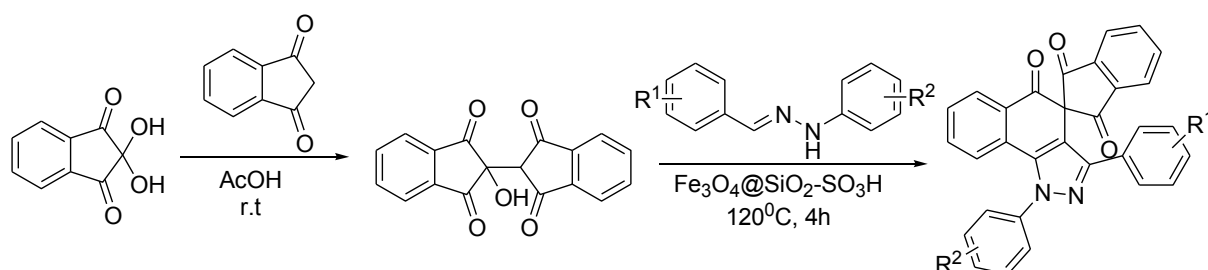
Scheme 5: CuFe_2O_4 catalyzed synthesis of coumarin and uracil fused pyrrole derivatives.

Sulfonic acid-functionalized silica-coated nano-Fe₃O₄ particles (Fe₃O₄@SiO₂-SO₃H) has been used as an efficient catalyst for the synthesis of a variety of tetraketone derivatives *via* the Knoevenagel condensation and Michael addition reactions of aromatic aldehydes to dimedone, 1,3-indanedione, and 1,3-dimethyl barbituric acid by Nemati *et al* (Scheme 6).²⁴



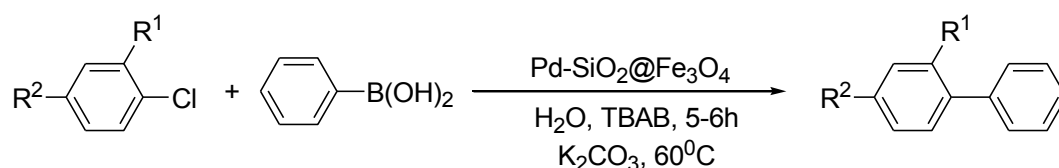
Scheme 6: Synthesis of the tetraketones catalyzed by Fe₃O₄@SiO₂-SO₃H.

Recently, Pramanik *et al.* have reported the synthesis of a new class of pyrazole embedded spirocyclic scaffolds in the presence of Fe₃O₄@SiO₂-SO₃H magnetic nanoparticles (MNPs) as acidic solid support under solvent-free conditions (Scheme 7).²⁵



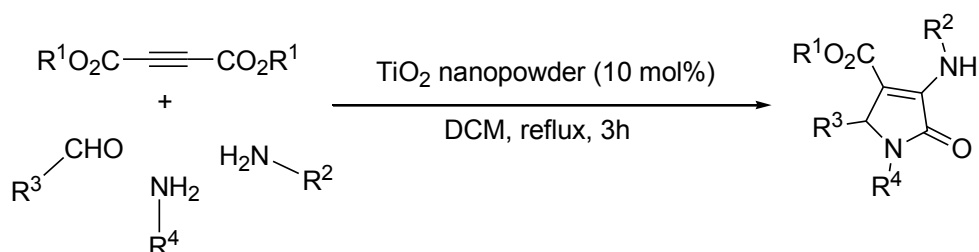
Scheme 7: Synthesis of 1,3-diaryl-4-spiro(1',3'-indanedione)-1,4-dihydrobenzo[g]indazol-5-ones.

Lee and co-workers demonstrated Suzuki coupling of a series of aryl chlorides with arylboronic acid in water and in the presence of K₂CO₃ as a base and tetrabutylammonium bromide (TBAB) as a phase-transfer agent using triethoxysilyl-functionalized palladium complex on the surface of robust SiO₂/Fe₃O₄ (Scheme 8).²⁶



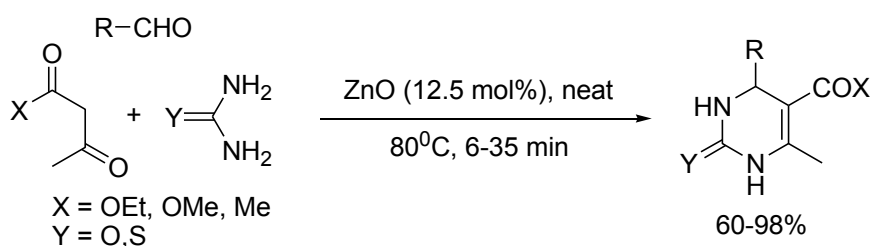
Scheme 8: Suzuki cross-coupling of deactivated aryl chlorides and phenylboronic acid.

Mukhopadhyay *et al.* reported the synthesis of densely substituted 2-oxo dihydropyrroles utilizing reusable and heterogeneous catalyst titanium dioxide (TiO₂) nanopowder through the four component coupling reaction of dialkyl but-2-ynedioate, two different amines, and an aldehyde (Scheme 9).²⁷



Scheme 9: TiO₂ nanopowder catalyzed multicomponent synthesis of fully substituted 2-oxo dihydropyrroles.

Bahrami *et al.* reported a simple, efficient and practical procedure for the Biginelli reaction using ZnO as a novel and reusable catalyst under solvent-free conditions. The reaction proceeds efficiently under these conditions, and the dihydropyrimidiones were produced in high yields (Scheme 10).²⁸



Scheme 10: Solvent-free synthesis of dihydropyrimidinones catalyzed by ZnO.

The main objective of the present thesis is to synthesis various biologically important molecular scaffolds *e.g.* ninhydrin and isatin based hydrazones, oxadiazoles, spiro and fused heterocycles such as isoindolone-1-ones, spiro[indoline-3,2'-quinoline] derivatives, spiro benzofuran-isobenzofurans and spiroindole fused dihydropyridines using solid supports and heterogeneous catalysts within the frame of *Green Chemistry* principles.

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