MULTI-COMPONENT SYNTHESIS OF HETEROCYCLIC COMPOUNDS OF BIOLOGICAL IMPORTANCE USING SURFACE COATED METAL NANOPARTICLES AND GRAPHITE OXIDE AS CATALYSTS

ABSTRACT

A THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

BY

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ABSTRACT:

The thesis entitled “Multi-component Synthesis of Heterocyclic Compounds of Biological importance using surface Coated Metal Nanoparticles and Graphite Oxide as Catalysts” consists of five chapters. First chapter consists of a brief review on synthesis of heterocyclic compounds catalyzed by surface coated metal nanoparticles and graphite based oxides. Remaining four chapters deal with the synthesis and characterization of various surface coated metal nanocatalysts and graphite oxide, and their catalytic application in multi-component reactions for the synthesis of various biologically important heterocycles like phthalazine, pyran, quinazolinone and dihydropyrimidines under green and sustainable conditions.

Chapter 1: A brief review on synthesis of heterocyclic compounds via multi-component reaction catalyzed by surface coated metal nanoparticles and graphite oxide

Green chemistry is a philosophy of modern day chemical research and engineering which deals with the development of eco-friendly procedures. Following principles of green chemistry, developing new methodologies symbolize the central topic in modern day research. Best way to achieve this is via one-pot multi-component reaction (MCR) which involves fusion of more than two reactants in one pot. It allows creation of several new bonds in a single step and products formed retain almost all the atoms which were present in reactants.

Catalysis is the essential component of many chemical protocols because it lowers the activation energy and makes the reaction more feasible. Generally there are two types of catalysts, homogeneous catalysts and heterogeneous catalyst. Homogeneous catalysts (in same phase to that of reactants) possess high TON and TOF, but the lack of applicability of homogeneous catalyst under sustainable condition is due to difficulty in separation and recyclability. Heterogeneous catalysts (in different phase to that of reactant) on the other hand can be easily recycled from the reaction mixture and can be re-utilised easily in subsequent reactions but their active sites are not easily accessible. In this sense, heterogenization of homogenous catalyst on solid supports has received utmost importance. Surface modified nano-catalyst which not only provides high catalytic activity (like homogeneous catalyst) but also possesses easy recyclability (like heterogeneous catalyst) is a desirable catalytic system for this purpose. But to recycle back something which is of $10^{-9}$ metre range is quite tedious.
and almost impossible by traditional methods like filtration. In order to overcome this issue application of magnetic nanoparticles are more viable.

Nanoparticles have gained lot of attentions recently as catalysts because of its high surface to volume ratio. But, when size of the active site gets reduced to nano range its surface energy increases. Because of this effect, particles get aggregated into small clusters and its catalytic activity decreases. In order to prevent this agglomeration, coating the surface of nanoparticles with appropriate coating agent is used. Surface coating technique with active homogeneous counterparts not only increases stability of the nano-catalyst but also increases its catalytic activity because of the presence of various active catalytic sites on its surface. Graphite oxide like nanoparticles acts as an efficient metal free carbocatalyst because of i) presence of various functional groups like epoxy (-O-), carboxyl (-COOH) and hydroxyl (-OH), ii) higher surface area etc. Further, easy recyclability of graphite oxide from the reaction mixture by centrifugation and its re-application are the added advantages of this carbocatalyst.

Heterocyclic compounds are important classes of organic compounds which are widely distributed in nature. They possess many medicinal activities like anti-cancer, anti-microbial, anti-tumour, anti-HIV, anti-fungal etc. They also make up structural framework of many naturally occurring organic compounds and are present in variety of drugs, vitamins, agrochemicals and veterinary products etc. Because of this, developments of newer routes for synthesis of these biologically relevant heterocycles are quite demanding. Chapter 1 of the thesis highlights some of the recent literature reports for the synthesis of biologically important heterocycles by the application of surface coated nanoparticles and graphite oxides.

**Chapter 2: Nano-ferrite supported glutathione as a reusable nano-organocatalyst for the synthesis of phthalazine –trione and -dione derivatives under solvent-free condition**

A magnetically separable nano-organocatalyst, nano-ferrite supported glutathione (nano-FGT) was synthesized from easily available starting materials. Synthesized nano-FGT was characterized by various analytical techniques like FT-IR, SEM, TEM, EDX, PXRD TGA and ICP-OES. After successful characterization, the synthesized catalyst was applied in one-pot multi-component synthesis of phthalazine-trione/dione derivatives. The methodology showed very good substrate scope and high degree of tolerance for a variety of aldehydes (including aliphatic and heteroaromatic aldehydes) and active methylene compounds. Moreover, catalyst can be easily separated from the reaction mixture by using external magnetic field and can be re-used in five consecutive runs without much decrease in catalytic
activities. Shorter reaction time, simpler work up procedure, easy handling of catalyst, and good yield of the products are few more advantages of this procedure.

Catalyst characterized by: FT-IR, SEM, TEM, EDX, PXRD, TGA, ICP-OES

Chapter 3: Magnetically recyclable Nano-FDP: A novel, efficient nano-organocatalyst for one-pot multi-component synthesis of pyran derivatives in water under ultrasound irradiation

Novel, highly stable, efficient and magnetically separable nano-ferrite supported L-proline (nano-FDP) was synthesized from readily available starting materials. Following that, nano-FDP was characterized by various analytical techniques like FT-IR, EDX, SEM, TEM, PXRD and VSM. After successful characterization, the catalyst was applied for the synthesis of pyran derivatives under ultrasonication, at room temperature using water as solvent. Shorter reaction time, higher yield of the desired products, easy recyclability of the catalyst by using an external magnetic field and its reusability in further consecutive runs, are the added advantages of this methodology.
Chapter 4: Preparation, characterization and catalytic application of nano-Fe₃O₄-DOPA-SnO₂ having high TON and TOF for sustainable synthesis of dihydroquinazolinone derivatives

A novel class of magnetically separable heterogeneous nano catalysts had been designed by encapsulating SnO₂ on nano-Fe₃O₄-DOPA. After successful characterization of synthesized catalyst by FT-IR, SEM, TEM, EDX, PXRD, XPS, VSM and ICP-AES, it was employed in the greener synthesis of dihydroquinazolinone derivatives using water as solvent. Nano-Fe₃O₄-DOPA-SnO₂ was found to have high TON (Turn Over Number) and TOF (Turn Over Frequency). It showed high catalytic activity which is validated by good to excellent yields of desired products. Application of present protocol was also carried out for the synthesis of bis-dihydroquinazolinone compound which lead to the formation of six new C–N bonds, two new C–C bonds, two new stereocentres and two new dihydroquinazolinone moieties in one step within a shorter period of time. Easy separation and reusability of the catalyst (five times), substrate variation, selectivity of desired products, shorter reaction time, green reaction medium (water), column chromatography free separation, gram scale reaction and easy workup procedures rendered this procedure environment friendly and sustainable. Furthermore, biologically important quinazolinones were synthesized from dihydroquinazolinone derivatives by a simple oxidation technique.
Chapter 5(A): Nano-Fe$_3$O$_4$@SiO$_2$@SO$_3$H as a reusable and magnetically separable potent solid acid catalyst for one-pot multi-component synthesis of dihydropyrimidine derivatives: A greener NOSE and SFRC approach

A product selective, highly efficient, eco-friendly, multi-component synthesis of dihydropyrimidine derivatives have been reported by using nano-Fe$_3$O$_4$@SiO$_2$@SO$_3$H as a catalyst. Reaction was carried out under solvent free reaction condition (SFRC) and it went smoothly with diverse range of aldehydes like aromatic, aliphatic and hetero-aromatic aldehydes, various $\beta$-dicarbonyl compounds and with different amine sources, thereby proving flexibility of this procedure. Catalyst was well characterized by various analytical techniques like FT-IR, SEM, EDX, TEM, VSM and TGA analyses. After completion of reaction, catalyst was recycled by using an external magnet and re-used up to five consecutive runs without much decrease in catalytic activity. Morphology of reused catalyst was characterized by various analytical techniques and it was found to be in accordance to that of freshly prepared catalyst.
Chapter 5(B): Graphite oxide catalyzed synthesis of dihydropyrimidine derivatives under solvent-free reaction condition

A green metal free carbocatalyst (graphite oxide) has been successfully exploited for the synthesis of dihydropyrimidine derivatives under solvent free reaction conditions (SFRC). Diversity in the formation of this heterocyclic moiety has been exhibited with the tolerance of a large number of functional groups establishing the generality of this protocol. The present metal free catalytic process eliminates the risk of metal contamination in product which is viable for pharmaceutical industries. Graphite oxide catalyst is very mild, easy to handle, non-corrosive and retains its catalytic activities till nine consecutive runs. The present methodology worked smoothly under gram scale condition thereby indicating its applicability in academic as well as industries in near future.
Catalyst characterized by:
FT-IR, SEM, HR-TEM, EDX, powder XRD, Raman, TGA and XPS analyses.

2. High substrate variability.
3. Gram Scale reaction.
4. Reusable heterogeneous catalyst upto nine consecutive runs