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Environmentaly benign chemistry: Synthesis of bioactive heterocycles

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Abstract

Heterocyclic compounds have gained significant attention because of their synthetic utility as synthetic intermediates, chiral auxiliaries, organ catalysts, protecting groups and metal ligands in asymmetric catalysts inorganic synthesis. Nowadays, ecofriendly approaches are obtained keeping the protection of the surroundings in mind, to investigate new green reagents (solvent and catalyst). The progress of eco-compatible multicomponent, one pot procedures are also fascinating the organic chemists. Green chemistry is accomplished by applying eco-friendly, some new and some traditional approach.

Keywords: Green chemistry, biologically active heterocycles, eco-friendly synthesis

Introduction

From last decade, green chemistry has been progressively documented as both culture and methodology for attaining sustainability. The principles of green chemistry are a significant beginning for the chemical profession in dealing with this novel concept for the environment.[1]The twelve principles of green chemistry was proposed by Paul Anastas and John Warner, cover all features of the product and the production level to develop more effective syntheses, from the design of less hazardous substances to the use of renewable feed-stocks.[2]In this context, the ideal synthesis should be a combination of a number of environmental, safe, health, and economic targets which obviously requires a balanced design of the target process based on primary understanding to deal with several green chemistry principles in a comprehensive manner.[3] For the past few decades, scientists have dedicated a great deal of research to replace toxic and harmful solvents by more environmentally benign alternatives. Polyethylene glycol (PEG), water, ionic liquids and supercritical carbon dioxide ($scCO_2$), are among the generally explored greener alternatives in recent years.[4]

Importance of Green Chemistry

The wide range of application of green chemistry includes new perceptions that reduce or remove the use of solvents since a basic purpose of green chemistry is to diminish or remove waste in the redesign of chemicals and related products. Green chemistry has also encouraged a several number of strategies to make conventionally petroleum-based chemicals from natural materials often plant matter or waste. Pharmaceutical industry was the first to acquire the advantage of green chemistry.[5]

The greener approach for the synthesis of biologically active heterocycles

Now a days, chemists are focusing their attention to propose an environmentally benign protocol in the field of synthetic organic chemistry. The development of a novel, greener and more sustainable methods by taking into account numerous subjects like asatom efficiency, energy, material consumption in chemical production is the demand of modern era in organic syntheses.[6]From past few decades, researchers have been involved extensively to produce heterocyclic compounds by designing new and green synthetic transformations. Some of the methods, which are used in organic synthesis, are mentioned below.

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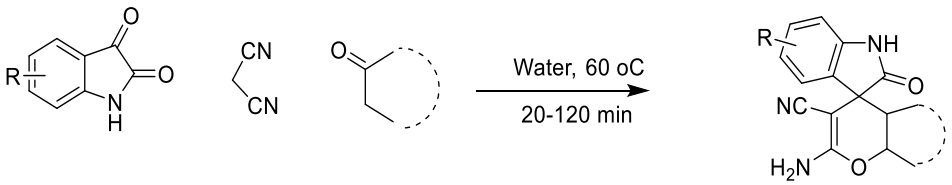
The breadth of this research is very broad and includes area such as:
1. Use of water
2. Use of Bio-based solvent
(i) Use of Glycerol
(ii) Use of PEG
3. Use of organocatalyst
4. Use of surfactant
5. Use of biopolymer
6. Use of heterogeneous catalyst
7. Visible light promoted synthesis

1. Use of water in synthesis

The utilization of water as a solvent was studied and its hydrophobic effects can strongly elevate the rate of various organic protocols. Earlier, the main cause that restricted the use of aqueous media in chemical transformation was the limited solubility of the reactants in water. However, in the study of new ‘‘green’’ methodology, high temperature water was found to be important in organic synthetic reactions.[7] Near-critical and supercritical conditions water act as a ‘‘pseudo-organic solvent’’ as its dielectric constant decreases significantly; the solvating tendency regarding organic compounds become comparable at room temperature with that of acetone or ethanol and acid or base-catalyzed reactions usually need minimum catalyst and generally proceed speedily.[8] Considering the importance of environmentally friendly protocols in organic chemistry, the applications of aqueous medium have fascinated noteworthy contribution in synthetic organic chemistry. A large number of organic synthesis are developed using water due to non-flammability, inexpensive and amply available, environmental friendly. It has unique and diverse physical properties such as high surface tension, high specific heat, high dielectric constant and large cohesive energy density, in comparison with common organic solvents.[9] Due to the above mentioned multipurpose and unique properties of water, rates and selectivities of organic reactions under on-water conditions can be improved, as well as a series of important organic transformations are reported in the absence of catalysts using water as organic solvent at room temperature/or high temperature.[10]

Zhao et al. reported a catalyst-free, one-pot, three-component reaction for the synthesis of biologically active spirooxindole derivatives in aqueous media.[11] (**Scheme 1**)



Scheme 1: Catalyst-free synthesis of spirooxindole

Potewar and Srinivasan synthesized various substituted 2-aminothiazoles in aqueous media in short reaction time and in good to excellent yields from substituted phenacyl bromide and thio-urea derivatives (**Scheme 2**).[12]

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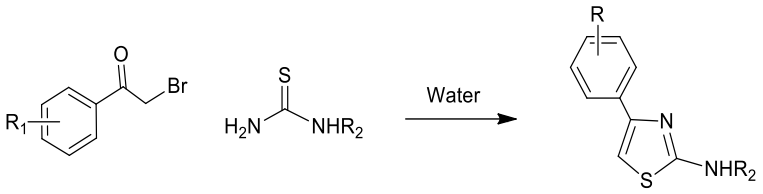
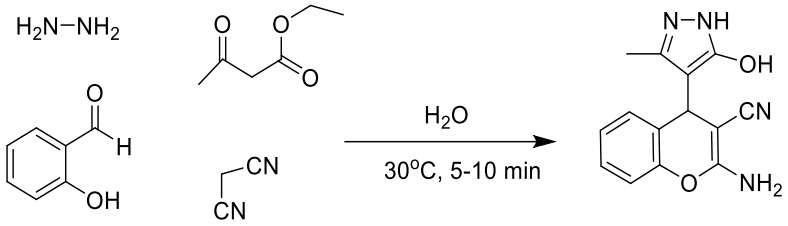


Scheme2: Catalyst-free synthesis of substituted 2-aminothiazoles in aqueous medium

Vasuki and Kumaravel synthesized a library of 2-amino-4-(5-hydroxy-3-methyl-1Hpyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives via a four component reaction between hydrazine hydrate, ethyl acetoacetate, 2-hydroxybenzaldehydes and malononitrile in-water at room temperature.[13] (**Scheme 3)**



Scheme 3: Catalyst-free, multicomponent synthesis of 4-pyrazolyl-4H-chromenes in aqueous media.

2. Use of Bio-based solvent

(i) Glycerol

The development of green and cleaner method is challenging task in synthetic organic chemistry. The use of eco-friendly solvents has gained much interest because the majority of waste and pollution generated by the chemical processes is directly related to solvents.[14]Scientists are using glycerol as a sustainable solvent for green chemistry since glycerol is a prototypical example of a "green solvent. Glycerol is growing considerable attention because it has similar characteristics like water such as biodegradability, abundant, non-toxicity, inexpensive, highly polar, immiscible with hydrocarbons, able to form strong hydrogen-bond networks and able to dissolve a wide range of organic and inorganic compounds.[15] In addition, compared to water, it has the advantage of its lower vapor pressure, higher boiling point and that it is able to dissolve organic compounds usually immiscible with water. Remarkably, the use of glycerol as solvent has resulted in few cases in an improved reactivity and/or selectivity, and also in an easier product separation and an improved catalyst recycling.[16]

Swastika *et al* reported a catalyst free, multicomponent-tandem, facile and glycerol mediated green approach for the synthesis of spirooxindole indazolone and spirooxindole pyrazoline. From the last few years, the synthesis of spirooxindoles-pyrazoline has received increasing attention due to the presence of the oxindole and pyrazoline skeletons in several bioactive molecules. Spirooxindoles-pyrazoline derivatives have also been reported as exhibiting very good anti-cancer activity. **(Scheme4)**[17]

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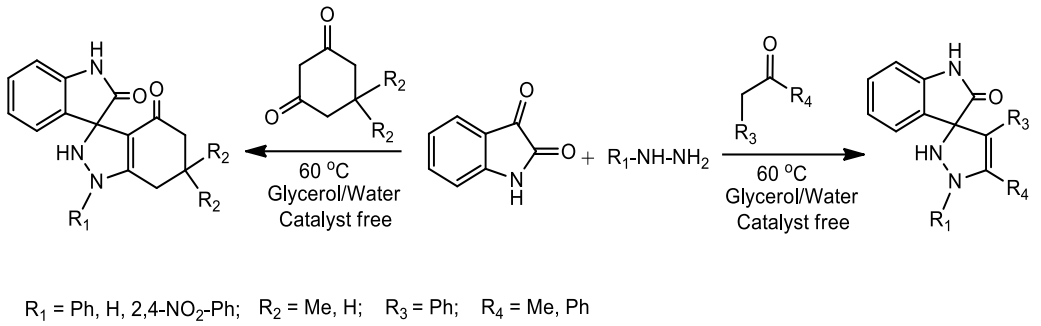
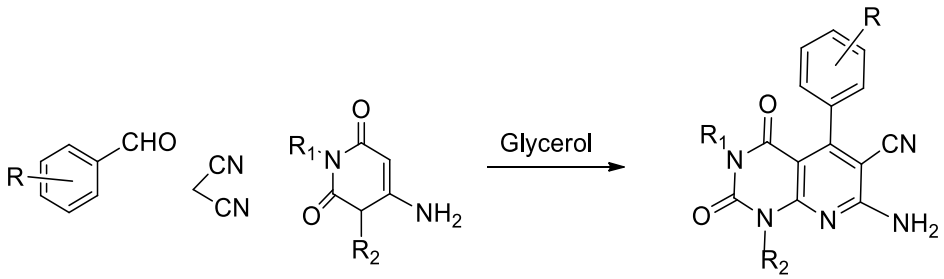


R_1 = Ph, H, 2,4-NO_2-Ph; R_2 = Me, H; R_3 = Ph; R_4 = Me, Ph

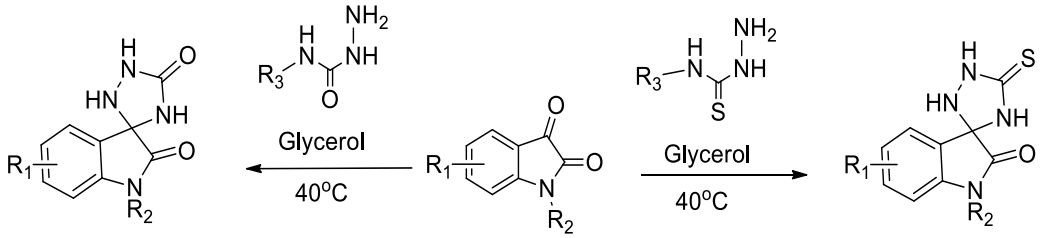
Scheme 4: Synthesis of spirooxindole indazolone and spirooxindole pyrazoline

Our group developed a catalyst free, multicomponent-tandem, facile synthesis of pyrido[2,3-d]pyrimidines using glycerol as recyclable promoting medium. Pyrido[2,3-d]pyrimidine is one such pyrimidine based hybrid scaffold, which has attracted considerable attention due to its broad biological and medicinal applications. (**Scheme 5)** [18]



Scheme 5: Multicomponent-tandem synthesis of pyrido[2,3-d]pyrimidines using glycerol as recyclable promoting medium

Recently our group described catalyst free glycerol mediated green synthesis of 5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-ones/spiro[indoline-3,3′-[1,2,4]triazolidine]-2,5′- diones (**Scheme 6)**[19]



Scheme 6: Catalyst free glycerol mediated synthesis of 5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-ones/spiro[indoline-3,3′-[1,2,4]triazolidine]-2,5′- diones

Fatima et al developed catalyst-free, glycerol-assisted facile approach to imidazole-fused nitrogen-bridgehead heterocycles. Imidazo[1, 2-a]pyridines, imidazo[1, 2-a] pyrimidines and imidazo[1, 2-a]pyrazines are a few important core structures of this class of molecules liberally distributed in many pharmacologically active compounds. (**Scheme 7)**[20]

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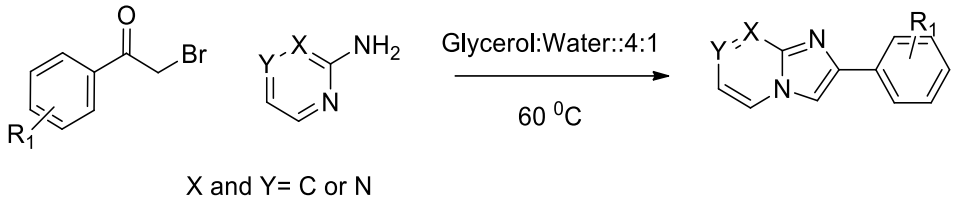
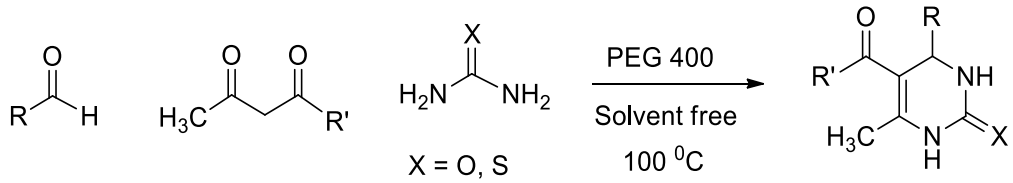


Scheme 7: Glycerol promotedfacile synthesis of imidazole-fused nitrogen-bridgehead heterocycles

(ii) Polyethylene glycol polymers:

Polyethylene glycol polymers (PEGs) have also been emerged as a new class of green solvents. PEG and PEG-supported catalysis is the alternative reaction media in the area of green chemistry which is providing benefitin recent innovation in utilizing bio-based chemicals. PEG and its aqueous solutions are considered as remarkable solvent systems for many other currently favored systems such as ionic liquids, glycerol, supercritical carbon dioxide, and micellar systems.[21] PEG is a hydrophilic polymer, easily soluble in water and many organic solvents as toluene, dichloromethane, alcohol, and acetone, but it is not soluble in aliphatic hydrocarbons such as hexane, cyclohexane, or diethyl ether. PEGs have been widely used as green solvents in several organic synthesis because PEGs are non volatile, recyclable, and stable to acid, base and also to high temperature, easily available in the market with low cast, PEGs concerning their toxicity and biocompatibility are well known, and, importantly, the low toxicity of PEGs allowed them to be used in many areas.[22]The main feature allows the recovery of PEGs by precipitation and filtration, which is extremely important in soluble polymer-supported chemistry. Polyethylene glycol polymers (PEGs) have been proved as eco-friendly reaction media as well as new route for the synthesis of important bioactive heterocyclic compound.[23]

Jain et al., described synthesis of 3, 4-dihydropyrimidinones using PEG-400 as promoter under solvent free and neutral conditions.(**Scheme 8)**[24]



Scheme 8: PEG-assisted solvent and catalyst free synthesis of 3,4-dihydropyrimidinones.

3. Use of organocatalyst in synthesis

Among the new and green synthetic routes, organocatalysis is the most attractive methodology for synthesizing biologically active heterocyclic compounds. Recently, organocatalysis has various benefits because of its eco-friendly and safer synthetic extent. The organocatalyst could be chiral or achiral and composed of C, H, N, S and P.[25] The organocatalyst without any metal, transports a definite advantage such as economical method and as well as environmentaly benign from green chemistry perspective. Organocatalysis is one of the most remarkable research topics in advanced organic chemistry.[26] Nowadays, organocatalysts are gaining significance due to their being, no-toxic, insensitive to moisture, cost-effective, easily available, efficient and selective. Their potential benefits become more appropriate in context of green

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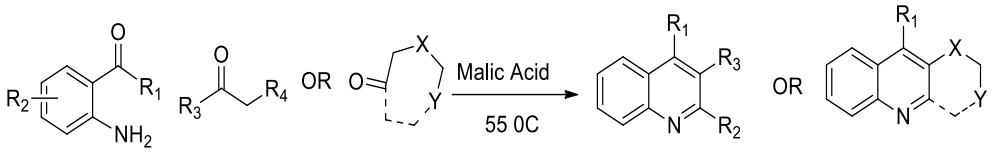
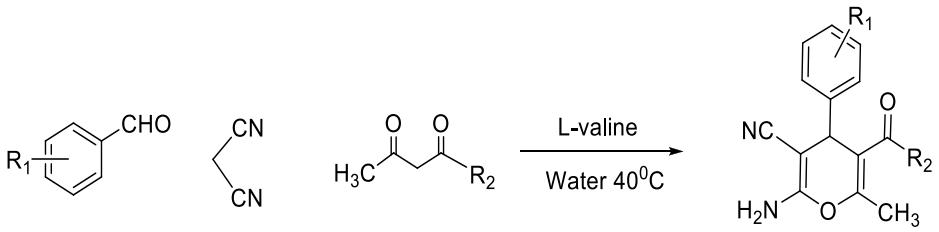
synthesis since the real advantage of organopromoters is best appreciated when used in combination with green solvents or solvent free conditions.[27] Therefore, researchers are on a continuous pursuit to design greener approach for the synthesis of medicinally important heterocyclic molecules using organocatalyst.

Fatima et al disclosed bioorganopromoted green,solvent free approach to multisubstituted quinolines using versatile new malic acid as an organopromoter. (**Scheme 9**)[28]



Scheme 9: Bioorganopromoted green, solvent free approach to multisubstituted quinolones.

Our group reported organocatalytic mediated green approach for the synthesis of diverse and densely functionalized 2-amino-3-cyano-4H-pyrans promoted by versatile new L-valine. (**Scheme 10**)[29]4H-pyran is a ubiquitous skeleton of various pharmaceuticals and bioactive natural products.



Scheme 10: Green synthetic approach to 4H-pyran using L-valine as an organocatalyst.

4 Organic Synthesis Using Surfactants

One of the most inspiring tasks is to search for alternates of commonly employed organic solvents which affect the health and environment. In this context, water is proved to be green solvent but the use of water certainly limited due to low solubility of most organic compounds in pure water.[30]For improving the solubility of organic substrates, surface-active agents (surfactants) have been emerged a powerful tool that may ultimately help in expanding the scope of water-based organic syntheses.[31]Incorporation of surfactants in aqueous media has been proved a vital method to enhance the reactivity of water mediated reactions via the formation of micelles or vesicular cavities. The use of micellar and vesicle forming surfactants as catalysts in water is widespread and has been studied for a number of different synthetic transformations/ multicomponent reactions in water.[32]

Madhulika et al reported DBU catalyzed eco-friendly synthesis of oxa-aza-phenanthrene and anthracene derivatives in aqueous micellar medium. **(Scheme 11)**[33]

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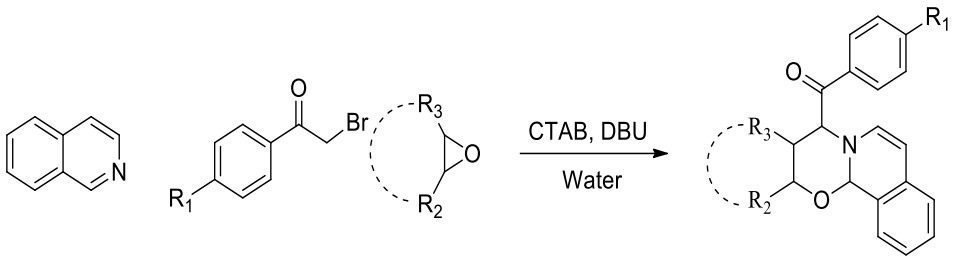
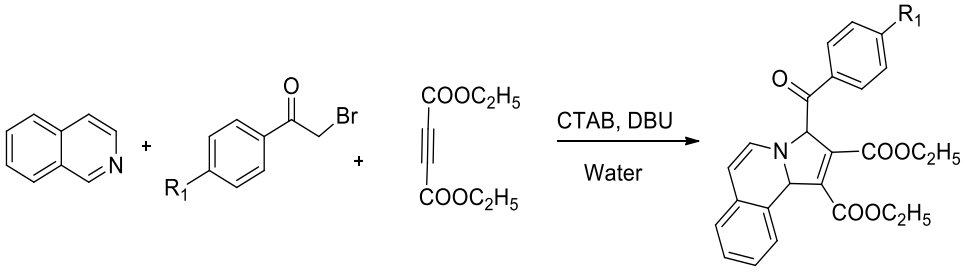


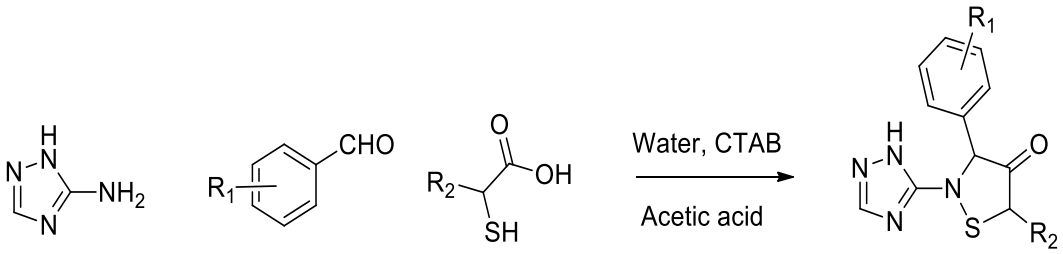
Scheme 11: Synthesis of oxa-aza-phenanthrene and anthracene

Mandavi et al described synthesis of diethyl 3-(4-chlorobenzoyl)-3, 10b-dihydropyrrolo[2,1-a] isoquinoline-1,2-dicarboxylate using cetyl trimethylammonium bromide (**CTAB)** as a micellar catalyst in aqueous medium. (**Scheme 12)**[34]



Scheme12: Synthesis of dihydropyrrolo[2,1-a] isoquinoline in aqueous micellar medium

Mandavi et al reported the environmentally friendly protocol for the efficient synthesis of biologically significant triazole-thiazolidinone hybrids in aqueous micellar medium, using acetic acid as an organocatalyst in the presence of cetyltrimethylammonium bromide (CTAB) as surfactant. (**Scheme 13)**[35]



Scheme 13: Multicomponent, efficient synthesis of triazolyl-thiazolidinones

Mandavi et al also described the synthesis of 1,2,4triazolo[1,5-a]pyrimidines with substituted aromatic aldehydes, malononitrile and 3-amino-1,2,4-triazole using boric acid as catalyst in aqueous micellar medium. Boric acid, a versatile catalyst, is inexpensive, easy to handle, and soluble in aqueous medium. **(Scheme 14)**[36]

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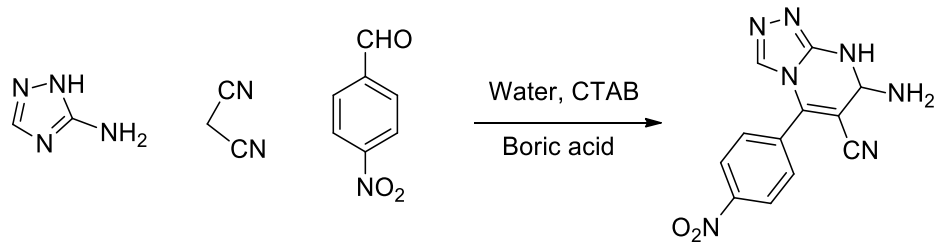
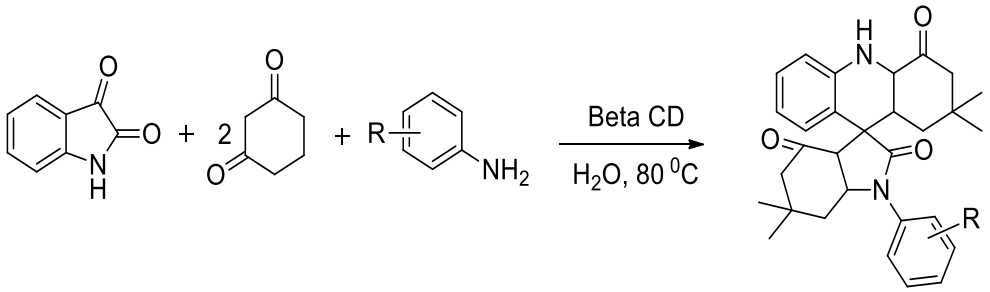


Scheme 14: Synthesis of 1,2,4triazolo[1,5-a]pyrimidine in aqueous micellar medium

3. Use of heterogeneous catalyst

In the last few decades, numerous efforts have been devoted towardsproposing heterogeneous catalysts able to work in water as the reaction medium. The use of water as solvent offers promising benefits with respect to environmental impact. In recentyears, chemists are focusing their major attention to develop a new synthetic protocol using heterogeneous catalysis by preventing the pollution in chemical industry.[37]Among all heterogeneous catalysts, Cyclodextrin has gained much attention due to its water-solubility and hydrophobic cavity. With respect to its excellent properties, cyclodextrins and its derivatives have been broadly applied as catalysts in various organic transformations.[38]

Asha et al, have developed a one-pot four component promising protocol for the synthesis of new spiro[acridine-9,30-indole]-20,4,40(10H,50H,10H)-trione derivatives through condensation of dimedone (2 equiv.), substituted anilines and isatin catalyzed by β-cyclodextrin in water within short reaction time at 80 °C in good to excellent yields. Synthesized compounds were evaluated for their antimicrobial activities against four bacteria and three fungi. All the spirooxindole derivatives exhibited significant antibacterial activity against bacteria and fungi. (**Scheme 15)**[39]



Scheme 15: β-Cyclodextrin catalyzed one-pot synthesis of spiro[acridine-9,30-indole]-20,4,40 (10H,50H,10H)-trione in aqueous medium.

6. Use of biopolymer

One of the most significant and diversified class of biomolecules are carbohydrates in nature. They are mostlyused in various applications such as absorbents, lubricants, adhesives, soil conditioners, textiles, drug delivery systems and high strength structural materials.[40] After cellulose, chitosan is the best polysaccharide pervaded abundantaly in nature and can also be found in industrial wastes. Chitosan shows several specific properties like as hydrophilicity, chemical reactivity due tohydroxyl and amino groups and having unique three-dimensional structure and excellent chelating properties. Moreover, chitosan is eco-friendly reagentas

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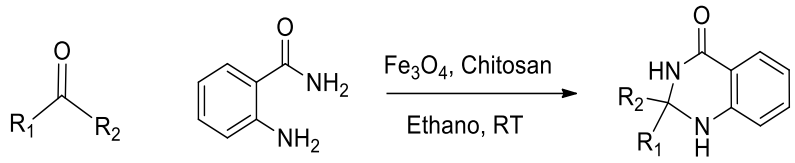
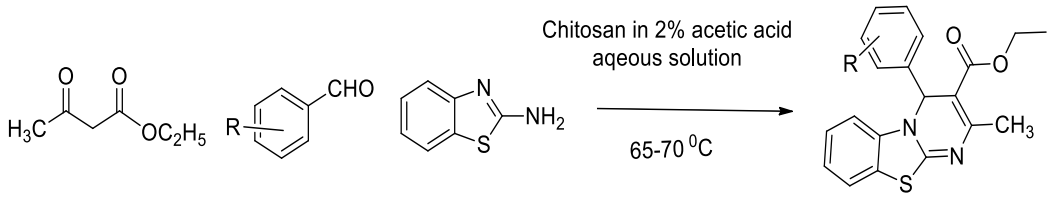
degraded by microorganisms in water and soil.[41]Therefore it can be studied as a potentially attractive biopolymer which is applied as catalysts in different organic syntheses.

A. Maleki et al have been developed an efficient and facile method for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from a condensation reaction of 2-aminobenzamide with various alkyl, aryl and alicyclic aldehydes or ketones using Fe_3O_4/chitosan as an eco-friendly, magnetically reusable nanocatalyst in ethanol at room temperature in high to excellent yields under milder conditions.(**Scheme 16)**[42]



Scheme 16: Synthesis of dihydroquinazolin-4(1H)-ones in the Presence of Ferrite/Chitosan

P. K. Sahu et al described a convenient and rapid method for the synthesis of nitrogen heterocyclic derivatives by one-pot three-component reaction of substituted aromatic aldehydes, dicarbonyl- and 2-aminobenzothiazole/3-amino-1,2,4-triazole/ urea/thiourea using commercially available chitosan in 2% acetic acid in aqueous media at 60−65 °C. Chitosan was used as an efficient biodegradable and reusable green catalyst for this multicomponent reaction. (**Scheme 17)**[43]



Scheme 17: Preparation of 4H-Pyrimido [2, 1-b]benzothiazole derivatives

7. Visible light mediated synthesis

From past decades, to conduct a visible light induced organic synthesis is one of the most essential purposes of researchers. Visible light has attracted extensively due to it's easy availability, renewable energy source as well as a valuable tool for a several green chemical reactions. Chemists have fascinated to perform a various visible light induced reactions since it is an outstanding tool for several synthetic organic chemistry.[44]Various research groups have applied compact fluorescent light and light emitting diodes as a source of visible light for synthesizing the target nucleus. Due to having safe handling, non-toxicity and cost effectiveness characterstics, the utilizations of visible light covers the all features of green chemistry.[45] Visible light is an indefinitely renewable source for numerous chemical transformations.

Deepali et al reported a visible light-initiated, one-pot, multi-component synthesis of 2-amino-4-(5-hydroxy-3-methyl-1Hpyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives under solvent and catalyst-free conditions. (**Scheme 18)**[46]

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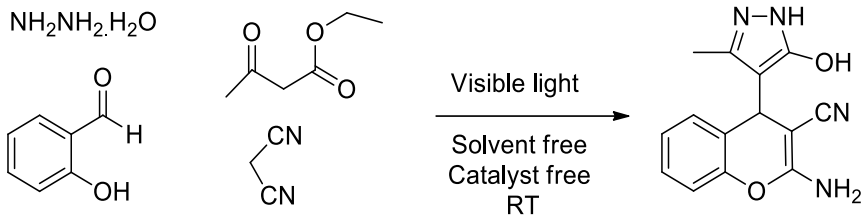
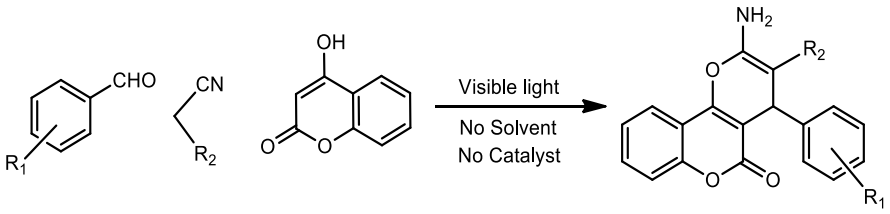


Scheme 18: Visible light utilized green synthesisof 2-Amino-4H-chromenes.

Our research group developed visible light promoted synthesis of dihydropyrano[2,3-c]chromenes via a multicomponent-tandem strategy under solvent and catalyst free conditions. The key feature of the present work is the utilization of visible light which is aubiquitous, inexpensive and eco-sustainable reagent for catalyzing the reaction. (**Scheme 19)**[47]



Scheme 19: Synthesis of highly functionalized dihydropyrano[2,3-*c*]chromenes under photochemical activation.

Conclusion: The synthesis of different complex molecules from bioactive natural products using principles of green chemistry inorganic synthesis is challenging task. After extensive analysis of heterocycles, the topic was found to be very fruitful and need to be explored. The synthesis of the library of biologically active heterocyclic compounds employing green protocols is challenging task. Consequently, number of synthetic environmentally benign methods was developed to synthesize biologically active heterocyclic compounds. Finally the syntheses were successfully completed and some delightful results were obtained for the synthesis of medicinally important heterocycles.

ACKNOWLEDGEMENTS

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