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Green Synthesis of Bioactive Molecules: A Review

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ABSTRACT

Most of the bioactive molecules are synthesized by the highly corrosive and time-consuming old conventional methods. The use of highly toxic chemicals harms the environment and human beings. In this review, we collect the different methods and procedures related to the green and environment benign synthetic methods. This data collected from the articles published in reputed journals dealing with the green synthesis of bioactive molecules. This review mainly focuses on the green synthesis of Indazoles, Benzimidazoles, Coumarins, Pyrazoles, and Imidazoles. In this review, we cover different green synthetic methods like microwave irradiation, green catalysis, solvent-free reaction condition.

INTRODUCTION:

Green chemistry is an eco-friendly and efficient method for the synthesis of most of the chemical entities. It is helpful to reduce the carbon footprint in the field of synthetic chemistry. Green chemistry prevents pollution at the molecular level. Green chemistry uses efficient solvents and catalysts for the synthesis of drug molecules. This innovative method reduces environmental pollution and prevents the toxic effect of chemicals on humans and animals. It involves different green methods useful in the field of organic chemistry, medicinal chemistry, and chemical engineering. Microwave irradiation and sonochemistry are a good source of heat as compared to the old conventional heating techniques. The effect of microwave irradiation creates a superheating effect directly inside the solvent. Sonochemical reactions produce an adiabatic process without affecting the molecule. These techniques are helpful in the minimization of waste products and the time required for the chemical reaction[2, 3]. These techniques reported with high yield and quality products in the synthesis of quaternary ammonium salts, quinalinimides and hydantoins.[4-6]

Solvents play a vital role in synthetic reactions as reaction media. In this category, green solvents are best as compare to petrochemical solvents. Green solvents like supercritical carbon dioxide, aqueous hydrogen peroxide play a vital role in green chemistry. These solvents are less toxic, biodegradable, and derived from renewable sources.[8, 9]

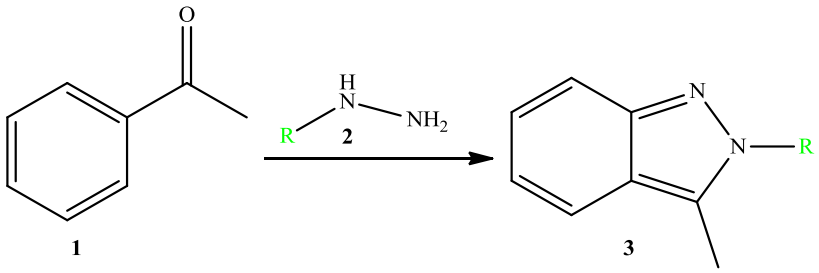
The requirement of more solvent for the reaction leads to the development of solvent-free reactions. This reaction condition reduces the effect of toxic solvents. Solvent free synthesis[10] is a highly successful green method in the field of synthetic chemistry.

Most of the synthetic reactions do not take place without a catalyst. Green catalysis[11] is a sustainable method to increase the rate of a reaction without any waste products. Green catalysts involve the use of biocatalysts, clays, Noble, and non-noble metal complexes.

Green synthesis without protecting groups[12] is more convenient to reduce the unnecessary generation of derivatives. These above all green methods used for the synthesis of the bioactive molecules to gain optimum yield in a shorter time. This review explores the different green and efficient techniques used for the synthesis of the various potent biologically active molecules.

Green Synthesis of the Indazole Derivatives

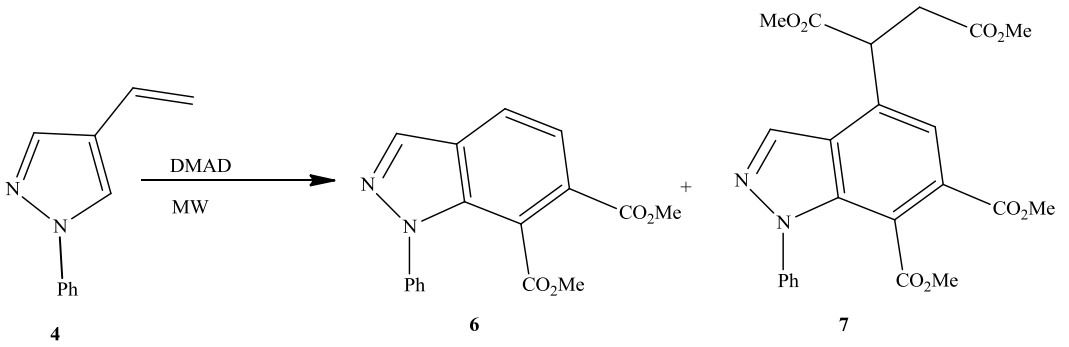
Substitutedtetrahydroindazole (3) derivatives were synthesized by Efrain Polo *et al* using paalknorr synthesis (scheme 1). The reaction between 1, 3-dicarbonyl compounds (1), and hydrazines (2) under microwave irradiation and reflux results in the production of good yield with fewer intermediates. These reactions were carried out using both polar protic-solvent (acetic acid) and an aprotic non-polar solvent (DMF). The comparative study shows the gradual increase in percentage yield from 85 to 90% by using microwave irradiation for 2 min.[13]



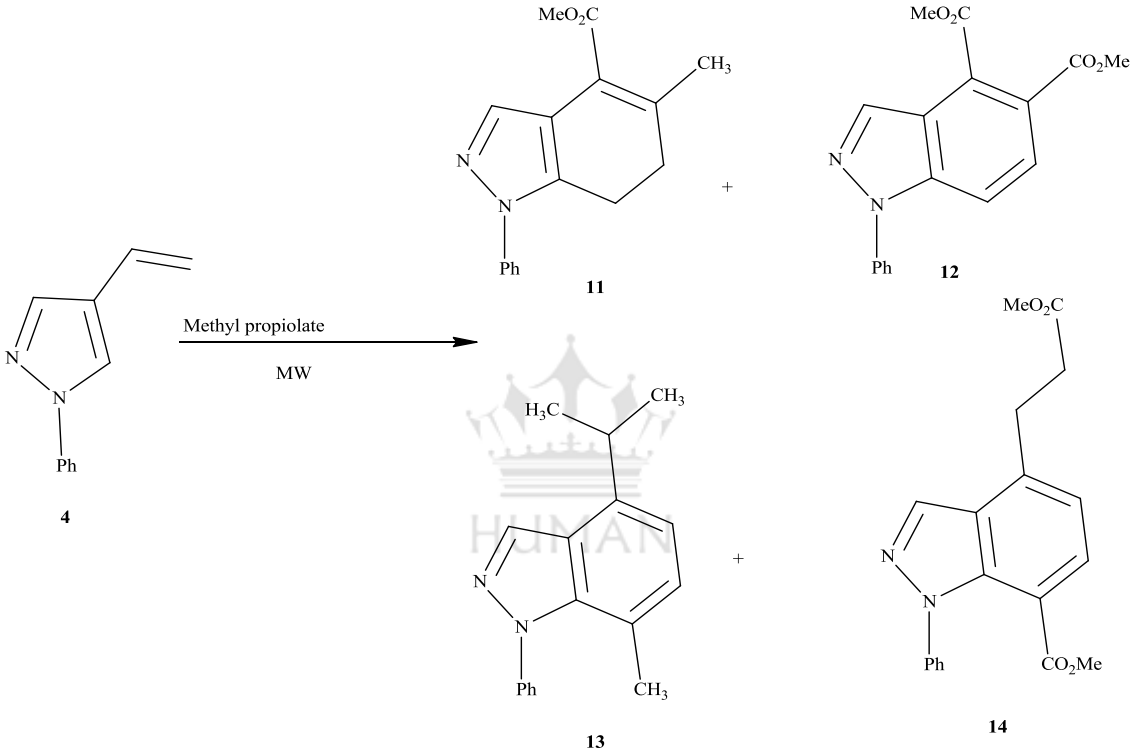
R = H-H_2O, C_6H_5, 4-BrC_6H4, 4-CNC_6H_4, $_4$-$CO_2HC_6H_4$, $_4$-FC_6H_4

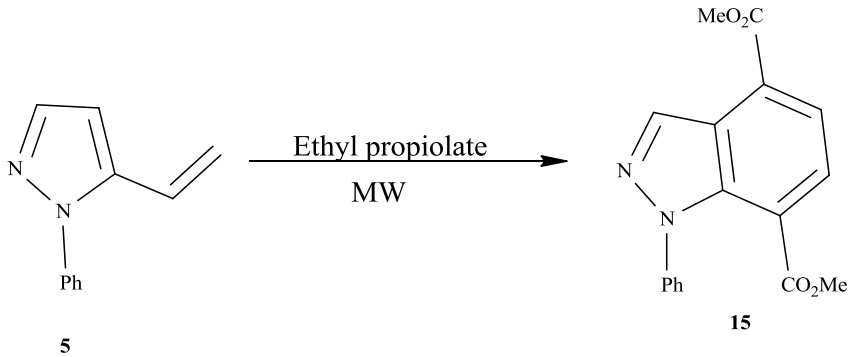
Scheme 1

Diels–alder cycloaddition reactions are carried out for the synthesis of some indazole derivatives. Angel Diaz-Ortiz et al used 4- or 5-vinylpyrazoles for the synthesis of Indazolederivatives by microwave irradiation technique and compared (% yield) with the conventional heating methods. Both 4-vinylpyrazole (4) and 5-methyl pyrazole (5) are consecutively undergoing addition reaction with DMAD for 6 and 30 min (scheme 2), Methyl propionate for 20 min, ethyl propionate for 25 min and ethyl phenylpropionate for 10 min and 15 min (scheme 3). Overall, these reactions the microwave irradiation (780 W) of vinyl pyrazole with DMAD at 130ºC for 6 min shows 62% yields (6). [14]



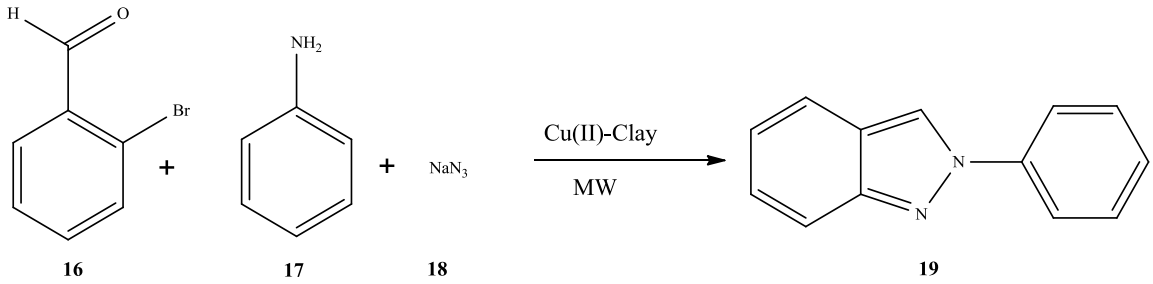
Scheme 2





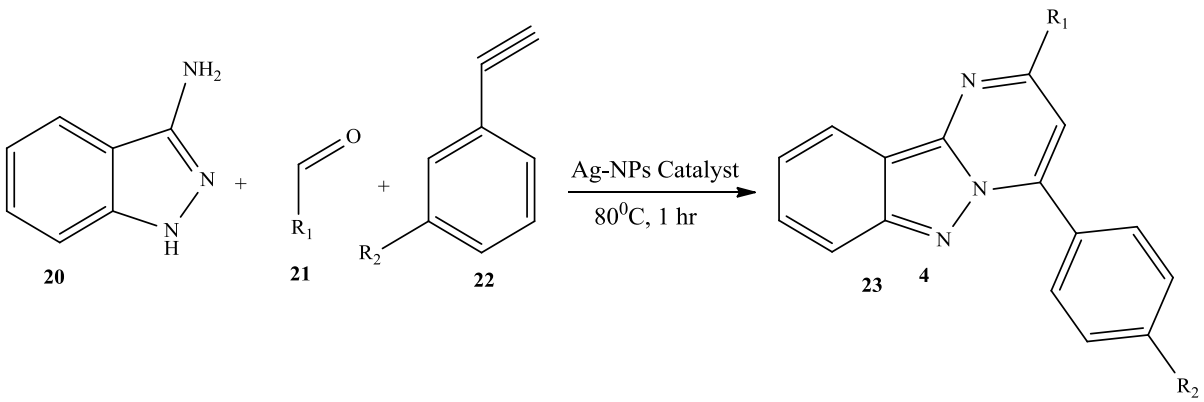
Scheme 3

Bashir Ahmad Dar and his group accomplish a profoundly proficient strategy for the synthesis of the 2H-indazoles (19) from bromobenzaldehydes (16), 2-essential amines (17), and sodium azide (18) through domino condensation. The combined effect of the Cu(II)-Clay catalyst, and microwave irradiation in solvent-free conditions produce high yield within a short period with fewer additives. The optimum result was produced at, 5 mg Cu-Clay catalyst, 1.0 mmol of 2-bromobenzaldehyde, 1.2 mmol of aniline, and 1.8 mmol of sodium azide-under solvent-free condition. The overall reaction completed within 8 min. Indeed, even the catalyst was recycled for around 5 consecutive reaction cycles.[15]



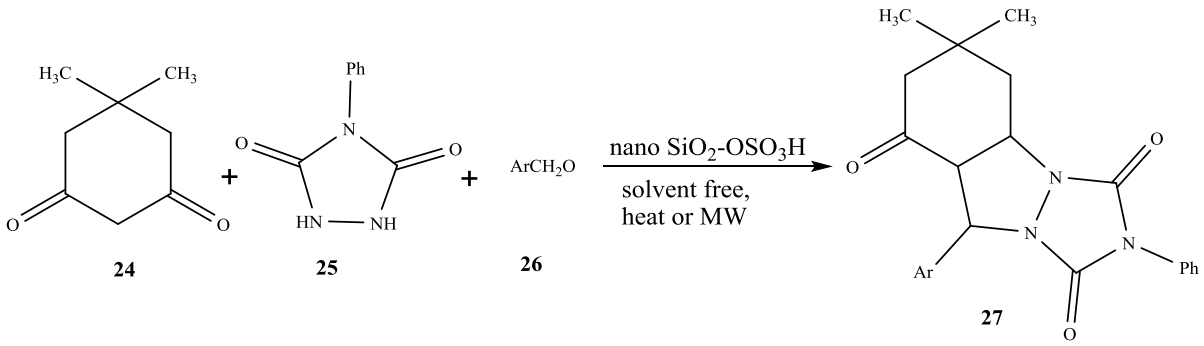
Scheme 4

Pyrimido-[1,2]-indazole (23) derivatives were synthesized by using silver nanoparticles (Ag-NPs) as catalyst under solvent-free conditions. A multicomponent A3-coupling reaction was carried out between aminoindazoles (20), 2-methoxy benzaldehyde (21), and ethylbenzene (22). These reactions were investigated for the activity of Silver-Nanoparticles for their catalytic activity under both solvent and solvent-free conditions. Among all these reactions, the solvent-free condition furnished the desired product in 96% yield at 80 °C in 1h. Even the various copper catalysts failed to achieve good yield at these reaction conditions. [16]



Scheme 5

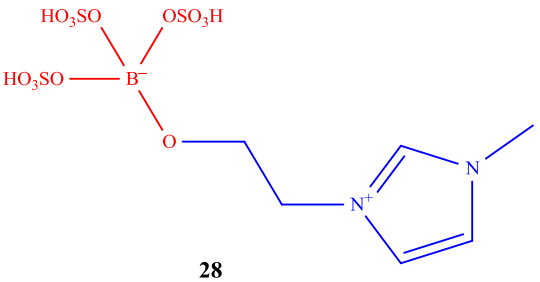
One-Pot and Efficient Synthesis of Triazolo [1,2] indazoletriones(27) carried out under a clean and green method (scheme 6). This reaction catalyzed by the Nano silica sulphuric acid under a solvent-free condition. The reaction between mixtures of dimedone(24), urazole(25), and aromatic aldehydes(26) was carried out under both conventional and microwave irradiation technique. The optimized condition yields 92%, under microwave irradiation in 5min. [17]



Scheme 6

Green Synthesis of the Benzimidazole derivatives.

The condensation of O-phenylenediamine (29) and Aldehydes (30) leads to Benzimidazoles (31). The direct condensation results in a complex intermediate, to overcome this problem a simple green synthesis was done by using [(MOEI)-BSA] as a catalyst (28) and water as a green solvent (Scheme 7). The best results occur in the presence of media contains a mixture of 5 mol% of [MOEI]-BSA with H_2O. Even the reactions were carried out using different solvents like Et-OH, chloroform for optimum yield at room temperature. Overall these solvents,water was found to be the best. [18]



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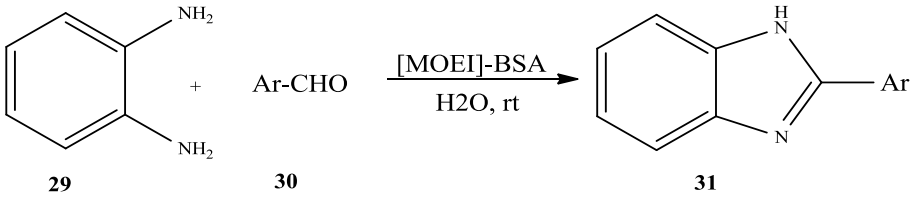
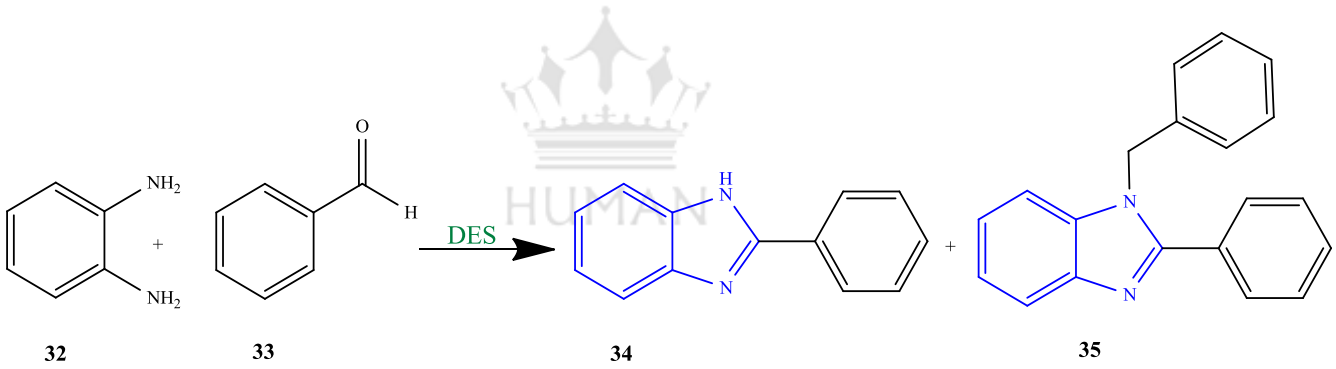


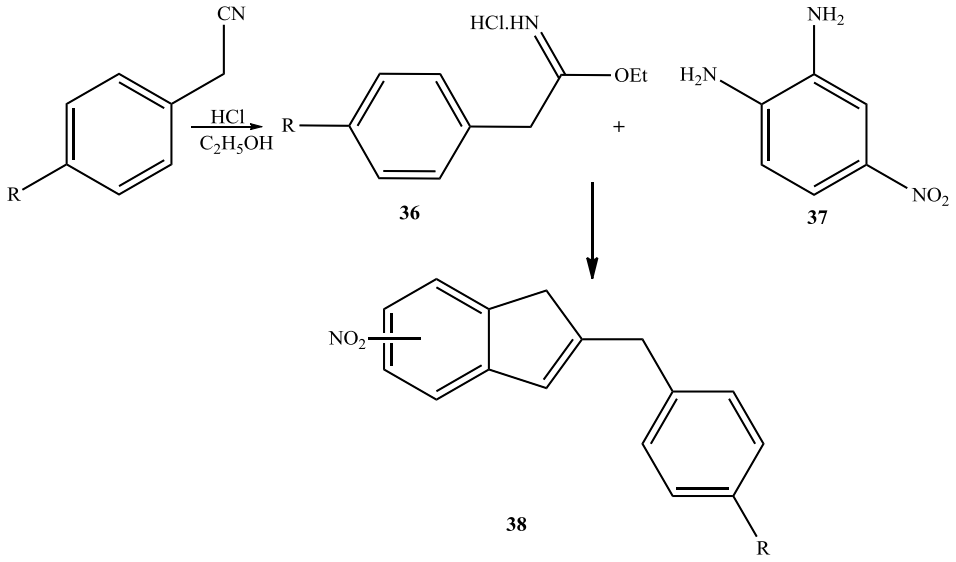
Scheme 7

Ionic liquids are highly toxic and harmful to the environment. This synthetic method contains deep eutectic solvents (DES) for the green synthesis of the benzimidazoles (34, 35). These Eutectic solvents are easy to produce and have less impact on the environment. Choline chloride/urea (ChCl: Urea) aDES, which is highly economic, biodegradable and non-toxic.The equimolar reaction between O-phenylenediamine (32) and an Aromatic aldehyde (33) inDES at 80^0C shows the best yield. The optimized ratio of O-PDA: Benzaldehydeshows the 80% yield within 10 min. [19]



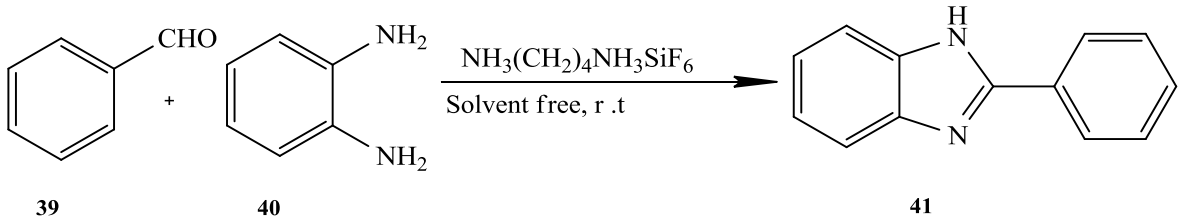
Scheme 8

Nitro-benzimidazoles (38) and their salicyl and isatin Schiff bases were synthesized by iminoester.hydrochloride (36) and 4-Nitro-o-phenylenediamine (37) under both microwave irradiation and conventional heating method. This reaction shows the best yield by microwave irradiation rather than the conventional heating. The optimized condition yield 70 to 93% in 10 min.[20]



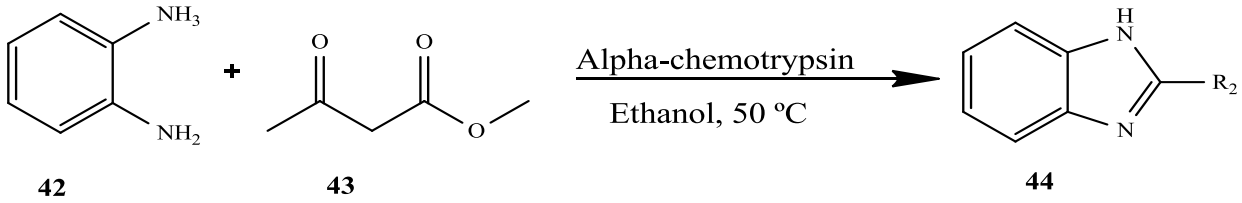
Scheme 9

Direct condensation of the1, 2-phenylene diamine (39), and Benzaldehyde (40) lead to different Benzimidazole derivatives (41). A hybrid compound $NH_3(CH_2)4NH_3SiF_6$ was used as a heterogeneous solid catalyst, yield around 93% of the product within 14 min. The optimized conditions at 1 mol% of the catalyst show 98% of the yield under solvent-free conditions. This recovered catalyst from the mixture by using methanol and used for further reactions.[21]



Scheme 10

A retro-Claisenreaction carried out between O-phenylenediamine (42) and β-keotester (43) for the synthesis of the Benzimidazoles (44). Anintroduction of the Chemotrypsin enzyme as a green catalyst in ethanol allows the reaction to proceed with the best yield within a short period. A higher yield of 93% was obtained at 50°C in 18 h. The optimum temperature (50^0C) avoids the energy consumption and deactivation of the enzyme. The recovered catalyst was recycled for further more reactions. [22]

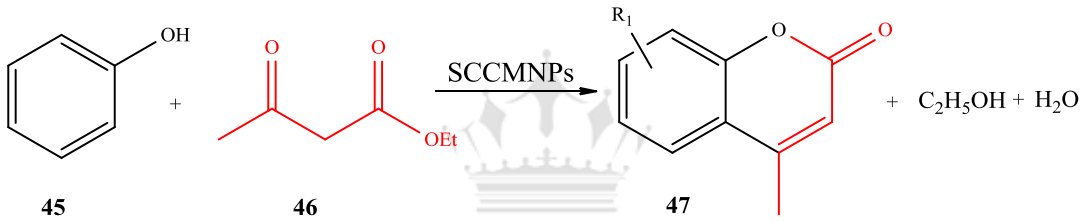


42 43 44

Scheme 11

Green Synthesis of the Coumarin Derivatives

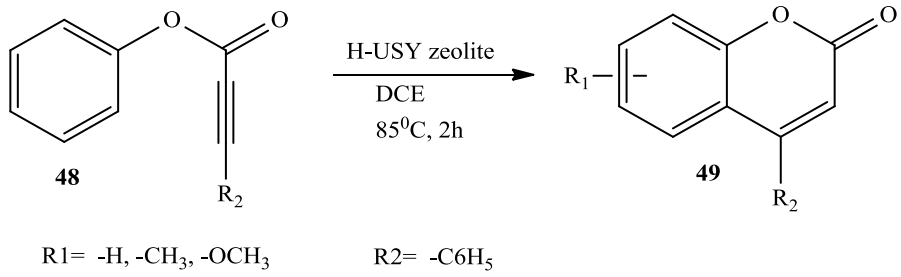
4-hydroxy methyl coumarins(47) were synthesized by the Pechmann condensation of the Resorcinol(45) and Ethyl-acetoacetate (46). This incomplete reaction was achieved by the use of sulfonated carbon-coated magnetic nanoparticles (Fe_3O_4@C@OSO_3H) as a green catalyst under solvent-free conditions. After overall reaction trials, an optimized amount of 6.5mol% of the catalyst at 120^0 C for 20 min yields 98% of the coumarin.[23]



45 46 47

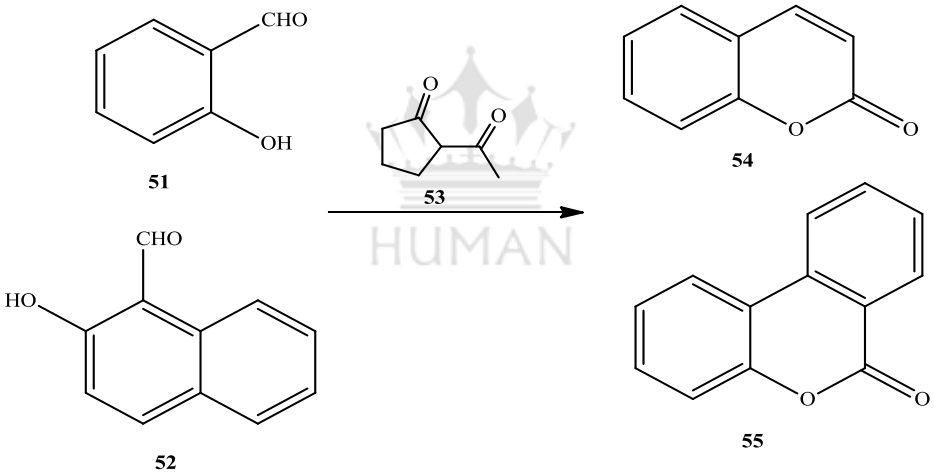
Scheme 12

A well-established green synthesis of the Coumarins(49) was carried out by the cyclization of the Aryl-propionates(48)in 1, 2-dichloroethane at 85°C for an hour. The maximum conversion of about 55% with a high yield of 40% occurs by the use of an acidic Zeolite (CBV 720) with a Si/Al ratio of 2:1. This ratio found best among the different types of zeolites because of its regardless porosity, acidity, and efficiency. The recovered green catalyst can be reused for 5 consecutive reactions without loss of their activity. [24]



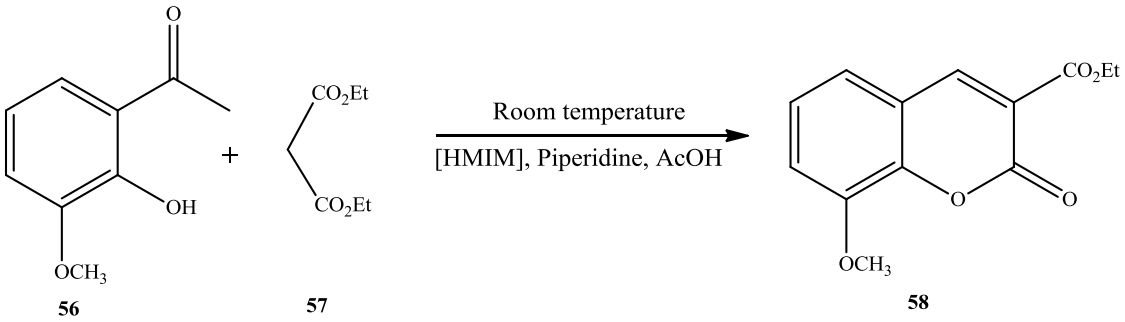
Scheme 13

Coumarins (54) and Benzocoumarins (55) were synthesized by microwave-assisted Knoevenagel condensation of the various Salicylaldehydes (51) and 2-hydroxy-1-naphthaldehyde (52) withDicarbonyl (53) derivatives. These reactions carried both under the solvent and solvent-free conditions. The optimized reaction occurs with the use of KF-Al_2O_3 as a green catalyst under solvent-free conditions. The maximum yield (71%) occurs at 15% weight of the catalyst. The recovered catalyst was reused for around four more reactions.[25]



Scheme 14

A series of the coumarins (58) were synthesized by2-hydroxy-3-methoxy benzaldehyde (56)and diethyl malonate/malononitrile (57) in the presence of the catalytic amount of Piperidine and acetic acid at room temperature. The reaction condition produces less yield and more by-products. Introduction of the ionic liquid, 1-hexyl-3-methylimidazolium-bromide [(HMIM)Br] as a green reaction medium shows better yield for around 98% in a short period .[26]

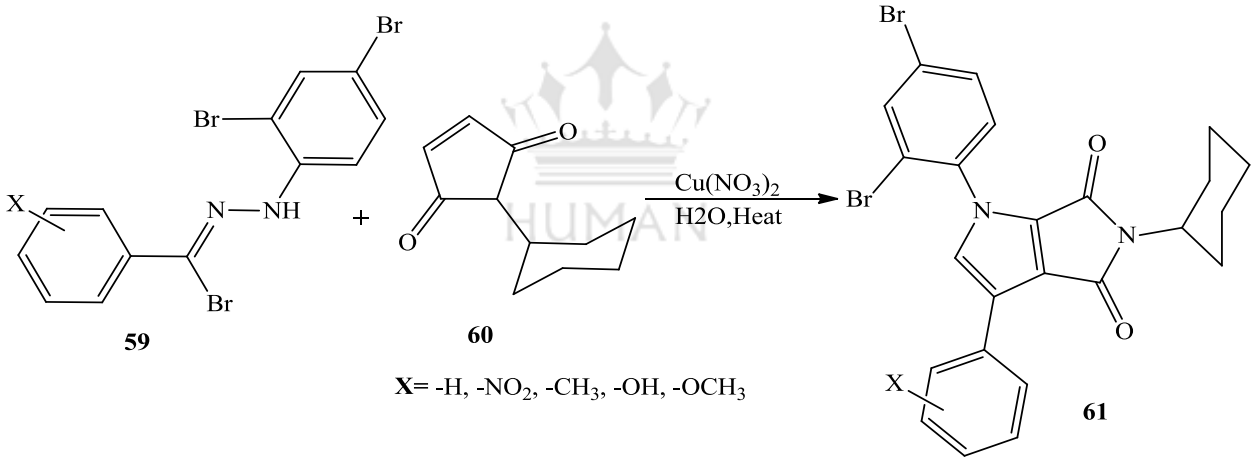


56 57 58

Scheme 15

Green Synthesis of the Pyrazoles

Pyrrolo-pyrazoles (61) were synthesized by the Hydrazonyl bromides (59) and N-cyclohexylmaleimide (60). This reaction completed by using different Lewis acid catalysts in an aqueous medium. A green catalyst, $Cu(NO_3)_2$ shows the best result (84%) among different Cu^{+2} salts in water. [27]

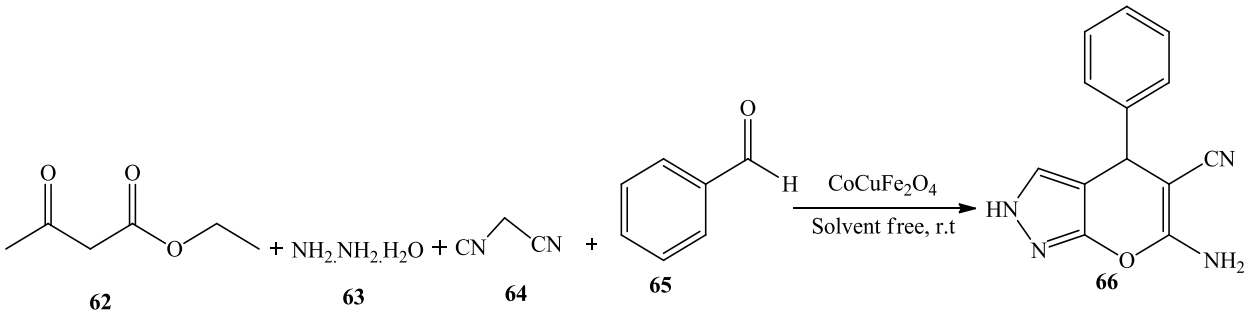


59 60 61

X= -H, -NO_2, -CH_3, -OH, -OCH_3

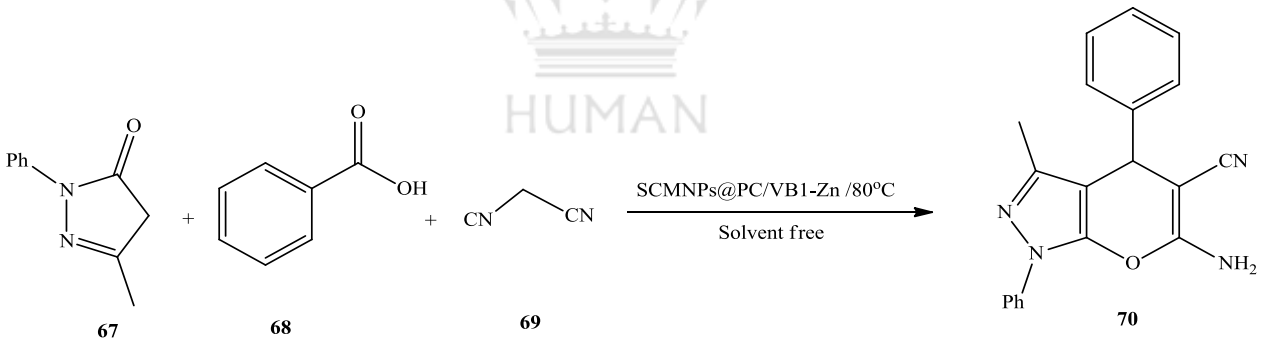
Scheme 16

A multicomponent reaction between Ethyl acetoacetate (62), Hydrazine hydrate (63), Malononitrile (64), and 4-Nitrobenzaldehyde (65) performed for the synthesis of the different Pyranopyrazoles (66). This complete reaction was catalyzed by the Cobalt-copper ferrite nanoparticles ($CoCuFe_2O_4$) at room temperature in solvent-free conditions. About 92% yield was obtained using 25mg of the catalyst. The extracted catalyst was reused for four more reactions. [28]



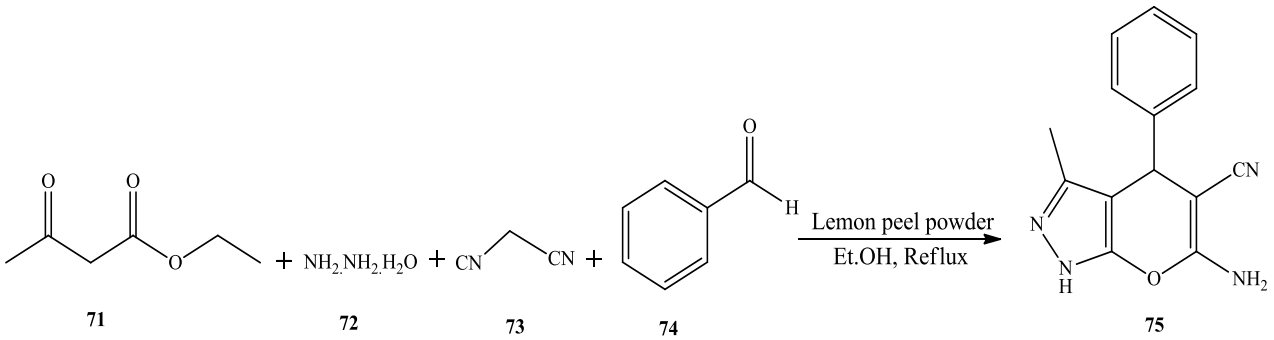
Scheme 17

Pyranopyrazole (70) derivatives were synthesized by the condensation of 3-methyl-1-phenyl-1H-pyrazol-5-one (67), Aromatic aldehyde (68) and malononitrile (69). This complete green reaction was carried by using silica-coated magnetic nanoparticles bonded at PC/VB1-Zn (P: 3-Chloropropyltriethoxysilane, VB1: Vitamin B1, Zn: Zinc) in solvent-free condition. The optimized reaction occurred at 10mg of the catalyst with a 96% yield in 15 min at 80 °C. The recovered catalyst was used for six more consecutive reactions with a decrease in catalytic activity. [29]



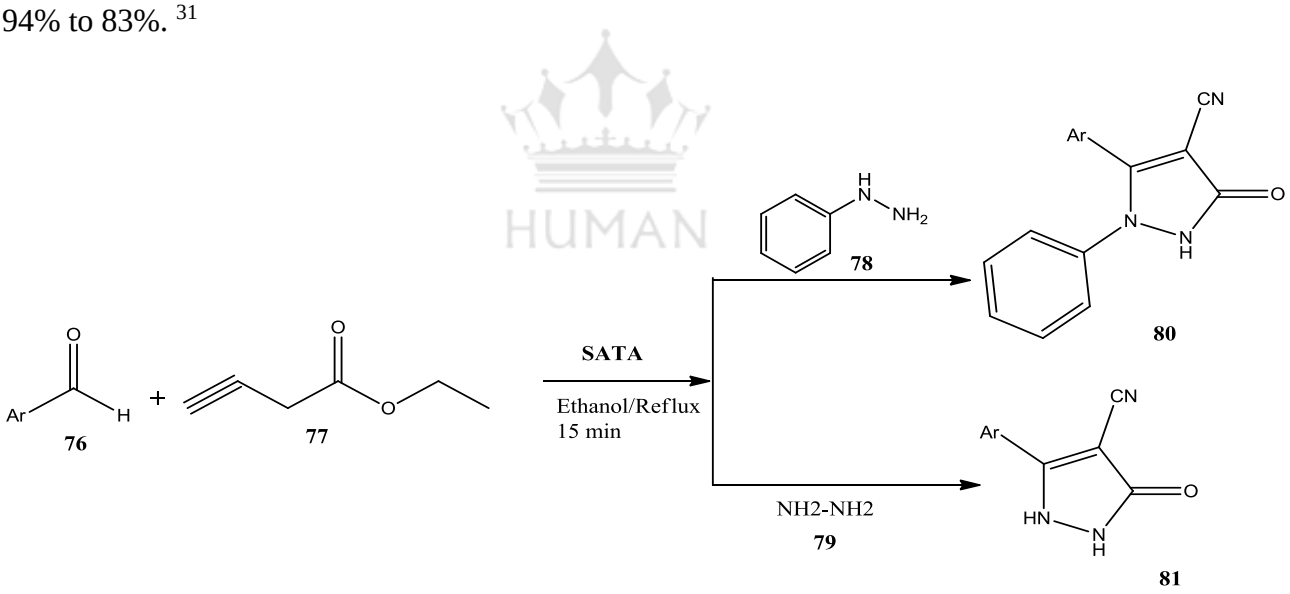
Scheme 18

A one-pot condensation of the 4-hydroxybenzaldehyde (71), Malononitrile (72), Ethyl acetoacetate (73), and hydrazine hydrate (74) in ethanol performed for the synthesis of the Pyranopyrazoles (75) with different Benzaldehydes (74). This reaction catalyzed by the lemon peel powder as a green catalyst to obtain a better yield. The optimized reaction occurs at 10wt% of catalyst in ethanol under reflux condition. [30]



Scheme 19

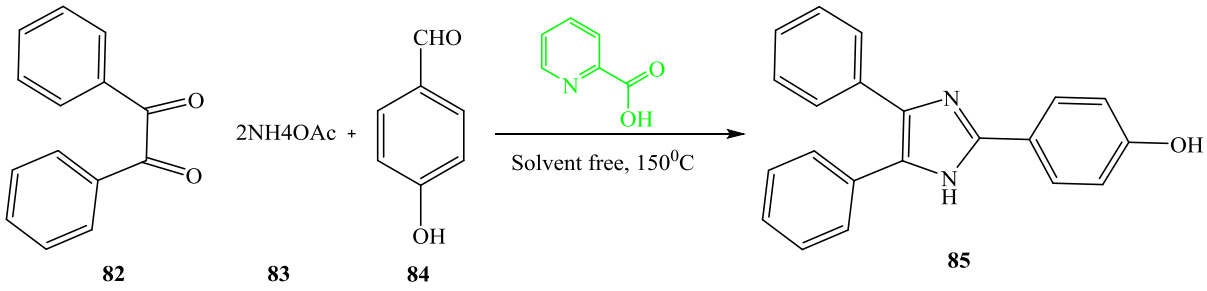
A series of Pyrazole-carbonitrile (80, 81) derivatives were synthesized by acid-catalyzed reflux condensation of Aromatic aldehydes (76), Ethylcyanoacetate (77), Phenyl hydrazine (78) /hydrazine hydrate (79) in alcohol. Among different acids, sulfated alumina tungstic acid (SATA) shows the best yield in ethanol. The optimized reaction condition shows a 94% yield in 15 min. The recollected catalyst used for five more reactions with a decrease in yield from 94% to 83%. [31]



Scheme 20

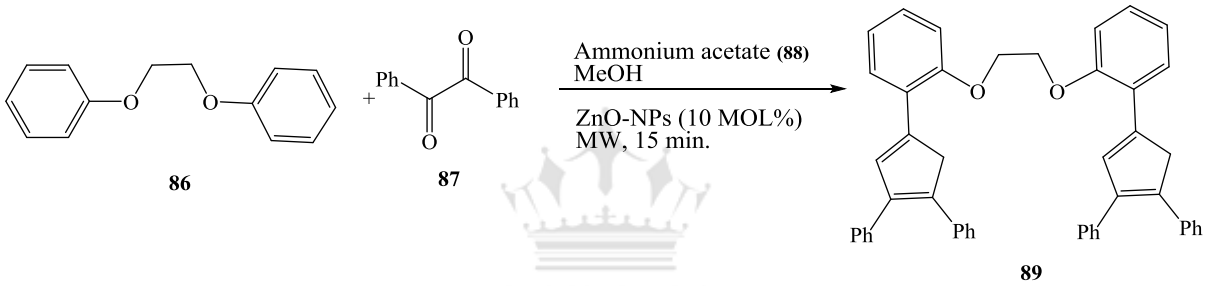
Green Synthesis of Imidazole derivatives

One-pot synthesis of the 2,4,5-trisubstituted imidazole (85) derivatives was carried by the direct condensation of the substituted Aromatic aldehydes (82), Benzil (83) and Ammonium acetate (84). In this reaction Pyridine-2-carboxylic acid (0.5 eq) used as a catalyst among other acids. The optimized reaction shows a 78% yield at 150^0C in 2-3 hours. [32]



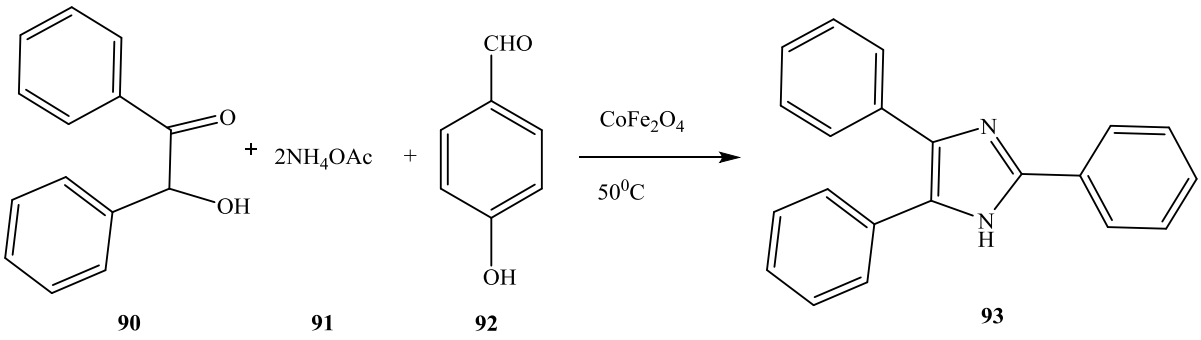
Scheme 21

One-pot synthesis of the Bis- and poly-imidazoles (85)was carried by three different methods. In these methods, the one-pot reaction between 1,2-diketone (87), Aldehydes (86), and Ammonium acetate (88) with a catalytic amount of ZnO-Nanoparticles in methanol show better yield. The optimized reaction yields 87% by microwave irradiation. [33]



Scheme 22

A multicomponent one-pot condensation of Benzoin (90), Benzaldehyde (91), and Ammonium acetate (92)performed for the synthesis of substituted Imidazole (93). This reaction catalyzed by different metal oxides in various time intervals. Among these $CoFe_2O_4$yields 99% in 10 min at 50^0 C. This green catalyst recollected and reused for several times.[34]



Scheme 23

SUMMARY

The old conventional methods for the synthesis are harmful to nature and human beings. The green synthesis is the area of interest for the synthesis of most of the bioactive molecules now a day. Most of the R&D centers, Pharmaceutical industries use these techniques for the rapid and environmentally benign synthesis of bioactive molecules. This leads to a step toward a sustainable future for the pharma sector.

ABBREVIATIONS:

DMAD: Dimethyl acetylene carboxylate

(MOEI)-BSA:1-Methyl-3-(2Oxyethyl) -1H-Imidazol-3-ium-Borate Sulfonic Acid

DMF: Dimethyl formamide

MW: Microwave

Cu (II) clay: Copper clay

O-PDA: O-phenylenediamine

$NH_3(CH_2)4NH_3SiF_6$: Butylene diammonium hexafluorosilicate

SCCMNPs: sulfonated carbon-coated magnetic nanoparticles

PC/VB1-Zn:PC: 3-Chloropropyltriethoxysilane, VB1: Vitamin B1, Zn: Zinc

$CoFe_2O_4$: Nanosized Cobalt ferrite

ZnO: Zinc oxide

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