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Review Article

Green Synthesis of Bioactive Molecules: A Review.

YUNUS PASHA THOPPALADA[1*], VIJAY PUJAR[2]
[1,2]Professor, Dept. Of Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy, BG Nagara, Mandya Dist-571448
*Corresponding Author
Email: thoppalada@gmail.com[1]*,vpujar707@gmail.com[2]
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ABSTRACT
Most of the bioactive molecules are synthesised by time-consuming conventional methods. The use of toxic chemicals harms the environment and human beings. In this review, an attempt has been made to introduce methods and procedures related to the green and environment benign synthetic process. Until 1980's the knowledge of the risks associated with using chemicals was quite poor among the chemists. This review mainly focuses on the green synthesis of Indazoles, Benzimidazoles, Coumarins, Pyrazoles and Imidazoles. As on today, toxicity of the chemicals can be explained to eliminate the cause of its toxicity without sacrificing the desirable properties of the chemical.

Keywords: indazoles, benzimidazoles, coumarins, imidazoles, green catalysis, solvent free reaction.

INTRODUCTION

Green chemistry is an eco-friendly and an 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 the pollution at molecular level. Green chemistry uses efficient solvents and catalysts for the synthesis of drug molecules. This method reduces the environmental pollution and prevents the toxic effect of chemicals on human and animals. It involves different green methods useful in the field of the organic chemistry, medicinal chemistry and chemical engineering. Microwave irradiation and Sonochemistry are good source of heat as compared to the conventional heating techniques. The effect of microwave irradiation creates superheating effect directly inside the solvent. Sonochemical reactions produce adiabatic process without affecting the molecule. These techniques are helpful in the minimisation of waste products and time required for the chemical reaction[2, 3]. These techniques reported with high yield and quality product 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 use of solvents in the organic synthesis is a common practice from decades. However, chemists concern to reduce the environmental pollution caused by solvents. These reactions achieved by use of the biocatalysts embedded in the clays, zeolytes, silica, alumina or other matrices with the thermal effect of UV, microwave irradiation or ultrasound effect.[10]

Most of the synthetic reactions do not take place without catalyst. Green catalysis[11] is sustainable method to increase the rate of reaction with fewer intermediates. The use of Biocatalysts, Clays, Noble and non-noble metal complexes leads a sustainable green syntheisis.

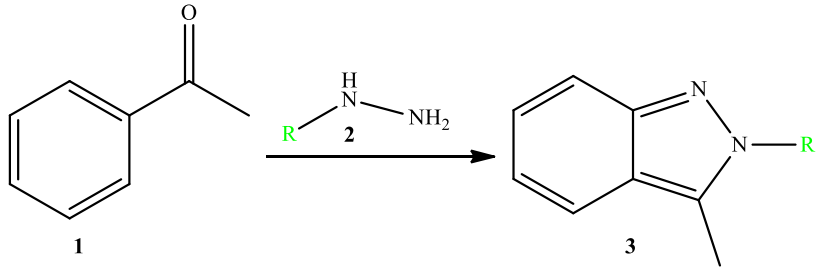
Green synthesis without protecting groups is more convenient to reduce the unnecessary generation of intermediates. A protection/deprotection lengthens the reaction steps, incurring the cost for additional reagents and waste disposal, and finally leads to a reduced overall yield. Here we present relevant historical context and highlight recent total syntheses that have developed new chemistry in an effort to exclude protecting groups.[12]

Overall, this review explores the different green and efficient techniques used for the synthesis of the various potent biologically active molecules like Indazoles, Benzimidazoles, Coumarins, Pyrazoles and Imidazoles.

Green Synthesis of the Indazole Derivatives

Substituted tetrahydroindazole (3) derivatives were synthesised by Efrain Polo et al using paalknorr synthesis (scheme 1). The reaction between 1, 3-

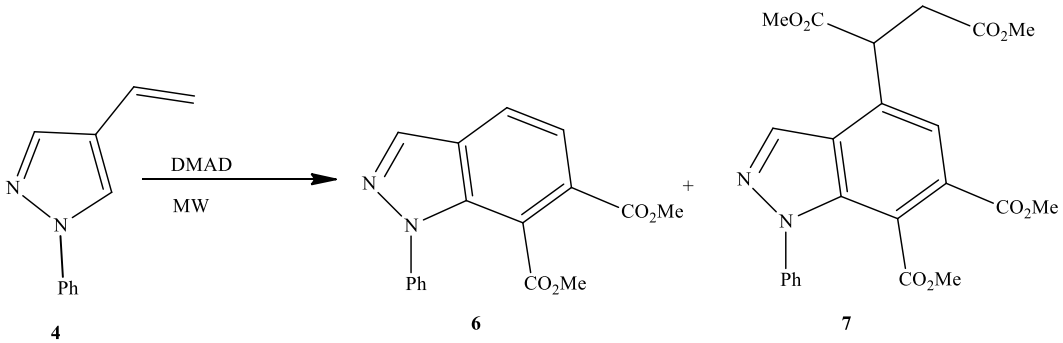
dicarbonyl compounds (1) and hydrazines (2) under microwave irradiation and reflux results in the production good yield with fewer intermediates. These reactions were carried out using both polar protic-solvent (acetic acid) and an aprotic non-polar solvent (DMF). The comparative study shows the gradual increase in percentage yield from 85 to 90% by using microwave irradiation for 2 min.[13]



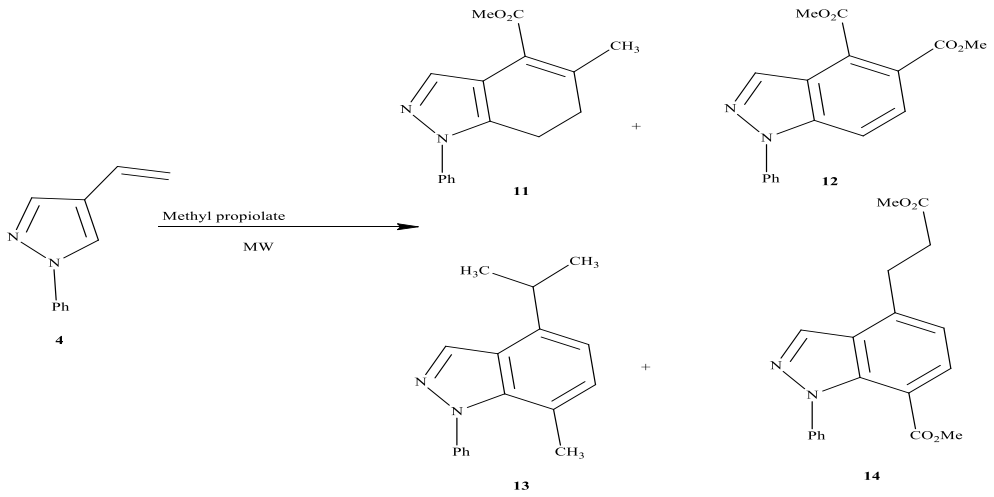
R = H-H_2O, C_6H_5, 4-BrC_6H4, 4-CNC_6H_4, $_4$-$CO_2HC_6H_4$, $_4$-FC_6H_4

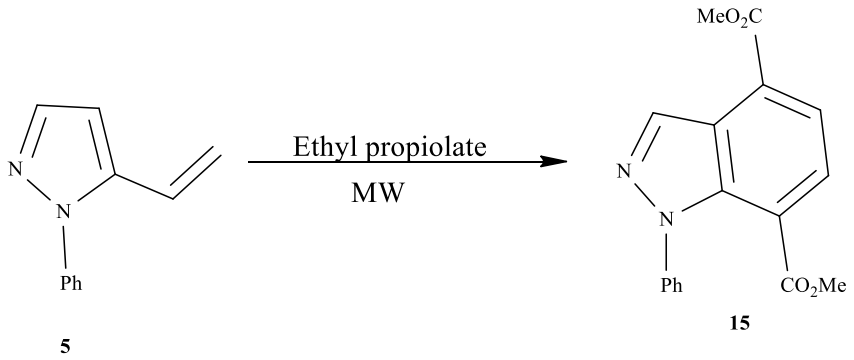
Scheme 1

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



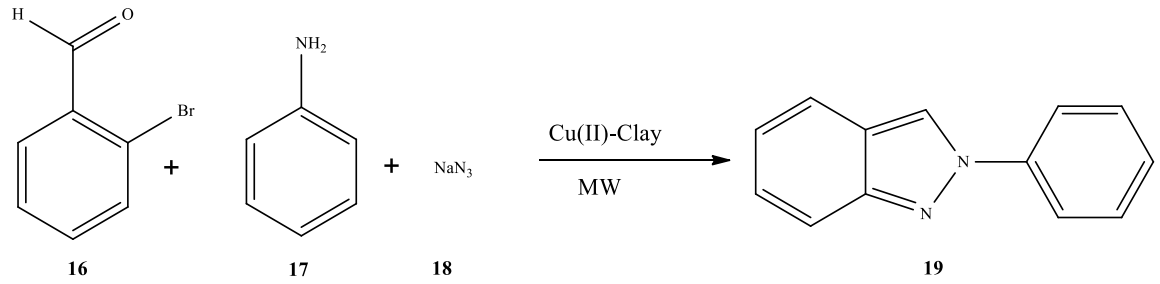
Scheme 2





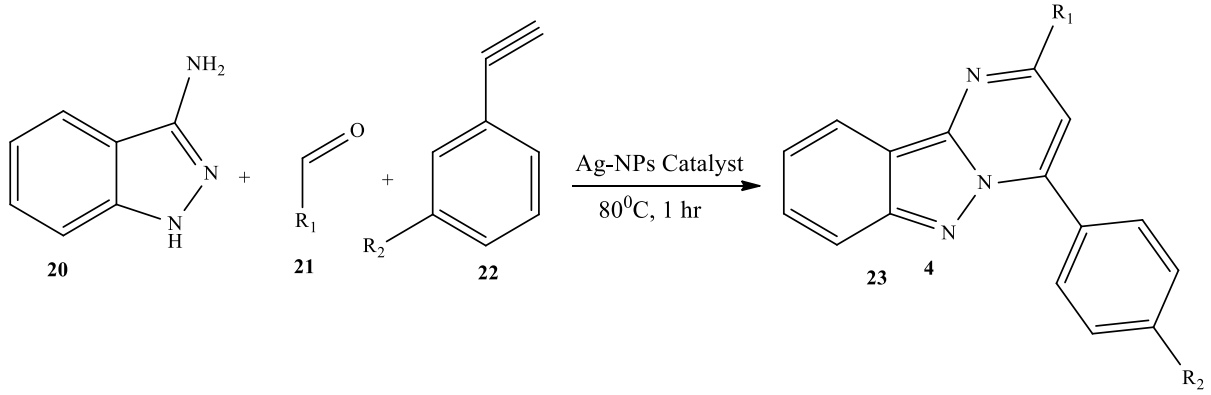
Scheme 3

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 produced high yield within a short span of time 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 azideunder solvent free condition. The overall reaction completed within 8 min of time. Indeed, even the catalyst was recycled for around 5 consecutive reaction cycles.[15]



Scheme 4

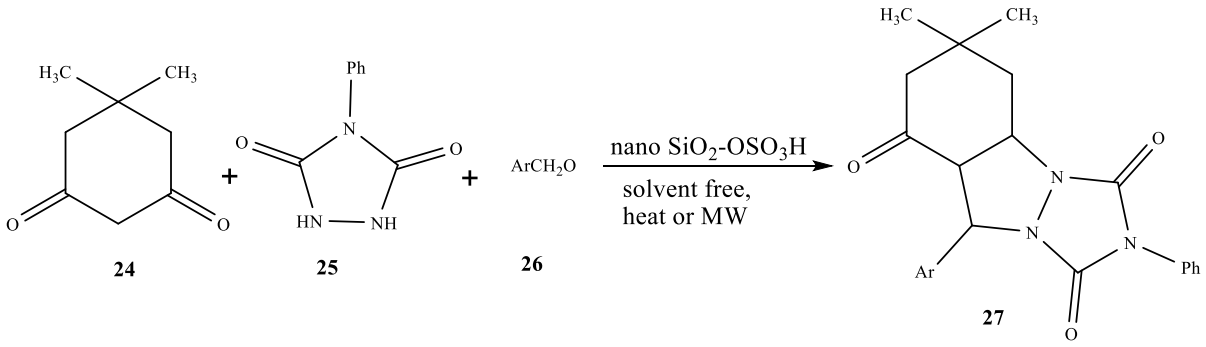
Pyrimido-[1,2]-indazole (23) derivatives were synthesised by using silver nanoparticles (Ag-NPs) as catalyst under solvent free conditions. A multicomponent A3-coupling reaction was carried out between aminoindazoles (20), 2-methoxybenzaldehyde (21) and ethynylbenzene (22). These reactions were investigated for the activity of Silver-Nanoparticles for their catalytic activity under both solvent and solvent free conditions. Among all these reactions, 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 catalysed by the Nano silica sulphuric acid under a solvent

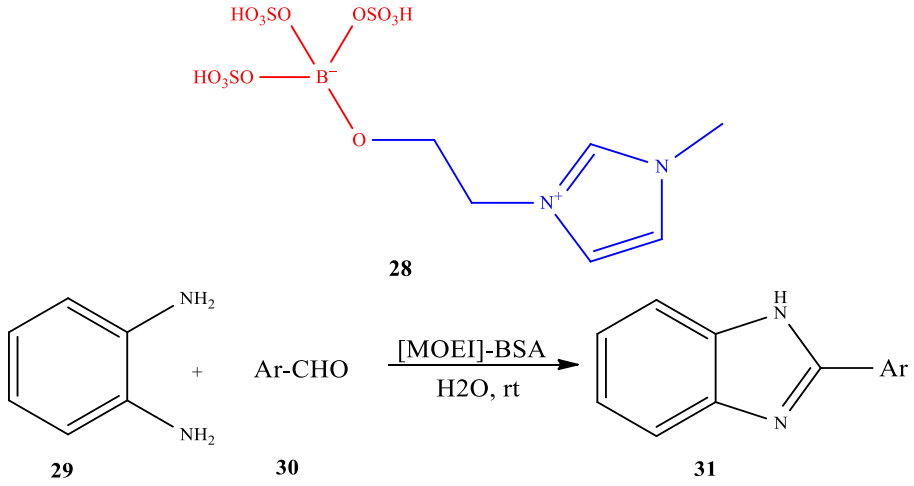
free condition. The reaction between mixtures of dimedone (24), urazole (25) and aromatic aldehydes (26) was carried out under both conventional and microwave irradiation technique. The optimised condition yield 92%, under microwave irradiation in 5min. [17]



Scheme 6

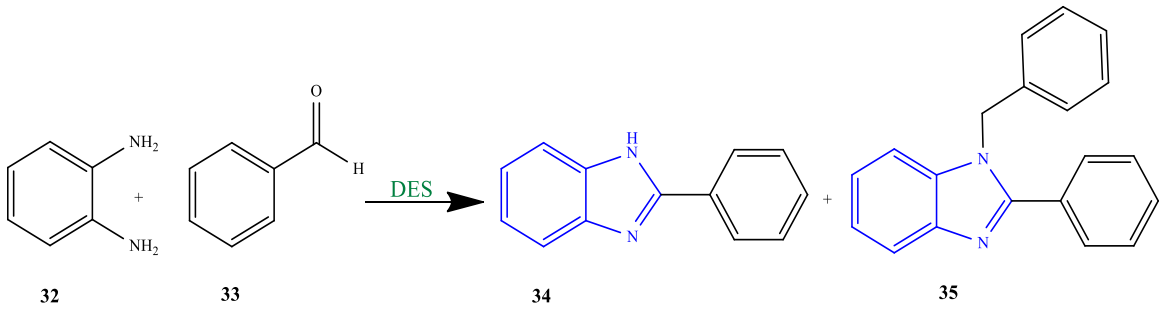
Green Synthesis of the Benzimidazole derivatives.

The condensation of O-phenylenediamine (29) and Aldehydes (30) leads to Benzimidazoles (31). The direct condensation results a complex intermediate, to overcome this problem a simple green synthesis was done by using [(MOEI)-BSA] as a catalyst (28) and water as green solvent (scheme 7). The best results occur in presence of media contains 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]



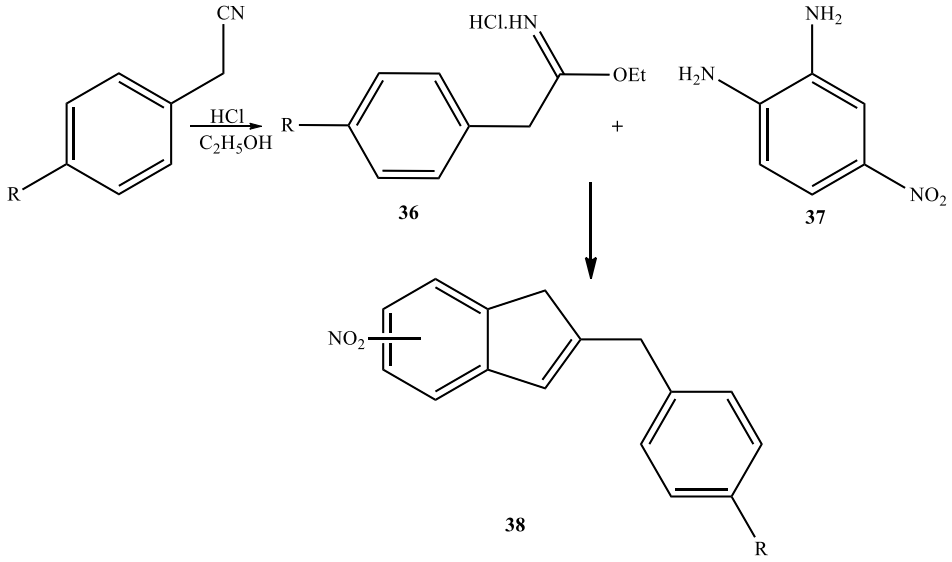
Scheme 7

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) a DES, which is highly economic, biodegradable and non-toxic.The equimolar reaction between O-phenylenediamine (32) and an Aromatic aldehyde (33) in DES at 80^0C shows the best yield. The optimised ratioof O-PDA: Benzaldehydeshows the 80% yield within 10 min of time. [19]



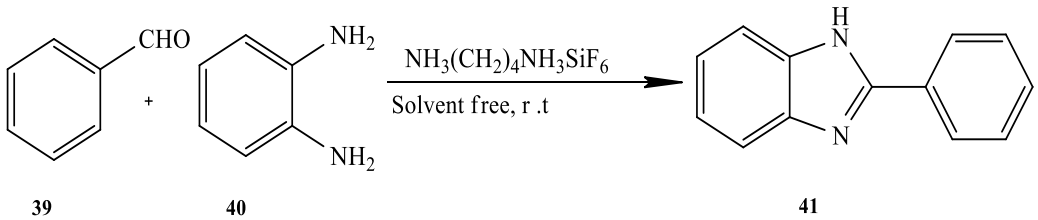
Scheme 8

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



Scheme 9

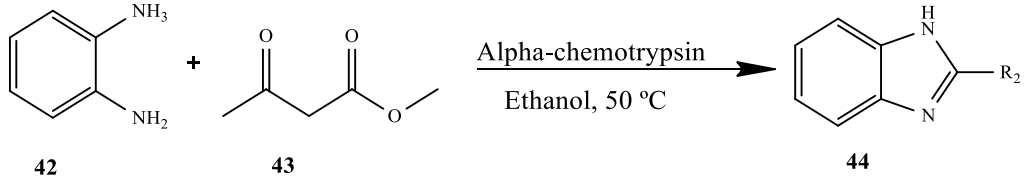
A direct condensation of the 1, 2-phenylene diamine (39) and Benzaldehyde (40) leads different Benzimidazole derivatives (41). A hybrid compound $NH_3(CH_2)4NH_3SiF_6$ was used as heterogeneous solid catalyst, yield around 93% of product within a 14 min of time. The optimised conditions at 1 mol% of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



Scheme 10

A retro-Claisen reaction 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 etahanol allows the reaction to proceed with a best yield within a short period of time. A higher yield of 93% was obtained at 50°C in 18 h. The optimum temperature (50^{0}C) avoids the energy consumption and deactivation of the

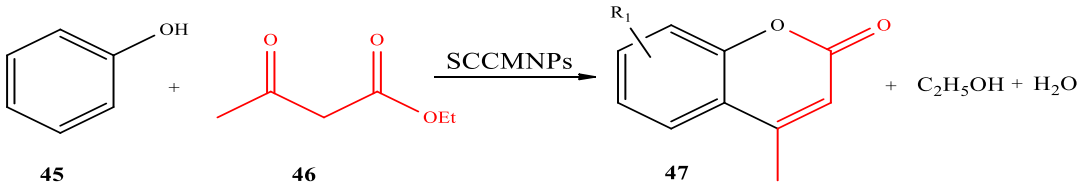
enzyme. The recovered catalyst was recycled for further more reactions. [22]



Scheme 11

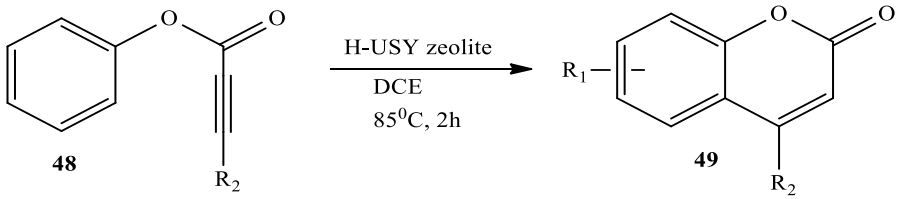
Green Synthesis of the Coumarin Derivatives

4-hydroxy methyl coumarins (47) were synthesised 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 optimised amount of 6.5mol% of the catalyst at 120^0 C for 20 min yields 98% of the coumarin.[23]



Scheme 12

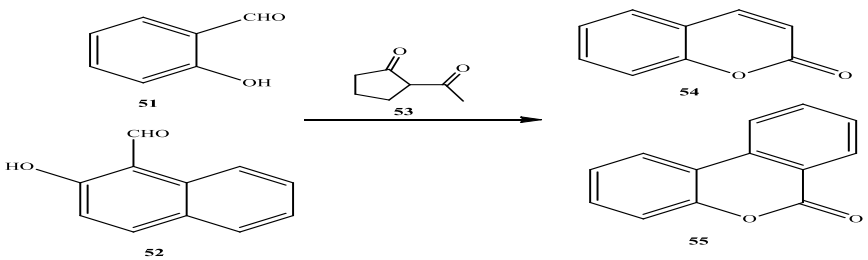
A well-established green synthesis of the Coumarins (49) was carried out by the cyclisation of the Aryl-propynoates (48) in 1, 2-dichloroethane at 85°C for an hour. The maximum conversion of about 55% with high yield of 40% occurs by the use of an acidic Zeolite (CBV 720) with a Si/Al ratio of 2:1. This ratio found best among the different type 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]



R1= -H, $-CH_3$, $-OCH_3$ R2= $-C6H_5$

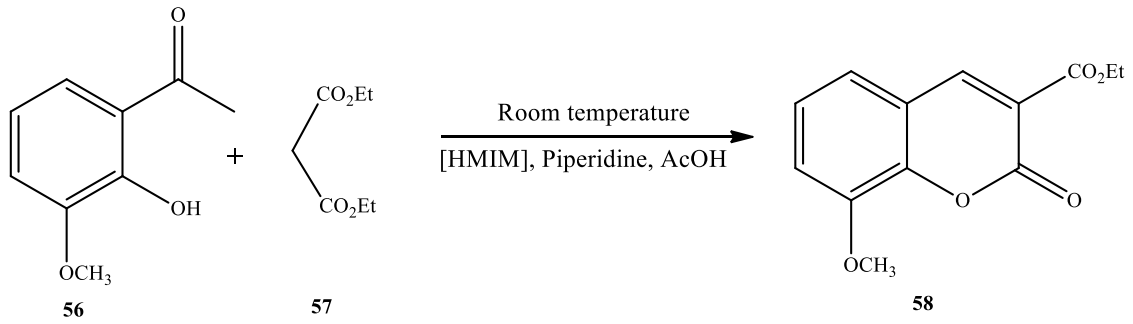
Scheme 13

Coumarins (54) and Benzocoumarins (55) were synthesised by microwave assisted Knoevenagel condensation of the various Salicylaldehydes (51) and 2-hydroxy-1-naphthaldehyde (52) with Dicarbonyl (53) derivatives. These reactions carried both under the solvent and solvent free conditions. The optimised reaction occurs by 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 synthesised by 2-hydroxy-3-methoxy benzaldehyde (56) and diethyl malonate/malononitrile (57) in 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 span of time.[26]

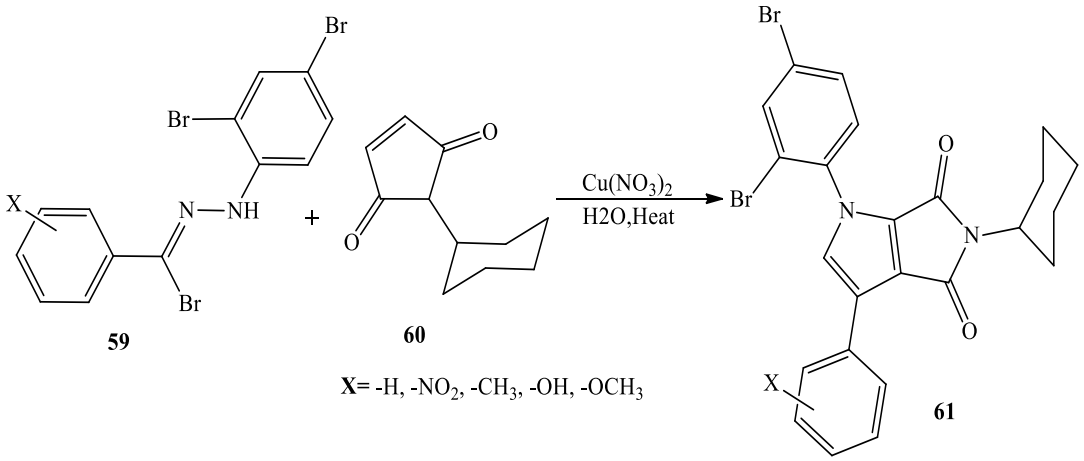


56 57 58

Scheme 15

Green Synthesis of the Pyrazoles

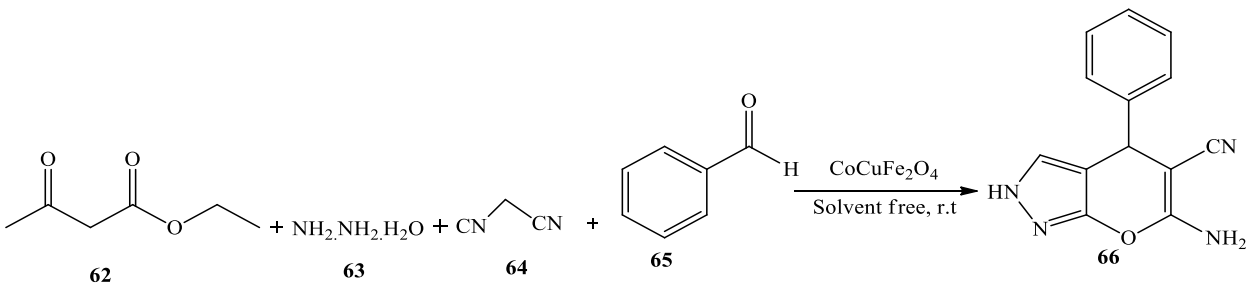
Pyrrolo-pyrazoles (61) were synthesised by the Hydrazonyl bromides (59) and N-cyclohexylmaleimide (60). This reaction completed by using different Lewis acid catalysts in an aqueous medium. A green catalyst, $Cu(NO_3)_2$ shows the best result (84%) among different Cu^{+2} salts in water. [27]



59 60 61

Scheme 16

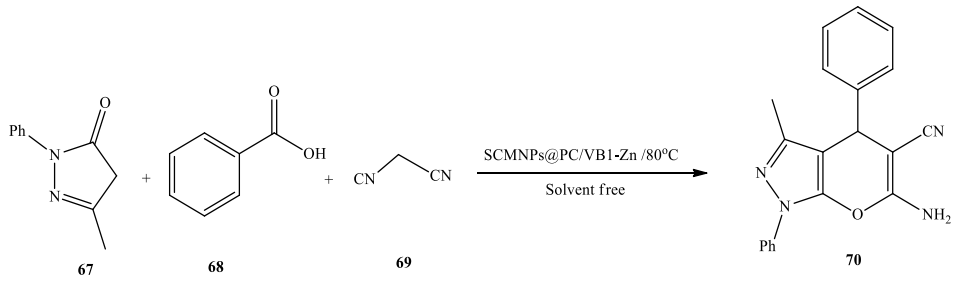
A multicomponent reaction between Ethyl acetoacetate (62), Hydrazine hydrate (63), Malononitrile (64) and 4-Nitrobenzaldehyde (65) performed for the synthesis of the different Pyranopyrazoles (66). This complete reaction was catalysed by the Cobalt-copper ferrite nanoparticles ($CoCuFe_2O_4$) at room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



62 63 64 65 66

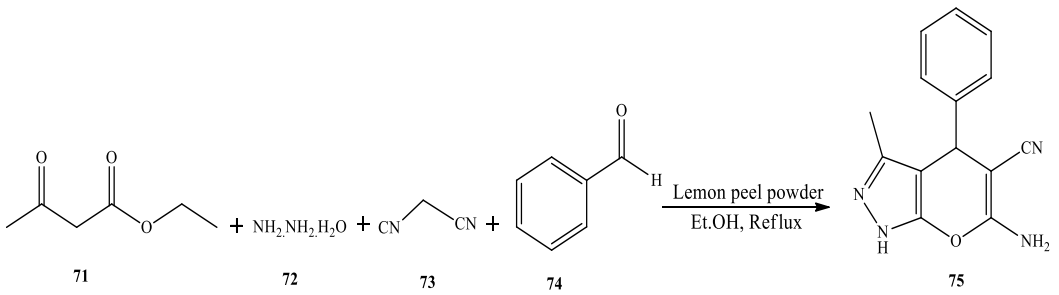
Scheme 17

Pyranopyrazole (70) derivatives were synthesised by the condensation of 3-methyl-1-phenyl-1H-pyrazol-5-one (67), Aromatic aldehyde (68) and Malononitrile (69). This complete green reaction was carriedby using silica-coated magnetic nanoparticles bonded at PC/VB1-Zn (P: 3-Chloropropyltriethoxysilane, VB1: Vitamin B1, Zn: Zinc) in solvent free condition. The optimised reaction occurred at 10mg of the catalyst with 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]



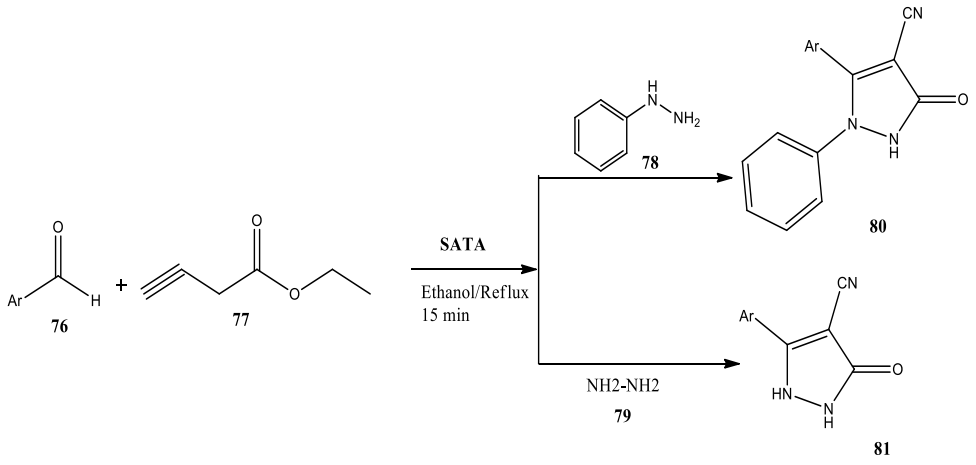
Scheme 18

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 catalysed by the lemon peel powder as a green catalyst to obtain a better yield. The optimised reaction occurs at 10wt% of catalyst in ethanol under reflux condition. [30]



Scheme 19

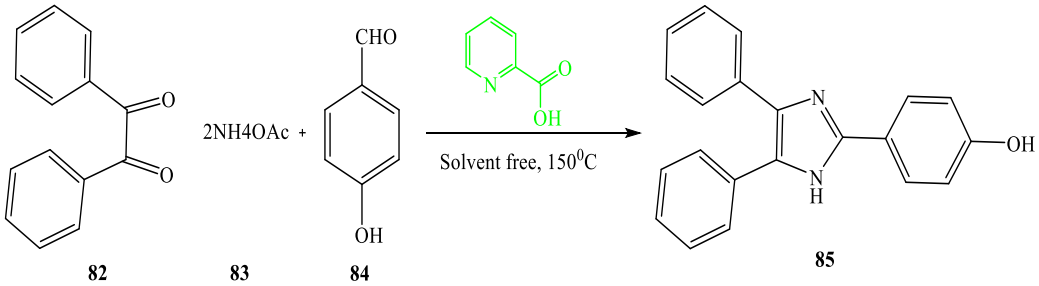
A series of Pyrazole-carbonitrile (80, 81) derivatives were synthesised by an acid catalysed reflux condensation of Aromatic aldehydes (76), Ethylcyanoacetate (77), Phenyl hydrazine (78) /hydrazine hydrate (79) in alcohol. Among different acids sulphated alumina tungstic acid (SATA) shows best yield in ethanol. The optimised reaction condition shows 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

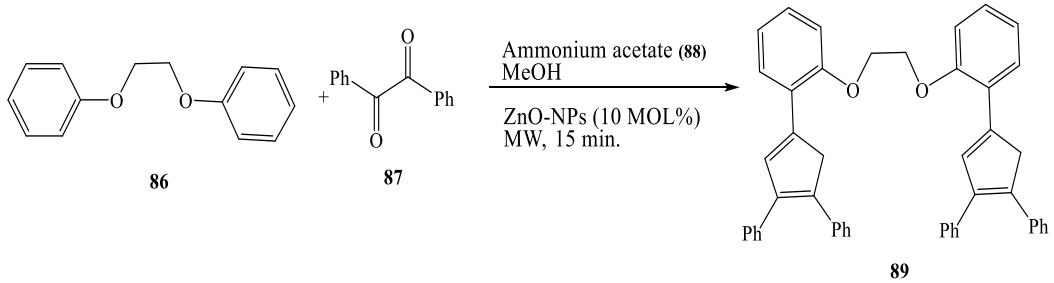
A one pot synthesis of the 2,4,5-trisubstituted imidazole (85) derivatives was carried by the direct condensation of the substituted Aromatic aldehydes (82), Benzil (83) and Ammonium acetate (84). In this reaction Pyridine-2-carboxlic acid (0.5 eq) used as a catalyst among other acids. The optimised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



82 83 84 85

Scheme 21

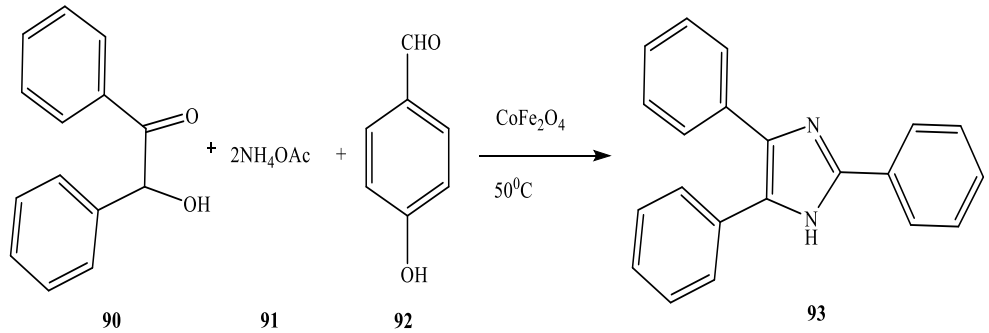
A one pot synthesis of the Bis- and poly-imidazoles (85) was carried by three different methods. In these methods, the one pot reaction between 1,2-diketone (87), Aldehydes (86) and Ammonium acetate (88) with a catalytic amount of ZnO-Nanoparticles in methanol show better yield. The optimised reaction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



86 87 89

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 catalysed 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]



90 91 92 93

Scheme 23

CONCLUSION

Green synthesis makes the medicinal chemist to derive a conclusion for the establishment of bioactive molecules in short of time. Conventional methods too , provides us the plat form for the synthesis of molecules , but amount of time , energy as well as exposure of reaction vapours with environment is comparatively very high and hereby risk of emission of pollutant. Keeping these environmental factors, pharma industries are applying green synthesis techniques to minimize the usage of solvents. World over there are rapidly growing activities in governments,

industries and academia in promoting green chemistry and offsetting carbon footprints.

Abbreviations

Dmad: Dimethylacetylenecarboxylate
(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
$CoFe_2O_4$: Nano sized Cobalt ferrite
ZnO: Zinc oxide

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