



ECO-FRIENDLY MULTICOMPONENT REACTION SYNTHESIS OF MOST PRIVILEGED PYRANO[2,3-C] PYRAZOLE DERIVATIVES: A REVIEW

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ABSTRACT: The pyran derivatives particularly, pyranopyrazole and pyranochromene are the important heterocyclic compounds, widely observed in natural product and biological systems of importance. The number of biological and medicinal properties of the heterocyclic pyran derivatives has attracted the interest of researchers and various synthetic methodologies have been reported in literature with numerous variations in catalyst and solvent systems. The review covers the study of the one-pot, multicomponent reactions (MCRs) synthesis of the pyranopyrazole derivatives to focus the present environment benign advancement in the field.

KEY WORDS: Multicomponent reactions; pyrano[2,3-c]pyrazole; catalyst-free; solvent-free; eco-friendly; aqueous medium synthesis; metal nanoparticles.

INTRODUCTION:

Heterocyclic compounds are widely found in natural products and exhibits an array of different biological and pharmaceutical properties. The pyranopyrazole derivatives are the fused heterocyclic compounds represents an interesting template for biologically active compounds in medicinal chemistry ⁱ. It is a fused heterocyclic compound consisting of five membered pyrazole and six membered pyran ring which are fused in four different ways and pyranopyrazoles exhibits four different isomers ⁱⁱ. Thepyrano[2,3-c] pyrazoles (**1**), pyrano[3,2-c] pyrazoles (**2**), pyrano[3,4-c]pyrazoles (**3**) and pyrano[4,3-c] pyrazoles (**4**) (Fig. 1).

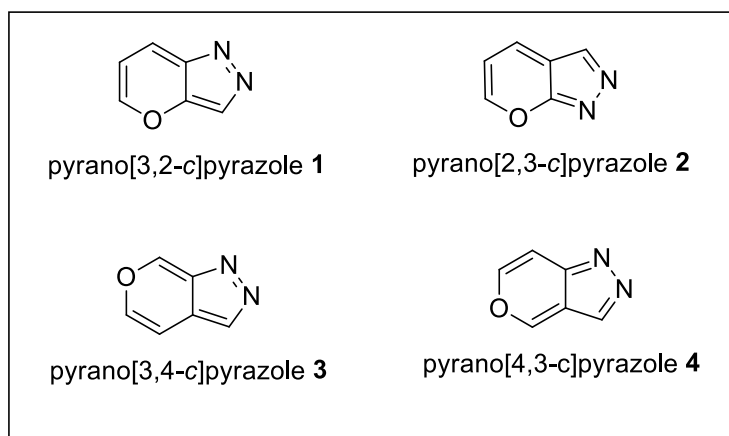


Fig. 1. Pyranopyrazole isomers

The pyrano[2,3-c] pyrazole (**1**) is the most important scaffold for the construction of bioactive derivatives among the four isomersⁱⁱⁱ. The polyfunctionalized pyranopyrazole nucleus occurs in many natural products^{iv}. The pharmacological and biological properties of pyranopyrazoles play an important role in medicinal field and precursors in drug discovery process^v. The derivatives of pyrano[2,3-c] pyrazole (**1**), shows numerous and wide range of biological activities such as antimicrobial (**5**)^{vi}, anti-inflammatory, analgesic (**6**)^{vii}, anti-cancer, antioxidant^{viii}, Chk1kinase inhibitor (**7**)^{ix} (Fig. 2), anti-coagulant, spasmolytic, diuretic^x, molluscicidal^{xi}, DNA binding^{iv}, cognitive enhancer, anti-HIV^{xii}, bovine brain adenosine receptor^{xiii}, photoactive material^{xiv} and biodegradable agrochemicals^{xv}.

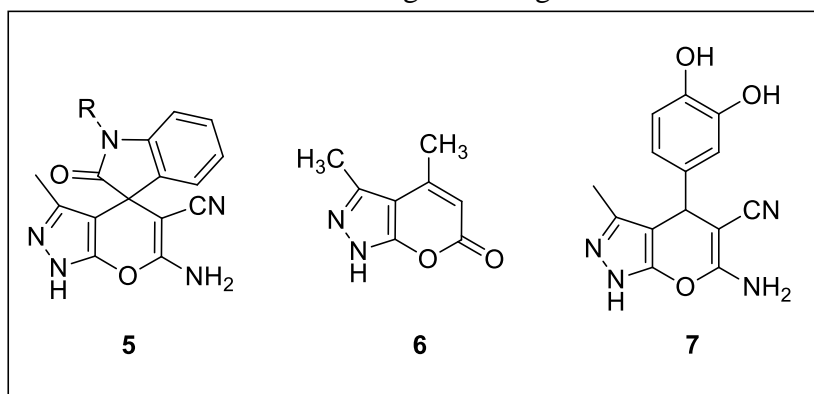


Fig. 2. Bioactive pyranopyrazole derivatives

The derivatives also find applications as fungicidal, herbicidal, and insecticidal activity in agrochemicals^{xvi}. Besides the pharmaceutical importance and agrochemicals pyranopyrazole derivatives are valuable heterocyclic compounds due to their commercial applications in cosmetics, dyestuffs, and food colouring industry^{xvii}.

The constitutes of natural products and an immense biological value of heterocyclic compounds, the synthesis of these compounds has always been among the most important research areas of synthetic and natural product chemistry^{xviii}. In this context, the design of the eco-friendly synthetic route to heterocyclic scaffolds of medicinal relevance that combine synthetic efficiency of green multicomponent reaction (MCRs) protocol with taking care of environment constitutes a very important challenge for green chemistry^{xix}.

The introduction of “Green chemistry” concept revolutionizes the way to carried out chemical reactions. The conventional way of doing chemical reactions by way of using non-aqueous solvents, high reaction temperature, longer reaction pathways, harsh reaction condition with generation of huge amount of waste are no longer be accepted due to environment concern. In many cases the usual syntheses provide reliable access to these scaffolds, however they are

simply no longer justified by current environment and safety standards [18]. Therefore, developments of sustainable alternative route to conventional methods are in high demand^{xx}. Many otherwise “known” reactions have been reinvestigated by green alternative routes^{xxi}.

The one-pot multicomponent reaction (MCRs) synthesis using green solvent and catalyst of desire product in single operation from three or more reactants molecules without exposure to toxic environment has been established beyond doubt^{xxii}. With the emphasis on the development of green reactions, organic reactions in water, aqueous ethanol is getting a lot of importance, due to advantages such as safety, cost, and easy product separation over conventional organic solvents^{xxiii}. Conceptually, one-pot, MCRs are potential candidates for the use of water as a solvent with or without surfactants since the multiple hydrophobic reactants are brought in closer proximity due to hydrophobic interactions such as enhanced hydrogen bonding in the transition state^{xxiv}.

Green MCRs are proved to be the best available methods for constructions of the biologically active scaffolds with number of advantages over the conventional multistep reaction^{xxv}. The environmental benign feature of the multicomponent reactions and diverse biological activities associated with pyranopyrazole derivatives, number of green MCRs synthetic routes have been reported in literature^{xxvi}.

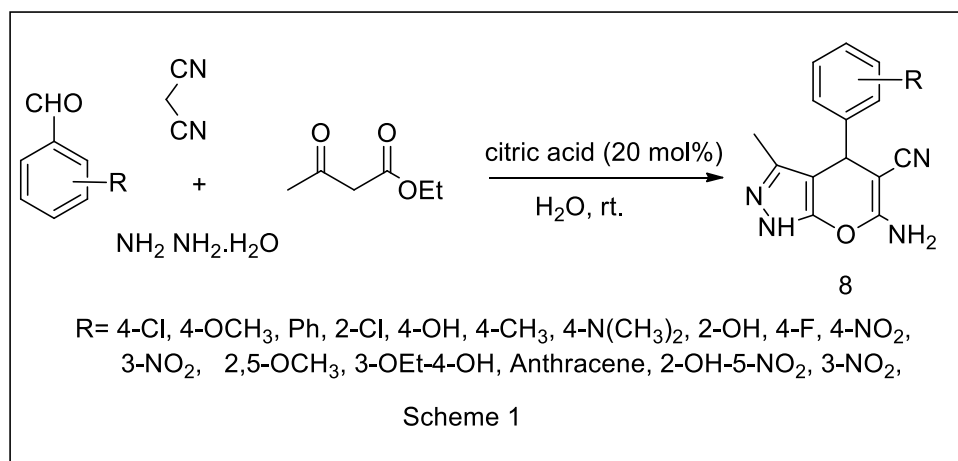
The most variations are in search of sustainable solvents and catalysts, such as use of water, green co-solvent, ethanol, polyethylene glycol (PEG), glycerol and ionic liquids (ILs) green catalyst, organocatalyst, biocatalyst and heterogeneous catalysts such as nanoparticles (NPs), clay, and heteropolyacids (HPA). ILs have emerged as a green solvent and catalyst performing dual role in organic synthesis due to their unique properties such as good solubility of organic and inorganic compounds, tunable polarity, immiscible with number of organic solvents^{xxvii}, recycled and reuse with easy isolation of products by filtration^{xxviii}. The eco-friendly nature of transition metal NPs and focus on development of environmentally benign reagents and catalysts, in recent years solvent-free and water mediated MCRs involving eco-friendly catalysts have gain importance^{xxix}.

This review article focuses on eco-friendly synthesis of amino, carbonitrile functionalized pyranopyrazole derivatives in view of recent published literature. To the best of our knowledge, it is the first review article devoted to eco-friendly synthesis of these heterocyclic derivatives.

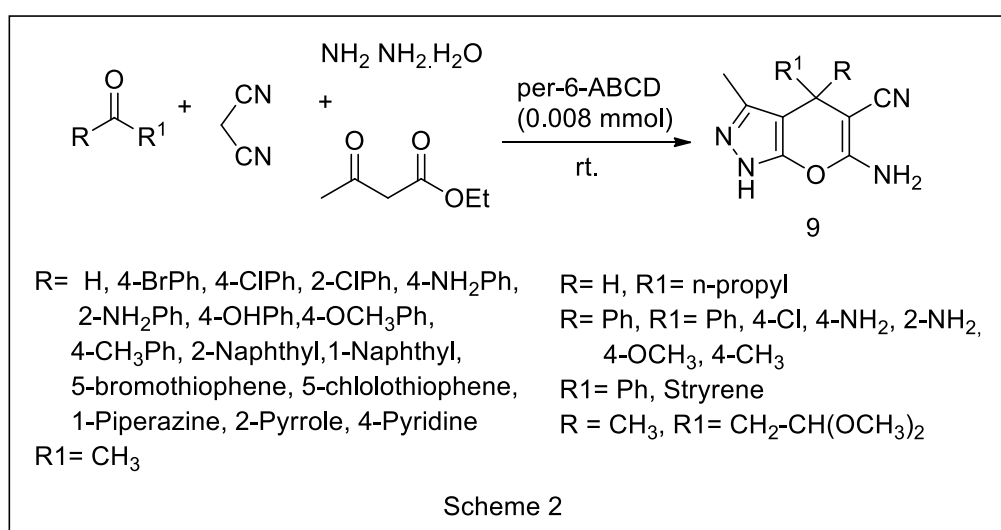
ORGANO AND BIOCATALYSTS:

The number of efficient MCRs synthetic protocols has been reported using various organocatalysts and biocatalysts for the synthesis of pyranopyrazole derivatives in green solvents such as water, aqueous ethanol at room temperature (rt.) and under reflux condition in short reaction time. The competent use of organocatalysts in MCR synthesis of pyranopyrazole derivatives are discussed in section below.

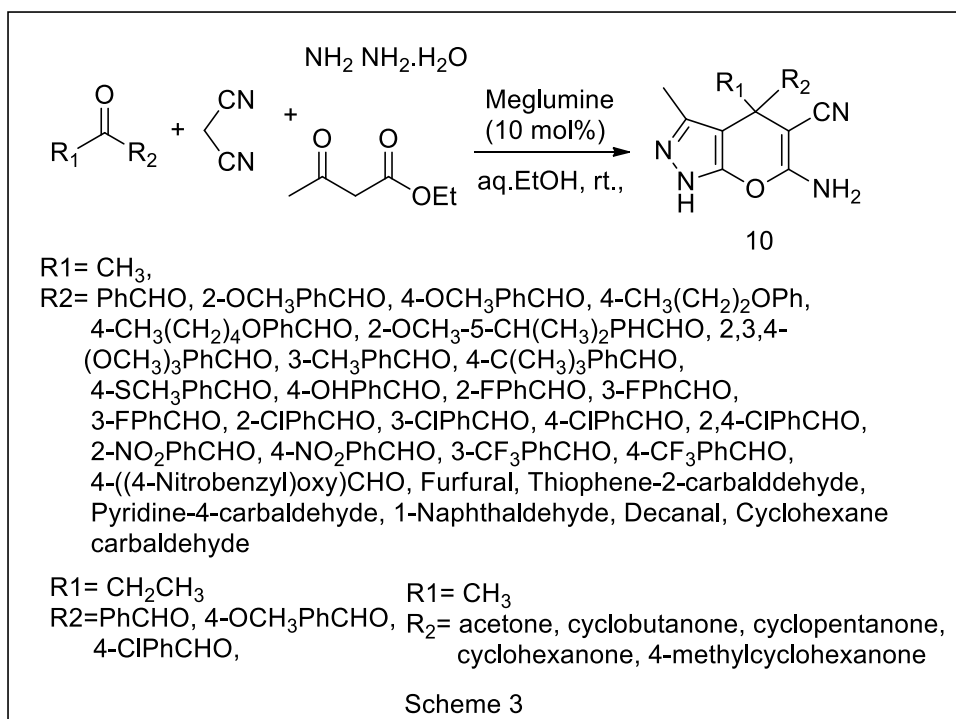
P. B. Pawar et al. reported the successful applications of inexpensive, readily available, and mild organocatalyst, citric acid by four components MCR in water. The equimolar reaction mixture of aldehyde, malononitrile, hydrazine hydrate, ethyl acetoacetate, with citric acid as homogeneous catalysts in co-solvent gave various pyranopyrazole derivatives **8**, in good yields^{xxx}. [Scheme 1]



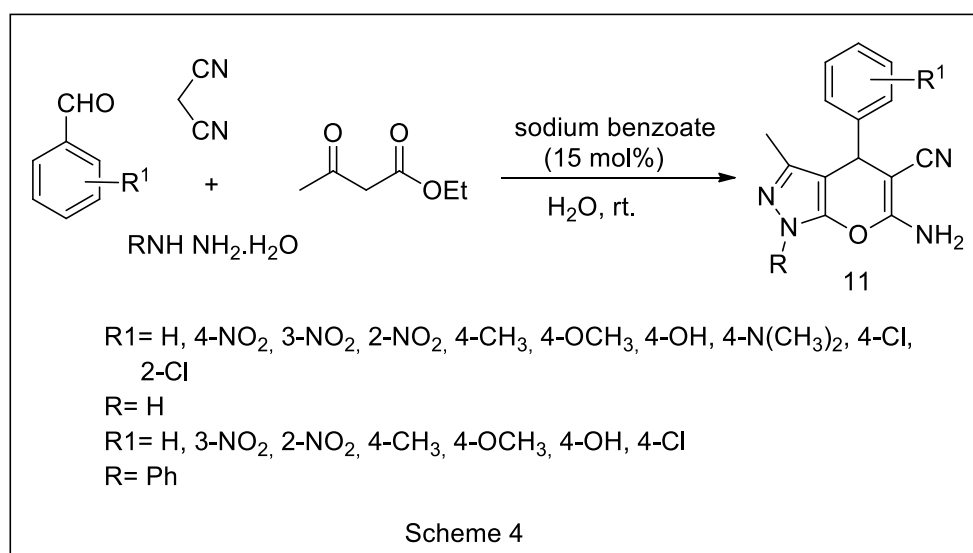
K. Kuppusamy et al. reported novel organocatalyst modified β -cyclodextrin, per-6-amino- β -cyclodextrin (per-6-ABCD) as an efficient supramolecular host and base catalyst for the synthesis of pyranopyrazoles. Per-6-ABCD is known to catalyze a wide range of chemical and photochemical reactions. The four components MCR of aldehyde, malononitrile, hydrazine hydrate, and ethyl acetoacetate, have been carried out in the presence of TEA, diethylamine, methylamine, and piperidine in solvent-free conditions but gave low yields. In DMF and DMSO also no yield improvement was seen while surprisingly in the presence of per-6-ABCD 100% yield is obtained on mixing the reactants and catalyst in solvent-free conditions. The pyranopyrazole derivatives **9**, obtained in excellent purity with no need of purification, this adds to the greenness of this method^{xxxii}. [Scheme 2]



R-Y. Guo et al. reported a related four-component MCR using natural amino-substituted sugar Meglumine. In search of a green reaction condition for the synthesis of pyranopyrazole derivatives **10**, from a carbonyl compound, malononitrile, hydrazine hydrate, and β -keto ester, in aq. ethanol reaction, meglumine was found an efficient catalyst. The catalyst after completion of the reaction was recovered from the filtrate, washed with diethyl ether, and dried to use in the next run. The authors beautifully harness the property of the amino group of meglumine as observed in per-6-ABCD showing electrostatic binding property of the pendant amino group^{xxxiii}. [Scheme 3]

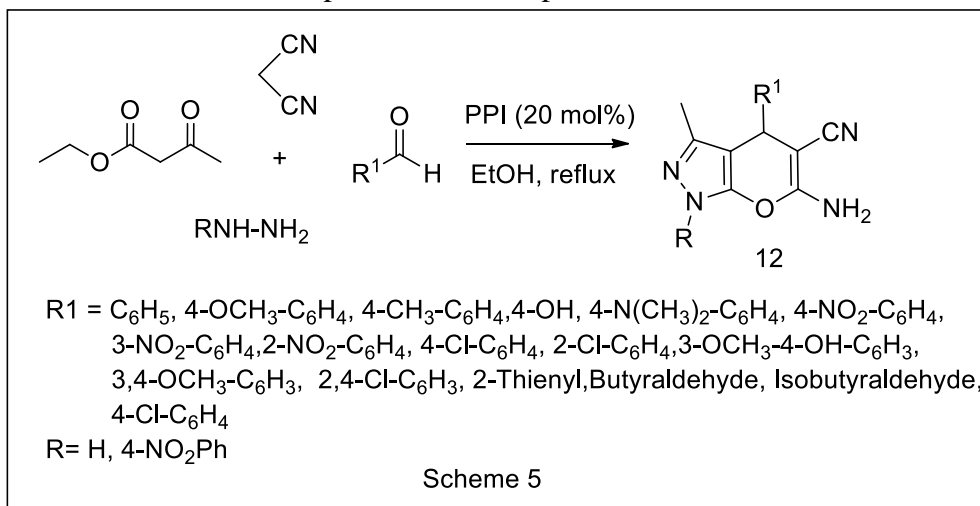


H. Kiyani et al. reported the synthesis of pyrano[2,3-c]pyrazoles catalyzed by sodium benzoate in water. The use of sodium benzoate as an eco-friendly organocatalyst has been reported in the synthesis of cyclic ketones, isoxazol-5(4H)-ones and substituted olefins. The four components MCR involving aryl aldehydes, malononitrile, substituted hydrazine hydrate and ethyl acetoacetate, takes place well in polar aqueous medium. The authors reported that reaction is slightly affected by nature and electronic effects of aryl aldehydes, electron donating group increases rate of reaction and yields than electron withdrawing groups. The MCR is simple in workup and products **11**, separate out from the aqueous medium by only filtration^{xxxiii}. [Scheme 4]

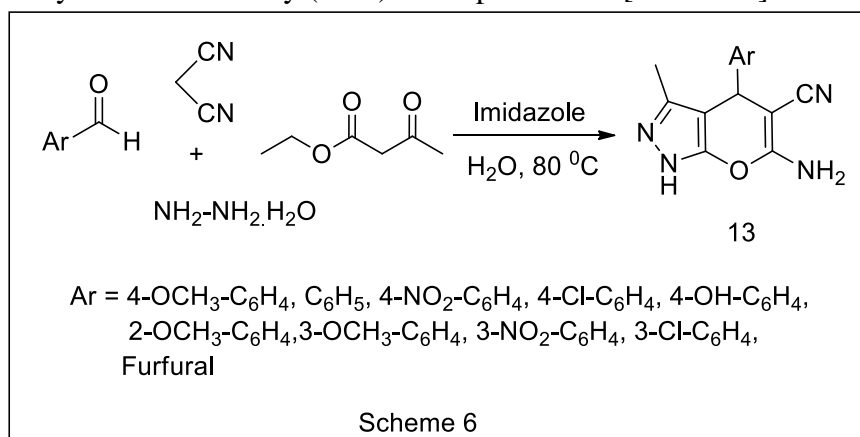


H. Kiyani et. al. further reported a four component MCR protocol using potassium phthalimide (PPI), as a mild, green, recyclable organocatalyst for the synthesis of 1,4-dihydro-pyrano[2,3-c] pyrazoles derivatives in ethanol. Under the optimized reaction condition, PPI (20 mol%) in

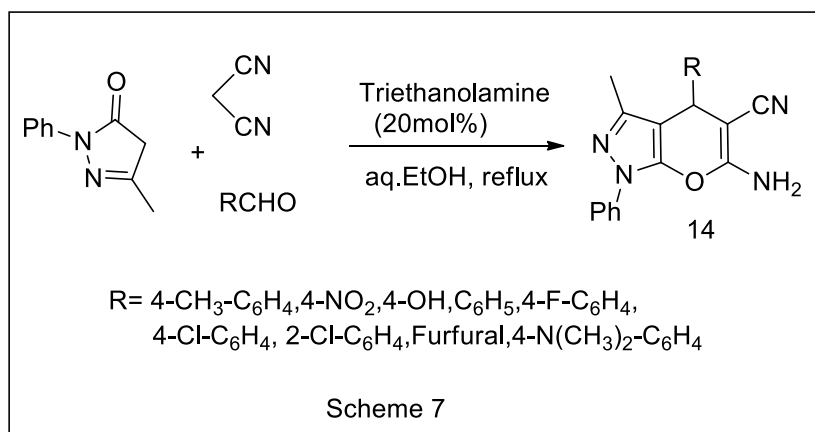
refluxed ethanol the various aldehydes, ethylacetoacetate, malononitrile, and substituted hydrazine hydrate, gave excellent yields of the product for aromatic and heteroaromatic aldehydes while in case of cyclic ketones and use of substituted hydrazine instead of hydrazine hydrate the yield obtained below 30%. In a simple work-up procedure, water was added to the cooled reaction mixture which separates out solid products^{xxxiv}. **12** [Scheme 5]



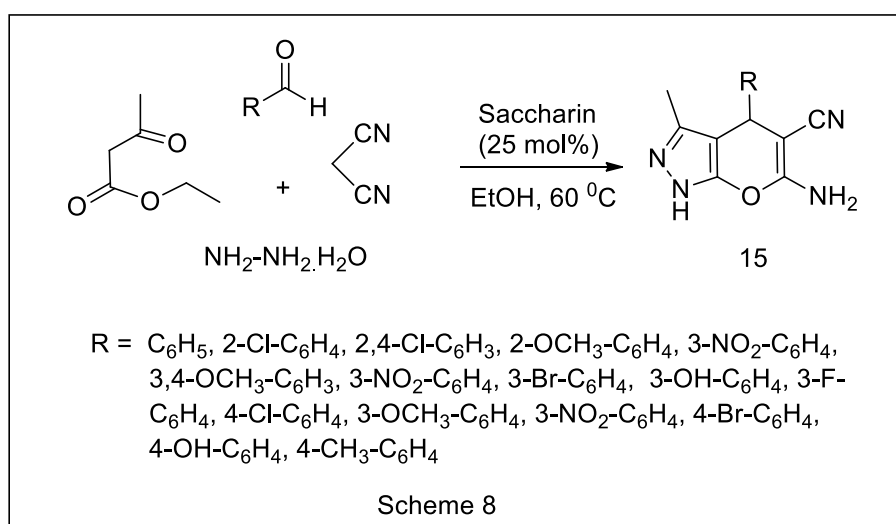
A. Siddekha et al. explored imidazole as an organocatalyst in aqueous medium for the synthesis of pyranopyrazoles by a simple, green MCR. The reaction took place well in few min. with excellent yields of the desired derivatives when various aromatic aldehyde, malononitrile, ethyl acetoacetate, hydrazine hydrate, and imidazole in water heated to 80 °C on hot plate. The frequency and intensity of IR bands of the selected pyranopyrazole derivatives **13**, have been studied by density functional theory (DFT) and reported^{xxxv}. [Scheme 6]



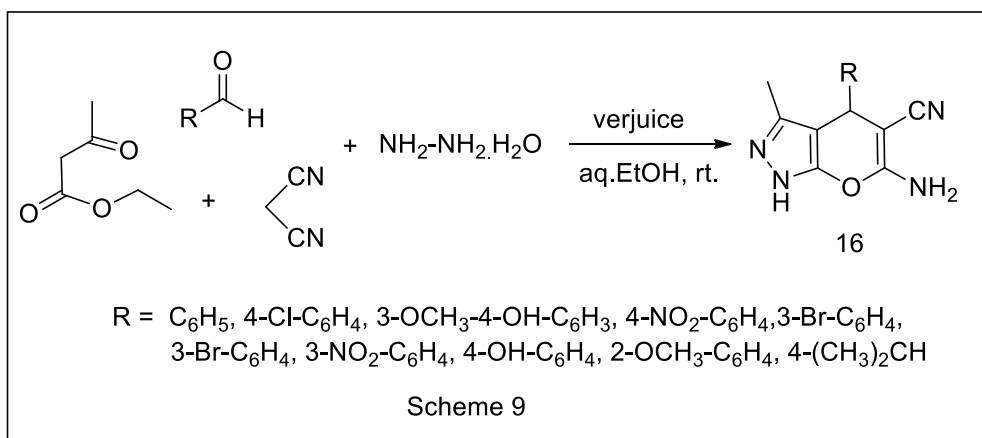
J. P. Sonar et al. successfully attempted an efficient, rapid, and green methodology for the synthesis of pyranopyrazole derivatives using triethanolamine as a catalyst in aqueous medium. Its application in synthesis such as ligand for copper ion, as a reaction medium in presence of L-proline as a catalyst in coumarin synthesis and as a catalyst in synthesis of pyran derivatives have been reported in the article. The substituted aromatic aldehydes, malononitrile, 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one and triethanolamine were stirred in ethanol-water (1:1) solvent and to stirred reaction mixture triethanolamine (20 mol%) was added and heated to 90 °C. The reaction procedure is short, simple, and solid product **14**, obtained in 15-20 min^{xxxvi}. [Scheme 7]



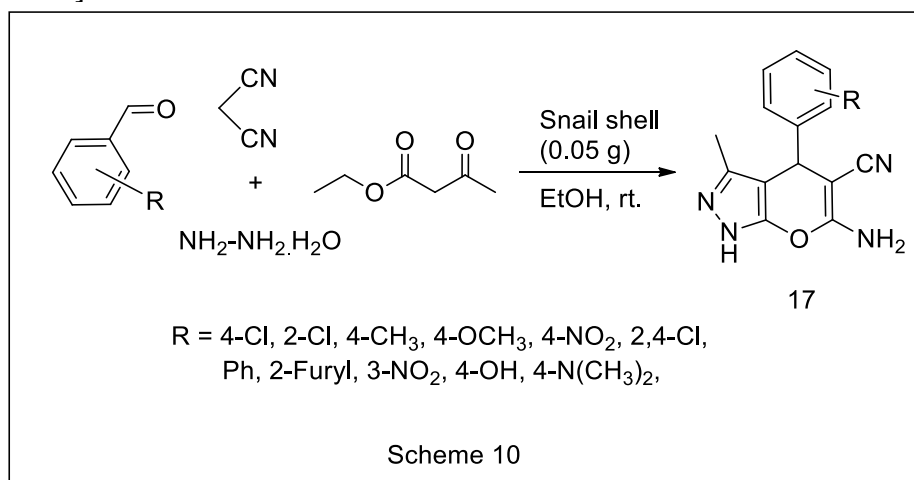
F. Mohamadpour et al. developed expedient and convenient MCR using saccharin as a catalyst in ethanol for the synthesis of series of pyranopyrazoles **15**, benzopyran and pyranopyrimidinone derivatives. The short reaction time, mild reaction condition and easy workup are the features of the protocol. In a simple reaction procedure saccharin (25 mol%) was added to reaction mixture of aromatic aldehyde, ethyl acetoacetate, malononitrile, and hydrazine hydrate, which heated to 60 °C for 10-35 min^{xxxvii}. [Scheme 8]



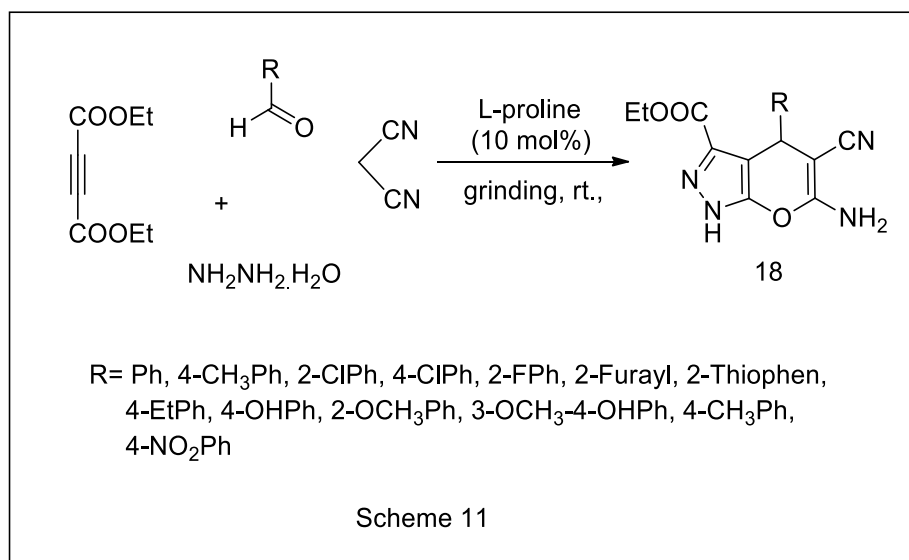
M. Mokhtary has explored unripe grape juice (verjuice) as a biocompatible natural acid catalyst for the synthesis of pyranopyrazole **16**, and quinoline-3-carboxamide derivatives at rt. The green MCR involving aromatic aldehyde, ethyl acetoacetate, malononitrile, hydrazine hydrate, and verjuice (5 drops) in ethanol-water at rt. was stirred for 15-35 min. The procedure for the preparation of verjuice was reported which has pH 2.^{xxxviii}. [Scheme 9]



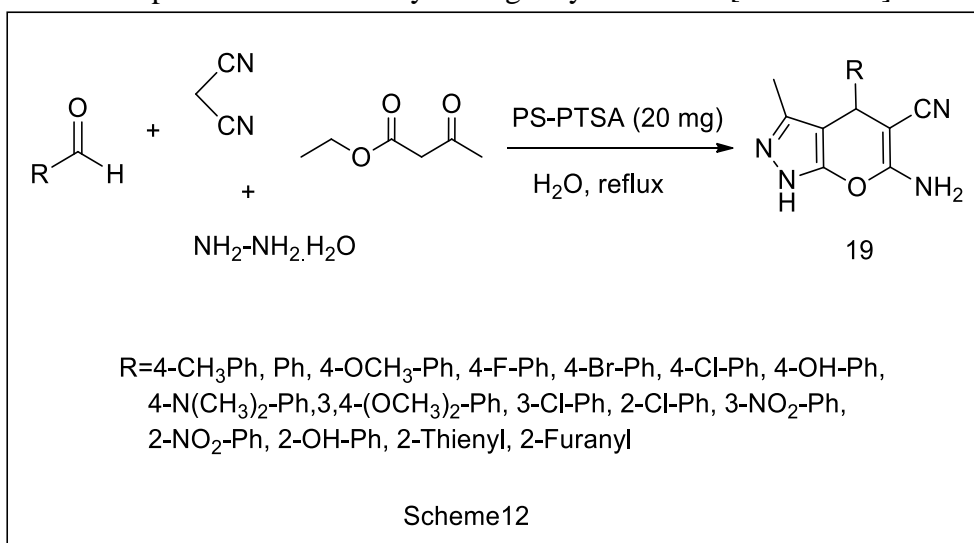
Z. Benzekri et al. reported Snail shell as a biocatalyst for the synthesis of pyranopyrazole derivatives. Snail shells composed of aragonite, which is most common crystalline form of calcium carbonate, catalyzed the Knoevenagel condensation reaction of malononitrile, and aldehyde, and Michael addition reactions of intermediates, arylidenemalononitrile and 3-methyl-5-pyrazolone which form from ethyl acetate, and hydrazine hydrate. The catalyst was prepared by drying shells at 100 °C for 24h and crushed into soft power. The white, soft power was used as such as a catalyst without calcination. The authors observed good catalytic activity of the catalyst and suggested to avoid calcination. The MCR took place in ethanol at rt. with excellent yields of the products **17**, as compared to number of reports cited in research article ^{xxxix} [Scheme 10].



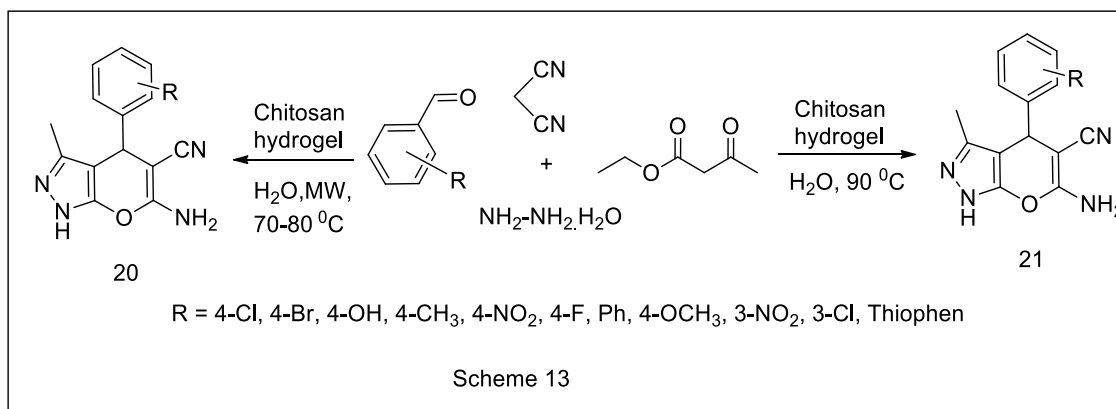
S. Ambethkar et al. 2015 reported green, facile, and efficient synthesis of pyranopyrazole derivatives using L-proline (10 mol%) as a catalyst under solvent-free by grinding method. In one-pot reaction, a mixture of aromatic aldehyde, and malononitrile, in presence of L-proline (10 mol%) grind for 2 min in mortar to this hydrazine hydrate, and diethyl acetylene dicarboxylate, were added and further grind until TLC shows completion of reaction. The reaction completed in 10 min with excellent yields of the derivatives **18**. The atom economy, short reaction time and high yields are the advantages of the protocol ^{xl} [Scheme 11].



M. A. Chaudhari et al. reported an eco-friendly, simple one-pot synthesis of pyranopyrazole derivatives using polystyrene-supported p-toluenesulfonic acid (PS-PTSA) as recyclable a heterogeneous catalyst. The reaction mixture of various aromatic aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate, in water in presence of PS-PTSA (20 mg) on refluxed gave desired derivatives **19**, in excellent yields in short reaction time. The catalyst recovered after completion of reaction by adding ethyl acetate ^{xli} [Scheme 12].



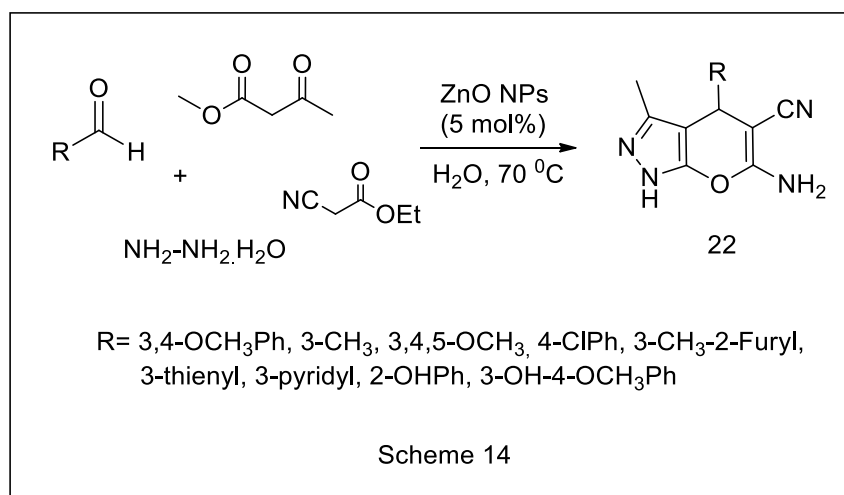
K. Patil et al. reported use of Chitosan hydrogel as a green and recyclable catalyst in aqueous medium for the synthesis of pyranopyrazole derivatives **20**, **21**, under conventional heating and MW methodologies in excellent yields. The reaction mixture of benzaldehyde, malononitrile, hydrazine hydrate, and ethyl acetoacetate, in water with Chitosan hydrogel (25 mg) was exposed to microwave power of 630W for 100 sec. While in conventional method the same reaction mixture stirred at 90°C for 1 h. The improvement in yield and short reaction time are the advantages of the MW method with green catalyst ^{xliii} [Scheme 13].



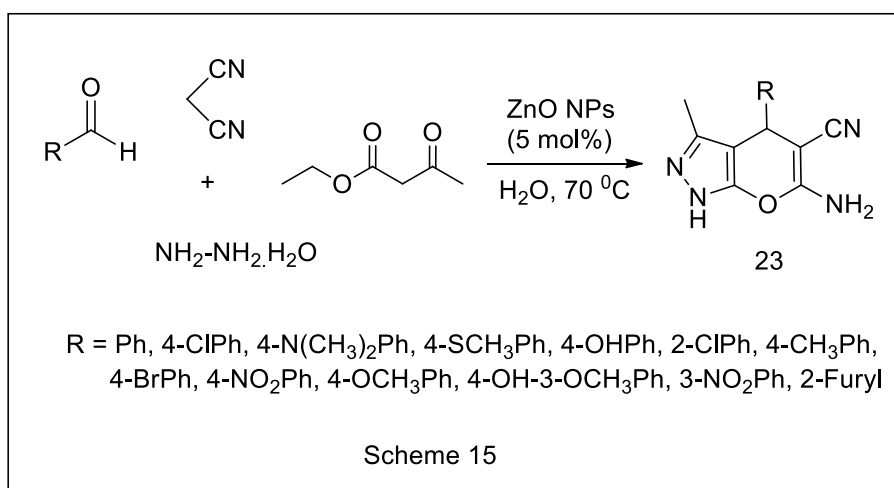
METAL NANOPARTICLES AS CATALYST:

In recent years, in search of green alternatives to reaction medium and environmentally benign catalysis, heterogeneous catalysts have received considerable importance in which nanoparticles become more popular because of their efficient, eco-friendly catalysis, short reaction time, excellent yields, reuse for number of run and easy recycling. Thus, green catalysis, MCRs took place in few minutes with high yields of the products mostly in green solvents. Below section highlights the efficient use of various NPs in MCR synthesis of pyranopyrazole derivatives.

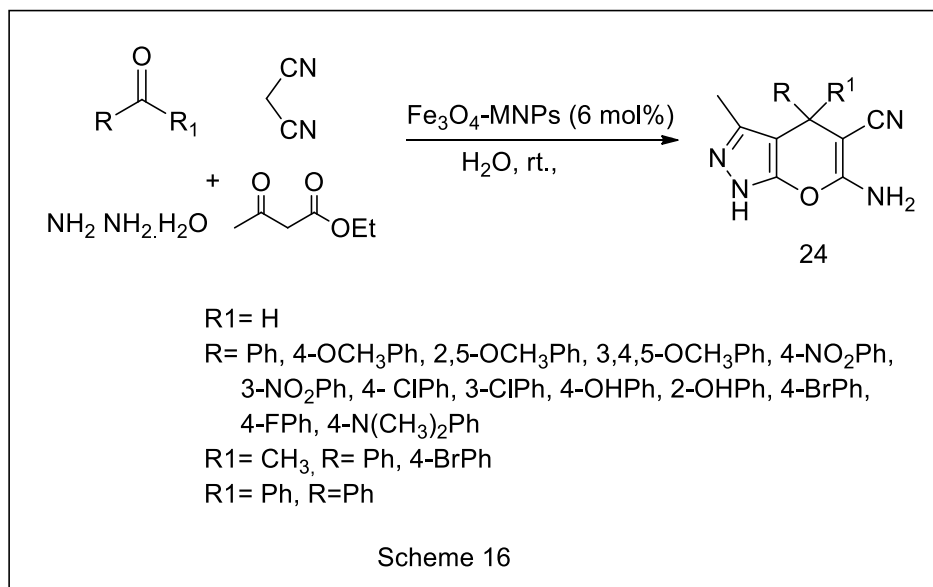
H. Sachdeva et al. reported ZnO NPs catalyzed green synthesis of 3-methylpyranopyrazole derivatives **22**, by using aldehydes, hydrazine hydrate, methyl acetoacetate, and ethyl cyanoacetate, as an efficient eco-friendly MCR in water with high yields. The authors reported preparation of ZnO NPs, taking zinc acetate ($\text{Zn}(\text{OAc})_2$) and potassium hydroxide in water^{xliii} [Scheme 14].



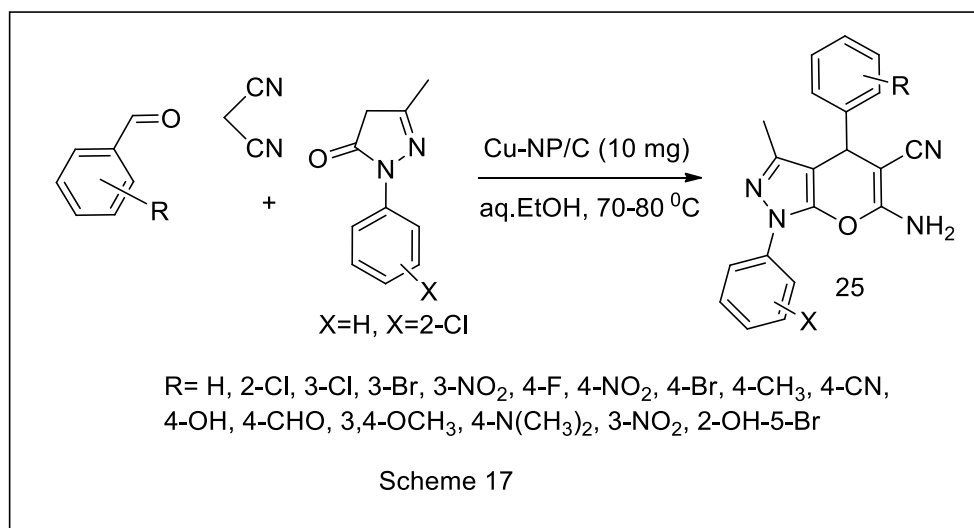
S. U. Tekale et. al. demonstrated similar an application of ZnO nanoparticles for green MCR synthesis of 6-amino-3-methyl-5-cyano-4-aryl-1,4-dihydropyrano[2,3-c]pyrazoles **23**, in aqueous medium. The author synthesized nano crystalline ZnO particles (NPs) and applied as a green heterogeneous catalyst for the four component MCR of various substituted aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate, in water at 70 °C. The reaction gave excellent yields of pyranopyrazole derivatives in short reaction time. The nature of substituent on aromatic aldehyde affects the yield of reaction, aldehydes having electron withdrawing substituent gave excellent yields of the derivatives. The ZnO NPs were characterized by TEM, XRD and FTIR analysis. TEM analysis shows particle size is in the range of 50-100 nm^{xliv}. [Scheme 15].



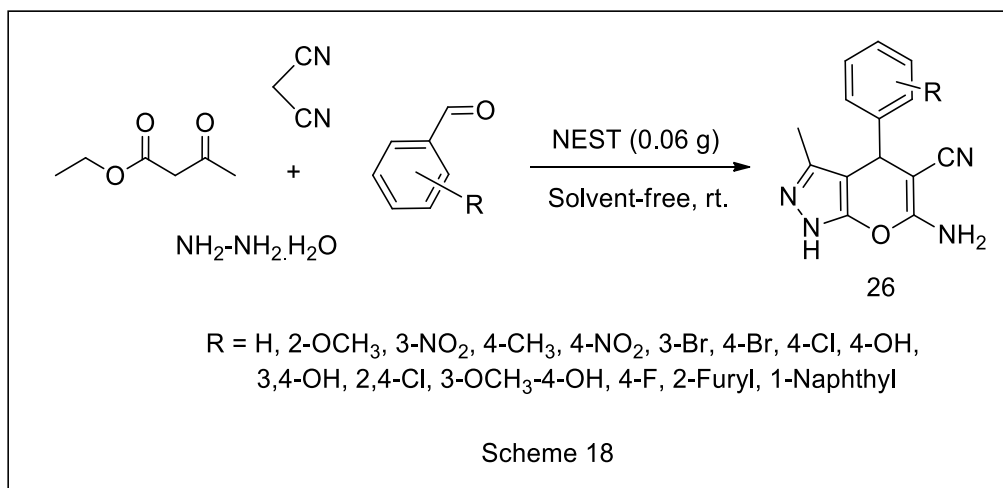
M. A. E. Aleem et al. reported a simple, rapid, room temperature MCR in water using magnetic Fe_3O_4 NPs. The magnetic NPs provide an additional advantage of recovery of the catalysts after reaction is over by means of an external magnetic field. The aqueous stirred mixture of aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate, and catalyst Fe_3O_4 MNPs gave the required derivatives **24**. The MNPs were prepared by coprecipitation method and were recovered from the reaction mixture by adding ethanol and separated using external magnet^{xlv} [Scheme 16].



N. S. Kaminwar et al. reported an eco-friendly methodology using copper nanoparticles grafted on carbon microsphere for the synthesis of series of pyranopyrazole derivatives **25**, in water-ethanol (1:1) solvent at 70-80 °C. The NPs are grafted on support to avoid self-aggregation under reaction condition which makes the protocol efficient in terms of catalytic activity, stability, and easy separation of NPs. The series of aryl aldehyde, malononitrile, and 1-phenyl 3-methyl pyrazolin-5-one, were refluxed in aq. ethanol solvent in presence of Cu-NP/C (10 mg) for short reaction time of 15-36 min^{xlvi}. [Scheme 17].



A. D. Tafti et al. recently a novel naturally based catalyst, nano-eggshell/Ti(IV) (NEST) was prepared and reported for the synthesis of dihydropyranopyrazoles **26**, to achieve high activity, selectivity and eco-friendly benefits. The NEST was obtained by simple addition of TiCl₄ to a suspension of eggshell (calcium carbonate 94%) in CH₂Cl₂ at room temperature. It was characterized by XRD, FE-SEM, EDX, FT-IR and TGA for its nature and thermal stability. The pyranopyrazole derivative obtained in excellent by four components MCR of aromatic aldehyde, ethyl acetoacetate, malononitrile, and hydrazine hydrate, in presence of NEST (0.06g) under solvent-free condition at room temperature in few min. The catalyst recovered from reaction mixture by adding acetone and filtration^{xlvi} [Scheme 18].

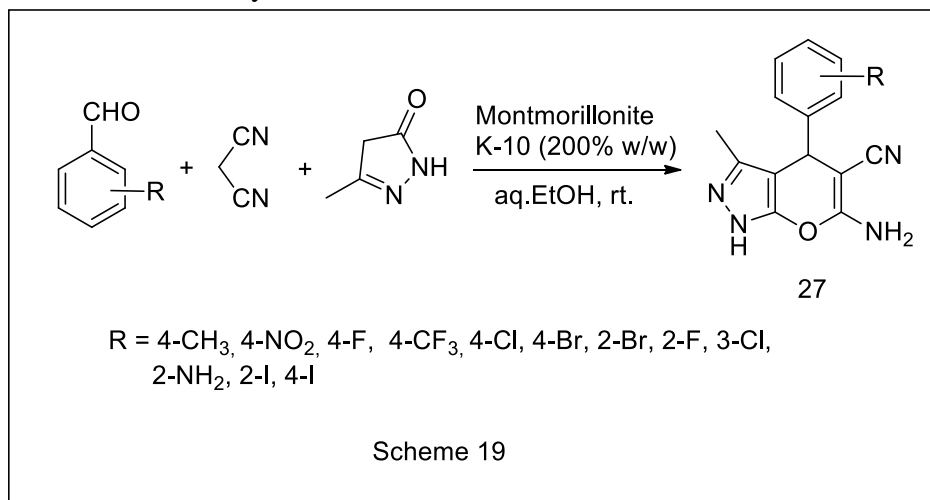


HETEROGENEOUS CATALYST:

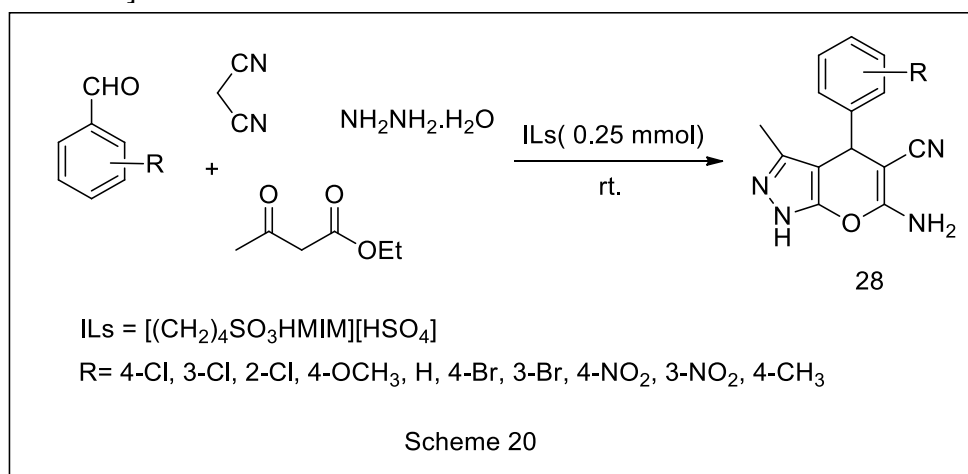
The heterogeneous catalysts such Bronsted acid, base and Lewis acid, bases is the another fascinating area of catalysis for the present day advancement in the green MCRs due to high catalytic activity, non-toxic nature, reusability and mild reaction condition. The most notable catalysts among these are montmorillonite K-10 clay, HPA and ILs. The application of these catalysts in MCR synthesis of pyranopyrazole derivatives are described below.

G. M. Reddy et al. discussed an eco-friendly MCR approach using montmorillonite K-10 catalyst in aq.ethanol solvent with stirring at room temperature. Montmorillonite K-10, an acid catalyst has received much attention and widely use in organic synthesis because of

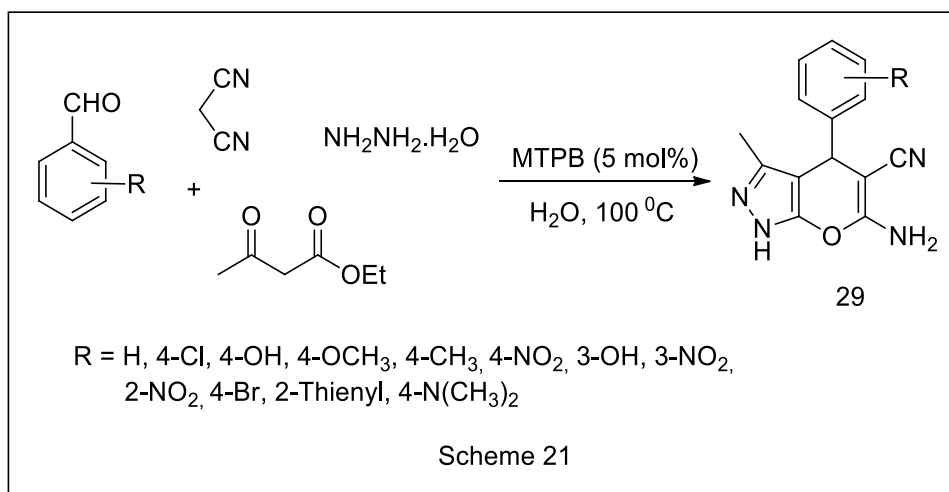
inexpensive, non-toxic, good reactivity, reusable, and ability to suppress side reactions. To stirred reactants at room temperature 3-methyl-1*H*-pyrazol-5(4*H*)-one, aromatic aldehydes, and malononitrile, was added 200% w/w montmorillonite K-10 clay catalyst gave derivatives **27**, in excellent yields. On completion of reaction the catalyst filtered and washed with EtOAc and recycled for use in next cycle of reaction^{xlviii} [Scheme 19].



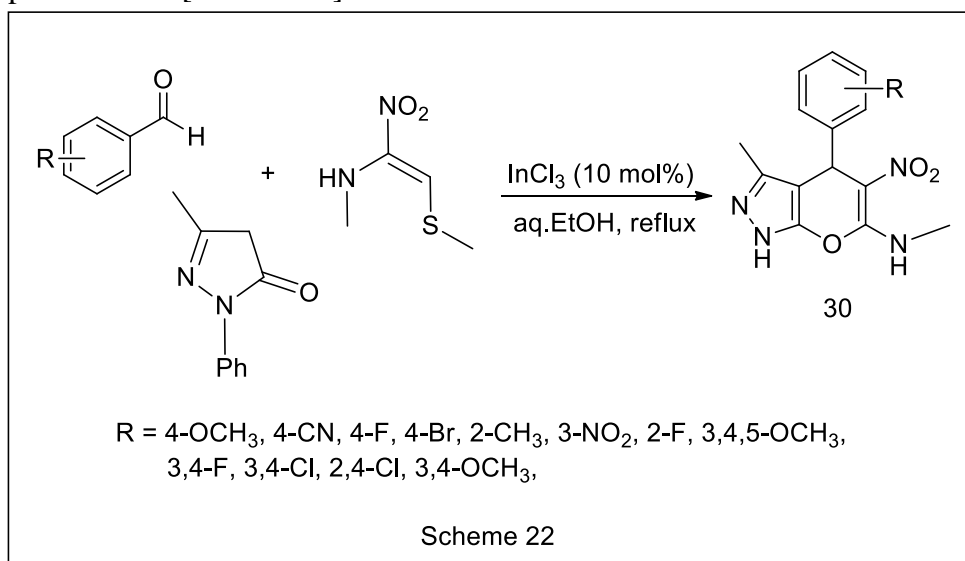
J. Ebrahimi et al reported an application of Bronsted-acidic task specific ILs, 3-methyl-1-(4-sulphonic acid)butylimidazolium hydrogen sulphate [(CH₂)₄SO₃HMIM][HSO₄], for the synthesis of pyranopyrazole derivatives. The authors prepared ILs according to reported procedure and applied for the MCR involving usual substrates, aryl aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate, to obtain the target pyranopyrazole derivatives^{xlix} **28** [Scheme 20].



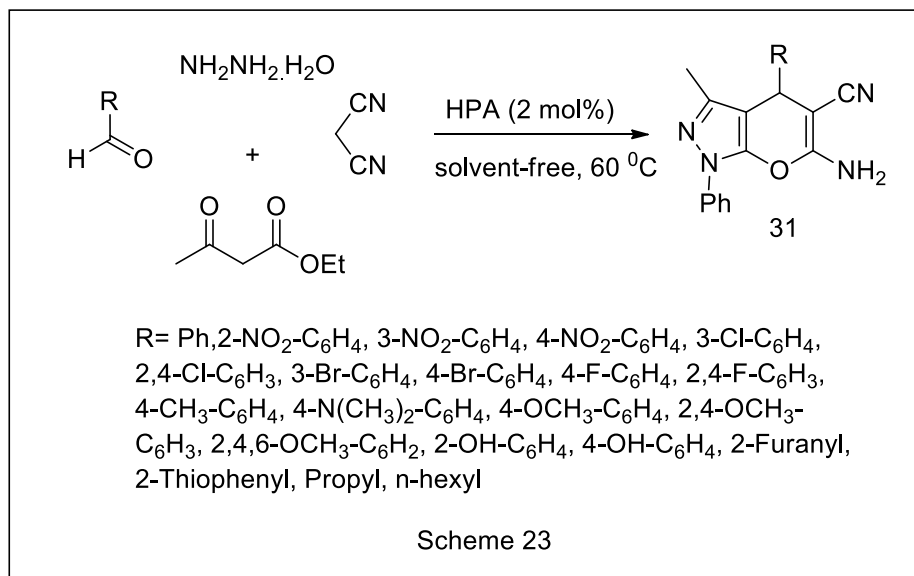
B. Faiza et al. reported a simple, green, four components MCR in aqueous medium using ILs, methyltriphenylphosphonium bromide (MTPB) for the synthesis of pyranopyrazole derivatives. The usual starting component and 5 mol% ILs were refluxed in water for 1hr., the product precipitate out from the reaction medium. The pyranopyrazole derivatives **29** obtained in good to excellent yields¹ [Scheme 21].



D. N. Survase et al. reported Lewis acid, indium chloride (InCl₃) catalyzed regioselective MCR for the synthesis of pyranopyrazole amine derivatives in aq. ethanol. The reaction mixture, aromatic aldehyde, 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, (E)-N-methyl-2-(methylthio)-1-nitroethenamine, and with catalyst was refluxed for 2-3 h which gave excellent yields of the solid products ^{li} **30** [Scheme 22].



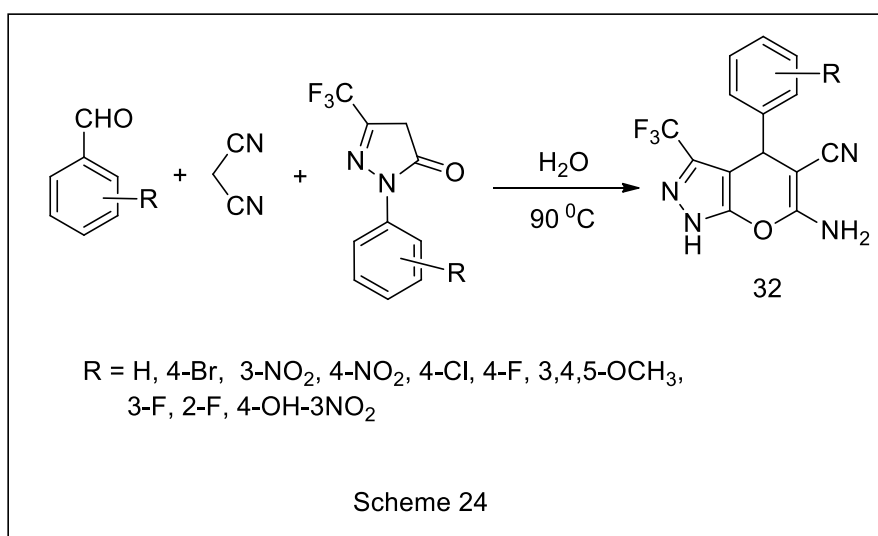
H. V. Chavan et al. developed a solvent-free, rapid four component MCR using heteropolyacid (HPA) for the synthesis of pyranopyrazole. HPA are acid heterogeneous catalyst found to apply in number of reactions. The reaction mixture of aromatic aldehyde **8**, ethyl acetoacetate, malononitrile, hydrazine hydrate, and silicotungstic acid (H₄[SiW₁₂O₄₀]) (2 mol%) as catalyst was heated to 60 °C for 10 min. in solvent-free condition. A series of aromatic aldehyde react well under the reaction condition leading to excellent yields of the products ^{lii} **31** [Scheme 23].



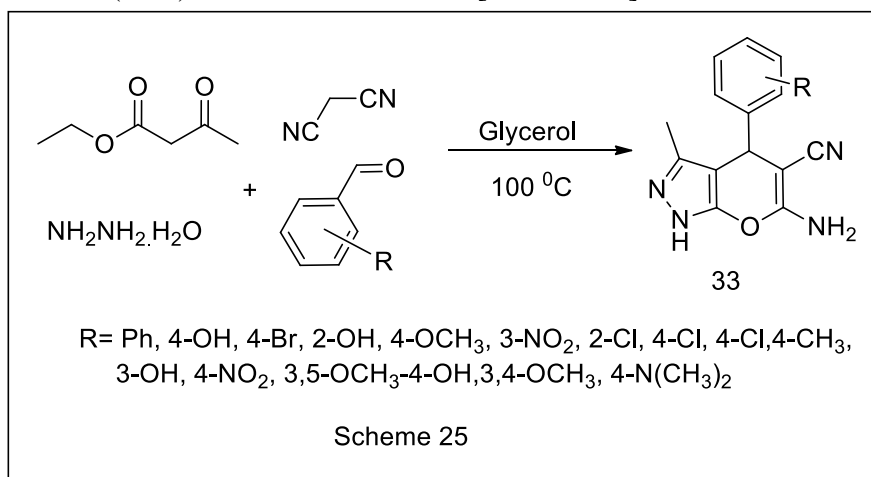
CATALYST FREE SYNTHESIS IN GREEN SOLVENTS:

Catalyst-free, solvent-free, high atom economy, solvent as only by product are the aim of development of green MCRs. Although difficult to achieve, few of green MCRs have been reported in this area using green solvents such as water, ethylene glycol and DES. Some of the significant MCR reported for the synthesis of pyranopyrazole derivatives are mentioned in below section.

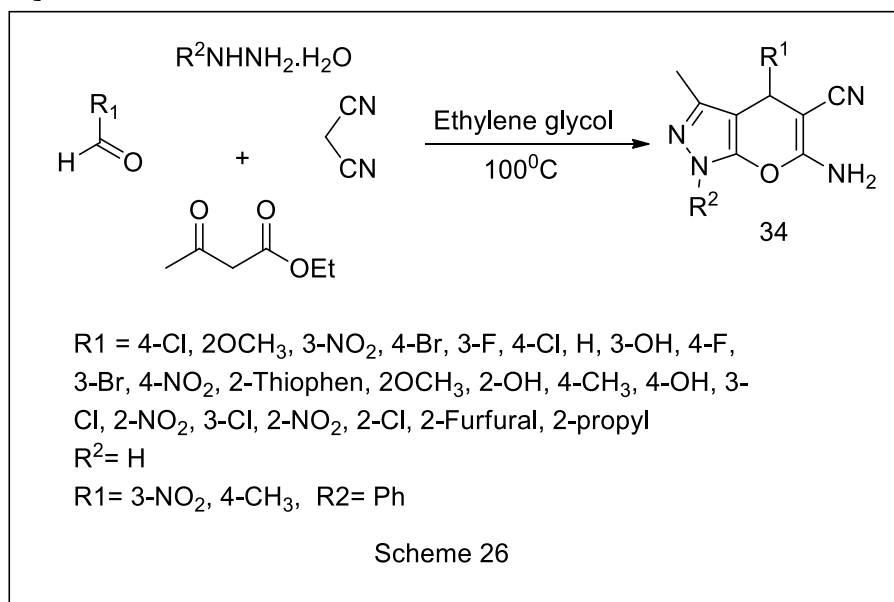
C. Yu et al. reported a green synthesis of organofluorinepyranopyrazole derivatives in water. In the present MCR, it has been seen that, the authors have taken one of the component of MCR as organofluorine compound, 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-(4*H*)-one with the intention to incorporate the unique properties of bulky and more electronegative trifluoromethyl group in the products **32**. The organofluorine component further represents the diverse nature of the MCR. The MCR gave good yields of pyranopyrazole derivatives for both classes of aryl aldehydes bearing electron-donating and electron-withdrawing groups. Notably the terephthalaldehyde gave pyranopyrazole derivatives incorporating two trifluoromethylated fused frameworks ^{liii} [Scheme 24].



R. H. Vekariya et al. reported a catalyst-free, green protocol using glycerol, a biodegradable, inexpensive solvent, and catalyst. Glycerol a by-product of biodiesel industry attracted great attention in green chemistry as an alternative reaction media. A series of pyranopyrazole derivatives **33**, were synthesised by one-pot MCR of aromatic aldehyde, ethyl acetoacetate, malononitrile, and hydrazine hydrate, in glycerol under stirring at 100 °C for 80-120 min. The derivatives were obtained in good yields and were separated from glycerol by adding hexane/ethyl acetate (95:5) in reaction mixture^{liv} [Scheme 25].

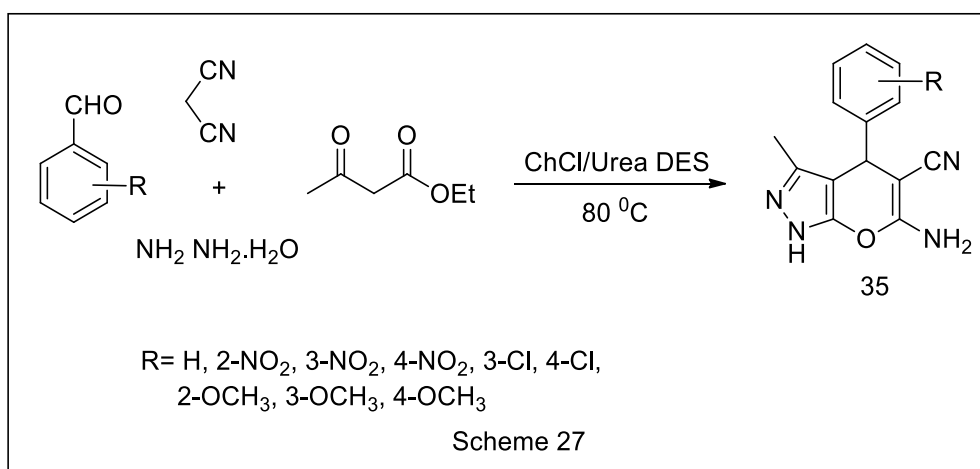


F. Mohamadpour et al. developed a green four component MCR using Ethylene glycol (EG) as a green, recyclable, biodegradable reaction media. EG works well both as solvent and catalyst, which gave excellent yields of derivatives **34**, in short reaction time. The aromatic aldehyde or aliphatic aldehyde, hydrazine hydrate, or phenyl hydrazine, were found equally reactive. The E-G was used for six runs and was recovered from reaction medium by distillation^{lv} [Scheme 26].



A. M. Zonouz et al. developed four component MCR using ammonium deep eutectic solvent (DES) for the synthesis of pyranopyrazole derivatives **35**. The choline chloride-urea DES act as both solvent and catalyst due to its basic nature and catalyzed MCR of benzaldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate, with stirring at 80 °C. The short

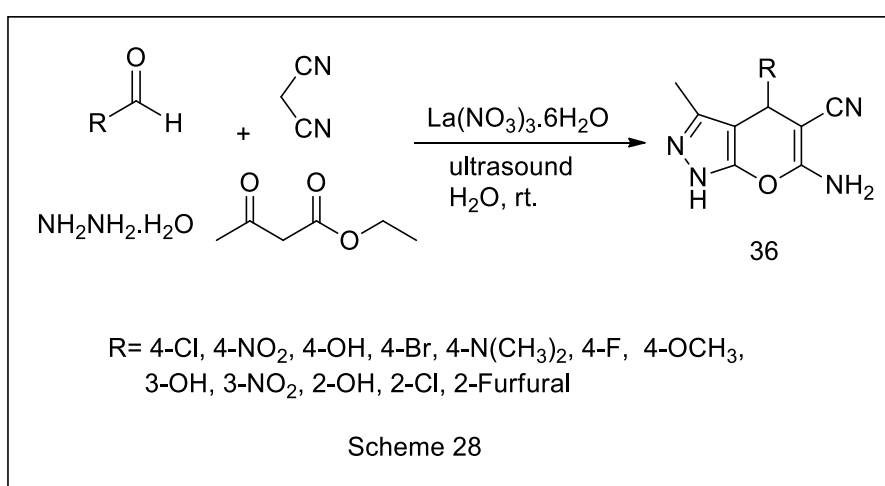
reaction time excellent yields and easy separation of products on completion of reaction are the advantages of the protocol^{lvi} [Scheme 27].



MICROWAVE, ULTRASOUND ASSISTED AND OTHER GREEN METHODS:

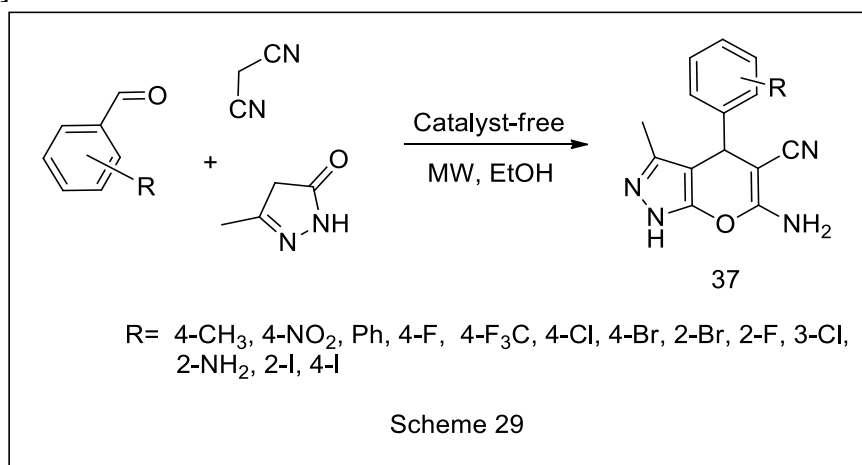
Microwave assisted organic synthesis (MAOS), Microwave-organic reaction enhancement (MORE) and Ultrasound assisted organic synthesis (UAOS) are the promising, energy efficient areas of the modern organic multicomponent reaction synthesis. The rapid reaction rate due to selective absorption of energy by polar molecules in MW and absorption of sound energy by elastic molecules in ultrasound, clean and neat synthetic procedures and enhancement in yields are the green features of these techniques. The efficient use of these techniques in MCR synthesis of pyranopyrazole derivatives are described below.

P. M. Khandare et al. reported the ultrasound mediated synthesis of pyranopyrazole derivatives in water using La(NO₃)₃.6H₂O as a Lewis acid catalyst. The mixture of aldehydes, malononitrile, ethyl acetoacetate, hydrazine hydrate, and catalyst, La(NO₃)₃.6H₂O in water sonicated for short reaction time. On completion of reaction, the solid products **36**, separated from aqueous medium in good yields^{lvii} [Scheme 28].

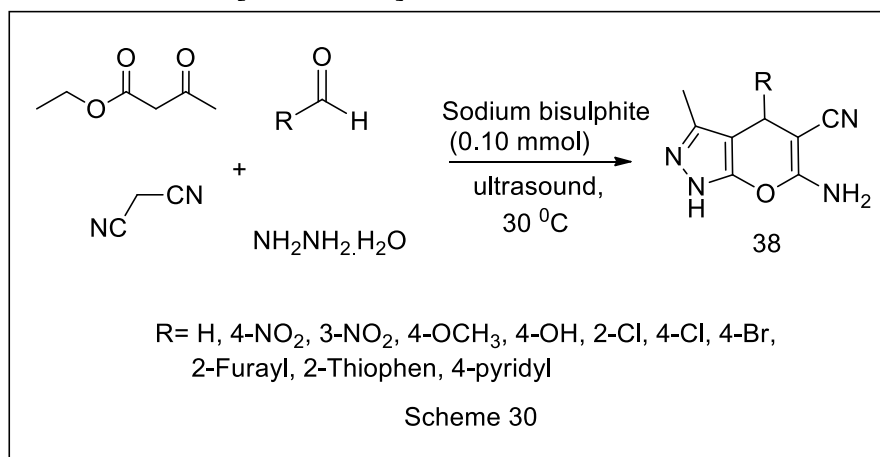


G. M. Reddy et al. developed similar MW assisted MCR for the synthesis of functionalized pyranopyrazole derivatives in short reaction time. The reaction mixture of aromatic aldehyde, malononitrile, and 3-methyl-1H-pyrazol-5(4H)-one, were irradiated with MW at the power of

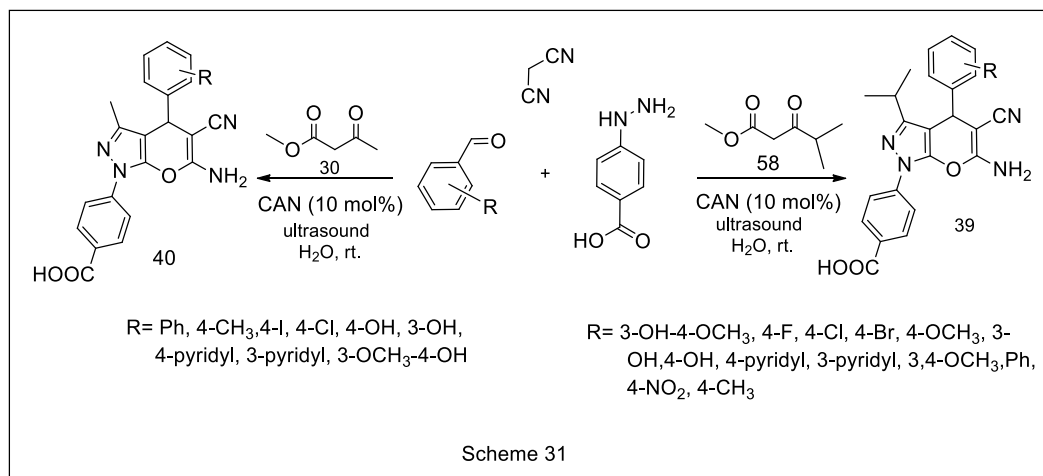
250 W at 130 °C for 10 min. The series of derivatives **37**, were obtained in excellent yields^{lviii} [Scheme 29].



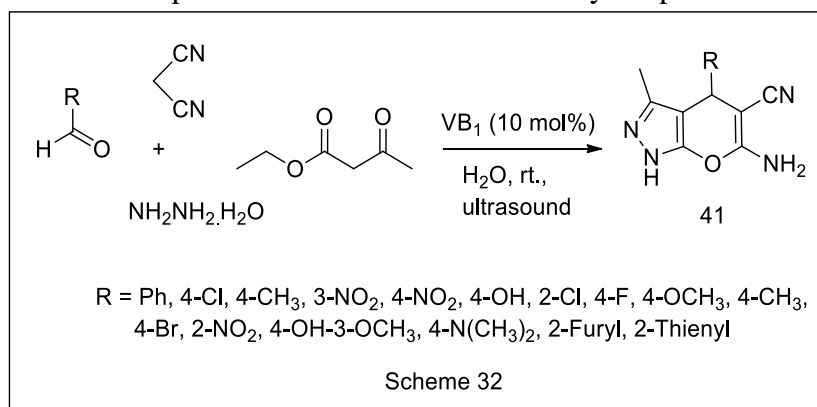
S. N. Darandale et al. developed new ultrasoundmediated solvent-free protocol for the synthesis of pyranopyrazole derivatives catalyzed by sodium bisulfite. An inexpensive weak acid, sodium bisulfite known to catalyzed organic reactions. The reaction mixture of aromatic aldehyde , ethyl acetoacetate , malononitrile , hydrazine hydrate , and sodium bisulfite was irradiated by ultra-sound bath sonicator at frequency of 35 kHz, power of 200 W in water bath with controlled temperature of 30 °C. A simple, practical green protocol gave quantitative yields of the derivatives^{lix} **38** [Scheme 30].



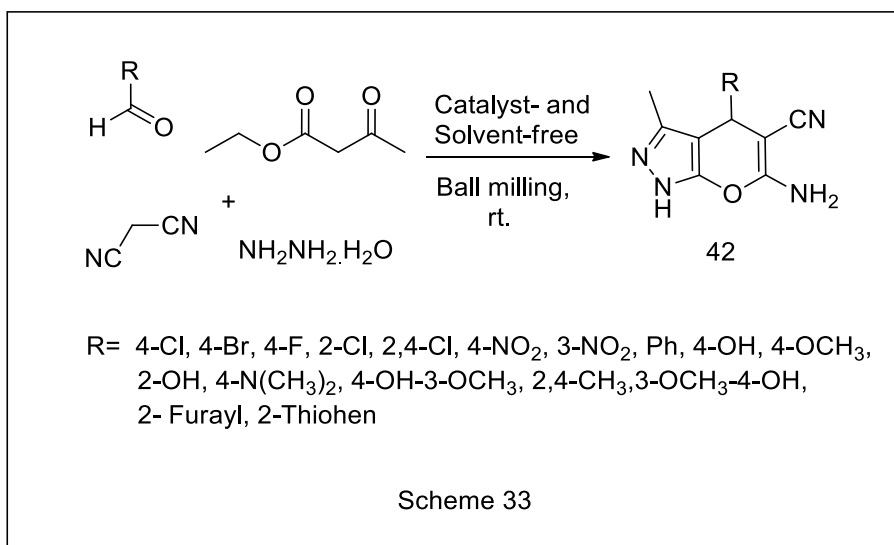
K. Ablajan et al. reported a one-pot, four component MCR for the synthesis of series of pyranopyrazole derivatives using cerium ammonium nitrate (CAN) (10 mol%) under ultrasound irradiation in water. CAN is as a versatile Lewis acid catalyst being non-toxic and environmentally compatible known to used for number of organic transformations. The reaction mixture of ethyl acetoacetate , and 4-hydrazinobenzoic acid , in water ultrasonicated at frequency of 25 kHz, power of 250 W at 30 °C for 5 min. The intermediate formed was allowed to react with aromatic aldehyde , and malononitrile , for 45-60 min under similar conditions which results into excellent yields of the products **40** similarly the reaction of methyl 4-methyl-3-oxopentanoate, gave derivatives **39** under same conditions of reaction^{lx} [Scheme 31].



M. D. Nikam et al. developed a one-pot an efficient and eco-friendly protocol using thiamine hydrochloride (VB₁) as a green catalyst for the synthesis of pyranopyrazole derivatives **41**. The short reaction time, simple workup and high yields are the features of the procedure both in conventional and ultrasound irradiation. The reactants aromatic aldehyde, ethyl acetoacetate, malononitrile, hydrazine hydrate 10, and catalyst, VB₁ (10 mol %) in water was stirred for 15-20 min at rt. while in ultrasound methodology the same reaction mixture was irradiated in water bath for 7-11 min. the solid product obtained was collected by simple filtration^{lxix} [Scheme 32].



M. G. Dekamin et al. developed a catalyst- and solvent-free efficient green protocol for the synthesis of pyranopyrazoles using ball milling technique at rt. The authors synthesized series of derivatives **42**, using various aromatic and heterocyclic aldehydes. The aromatic aldehyde having an electron withdrawing group reacts more efficiently than the aldehydes having an electron releasing group. In a ball mill vessel having two stainless steel balls ethyl acetoacetate, and hydrazine hydrate, were added and ball milled run at rt. at a speed of 28 Hz for 30s. To this malononitrile, and aromatic aldehyde, were added and ball mill run for another 30-120 min which results into excellent yields of the derivatives^{lxxii} [Scheme 33].



CONCLUSION:

This review discussed the recent updates of green multicomponent reactions protocols applied for the synthesis of biologically important pyrano[2,3-c]pyrazoles derivatives. The number of green alternatives are described in literature with use of green solvents, eco-friendly catalysts, microwave and ultrasound irradiation, ambient reaction temperature and use of diverse reactant molecules are the notable. The short reaction time, simple workup by filtration of solid products formed in reaction medium, energy efficient and high yields are the features of the reported procedures.

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