

Recent Trends in Green and Multicomponent Approaches for the Synthesis of Pyrano[2,3-c] pyrazoles

Attreyee Mukherjee

Department of Chemistry, Ananda Mohan College, Kolkata 700009, West Bengal, India

Corresponding Author's Email: attreyee.m@gmail.com

Abstract

Among the fused heterocycles, pyrano[2,3-c]pyrazoles are the most significant scaffold because of their biological potential. Recently, growing interest in sustainability has strengthened the green methodology of the multicomponent reactions for the synthesis of these frameworks. This review summarizes an extensive and updated overview of the advancement of green synthetic strategies of these pyrazole-fused heterocycle derivatives in the period of ten years. The use of alternating energy sources, e.g., microwave and ultrasound irradiation, recyclable nano catalysts, metal-free organic and biocatalysts, ionic liquids, water as a green solvent and solvent-free and catalyst-free conditions are highlighted in the review. The descriptive and comparative study of these methodologies unveils significant improvements in the atom economy of the reactions, reduced energy consumption and catalyst recyclability. The critical analysis of the current trends and limitations, this review aims to guide the future design of sustainable, high atom economy synthetic strategies for this biologically significant heterocycle.

Keywords: Green Solvent; Green Synthesis; Microwave; Multicomponent; Nanocatalyst; Solvent Free Ultrasound

Introduction

Heterocyclic molecules are abundantly found in nature, and these are very essential in our biological systems. Due to their structural diversity and functional versatility, they became the indispensable components of pharmaceuticals, agrochemicals, dyes, and advanced materials (Pozharskii *et al.*, 1997; Biswas *et al.*, 2022). Over the last two to three decades, the chemistry of heterocyclic compounds has been extensively studied (Katritzky *et al.*, 2001). The synthesis and application of medium-sized heterocyclic rings, especially the fused heterocyclic rings, have attracted significant attention among the researchers involved in pharmaceutical chemistry as well as drug discovery. The pyrano-fused pyrazoles have four isomers (Figure 1), and among them, pyrano[2,3-c]pyrazole is reported to be the most biologically significant and so the synthesis of this heterocycle becomes of great interest. The incorporation of the pyrazole nucleus imparts diversified applications in different areas such as technology, medicine and agriculture (Abhinav *et al.*, 2020) and agrochemical research (Nassar *et al.*, 2022).

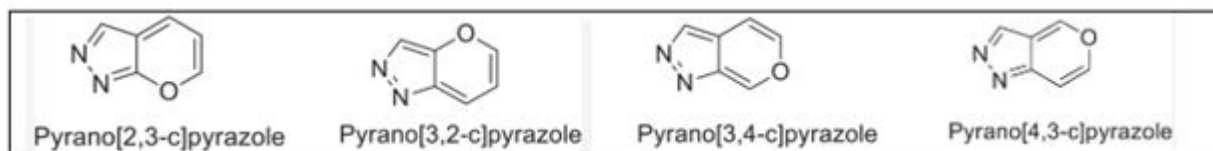


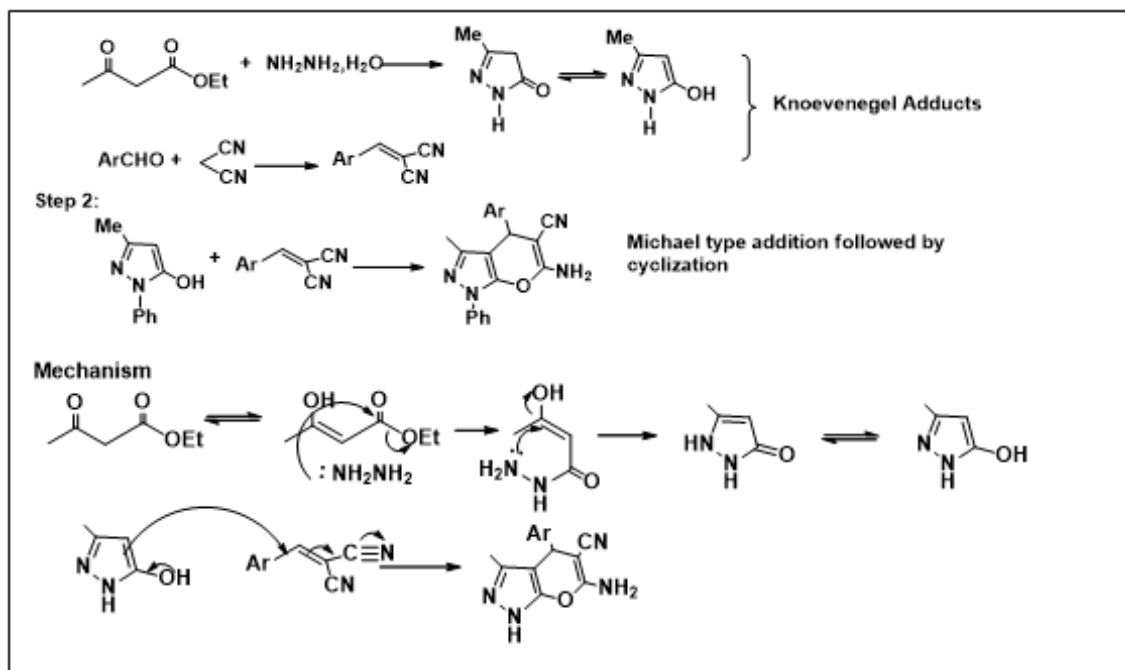
Figure 1: Isomers of Pyrano[2,3-c]pyrazole

The molecules having a pyranopyrazole nucleus are found to exhibit a broad spectrum of biological activities such as cholinesterase inhibitory activity (Derabli *et al.*, 2018), antibacterial (El-Assaly *et al.*, 2021), antimicrobial (Alzahrani *et al.*, 2025; Nguyen *et al.*, 2022), anticancer (Fouda *et al.*, 2022), anti-inflammatory, and analgesic (Kumar *et al.*, 2012) properties. Recent studies have also highlighted their

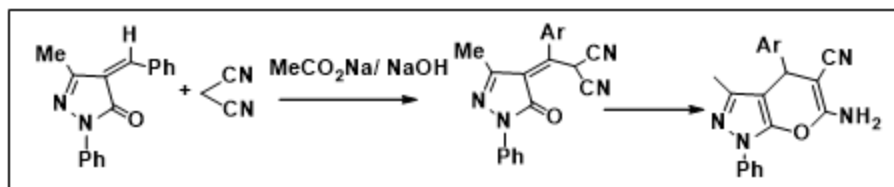
fungicidal, bactericidal, and herbicidal properties (Nicolaou *et al.*, 2002), which make the molecules agrochemically important. Interestingly, recent research of these molecules reveals that these derivatives may be used as the inhibitor of human coronavirus 229E (Allayeh *et al.*, 2024). Such wide-ranging activities have encouraged extensive research on the synthesis of this valuable scaffold in efficient and sustainable methods.

Multicomponent reactions (MCRs) are recognized as the most powerful tool in synthesizing pyranopyrazole due to their inherent benefits—operational simplicity, increased atom economy, reduced waste production, minimization of reaction time and energy consumption. The conventional methods often involve hazardous solvents, strong acids, and extended reaction time (Kharissova *et al.*, 2019). The modern green technologies (Mamaghani *et al.*, 2021; Bhaskaruni *et al.*, 2020) encourage the use of recyclable catalysts, alternating energy sources, green solvents, etc. Consequently, numerous green methodologies have been reported using bio- and asymmetric catalysis (Varma, 2016; Kate *et al.*, 2022), microwave, ultrasound, ultraviolet, green solvents, e.g., water and ionic liquids (ILs) (Romney *et al.*, 2018).

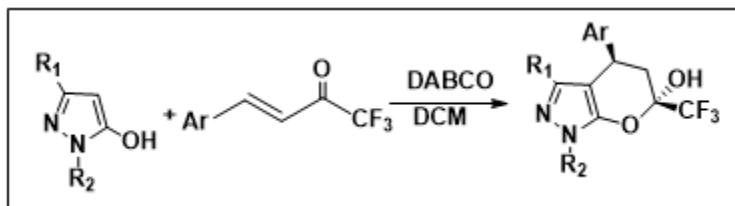
This review will cover a detailed and updated account of the green MCR strategies for synthesizing pyranopyrazole derivatives by using MW, organo or biocatalysts, or nanocatalysts. solvent-free or using water and ultrasound technique. The MCR synthesis of this molecule involves generally four components – (i) aldehyde, (ii) malononitrile, (iii) β -ketoester, e.g., ethyl acetoacetate and (iv) hydrazine hydrate. The reaction takes place in the presence of an appropriate catalyst or promoter (Bhope *et al.*, 2022). The conventional method of synthesis of pyranopyrazole is the Michael addition of a pyrazolone nucleus with malononitrile in the presence of a base (Scheme 1). This is the first approach to synthesizing this molecule by Otto (1974). The cyclization reaction of 4-arylidene-5-pyrazolone with malononitrile was carried out in the presence of base (Scheme 2). Wang *et al.* (2015) further modified the synthesis where the base used was DABCO and the reaction of pyrazolone and α,β -trifluoromethyl ketones took place in DCM as a solvent (Scheme 3).



Scheme 1: General Multicomponent Synthesis



Scheme 2: First synthetic approach of pyrano[2,3-c]pyrazole



Scheme 3: Modified Approach of Synthesising Pyrano[2,3-c]pyrazole Using DABCO as Base

Methodology

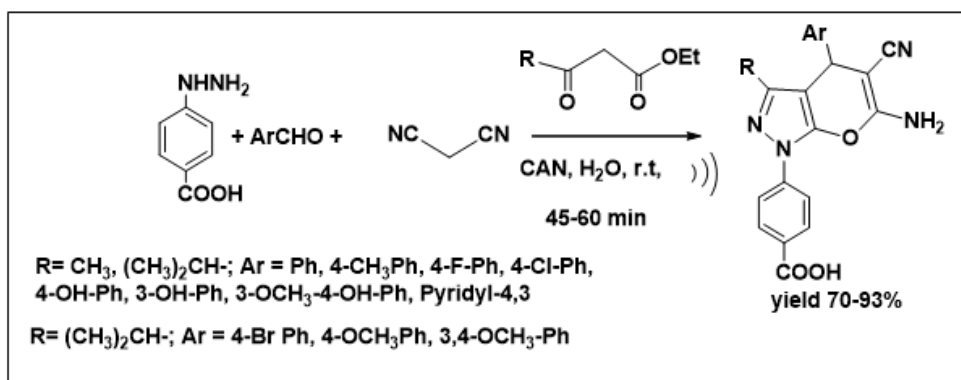
By Using Ultrasonic Sound Technique

Ultrasound irradiation increases the reaction rate and selectivity of the reaction by acoustic cavitation and reduces the reaction time and temperature (Puri *et al.*, 2013). Several catalyst-based and catalyst-free ultrasonically driven MCRs have been developed, providing excellent yields under mild and eco-friendly conditions.

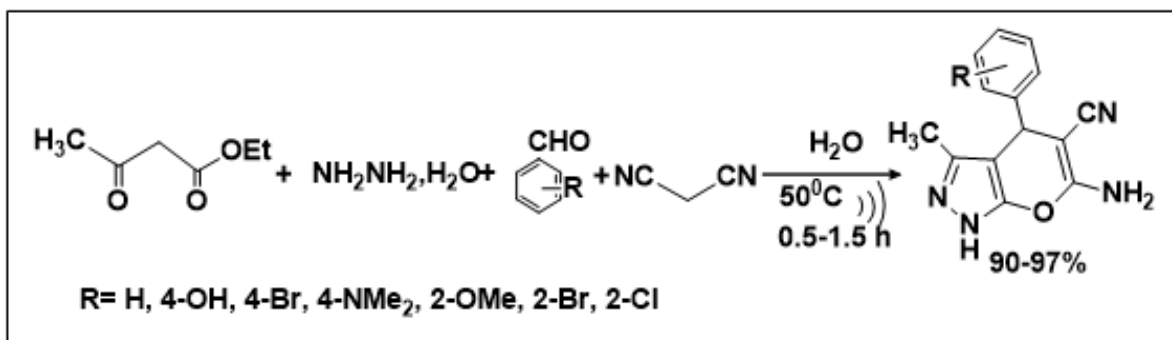
Ablajan and his team (Ablajan *et al.*, 2013) recently outlined a method for synthesizing pyrano [2,3-c] pyrazole derivatives from phenylhydrazine-4-carboxylic acid at 250°C in aqueous medium in the presence of CAN by using ultrasound techniques (Scheme 4).

Shabalala and his group synthesized pyran pyrazoles from different aromatic aldehydes via four-component synthesis in a water medium under ultrasonic irradiation (Shabalala *et al.*, 2015) (Scheme 5). Gujar *et al.* (2014) invented a new approach by using molecular sieves (40 Å) as a catalyst. The advantage of this catalyst is that it can be reused with the same efficiency up to the third run (Scheme 6).

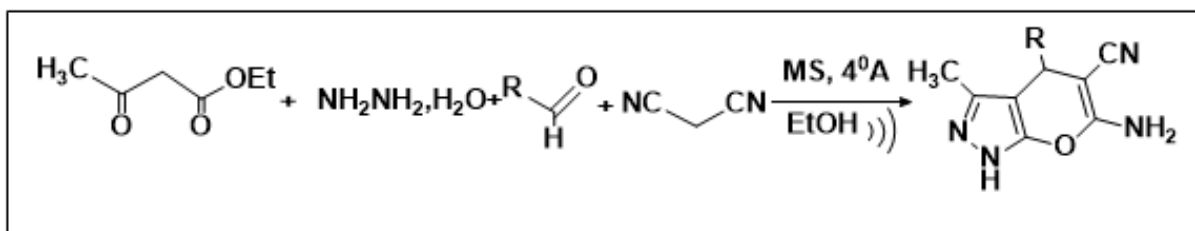
Four-component synthesis of the molecule was also reported using Mn-doped zirconia (Mn/ZrO₂) in aqueous ethanol at room temperature and the recovered catalyst was reported to be recycled for six consecutive times (Maddila *et al.*, 2019). (Scheme 7).



Scheme 4: Pyranopyrazole Derivatives Synthesis in Presence of CAN under Ultrasonic Technique

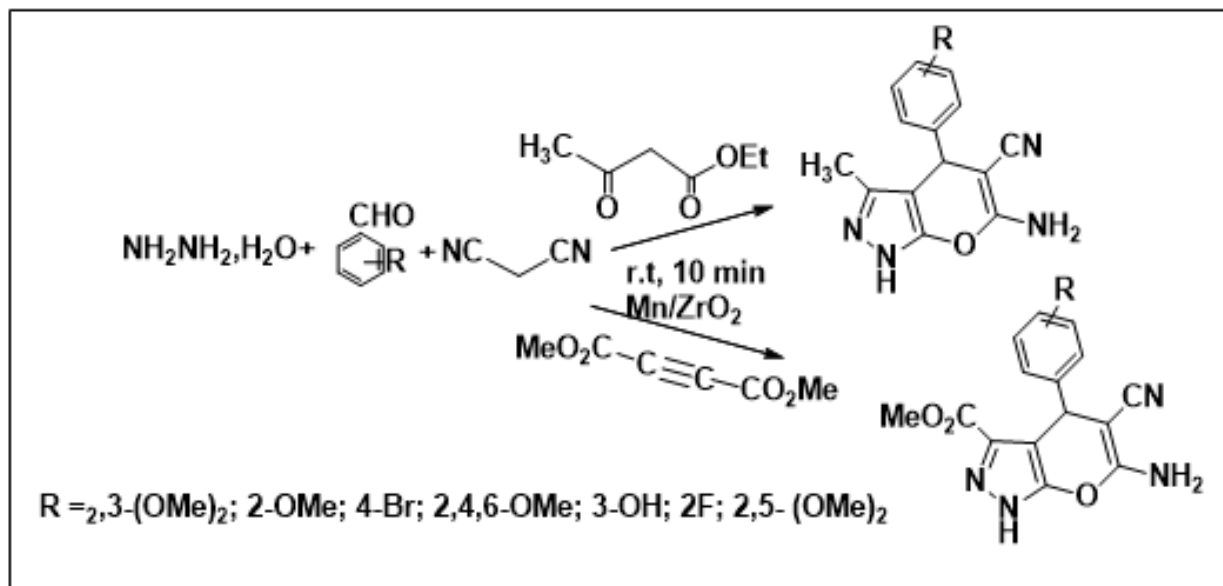


Scheme 5: Pyranopyrazole Synthesis Under Catalyst-Free Condition in Water

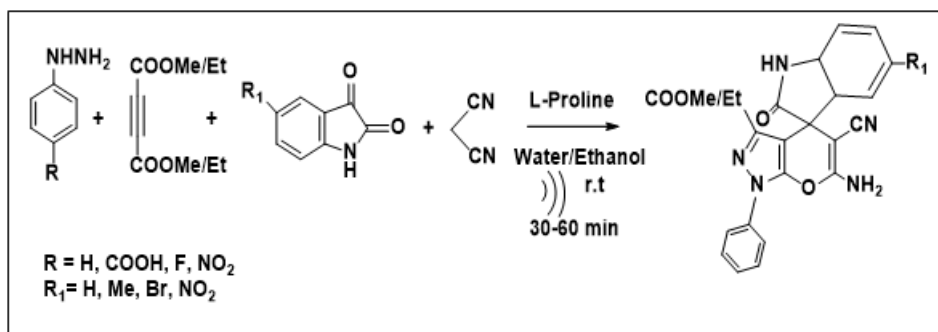


Scheme 6: Pyranopyrazole Synthesis Using Molecular Sieves

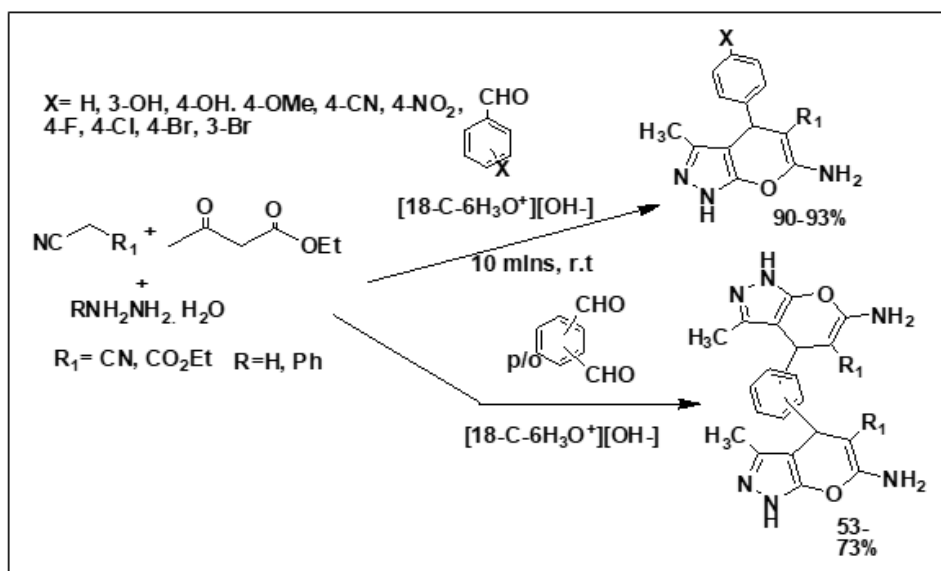
Water is found to be the best medium among other ecofriendly solvents like methanol, acetonitrile, toluene, DMF and DMSO. Spiro pyrano [2, 3-*c*] pyrazoles were reported to be prepared under ultrasound using L-proline with 1:1 v/v ethanol/water at room temperature (Liju *et al.*, 2015) (Scheme 8). Mishra *et al.* reported the generation of the hydronium ion of crown ether in situ and its catalytic activity towards the preparation of pyranopyrazoles (Mishra *et al.*, 2020) (Scheme 9). Khare *et al.* introduced 1,2,3-triazolyl pyranopyrazoles (Scheme 10) with 92–98% yield at 30°C in water with NaHCO₃ as a catalyst (Khare *et al.*, 2019).



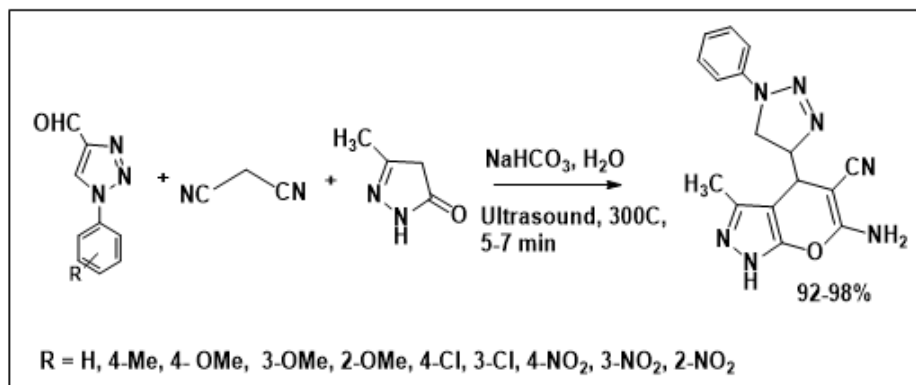
Scheme 7: Preparation of pyrano[2,3-*c*]pyrazole Derivatives Using Mn/ZrO₂ as Catalyst



Scheme 8: Synthesis of Spiropyranopyrazole Derivatives in Presence of L-proline Catalyst



Scheme 9: Bispyrano[4,3-*c*]pyrazole from Benzene Dicarboxaldehyde (*o/p*)



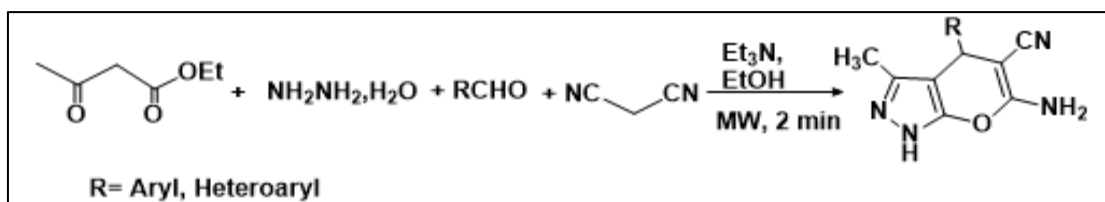
Scheme 10: Preparation of 1,2,3-triazolopyrano[2,3-*c*]pyrazole

Microwave Technique

Microwave irradiation accelerates chemical transformations by rapid internal heating and improved reaction kinetics. Numerous microwave-assisted MCRs for pyranopyrazoles have been reported,

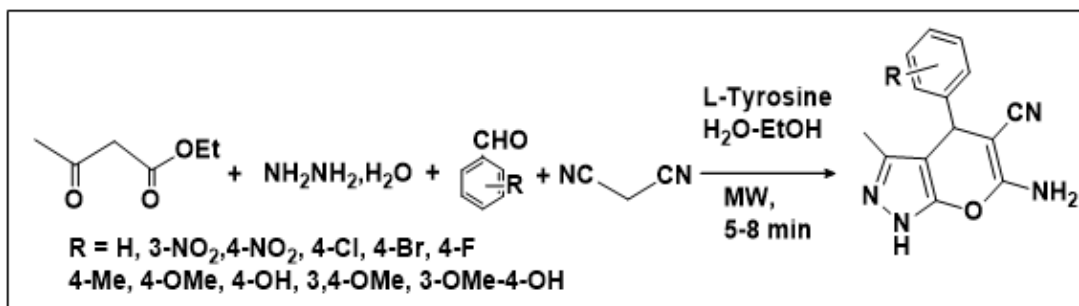
demonstrating shortened reaction times, excellent yields, and operational simplicity. The microwave irradiation increases the rate of reaction and decreases the time of reaction and makes the reaction eco-friendly.

A comparison was made between the microwave method and the conventional method of synthesizing a series of pyrano [2,3-c] pyrazoles by Shukla and his team and they concluded that the conventional method ended with good yields of the product, whereas microwave irradiation reduces the duration of the reaction (Shukla *et al.*, 2015) (Scheme 11). Some of the compounds in this series showed cytotoxic activity against the Hep3B cancer cell lines (Sharma *et al.*, 2016).



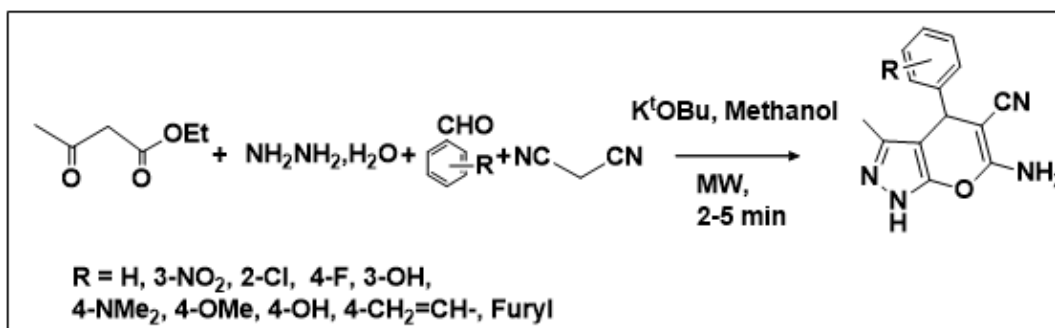
Scheme 11: Base Catalyzed Synthesis of Pyranopyrazoles Under Microwave Condition

The eco-friendly synthetic approach was reported to synthesise pyranopyrazoles under MW technique using solvent mixture water-ethanol system in the presence of L-tyrosine (Rupnar *et al.*, 2017) (Scheme 12).



Scheme 12: MW Preparation of pyrano[2,3-c]pyrazoles in Presence of L-tyrosine

Yallappa *et al.* recently introduced a new method of synthesis of the compounds via four component MCR in presence of K^tOBu under MW condition and found the excellent yield of product in 5-7 mins (Yallappa *et al.*, 2022) (Scheme 13).

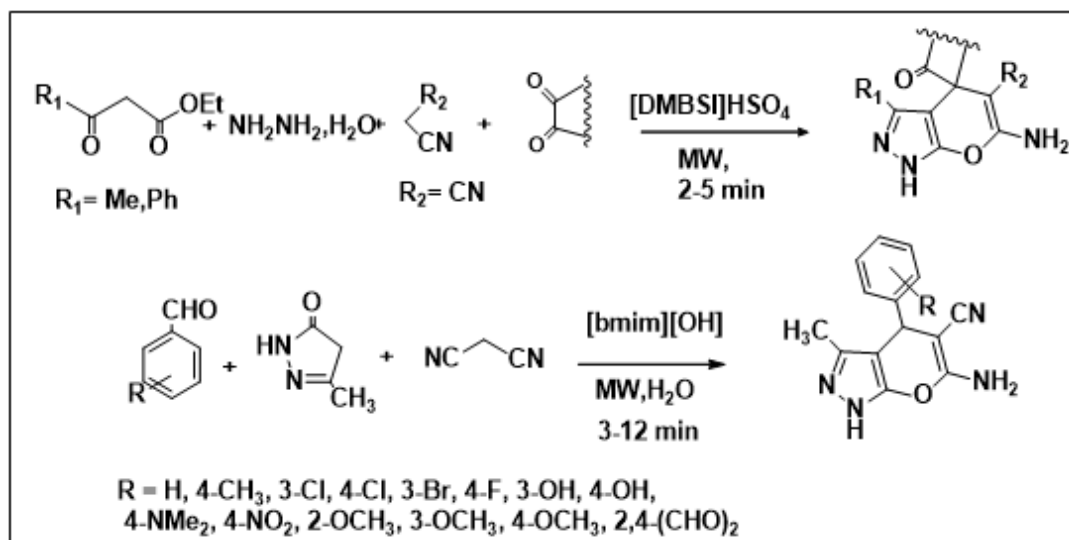


Scheme 13: Base Catalyzed Synthesis Under MW Condition

In the green MCR, ionic liquids have played the excellent role of green solvent in place of common organic solvent due to their favorable properties (Becerra *et al.*, 2022). A rapid, straightforward, one-pot

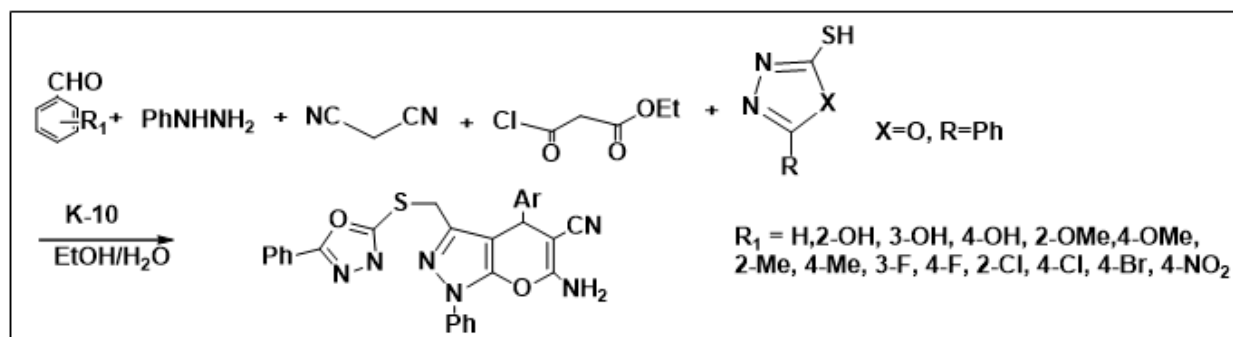
approach using [DMBSI][HSO₄] was reported by Mamaghani and his team (Mamaghani *et al.*, 2015). The reaction was placed at 60°C in MW without solvent (Scheme 14). The spirodiketones were taken by the researchers to produce spiropyranopyrazoles. These compounds showed antibacterial activity against gram-positive and gram-negative bacteria in in-vitro studies using tetracycline and erythromycin as standard drugs.

Imidazole-based ionic liquid [bmim][OH] was also used in the synthesis of pyranopyrazoles under microwave conditions (Aliabadi *et al.*, 2016). The synthesised compounds (Scheme 15) were found to exhibit antioxidant activity.



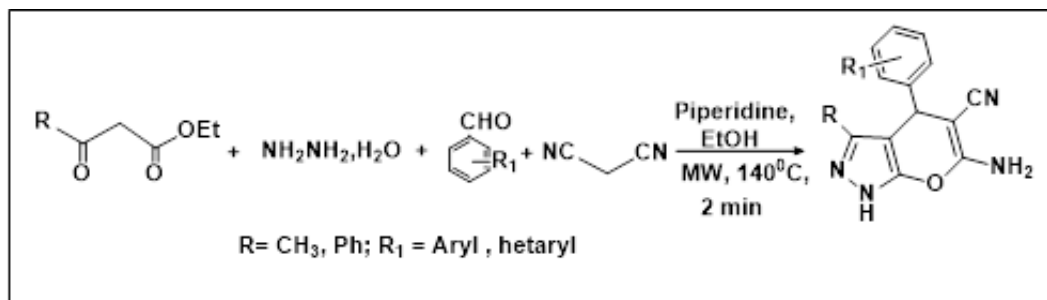
Scheme 14 & Scheme 15: Synthesis of Spiropyranopyrazoles Derivatives in Presence of IL Under MW

There has been a growing emphasis on developing eco-friendly reaction pathways, environmentally sustainable catalysts, and solvents, as well as synthesizing novel biologically active heterocycles. These areas have become crucial focal points in numerous ongoing research programs (Reddy *et al.*, 2017). The new pyranopyrazoles linked with thioether were prepared in the presence of Montmorillonite K-10 clay (Reddy *et al.*, 2019) (Scheme 16). Due to the acid-catalytic nature of the catalyst, the reaction was initiated rapidly. The catalyst K-10 can be reused, is inexpensive, is eco-friendly, and increases the yield of the product. The antibacterial activity was also reported for these compounds.



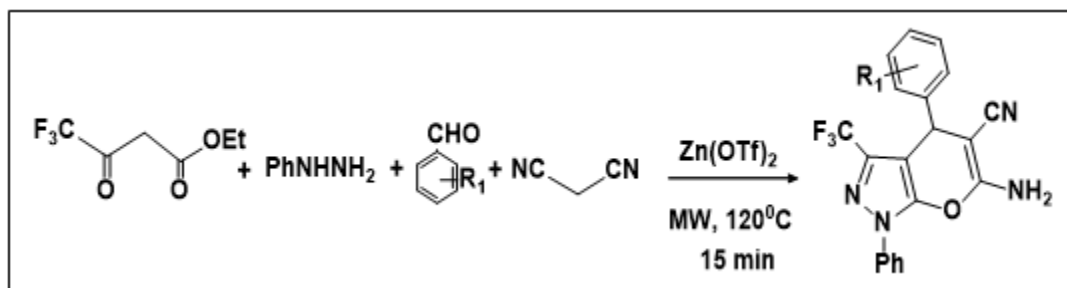
Scheme 16: Thioether-linked Pyranopyrazoles via a Five-Component Reaction

Recently, microwave synthesis of these molecules were reported using piperidine as catalyst at 140°C in 2 min in good to excellent yields (El-Agrody *et al.* 2022) (Scheme 17).



Scheme 17: MW Synthesis in Presence of Piperidine

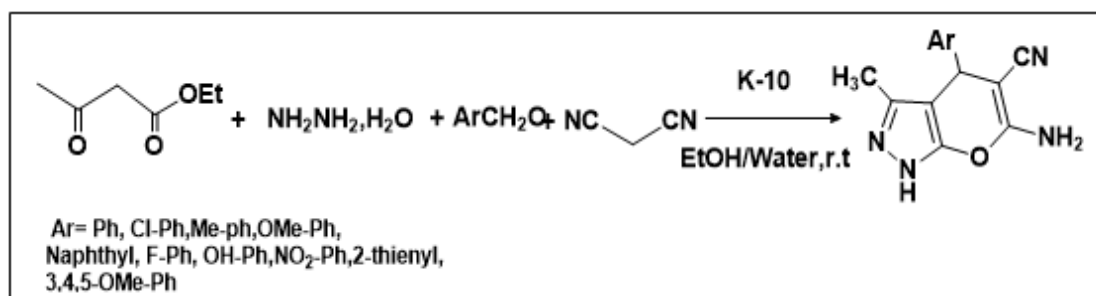
Another multicomponent approach under MW technique was successfully done in two steps: (i) β -ketoesters and aryl hydrazines were irradiated for 10 min at 80°C in the presence of Lewis acid catalyst zinc triflate, (ii) then addition of aromatic aldehydes and malononitrile and after irradiation, the mixture at 120°C for 15 min produced the desired product (Parikh *et al.*, 2022) (Scheme 18).



Scheme 18: Preparation of Pyranopyrazole Derivatives in Presence of Lewis Acid Zinc Triflate Using Nanocatalyst

Among the wide range of catalysts, nanoparticle-derived nanocatalysts are found to be excellent alternatives to conventional catalysts as their surface-to-volume ratio is increased and also for their robustness and stability (Yang *et al.*, 2017; Saxena *et al.*, 2017). Due to the presence of more open active surfaces than bulk catalysts, the contact between the reactant and catalyst becomes very efficient (Narayan *et al.*, 2019). The nanocatalysts show high selectivity, reusability, and control over the reaction routes (Ahmad *et al.*, 2023) and minimize the byproducts. Recently heterocyclic compounds are synthesized by using the nanocatalysts.

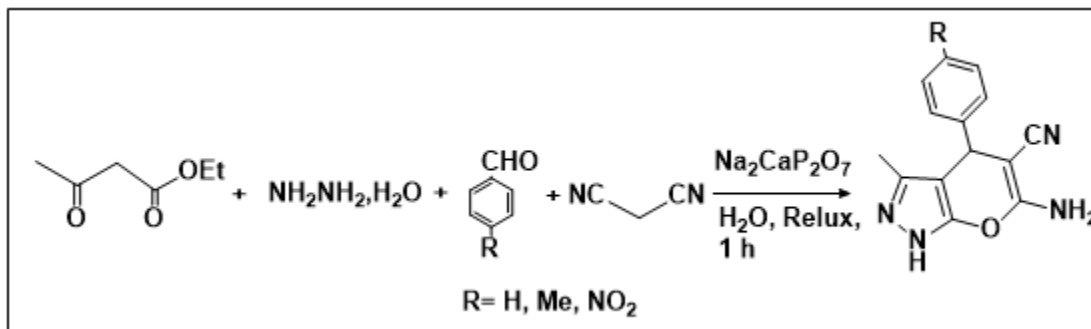
The green heterogeneous acid catalyst Montmorillonite-K10 is used to prepare pyranopyrazole derivatives at 100°C (Moosavi-Zareet *et al.*, 2016) (Scheme 19).



Scheme 19: Preparation of Pyranopyrazole Derivatives in Presence of Montmorillonite-K10 Catalyst

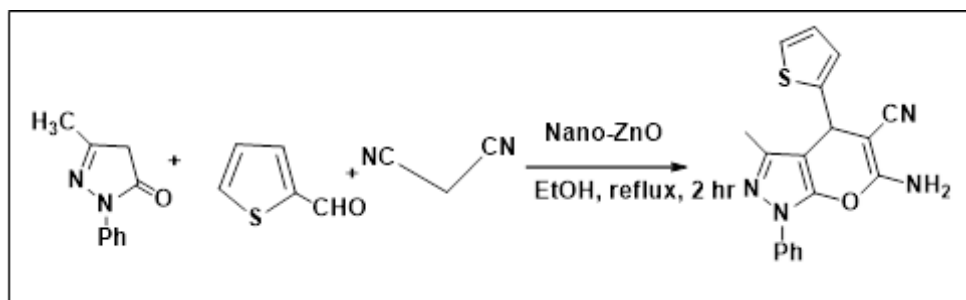
MNPs are now very popular as catalysts in MCRs and another widely used nanocatalyst is heterogeneous magnetic nanocatalysts.

Pyranopyrazoles were successfully prepared in the presence of a $\text{Na}_2\text{CaP}_2\text{O}_7$ catalyst via a four-component reaction in refluxing water for 1 h (Addoum *et al.*, 2021) (Scheme 20).



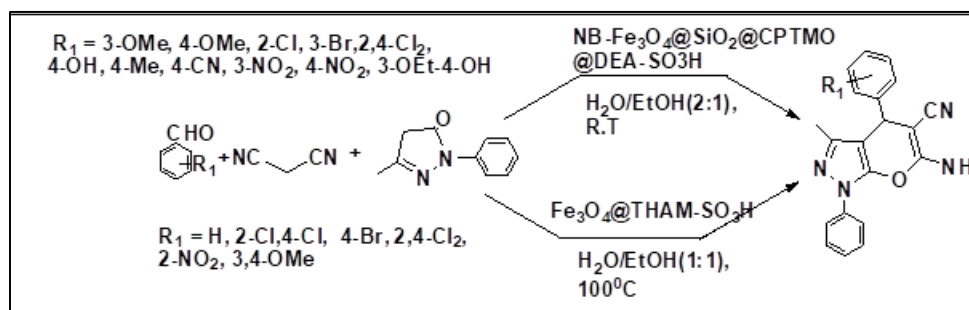
Scheme 20: Pyranopyrazole Derivatives in Presence of $\text{Na}_2\text{CaP}_2\text{O}_7$ catalyst

The thiophene-based pyranopyrazole derivatives were prepared by taking thiophene-2-carbaldehyde and refluxing it with pyrazol-3-one and malononitrile in ethanol in the presence of a nano-ZnO catalyst (Amer *et al.*, 2021) (Scheme 21).



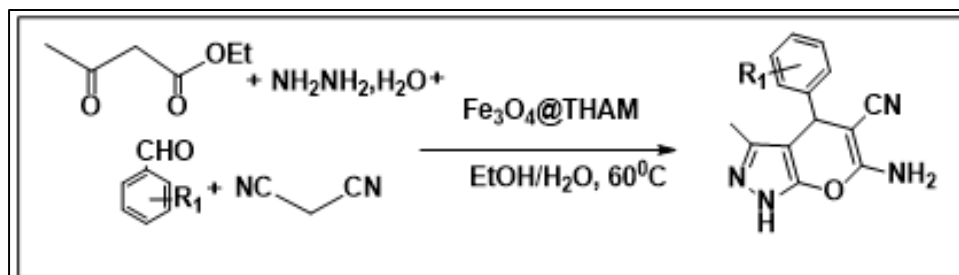
Scheme 21: Pyrano[pyrazole Derivatives Synthesis in Presence of Nano-ZnO catalyst

The nanomagnetic catalysts, e.g., $\text{NB-Fe}_3\text{O}_4@\text{SiO}_2@\text{CPTMO}@\text{DEA-SO}_3\text{H}$ (Eftekhari-Far *et al.*, 2020) and tris(hydroxymethyl)aminomethane (THAM), were prepared and successfully used to synthesize the pyranopyrazole framework (Scheme 22).



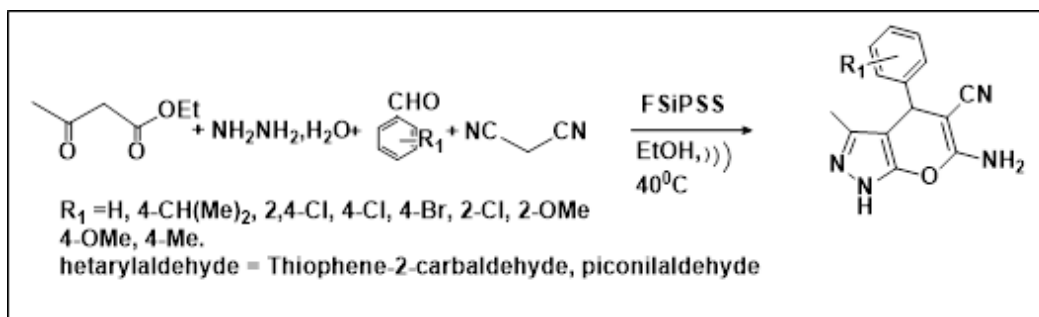
Scheme 22: Pyrano[2,3-c]pyrazole Synthesis in Presence of Nanomagnetic Catalyst

Recently, Fatemeh Mir and her team used another reusable nanocatalyst, $\text{Fe}_3\text{O}_4@\text{THAMP}$ piperazine, in an ethanol/water medium to prepare the dihydropyranopyrazole (Mir *et al.*, 2023) (Scheme 23).



Scheme 23: Preparation of Pyrano[2,3-*C*]Pyrazole Derivatives with $\text{Fe}_3\text{O}_4@\text{THAM}$ Nanocatalyst in Aqueous Medium

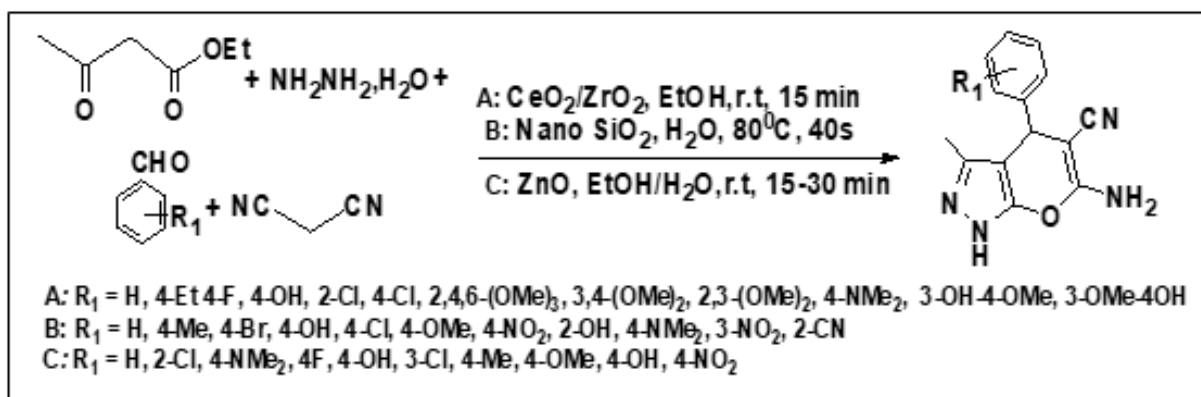
Another efficient and recoverable nanomagnetic catalyst $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{OSi}(\text{CH}_2)_3\text{-N(3-pyridoyl sulfonic acid)}$ semi carbazide (FSiPSS) was synthesized and characterized by Beiranvand *et al.* (2022) and used in MCR under ultrasonication and produced the desired molecules in very short reaction time. (Scheme 24).



Scheme 24: Pyranopyrazole Derivatives Preparation in Presence of Nanomagnetic Catalyst

The ceria-doped zirconia catalyst introduced by Maddila *et al.* (2017) showed excellent yields of pyranopyrazole derivatives at room temperature within 15 mins. Another nanocatalyst, nano- SiO_2 , was used successfully in water for only 40s by the sol-gel process from wheat-straw agricultural waste. This synthesis took place at room temperature using the ultrasonic technique and leads to good to excellent yields as reported by Patel and his team (Patel *et al.*, 2018).

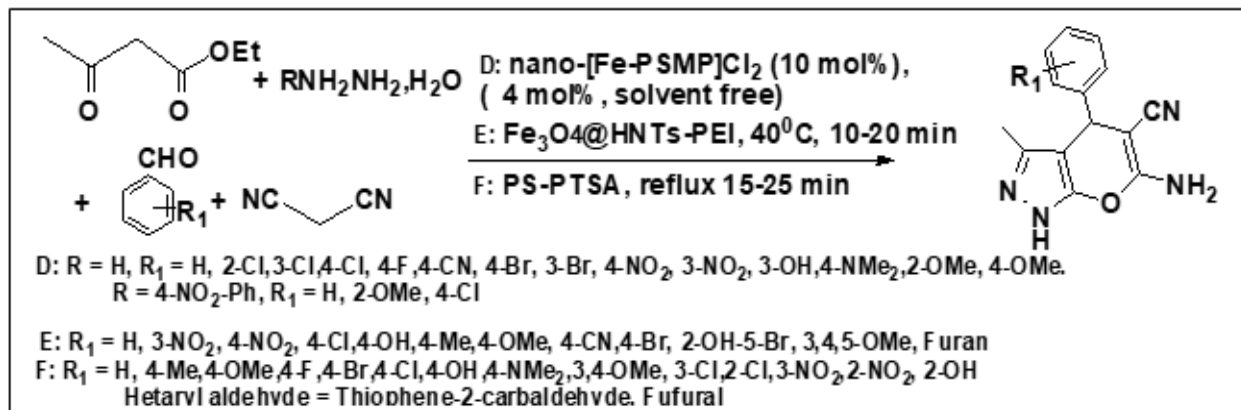
Another synthetic route of pyranopyrazole was designed by Chhattise *et al.* (2020) with four component reagents at room temperature within 15-30 mins, resulting in a high yield of product (Scheme 25).



Scheme 25: Pyrano[2,3-*c*]pyrazole Derivative Synthesis with Different Nanocatalysts

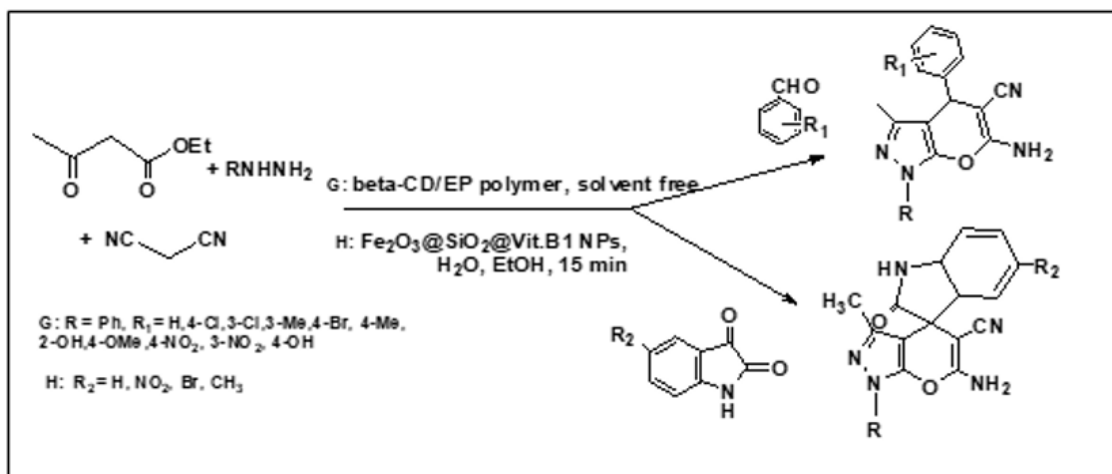
The nano-Schiff base nano-[Fe-PSMP]Cl₂ was applied by Moosavi-Zare *et al.* to prepare a pyranopyrazole derivative under solvent-free conditions at 1000°C (Moosavi-Zare *et al.*, 2018) (Scheme 26).

The heterogeneous nanocomposite Fe₃O₄@HNTs-PEI (Hajizade *et al.*, 2018) was used as a catalyst for the preparation of pyranopyrazole derivatives (Scheme 26). This catalyst can be reused without reducing yield of the product and catalytic activity. A polymer-supported catalyst (Gujaret *et al.*, 2014) was also reported for synthesizing pyranopyrazole derivatives.



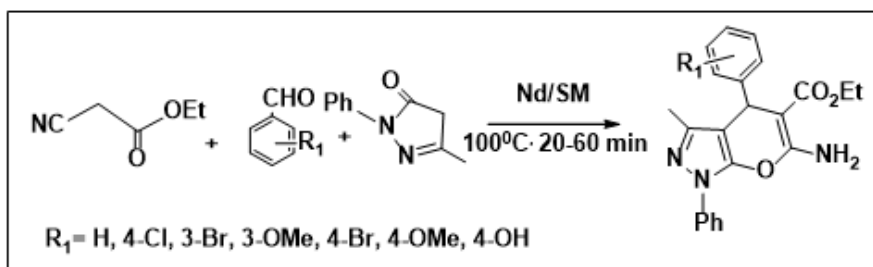
Scheme 26: Pyranopyrazole Derivatives Preparation in Presence of Heterogeneous Nanocomposite

The target molecules were reported to be synthesized in the presence of a heterogeneous catalyst, β -cyclodextrin-epichlorohydrin (β -CD/EP), a nano-sponge polymer, at 1000°C under solvent-free conditions (Jafari Nasab *et al.*, 2018) (Scheme 27). The pyranopyrazoles and spiropyranopyrazoles were also prepared by applying magnetic organo nano catalyst Vit B1 supported Fe₂O₃@SiO₂ NPs (Rahman *et al.*, 2018) in aqueous ethanol at 250°C. This NP increases the electrophilicity of carbonyl carbon and nitrile nitrogen by coordinating with them and facilitates the nucleophilic attack (Scheme 27).



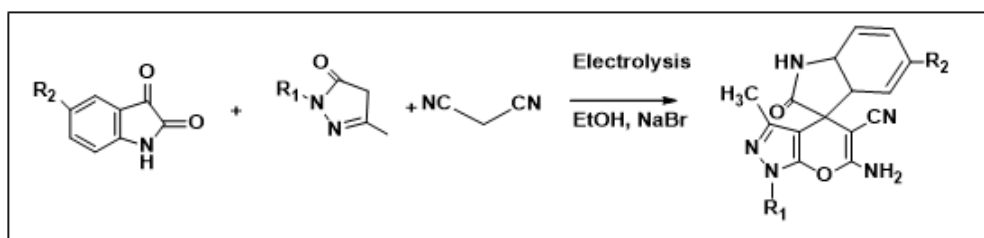
Scheme 27: Pyrano[2,3-c]pyrazole and Spiropyranopyrazoles Derivatives in Presence of Organonanocatalyst

Rather *et al.* (2018) applied a novel Nd-Salen Schiff base complex as a catalyst, prepared on mesoporous SiO₂ by adsorption of NdCl₃, to prepare pyranopyrazoles (Scheme 28).



Scheme 28: Pyrano[2,3-*c*]pyrazole Derivatives in Presence of Nd-Salen Schiff Base Complex

The novel electrolytic method was applied by Elinson *et al.* (2009), where he used sodium bromide as an electrolyte and indolone derivative as one of the components to synthesize spirocyclic indole-linked pyranopyrazole compounds (Scheme 29).



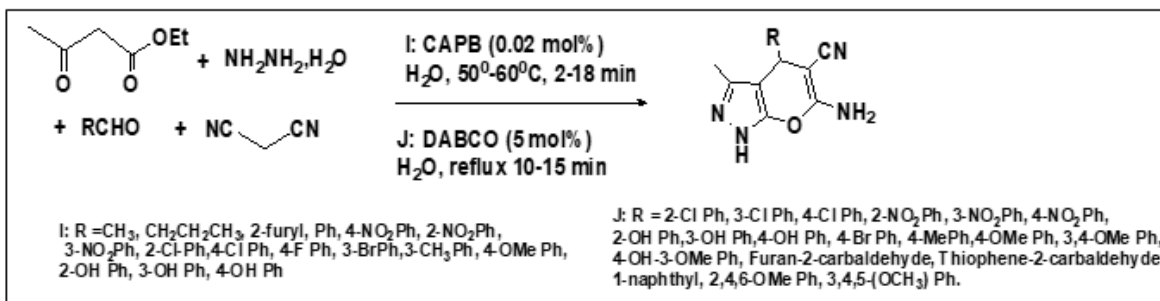
Scheme 29: Electrolytic Method of Pyrano[2,3-*c*]pyrazole Derivatives Synthesis

Using Organ Catalysts

Recently, organ catalysts are very popular for chemical reactions and have become an emerging area in green chemistry. Organocatalysis method is extensively used in organic and medicinal chemistry to design MCRs to avoid heavy transition metals.

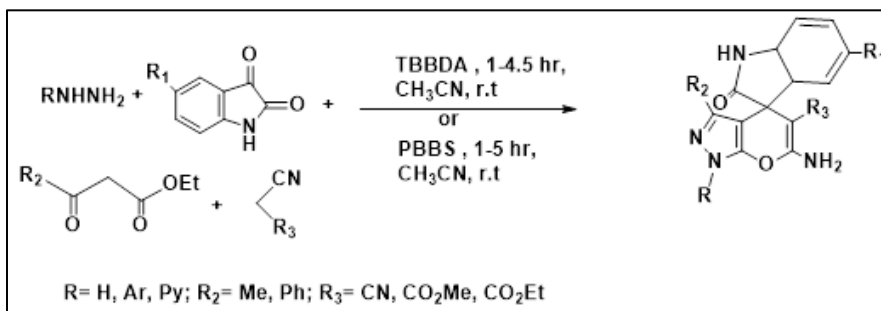
Organocatalysis offers metal free and environmentally friendly alternatives for facilitating MCRs. Catalysts such as DABCO, aspirin, maltose, sodium lactate, and zwitterionic surfactants have been successfully employed to achieve high yields with benign conditions (Tao *et al.*, 2016; Fiorani *et al.*, 2015).

Tamaddon and Alizadeh (Tamaddon *et al.*, 2014) designed a synthetic method of pyranopyrazoles using zwitterionic surfactant CPBA in water at 50^o-60^oC. The advantages of the use of CAPB as reported by them are (i) reaction condition became milder, (ii) catalyst may be reused, (iii) products were isolated easily (Scheme 30). DABCO is the most popular organo catalyst used in the MCRs to synthesize pyranopyrazoles. DABCO was applied by Waghmare *et al.* for one pot synthesis from four component reactions in water (Waghmare *et al.*, 2017) (Scheme 30).



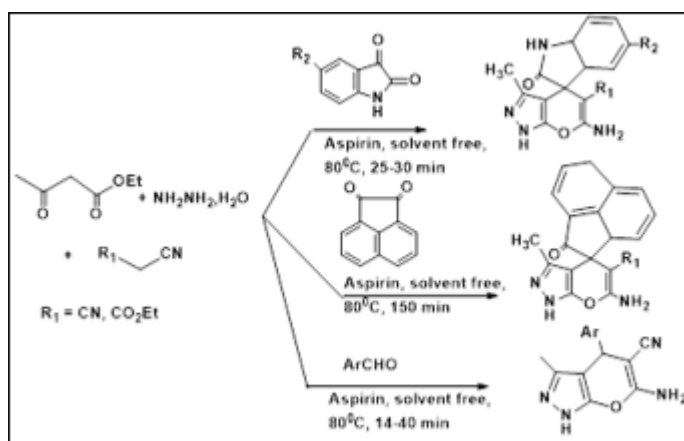
Scheme 30: Pyrano[2,3-*c*]pyrazole Synthesis Mediated by Organocatalysts

A new series of pyranopyrazoles from isatin derivatives was prepared successfully when TBBDA (N,N,N,N'-tetrabromobenzene-1,3-disulfonamide) and PBBS poly(N,N'-dibromo-N-ethyl-benzene-1,3-disulfonamide) were employed as organocatalysts (Ghorbani-Vaghei *et al.*, 2017). These catalysts were recovered and reused easily several times. The reuse of these catalysts did not change the yield of the desired product (Scheme 31).



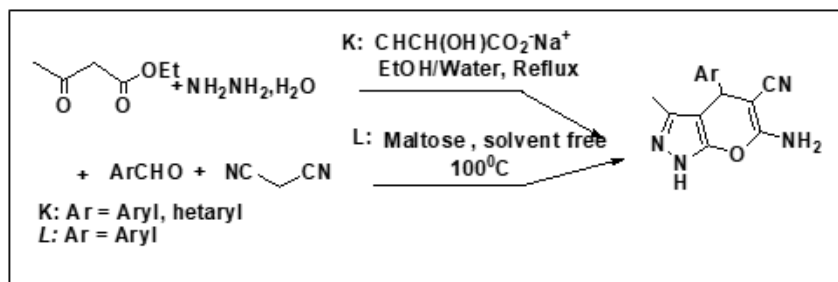
Scheme 31: Pyrano[2,3-*c*]pyrazoles from Isatins Mediated by Organocatalysts

Fatahpour *et al.* (2017) used aspirin as organo catalyst under solvent-free conditions at 80°C (Scheme 32).



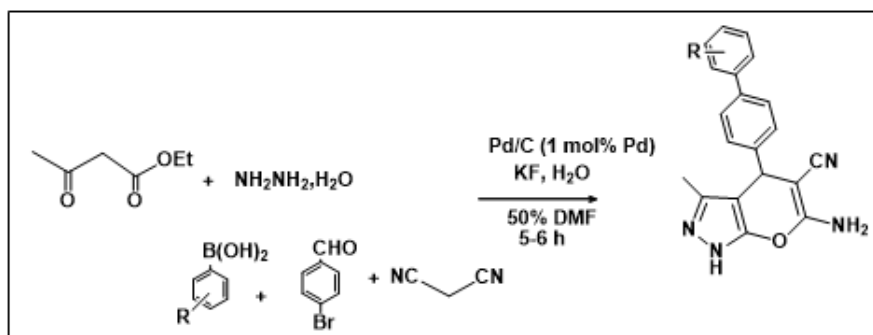
Scheme 32: Preparation of Pyrano[2,3-*c*]pyrazole Derivatives Employing Aspirin

Sonar *et al.* conducted the condensation reaction under reflux conditions in an aqueous ethanolic solution involving sodium lactate as an organocatalyst to synthesize pyranopyrazoles (Sonar *et al.*, 2019). Salahi and his team performed this reaction using maltose as a catalyst under solvent-free conditions (Kangani *et al.*, 2015) (Scheme 33).



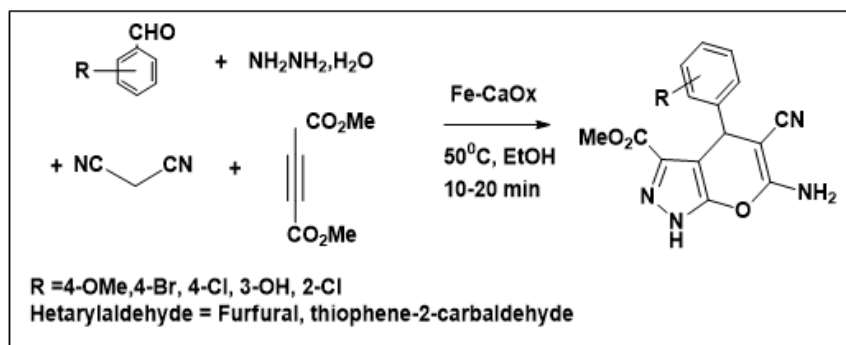
Scheme 33: Synthesis of Pyrano[2,3-*c*]pyrazole Derivatives Using Sodium Lactate, Maltose

A new series of biaryl-substituted pyranopyrazole derivatives was synthesized by using the inorganic catalyst $\text{KF} \cdot 2\text{H}_2\text{O}$ (Lu *et al.*, 2015). The biaryl system was prepared in situ by a Suzuki coupling reaction (Scheme 34).



Scheme 34: Using Inorganic Catalyst KF to Synthesise Pyranopyrazoles

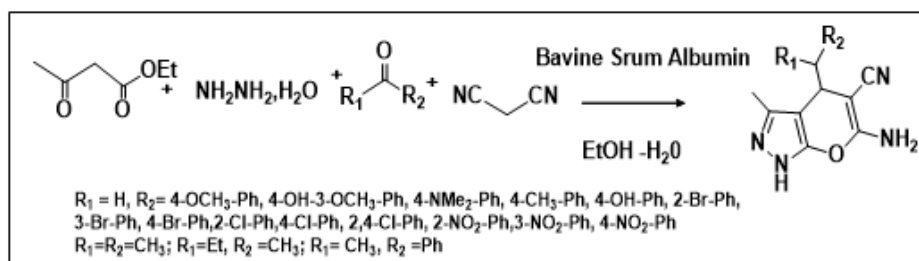
Gangu *et al.* (2017) performed a new synthetic approach by using dimethyl acetylene dicarboxylate as one of the components in presence of heterogeneous catalyst Fe-CaOx (Scheme 35).



Scheme 35: Pyranopyrazole Derivatives Synthesis Under Heterogeneous Catalyst Fe-CaOx

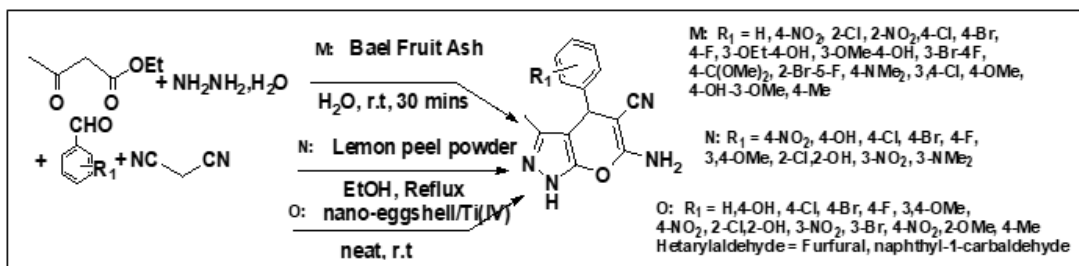
Using Biocatalyst

Biocatalysts are natural catalysts, such as enzymes, and they can catalyze chemical transformations. Biocatalysts have become increasingly popular because these are environmentally friendly and reduce the formation of by-products and waste in a chemical reaction. Biocatalysts also offer region and stereoselectivity, allowing for precise and complex transformations (Jumbam *et al.*, 2020). Xingtian *et al.* synthesized pyranopyrazole derivatives from various carbonyl compounds catalyzed by bovine serum albumin (BSA) at 45°C for 45 min in ethanol and reported good to excellent yield of the products (Huang *et al.*, 2016). BSA recovered easily and used another five times without affecting the yield (Scheme 36).



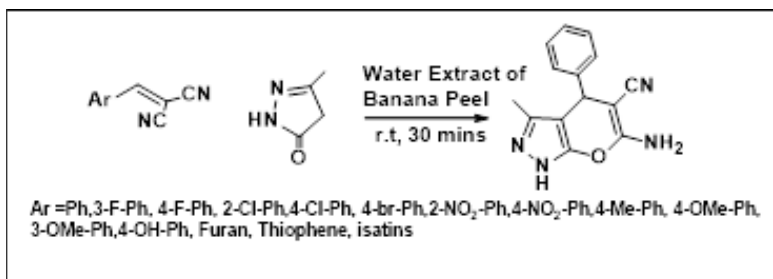
Scheme 36: Preparation of Pyrano[2,3-*c*]pyrazole Derivatives Employing BSA as a Catalyst

The successful application of natural catalysts, e.g., bael fruit ash (Shinde *et al.*, 2017), lemon peel powder (Ghodke *et al.*, 2020), and nano-eggshell/Ti(IV) (Tafti *et al.*, 2021), was reported for the synthesis of pyranopyrazole derivatives in mild conditions (Scheme 37).



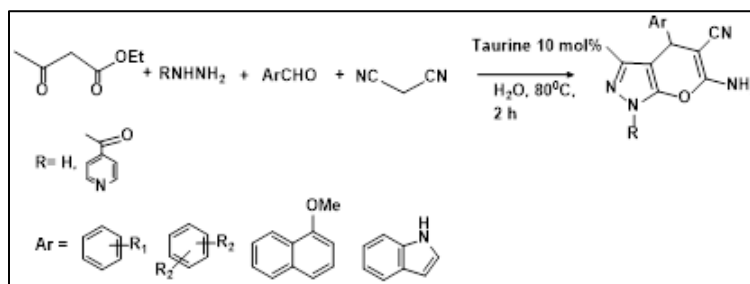
Scheme 37: Some Natural Catalysts to Synthesise Pyranopyrazole Derivatives

Another excellent natural catalyst, Water Extract of Banana Peels (WEB) was reported in the preparation of pyranopyrazoles by Chowhan and his group (Dwivedi *et al.*, 2020) (Scheme 38).



Scheme 38: Water Extract of Banana Peels used as natural catalyst

The use of taurine as a catalyst in the production of densely substituted Pyrano[2,3-c]pyrazoles has been described recently (Mali *et al.*, 2021) (Scheme 39).

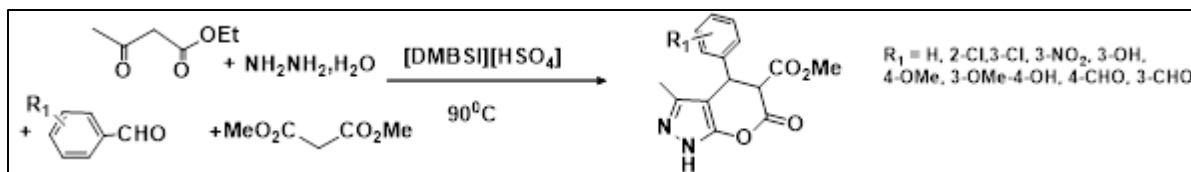


Scheme 39: Synthesis of Pyrano[2,3-C]Pyrazole Derivatives in Presence of Taurine

The biocatalysts, being biodegradable with minimal waste, have excellent selectivity. The challenges include issues related to enzyme stability and the difficulty of reusing enzymes compared to nanocatalysts.

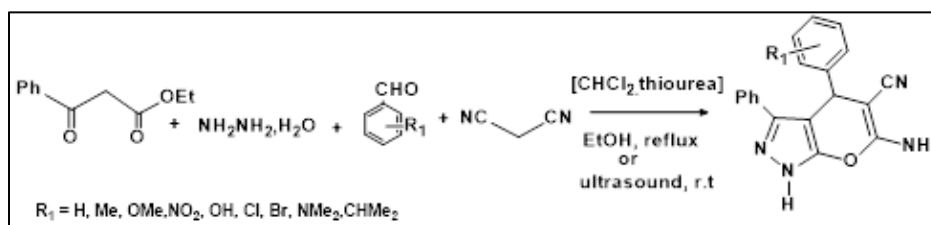
Using Ionic Liquids

In modern research, ionic liquids (ILs) are being successfully utilized as environmentally friendly catalysts and solvents in chemical reactions. The SO₃H-functionalized ionic liquid ([DMBSI]HSO₄) was reported to be employed in the synthesis of pyranopyrazoles under different green technical conditions (Farokhian *et al.*, 2018) (Scheme 40) (Zakeri *et al.*, 2017) (Scheme 42).

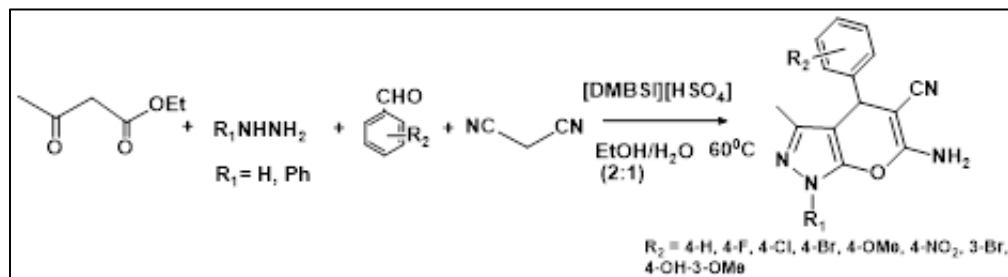


Scheme 40: Pyranopyrazole Derivative Synthesis Applying Ionic Liquid ([DMBSI]HSO₄)

Alikarami and his team described a synthetic route of a new series of substituted pyranopyrazoles using choline chloride-based thiourea (ChCl₂.Thiourea) (Dehbalaei *et al.*, 2017). The synthesis was carried out at room temperature under ultrasound, and the catalyst was recovered easily from the reaction mixture and reused successfully for the next reaction (Scheme 41).

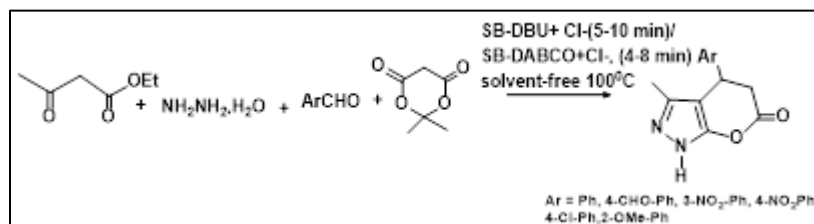


Scheme 41: Preparation of Pyranopyrazole Derivatives Mediated by Choline Chloride-Based Thiourea



Scheme 42: Pyranopyrazole Derivative Synthesis Catalyzed by [DMBSI]₂HSO₄

The silica-supported ionic liquids have become very popular ILs recently (Mamaghani *et al.*, 2021), and a number of synthetic strategies were developed by applying these catalysts, resulting in a high yield of the products (Rigi *et al.*, 2017). (Scheme 43).



SB-DBU⁺Cl⁻ = silica bonded diazabicycloundec-7-enium chloride;

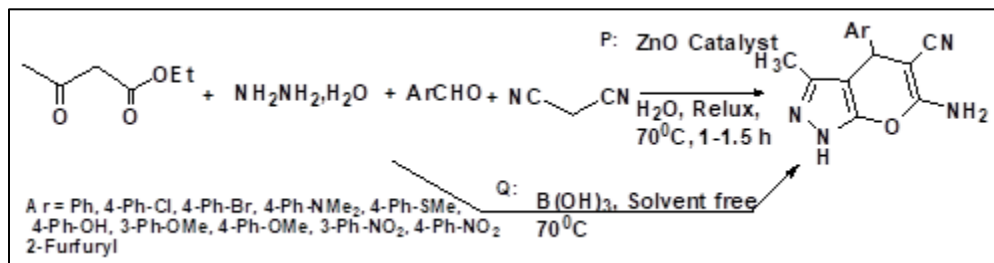
SB-DABCO⁺Cl⁻ = silica bonded *n*-propyl-4-aza-1-azoniabicyclo [2.2.2] octane chloride

Scheme 43: Synthesis of Pyrano [2,3-*C*] Pyrazole Derivatives Using Silica-Supported Ionic Liquids

Ionic liquids play dual role as solvent and catalyst. But high cost, toxicity is considered as the limitations of using these.

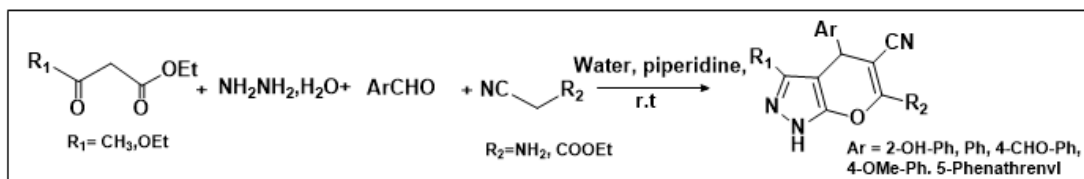
Using water as green solvent and solvent free condition

Recently, water has been widely used as a green solvent since it is inexpensive, environmentally friendly, non-toxic and cost-effective. The S. U. Tekale group reported new pyranopyrazole derivatives in water in the presence of a ZnO catalyst (Tekale *et al.*, 2013). A new approach to using boric acid solution in solvent-free conditions was applied as a green acid catalyst (Scheme 44).



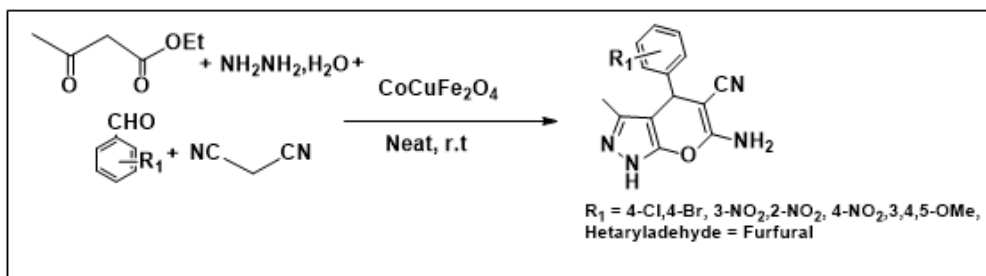
Scheme 44: Synthesis of Pyranopyrazole Derivatives Using ZnO and Boric Acid as Acid Catalysts

A base-catalyzed one-pot preparation of pyrano[2,3-c]pyrazole derivatives in a water-piperidine system has recently become very effective owing to its simplicity (Scheme 45).



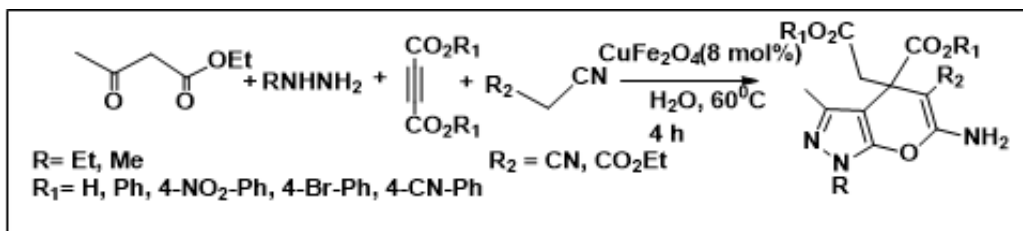
Scheme 45: Pyranopyrazole Derivative Synthesis in Water

Another solvent-free synthetic route was described by Dadaei where amagnetic nanocrystals CoCuFe₂O₄ were applied (Dadaei *et al.*, 2022) (Scheme 46).



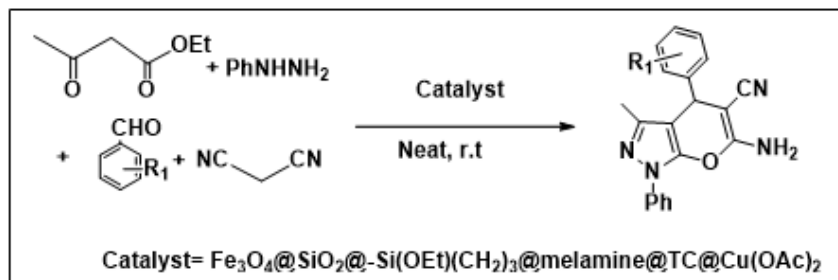
Scheme 46: Pyranopyrazole Derivatives Using CoCuFe₂O₄

Pradhan *et al.* synthesized pyrano[2,3-c]pyrazoles in the presence of a CuFe₂O₄ nanocatalyst in aqueous medium (Pradhan *et al.*, 2014) (Scheme 47).



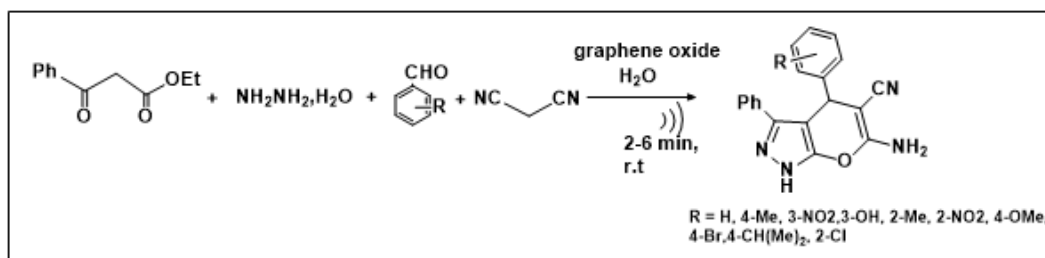
Scheme 47: Pyranopyrazole Synthesis in the Presence of Nanocatalysts in an Aqueous Medium

Nanomagnetic catalyst $\text{Fe}_3\text{O}_4@\text{SiO}_2@-\text{Si}(\text{OEt})(\text{CH}_2)_3@\text{melamine}@\text{TC}@\text{Cu}(\text{OAc})_2$ was used to produce pyranopyrazole in high yield under solvent-free conditions. (Soleimani *et al.*, 2024) (Scheme 48).



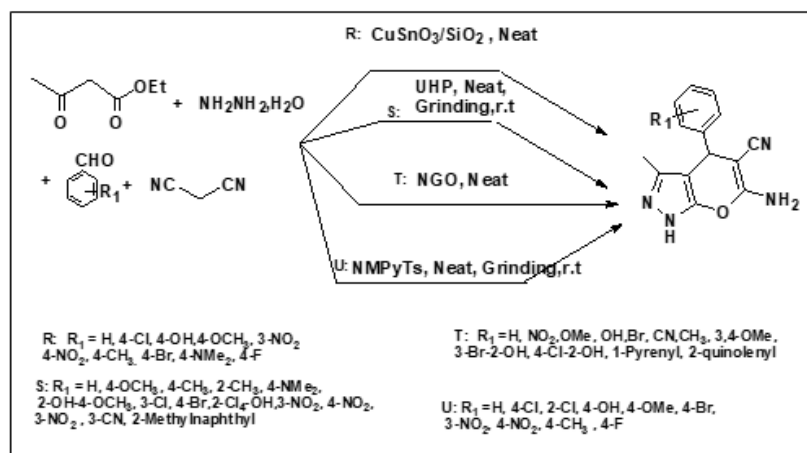
Scheme 48: Pyranopyrazole Derivatives Preparation Using Nanomagnetic Catalyst

Foroughifar's group synthesized, under ultrasound assistance, the target molecules catalyzed by 10 mol% graphene oxide with vigorous stirring. The reaction was performed at room temperature in an aqueous medium for 2–6 min with excellent yield (Dehbalaei *et al.*, 2018) (Scheme 49).



Scheme 49: Pyrano[2,3-*c*]pyrazole Derivatives on Graphene Oxide

The pyranopyrazole derivatives were synthesized in solvent-free conditions by applying the $\text{CuSnO}_3:\text{SiO}_2$ catalyst (Sangle *et al.*, 2022). Verma *et al.* (2022) designed a solvent-free, eco-friendly synthesis of pyranopyrazole derivatives mediated by urea hydrogen peroxide. The solid-base heterogeneous catalyst nitrogen-doped graphene oxide (NGO) was utilized by S. Ganesan and his team (Saravana *et al.*, 2020), whereas Sapkal *et al.* (2020) introduced ionic liquid (NMPyTs) as a catalyst to prepare pyranopyrazole derivatives by grinding technique at room temperature (Scheme 50).



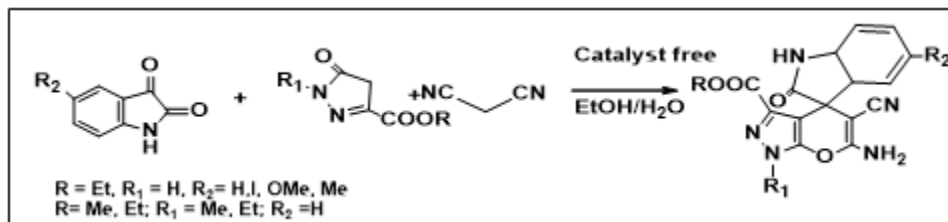
Scheme 50: Pyrano[pyrazole] Derivative Synthesis Without Solvent

Pyrano[pyrazole] derivative synthesis without solvent Most of the reactions, except reactions with hydrophobic substrates, have taken place in water with excellent atom economy. The advantages of using water as a green solvent are that (i) it is non-toxic and (ii) inexpensive.

Using Catalyst Free Condition

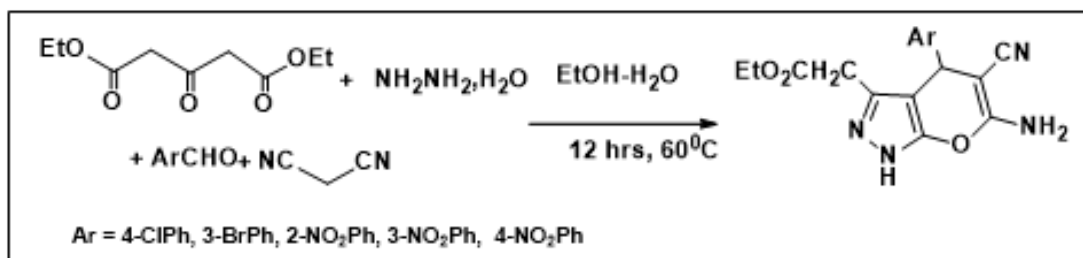
Several catalyst-free protocols—including ball milling, magnetized water, and thermal MCRs—have been introduced as the ultimate expression of green chemistry, eliminating the need for added reagents while achieving high efficiency.

Pore *et al.* designed a green catalyst-free synthesis for pyranopyrazole using isatin and DMAD (Pore *et al.*, 2013) (Scheme 51).



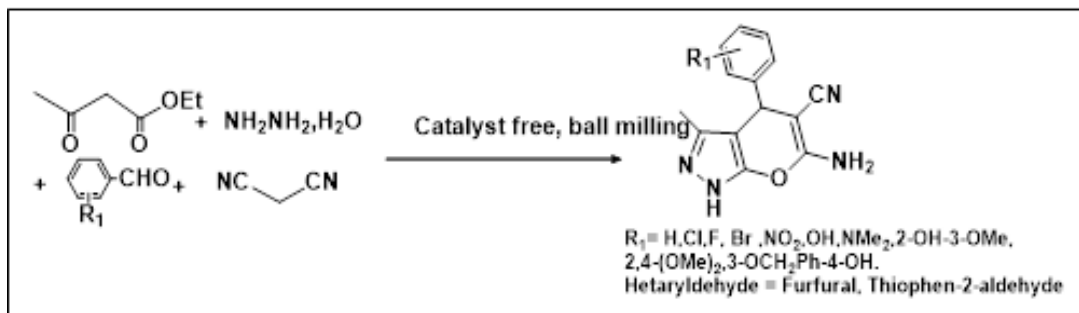
Scheme 51: Pyranopyrazole Derivatives from Isatins without Using Any Catalyst

A region and stereoselective synthesis were done taking dialkyl 3-oxopentanedioate in water/ethanol without catalyst. It took 12 hours to get to the target molecules (Kooreshari *et al.*, 2014) (Scheme 52).



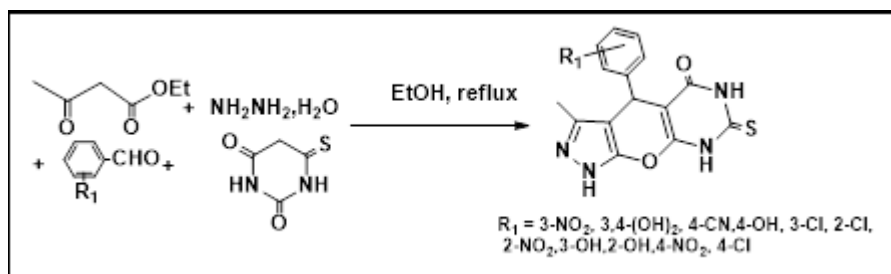
Scheme 52: Catalyst Free Synthesis of Pyranopyrazole Derivatives Using Aqueous Ethanol

Ball milling technique (Dekamin *et al.*, 2016) was used to synthesize pyranopyrazole (Scheme 53).



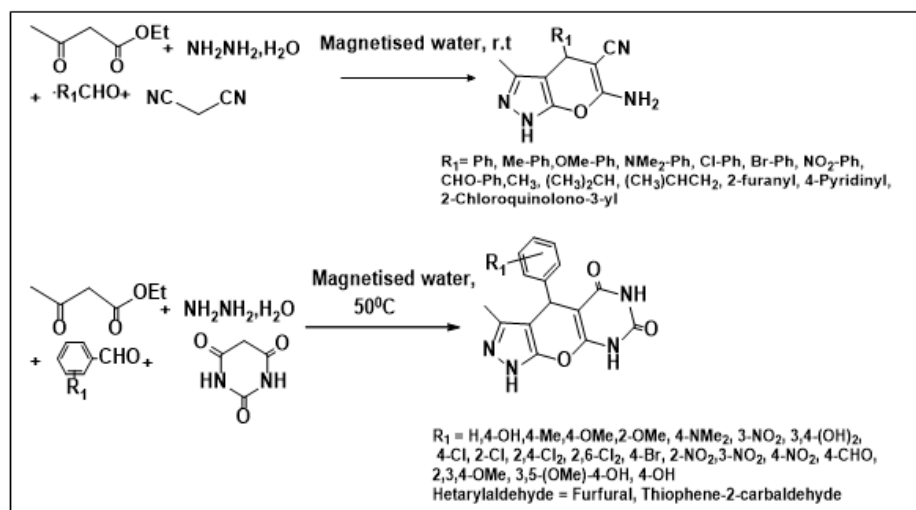
Scheme 53: Catalyst Free Preparation of Pyranopyrazole Derivatives with Ball Milling Technique

A catalyst-free four component synthesis of pyrazolo thiopyrimidines was reported (Patil *et al.*, 2017) and the compounds were found to exhibit antituberculosis activity (Scheme 54).



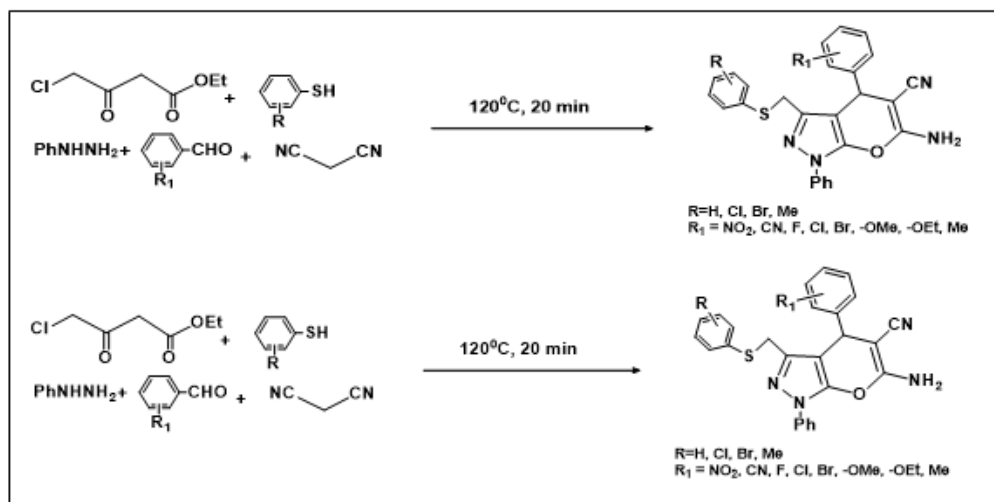
Scheme 54: Catalyst Free Synthesis of Pyrano[Pyrazoles from Thiopyrimidine

The synthesis of the new series of pyranopyrazole and pyranopyrimidine was also reported using magnetized water at room temperature (Bakherad *et al.*, 2017) (scheme 55).



Scheme 55: Synthesis of Pyrano[2,3-*C*]Pyrazole and Pyrano[2,3-*C*]Pyrazolo[2,3-*D*]Pyrimidine Using Magnetized Water without Using a Catalyst

Ramesh *et al.* (2016) described a solvent-free as well as catalyst-free synthetic route for the synthesis of thioether-linked pyranopyrazoles (Scheme 56).



Scheme 56: Catalyst-free Preparation of pyrano[2,3-*c*]pyrazole Derivatives

Catalyst free reactions are free from the contamination of catalysts and often takes longer time.

Table 1: Critical Comparison of Green Multicomponent Strategies for the Synthesis of Pyrano[2,3-*c*]pyrazoles

Green Technique	Conditions	Advantages	Major limitations	Sustainability Assessment
Ultrasound-assisted MCRs	Aqueous /aqueous–alcoholic media, r.t.–60 °C	- Short reaction times; - enhanced mass transfer; - often catalyst-free or mild catalysts	- Limited scalability; - Equipment dependency; - reduced efficiency for poorly soluble substrates	High
Microwave-assisted MCRs	Solvent-free or green solvents; short irradiation time	- Dramatic reduction in reaction time; - high yields; - energy efficiency	- Scale-up challenges; - uneven heating in some systems	High–Moderate
Nanocatalyst-based MCRs	Water or ethanol; r.t.–reflux	- High catalytic activity; - recyclability; - mild conditions	- Catalyst synthesis may be multistep; - long-term environmental impact uncertain	Moderate
Organocatalyst-based MCRs	Water, ethanol, or solvent-free; mild temperatures	- Metal-free; - inexpensive catalysts; - operational simplicity	- Catalyst loading sometimes high; - limited asymmetric versions	High
Biocatalyst-based MCRs	Aqueous or aqueous–alcoholic media; mild temperatures	- Excellent selectivity; - biodegradable catalysts; - minimal waste	- Narrow substrate scope; - enzyme stability - reuse issues	Very High
Ionic liquid-mediated MCRs	Solvent-free or aqueous systems; moderate heating	- Dual role as solvent and catalyst; - high efficiency; - recyclability	- Toxicity concerns; - high cost; - challenging purification	Moderate–Low
Water as green solvent	r.t.–reflux; simple bases or acids	- Non-toxic; - inexpensive; - excellent atom economy	Poor solubility of hydrophobic substrates	Very High
Solvent-free protocols	Thermal, MW, grinding	- Minimal waste; - high atom economy; - fast reactions	- Mixing issues; - temperature control limitations	High
Catalyst-free approaches	Water, ethanol, ball-milling, magnetized water	- Ultimate green strategy; - no catalyst contamination	- Often longer reaction times; - limited substrate scope	Very High

Scope and Outlook

From a comparative perspective, the recent study reveals that the multicomponent reactions offer distinct advantages in terms of green chemistry principles. Nevertheless, the sustainability of certain methodologies remains limited by some factors such as catalyst synthesis complexity, scalability constraints and also long-term environmental impact of some nanomaterials and ionic liquids.

Looking ahead, the recent studies will help the researchers to prioritize the development of genuinely benign and scalable catalytic systems derived from renewable and biodegradable resources along with mechanistic understanding. Improving catalyst durability and recyclability as well as expanding

asymmetric and enantioselective multicomponent protocols may lead the future research on the synthesis of these heterocycles to promising directions.

Conclusion

This review critically summarizes the recent trends in green multicomponent approaches to biologically active pyrano[2,3-c]pyrazole derivatives. The integration of alternative energy sources like MW and ultrasound together with nanocatalysts, organocatalysts, biocatalysts and ionic liquids has increased the efficacy of the reaction.

Instead of high yield, shortened reaction times, and mild reaction conditions, challenges remain with respect to nanocatalyst preparation as well as the use of ionic liquids. So, researchers should focus strongly on developing universally benign catalysts in the future to improve the industrial applicability.

Overall, the study discussed herein underscores the potential of green multicomponent reactions as powerful tools for the sustainable synthesis of pyrano[2,3-c]pyrazole derivatives.

The author looks forward to this review encouraging the researchers to embrace these eco-friendly methods, paving the way for cleaner and more sustainable practices.

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Conflict of Interest

The author declares no conflict of interest.

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