Green Synthesis of Pyrazoles: Recent Developments in Aqueous Methods

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Abstract:
Abstract Organic syntheses by adopting green protocols such as sonochemical procedures, microwave technologies, solvent-free conditions, green solvent, heterogeneous catalysis particularly nanocatalysts, ionic liquids have replaced the traditional procedures due to concerns pertaining especially to environment. The heterocycle, pyrazole, due to its multifaceted applications has been the cyanosure of the chemists and therefore various synthetic approaches have been developed to synthesize the pyrazole containing molecules. In the present compilation, we have summarized the recent water-based research work on the synthesis of pyrazoles.

Key words: Green chemistry, environment friendly, water based synthesis, pyrazoles

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Green Synthesis of Pyrazoles: Recent Developments in Aqueous Methods

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Abstract: Organic syntheses by adopting green protocols such as sonochemical procedures, microwave technologies, solvent-free conditions, green solvents, heterogeneous catalysis particularly nanocatalysts, ionic liquids have replaced the traditional procedures due to concerns pertaining especially to environment. The heterocycle, pyrazole, due to its multifaceted applications has been the cyanosure of the chemists and therefore various synthetic approaches have been developed to synthesize the pyrazole containing molecules. In the present compilation, we have summarized the recent water-based research work on the synthesis of pyrazoles.

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1. Introduction
There is great concern in the utilization of chemicals and polymers for production processes, which have detrimental effects on public health and the global environment. For the society and human wellbeing, various environmentally benign organic transformations are being devised, with minimization of chemical waste, atom economy, energy savings, easy work ups, alternative catalysts and procedures, chromatography free isolation of the products. The utilization of eco-friendly synthetic techniques like “Green chemistry” came into consideration for the synthetic chemist to develop products in the desired quantity.

The green approaches which are mainly considered for the organic synthetic reactions are (i) use of green solvents like nature’s solvent, the water, as reaction medium instead of organic solvent (ii) reactions in solid state without using any solvent at all (iii) using catalytic amount of organometallic reagents instead of stoichiometric amounts (iv) preference for biosynthetic processes. For the synthesis of heterocyclic compounds, many green methods have been applied6–9 performing the reactions at ambient temperature and using alternative energy sources being the methods of choice.

The organic reactions are mainly performed in organic solvents thus giving rise to huge amount of the solvent waste which is hazardous to the aquatic organisms and pollutes the underground water. Use of aqueous media, a non-polluting abundant solvent, for organic syntheses is very important area of the green chemists which is receiving special attention in the past three decades.10–14

The present compilation elaborates the water-based synthesis of pyrazoles including the fused ones with and without catalyst. Pyrazole is a versatile ring among heterocyclic compounds as pyrazole compounds are involved in plethora of applications, including; industries, medications, pharmaceutics, agriculture, polymers, luminophores, dyes, etc.15 Pyrazole containing compounds have various therapeutic and pharmaceutical properties and represent important building blocks for, insectoacaricidal,16 antibacterial,17 antifungal, analgesic, antiviral, anticancer, antioxidant, anti-HIV, COX-2 inhibitor, anti-inflammatory, antiproliferative drugs.18–26 Many of the derivatives are of great interest due to their pharmacological properties, for instance, Celecoxib (4-[5-(methylphenyl)-3-fluoromethyl] pyrazol-1-yl) benzene sulphonamide) acts as inhibitor of cyclo-oxypenate-2 (COX-2) and reduces side effects in the gastrointestinal tract. Methyliopryazolopeithione B shows strong antitumor activity. Functionalized pyrazoles and suitably substituted pyrazoles such as Pyrano[2,3-c]pyrazole, benzopyrano[2,3-b]pyrazoles, pyrazolopyrimidines, furanopyrazoles, Tetrahydropybenzo[b]pyrans and many others show a wide range of biological activities [Fig. 1].27–30

![Figure 1 Medicinally important pyrazole derivatives](image)

Due to multifacetted applications of the pyrazole derivatives, a quite good number of methods for the attainment of the heterocycle have been developed using A1O2s/clay (montmorillonite K10), Amberlyst-70, polymer bound PTSA, silica-supported sulphuric acid (H2SO4/SiO2), Sc(OTf)3, sulphamic acid as catalysts. Various environmentally benign protocols using green solvent have also been reported in the literature including the synthetic methods using water as solvent. The current review paper is an effort towards compiling the recent work done on the water-based syntheses of pyrazole derivatives (from 2015 till 2022) to facilitate the scientists working or intended to work in this important field.

1. Synthesis of Polyfunctionalized Pyrazoles

Synthesis of the pyrazolone derivatives 5 was reported in water by Akondi et al. in 2016 and the yield obtained was 85–92%. For the multicomponent reaction, the heterogeneous Lewis acid, CeO2/SiO2 (0.9%) was used as catalyst (Scheme 1). All the newly synthesized compounds 5 were evaluated for in vitro antimicrobial activity. For antibacterial activity, the derivatives containing halogen and nitro groups were found to be more useful. For antifungal activity, the dinitro substituted pyrazolone derivatives were found to be even better than the standard drug, ketoconazole used for the work.27

![Scheme 1 Synthesis of 3-pyrazolone derivatives using CeO2/SiO2 in water](image)

The room temperature reaction of different aryl hydrazines with malononitrile derivatives offered the synthesis of several 5-amino-4-cyanopyrazoles in high yield of 89–97%. The reaction executed by Elnagdy and Sharma in 2019 became successful by using the homogeneous catalyst FeCl3-PVP (5 mol % FeCl3) in the water/PEG-400 (2:1) medium for 2–4 h (Scheme 2).30
Ceric ammonium nitrate catalyzed synthesis of substituted polyfunctionalized pyrazoles 8 has been achieved starting from aromatic aldehydes, malononitrile and aryldiazonitriles by Kadu et al. in 2019. The solvent system used herein is PEG-400: H₂O, PEG plays the role of solvent as well as promoter [Scheme 3].

Dehghan-Manshadi et al. in 2021 have reported the CeO₂/CuO@GQDs@NH₃ nanocomposite catalyzed reaction of phenylhydrazine, dimethyl acetylenedicarboxylate and arylaldehyde at ambient temperature in water solvent to obtain the bispyrazole derivatives 9 in good yield (82-94%). Initially, the reaction was attempted in the presence of p-TSA, Et₃N, CeO₂/CuO, CeO₂/CuO@GQDs and CeO₂/CuO@GQDs@NH₃ nanocomposite. Different concentrations of the catalyst under different solvents were attempted. The nanocomposite acted as the best catalyst for the synthetic protocol using the nature’s solvent [Scheme 4].

An environment friendly aqueous synthesis of tetrasubstituted pyrazoles 10 is achieved in the presence of cetyltrimethylammoniumbromide (CTAB) by using aldehydes, EAA, PhNHNH₂/ NH₂NH₂·H₂O in one pot [Scheme 5]. The reaction developed by Bansal et al. has also been used for the synthesis of sullinic esters. The work has also elaborated the application of electrochemistry.

3. Synthesis of Fused pyrazoles in water without catalyst

3.1 Fused [5-5]system (3 heteroatoms): Furo[2,3-c]pyrazole

Synthesis of some new fused furopyrazoles 11 has been done using a four component system without involving any catalyst in the reaction at room temperature by Noruzian et al. [Scheme 6]. The domino reaction when applied to amines with electron withdrawing groups furnished the unexpected bis(pyrazole-5-ol) products.

3.2 Fused [5-6]system (3 heteroatoms): Pyrano[2,3-c]pyrazoles

The reaction of ethylacetatoacetate, aromatic aldehydes and hydrazine was carried out with malononitrile or pyrimidine trione under magnetized water to offer pyrano[2,3-c]pyrazoles 12 or pyrano[4',3':5,6]pyrazolo[2,3-d]pyrimidines 13 respectively [Scheme 7]. The reaction could not be commenced in non polar solvents and in polar-prootic solvents (EtOH, MeOH) yield was poor. It was suggested that hydrogen-bond interactions at the organic-water interface are responsible for the stabilization of the intermediate. The reaction has the wide applicability for differently substituted aromatic and hetaromatic aldehydes such as furan-2-, thiophene-2-, pyridine-4- and 2-chloro quinolone-3-carbaldehydes.

3.3 Fused [5-6]system (3 heteroatoms): Pyrazolo[3,4-b]quinolone
Zhu et al. in 2018 have synthesized the spiro compounds, spiro[indoline-3,4'-pyrazol][3,4-b]quinoline]-2,5'- (6'H)-diones 14 by taking different isatins, 3-aminoypyrazole, cyclohex-1,3-dione or dimerone as reactants and H2O:AcOH (4:1) as the solvent system at 90 °C for 5-7 h. The reaction was also attempted at lower temperature but in vain. The pure solvents, pure water or pure acetone were also tried but the yields were poor. (Scheme 8).

4.2 Fused [5-6] system (3 heteroatoms): Pyrano[2,3-furopyrazoles]

Aromatic aldehydes and 1,3-disubstituted pyrazolones underwent condensation while refluxing in water for a time period of 30 min. To the reaction mixture, 2-[bis(acetoxymethyl)iodo]benzene (BAIB) was added and the reaction mixture was stirred for 5 min at room temperature to get spirofuropyrazole derivatives 16. In the same year using the above reactants and pyridinium salt, the synthesis of furopyrazoles 17 was achieved by Yazdani-Elah-Abadi et al. 2018 by employing the catalyst 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction was performed in water using microwaves (Scheme 9, Scheme 10).

ZrO2 nanoparticles were used as reusable catalysts for the multicomponent synthesis of derivatives of dihydropyran[2,3-c]pyrazoles 12 (yield 90-98%) at room temperature within 2-10 minutes by Saha et al. Liu et al. have utilized L-proline as catalyst in the synthesis of spiro[indoline-3,4-pyra-[2,3-c]pyrazole derivatives 15 in 84-93% yield. For the multicomponent synthesis 1:1 v/v EtOH/H2O was used as solvent and the reaction was performed under ultrasonication to obtain the targeted compounds within 60 min time period (Scheme 11).

4.2 Fused [5-6] system (3 heteroatoms): Pyrano[2,3-c]pyrazole

Scheme 8 Preparation of spiro[indoline-3,4'-pyrazol][3,4-b]quinoline]-2,5'(6'H)-diones in water: acetone

Scheme 9 BAIB mediated fusion of pyrazolones with aldehydes

Scheme 10 DABCO mediated synthesis of furopyrazoles

4.3 Synthesis of Fused pyrazoles in water using catalyst

4.1 Fused [5-5] system (3 heteroatoms): Furo[2,3-c]pyrazoles

Two series of pyrazole products, pyrazolopyridines 19 and pyranopyrazoles 12 were obtained by performing the reactions at 50 °C under ultrasonication by Shabalala et al. in 2015. The pure products were achieved without the need for chromatography (Scheme 12).

Various nanoparticles have been applied as catalysts for the synthesis of fused pyranopyrazoles. Fe@SiO2 core-shell NPs have been used by Soleimani et al. for constructing the fused pyrazole derivatives in H2O:EtOH.

The application of biodegradable β-cyclodextrin (β-CD) as a catalyst in the four-reactant domino synthesis of pyran[2,3-c]pyrazoles 12 and spiro[indoline-3,4-pyra-[2,3-c]pyrazole] products 15 & 18 has been explored by Tayade and his co-workers in 2015. The reaction progressed successfully with EAA, malononitrile, hydrazine hydrate and aldehydes (aryl or hetaryl) 1,5-disubstituted isatins/1,1-(butane-1,4-diy)bisis(indole-2,3-dione) in H2O-EtOH (9:1) at 80 °C (Scheme 13).

Template for SYNTHESIS
In the year 2016, Javad et al. prepared Preyssler-heteropoly acid (H₃NaP₆W₁₄O₄₉) supported silica coated NiFe₂O₄ magnetic NPs (NiFe₂O₄@SiO₂-Preyssler/NPS-PRS) and employed it for the synthesis of 25 pyrano[2,3-c]pyrazole derivatives 12 under green conditions using water as a solvent.

The preparation and application of nano structured diphosphate, Na₂CaP₂O₇ has been done by Maleki et al. in 2016 for synthesizing two series of dihydropyran[2,3-c]pyrazoles 12 and spiro[indoline-3,4-pyrano[2,3-c]pyrazole] products 15 (Scheme 14) ³5. All the reactions were performed under reflux condition in water solvent. The catalytic approach is efficiently extendable to a wide variety of aromatic aldehydes to produce the solo expected product.

Several 5-substituted 6-amino-3-methyl-4-aryl-1,4-dihydropyran[2,3-c]pyrazoles have been synthesized by many research groups by applying different catalysts. The group of Vekariya in 2016 used the juice of Citrus Limon (lemon juice) in aqueous ethanol³⁶. The research group in the very same year applied the organocatalyst thiourea dioxide (TUD) for this reaction conducted in water³⁷. The biocatalyst, bovine serum albumin (BSA) was used by Dalal et al. for making different types of pyrano[2,3-c]pyrazoles 12 and spiro pyrano[2,3-c]pyrazoles 15 (Scheme 15)³⁸.

Zhou et al. worked with Lewis acid catalyst morpholine trflate (MorT)³⁹ (Scheme 16).

Moeinpour, and Khajastehnezhad⁴⁰ in 2017, have also reported the synthesis of 5-cyano-1,4-dihydropyran[2,3-c]pyrazoles 12 in water and the catalyst used was Ni₃Zn₅Fe₄O₄PPAnanoparticles (0.03 g, 0.015 mmol H⁺) in 86-94% yield. The catalyst was recyclable at least up to six times.

Similarly Abad and Farooqui in 2017 have made a range of the pyrano[2,3-c]pyrazole compounds 12 in aspartic acid as an efficient organocatalyst in EtOH/H₂O solvent system (Scheme 17)⁴¹.

Cyclocondensation of EAA, NH₂NH₂·H₂O, CH₃(CN)₂ and chromene-carbaldehyde resulted in the construction of several coumarin-based dihydropyran[2,3-c]pyrazole derivatives by using the base catalyst 4- dimethylamino pyridine (DMAP) in the dual solvent EtOH/H₂O at ambient temperature condition. The plausible mechanism that explains this transformation involves Knoevenagel condensation, intramolecular cyclization and tautomerization to offer the title compounds in 82-92 % yield (scheme 18)⁴².
Waghmare et al. developed the four component cyclocondensation reaction for obtaining twenty dihydropyranopyrazole derivatives 12 using DABCO catalyst (5 mole%) in aqueous medium (Scheme 19) by refluxing the reaction mixture. The reaction did not work with the other solvents attempted for the reaction like THF, EAA, EtOH, MeCN and the percentage yield obtained was very poor.

Similarly, the group of Fatahpour applied Ag/ TiO₂ nano films as heterogeneous catalysts for the reaction. Ghorbani-Vagheh et al. studied the application of Fe₃O₄/SiO₂ nanoparticle supported ionic IL, Fe₃O₄@SiO₂@piperidinium benzene-1,3-disulfonate, for this very reaction conducted in water (Scheme 20).

The reaction of EAA, NH₂NH₂.H₂O, CH₂[CN] is accomplished with variously substituted aromatic aldehydes or isatins to provide dihydropyran[2,3-c]pyrazole 12 & spiro[indoline-3,4-pyrazole] derivatives 15 by using the Fe₃O₄/SiO₂ NPs functionalized with vitamin B1. The reaction was carried out in aqueous ethanol at room temperature while stirring the reaction mixture by Rahman et al in 2018 (Scheme 21).

Devi et al. have employed the sodium dodecyl sulfate (SDS) catalyst for the three-component room temperature synthesis of spiro[indoline-3,4-pyrazole] compounds 15 in water solvent. The reaction offered the spiro products in 80-91% yield (Scheme 22).

Konalanchi and his research group has described the use of sodium fluoride for making the derivatives of 12 by applying ultrasonic waves for 5-10 min. The water-ethanol solvent was used to obtain the target compounds in 88-98% yield (Scheme 23).

The use of green and ecofriendly natural catalyst, Bael fruit ash (BFA) along with the substrates aromatic/betaaromatic aldehyde, EAA, NH₂NH₂.H₂O, CH₂[CN] offered an efficient aqueous synthesis of pyrano[2,3-c]pyrazole 12 at RT by Shinde et al. (Scheme 24). The reaction is successful to make twelve derivatives of the fused pyrazoles in 86-94% yield at room temperature.
In 2017, Patel et al. have utilized the agricultural waste wheat straw and derived nano-silica from it which was used as catalyst for the formation of fused pyranopyrazoles in aqueous medium at 80 °C. Different monosubstituted aromatic aldehydes have been used successfully by using the green catalyst (Scheme 25)\(^1\).

Kiyani et al. revealed the utility of the environment-friendly heterogeneous catalyst sodium ascorbate for the synthetic reaction of derivatives of 12 in water (Scheme 27)\(^2\).

Jayant P Sonar et al. worked with triethanolamine as well as sodium lactate catalyst (Scheme 29) and Khande Bharad et al. with the recyclable organocatalyst sodium gluconate (Scheme 30)\(^3\).

Reddy and co-workers constructed thirteen dihydropyran[2,3-c]pyrazole derivatives 12 from the reaction of ortho/meta/para monosubstituted aromatic aldehydes, malononitrile and pyrazolone by using the green and reusable catalyst montmorillonite K-10 in aqueous ethanolic solvent\(^4\).

The use of manganese doped zirconia as an efficient catalyst for the ultrasound-assisted four component water-ethanol RT synthesis of dihydropyran[2,3-c]pyrazole products 12 has been reported by Maddila et al. in 2016. The reaction was well tolerated with different aromatic aldehydes containing electron-releasing or withdrawing groups without any effect on the yield of the products (Scheme 28)\(^5\).
organocatalyst melamine modified chitosan (Gx-Pr-Me) was done by the Valiey's research group (Scheme 31, Scheme 32)[76,77].

\[ \text{Scheme 31 Pyrazole-ring formation reaction in the presence of taurine catalyst} \]

\[ \text{Scheme 32 Melamine modified chitosan catalyst for pyrazole construction} \]

α-Casein has also been used for the synthesis of pyrazole 12 and 15 derivatives by Milani et al. in EtOH/H2O at 60 °C (Scheme 33)[78].

\[ \text{Scheme 33 Cyclocondensation in the presence of α-casein} \]

In the same year 2019, phosphoric acid-functionalized graphene oxide (GO-Po-H2O-II) was put in the reaction by Zakeri et al. to catalyse the aqueous reaction. The nanocatalyst was found to be compatible with various meta and para substituted aryl aldehyde substrates (Scheme 34)[79].

\[ \text{Scheme 34 Implementation of phosphoric acid-functionalized graphene oxide catalyst for pyrazoles construction} \]

Khare et al. in 2019 generated 1,2,3-triazolyl derivatives of pyrano[2,3-c]pyrazoles 12 (Scheme 35) from the reaction of 1-aryl-4-formyl-1,2,3-triazole, malononitrile and 3-methyl-5-pyrazolone with NaHCO3 catalyst in water at 30 °C by using ultrasonic irradiation[80].

\[ \text{Scheme 35 Synthesis of triazolyl pyranopyrazole derivatives by applying Sonochemical method using base} \]

The synthesis of some pyrano[2,3-c]pyrazole compounds have been carried out starting from the four component system using natural mesoporous silica as a support for H3PW12O40 immobilized on aminated epibromohydrin functionalized Fe3O4@SiO2 NPs. The reaction was carried out in aqueous medium at the room temperature by Mohtasham and Gholizadeh[81] in the year 2020 (Scheme 36).

\[ \text{Scheme 36 Synthesis of dihydropyrano[2,3-c]pyrazole derivatives using nanocatalyst} \]

Titanium dioxide (10 mol %) have also been used for the aqueous synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate derivatives 12 by using the four reactants in one pot. The reaction was successfully performed at room temperature within 30 min time period by Pathan et al. in 2020 (Scheme 37) and offered the products in 85-90% yield (TiO2)[82].

\[ \text{Scheme 37 TiO2 catalyzed single vessel synthesis of methyl pyrano[2,3-c]pyrazole-3-carboxylate derivatives} \]

The use of 18-Crown-6-ether was made by Mishra et al., in 2020 to develop water mediated multistate synthesis of 14
pyranopyrazoles 12 (Scheme 38) in 89-96% yield in water using ultrasoundation within 10 min. Many other solvents such as MeOH, MeCN, DMF, DMSO, DCM have also been attempted in the synthetic protocol however the water was found to be the best among all the solvents under study\(^{83}\).

A two component synthesis of seventeen derivatives of pyrano[2,3-ç]pyrazoles has been achieved using the natural waste, water extract of banana peels (WEB) by Diwedi et al. in 2020 (Scheme 39) starting from arylidene malononitriles and methyl pyrazolone. The reaction has efficiently been performed with variously substituted arylidene malononitriles possessing ortho/meta/para aryl or hetaryl groups at room temperature and the products were obtained in excellent 91-96% yield\(^{84}\).

The reaction by the use of boric acid catalyst is successfully conducted by Moosavi-Zare et al. 2017. The reaction is compatible with many electron releasing and withdrawing substituents on the aromatic aldehydes and also with halogen substituents. The reaction occurs within 20 min at 70 °C (Scheme 40)\(^{85}\).

Aqueous ethanolic solution (9:1) of benzaldehyde derivatives, propanedinitrile, ethyl 3-oxobutanoate and hydrazine hydrate upon heating at 90 °C with the natural catalyst L-cysteine (0.5 mol) produced the desired compounds 12 in excellent yields (Scheme 41)\(^{86}\).

Dhakar et al. applied sodium lauryl sulphate (SLS) (15 mol%) in their work towards the multicomponent preparation of spirifindoline-3,4'-pyrano[2,3-ç]pyrazole) products 15 using water as solvent. In the micelle promoted surfactant catalyzed reaction, isatin was used along with EAA, hydrazine, ethyl cyanoacetate (Scheme 42)\(^{87}\).

The base catalyst sodium benzoate have also been applied in the synthesis of biologically active pyrazopyrazoles by Sadegh Talaiefar et al. (Scheme 43)\(^{88}\).

Amiri-Zirtol and Anrollahi in 2021 has introduced sodium tetraborate pentahydrate (Borax) as ecofriendly natural catalyst in the reaction and successfully obtained the fused heterocyclic products in 85-95% yield while refluxing the aqueous reaction mixture (Scheme 44)\(^{89}\).

### 4.3 Fused [5-6-6]system (2 heteroatoms): Pyrazolo[1-b]phthalazine

Water mediated synthesis of 1H-pyrazolo[1-b]phthalazine-5,10-diones 20 was efficiently achieved by refluxing the reactants for 1-1.5 h. InCl\(_3\) catalyst was used by Esvarara Rao et al. 2017 to obtain the pyrazolophthalazines in good yields. The
reaction was also performed by Kerr et al. in the same year by using the heterogeneous catalyst, eggshell powder. The biodegradable and inexpensive catalyst allowed the reaction to occur in water through Knoevenagel-Michael pathway with 98% atom economy and 100% carbon efficiency (Scheme 45, Scheme 46)\(^9\)\(^2\)

![Scheme 45](image)

**Scheme 45** \(\text{InCl}_3\) catalyzed cyclocondensation to obtain pyrazolo[1-b]phthalazine derivatives

4.4 Fused [5-6-6] system (3 heteroatoms): Benzopyranopyrazoles

The synthesis of chromeno[4,3-c]pyrazole derivatives 21 has been successfully attempted by Muthusamy and Gangadurai in the year 2018 starting from propargylated salicylaldehydes via intramolecular [3+2]-cycloaddition reaction in aqueous medium while heating at 70 °C for 12 h (Scheme 47)\(^9\)\(^2\).

![Scheme 46](image)

**Scheme 46** Formation of derivatives of pyrazolophthalazines using eggshell powder

![Scheme 47](image)

**Scheme 47** Base catalyzed preparation of benzopyranopyrazoles


A simple, and eco-friendly approach for the multicomponent production of many derivatives of pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-diones 22 from the reactants EAA, aldehyde, hydrazine hydrate, and 6-amino-1,3-dimethyl uracil catalyzed by triethylamine (TEA) and L-Proline in water as solvent is reported by Daraie and Heravi in 2016 (Scheme 48). The generality of this method was established by using differently substituted aromatic aldehydes possessing either electron donating or electron withdrawing groups to acquire successfully the corresponding expected products in excellent yields (82-92% with TEA and 75-90% with L-Proline)\(^9\)\(^2\).

![Scheme 48](image)

**Scheme 48** TEA/L-proline: Catalytic formation of pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidine-diones

Polyfunctionalized pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines 23 were conveniently obtained in aqueous medium by applying the multireactant approach. Derivatives of arylglyoxal, barbituric acid, β-aminoacetonitrile, phenyldrazine underwent the reaction efficiently in the presence of triethylamine catalyst under refluxing condition (Scheme 49). The protocol offered easy isolation and high yield of the products.\(^9\)\(^4\)

![Scheme 49](image)

**Scheme 49** TEA mediated synthesis of polyfunctionalized tricyclic derivatives

Sagir et al. have reported the reaction using iodine (10 mol%) efficiently for preparing variously substituted pyridopyrimidines 24 in aqueous medium (Scheme 50). Many Bronsted and Lewis acid catalysts such as FeCl\(_3\), I\(_2\), CoCl\(_2\), Cu(OAc)\(_2\), HCl, p-TSA were screened for this process. Among all the tested catalysts, molecular iodine was found to be best for the pursuance of the reaction. Many solvents such as chloroform, tetrahydrofuran, methanol, ethanol, water were attempted for this particular reaction varying the temperature. The method worked well with some of the solvents used like methanol, ethanol, acetonitrile and water. However, the preferred solvent was water both in terms of environmental compatibility and yield. Furthermore, performing the reaction in the aqueous medium was also advantageous for the separation of the product which could be possible just by filtration because of the solubility-difference of the product from the reactants. It was also perceived that the different isatin derivatives containing electron donating/electron withdrawing groups smoothly offered the products. The workup of the reaction involved only filtration and chromatography or recrystallization was not needed.\(^9\)\(^5\)
Halloysite clay nanotubes (HNTs) were functionalized by c-aminopropyltriethoxysilane and then immobilized by using phosphotungstic acid. The hybrid catalyst was used for the synthesis of fused tricyclic system containing pyrimidine, pyran and pyrazole. This reaction was executed by refluxing in water (Scheme 51). The synthesis was also conducted under microwave and ultrasonic conditions. By applying microwaves for this very reaction, the time was reduced to 5 min. but yield was low due to many by-products. Under ultrasonication, the reaction could be brought about within 15 min at 60 °C and the yield was excellent.

Conclusion

The review is directed towards summarizing the literature on the synthesis of pyrazole derivatives (pyranopyrazole, spiro-pyranopyrazole, furopyrazole, pyrazolopyrimidine) using water as green solvent. The synthetic work on pyrazoles under water is mainly performed in the presence of catalysts. A wide variety of catalysts such as nanoparticles, nanothin films, bronsted and Lewis acid catalysts, bases, amino acids and natural catalysts have been applied to achieve the formation of the pyrazole nucleus. A little work has also been carried out under ultrasonication and microwave. It is to highlight that the reported work is inclined towards the synthesis of two fused pyrazole systems, furo[2,3-c]- and pyrano[2,3-c]pyrazoles. It is also found that the majority of the reactions are performed involving multicomponent reaction system. Surely, there is good deal of scope to work in this particular area and this focused compilation will be very advantageous for the scientists interested to work in the area of green synthesis of pyrazoles.

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Conflict of interest

Authors have no conflict of interest.

Abbreviations

PEG Polyethylene glycol
CAN Ceriacummonium nitrate
PSSA Polystyrene Supported Sulfonic Acid
COX-2 Cycloxygenase-2
PTSA p-toluene sulphonylic acid
CTAB Cetyltrimethylammoniumbromide
DMSO Dimethylanilpyridine
SDS Sodium dodecyl sulfate
TUD Thiourea dioxide
RT Room temperature
EAA Ethyl acetoacetate
BFA Bael Fruit Ash
WEB Water Extract of Banana Piece
DABCO 1,4-diazabicyclo[2.2.2]octane
BAIB [bis(acetoxy)iodo]benzene
TEA Triethylamine
β-CD β-cyclodextrin
BSA Bovine serum albumin
SLS Sodium lauryl sulphate
HNTs Halloysite clay nanotubes

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