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Applications of pyrazolone in multicomponent reactions for the synthesis of dihydropyrano[2,3-*c*]pyrazoles and spiro-pyrano[2,3-*c*]pyrazoles in aqueous medium

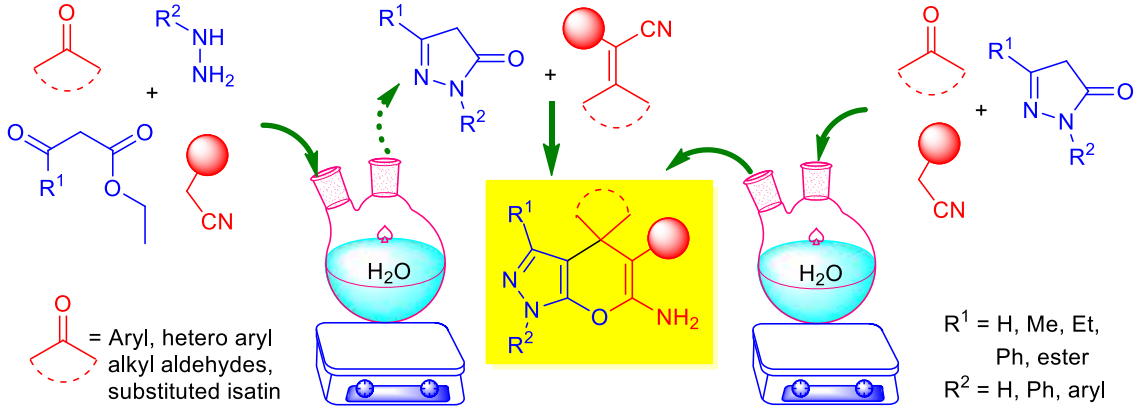
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Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Abstract

Pyrazolone is an important class of heterocyclic compounds with numerous applications in the fields of organic/material/pharmaceutical chemistry, food/textile industry and cosmetics. Dihydropyrano[2,3-*c*]pyrazoles and spiro-pyrano[2,3-*c*]pyrazoles are synthesized from pyrazolone and hold huge potential in the field of medicinal chemistry because of their wide-ranging biological activities. This review article will summarize the up to date advances on the application of pyrazolone in multicomponent reactions for the synthesis of pyrano[2,3-*c*]pyrazoles in an aqueous medium.



Keywords: Pyrazolone, dihydropyrano[2,3-*c*]pyrazole, spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole, aqueous medium, multicomponent reactions

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1. Introduction

Due to increasing apprehension about an environmental issue, the design and development of a chemical transformation that directs the efficient and practical synthesis of molecular complexity has emerged as one of the most significant ambitions for chemists in industry and academia.[1] In recent years, compared to other step-wise synthetic methods which involved separation, complex purification techniques which utilizes large amount of solvent, reagent, and byproduct, multicomponent reactions (MCRs) have increasingly gained favor as they avoid the waste of solvent, reagent, and product. Multicomponent reactions (MCRs) have provided a useful and important influential implement for the construction of organic compounds and biologically active molecules, in which three or more reactants are mixed in a single operation and result in the formation of a product with the creation of several new bonds.[2,3] From the viewpoint of green chemistry, organic synthesis /organic transformation *via* multicomponent reaction (MCRs) should need to be designed in such a way that utilizes alternative pathway and materials which are not only environmentally friendly but also be easily available anywhere in bulk quantities at very cheap price.[4] Also, one of the major risks to the environment is due to the chemical waste produced during a chemical process, which is mainly generated from hazardous organic solvents, and therefore, avoiding or minimizing the use of hazardous organic solvents by using green ones is a critically important goal of modern synthetic chemistry.[5,6] In this context, Breslow[7] rediscovered the use of water as a green solvent in organic reactions in the 1980s, and currently, the utilization of water as a reaction medium in catalytic process for the synthesis of either natural products or pharmaceutically active compounds has received considerable attention due to the abundantly available, non-hazardous, non-flammable, unique redox stability and its cheap nature.[8,9,10]

Heterocyclic compounds are important bioactive molecules found in nature. Due to their characteristic properties, heterocyclic compounds have a significant application in the pharmaceutical industry. Among heterocyclic compounds, pyrazolones are important compounds with numerous applications in the fields of synthetic organic chemistry, material science, medicinal and pharmaceutical chemistry, food industry, textile industry, cosmetics products, chemical industry, and also as powerful synthon for generating biologically active heterocycles.[11] The medicinal application of pyrazolone includes antipyretic activity (**A**, **B**, **H**) and

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analgesic activity (**A**, **B**, **F**),[12,13,14,15] antibacterial (**G**),[16] anti-inflammatory activity (**H**), antitumor activity (**D**),[17,18] neuroprotective and cardiovascular agent (**C**),[19,20,21] antidepressant activity,[22] phosphodiesterase inhibitors (**E**),[23] p38 inhibitors (**I**)[24] and so on (Figure 1).

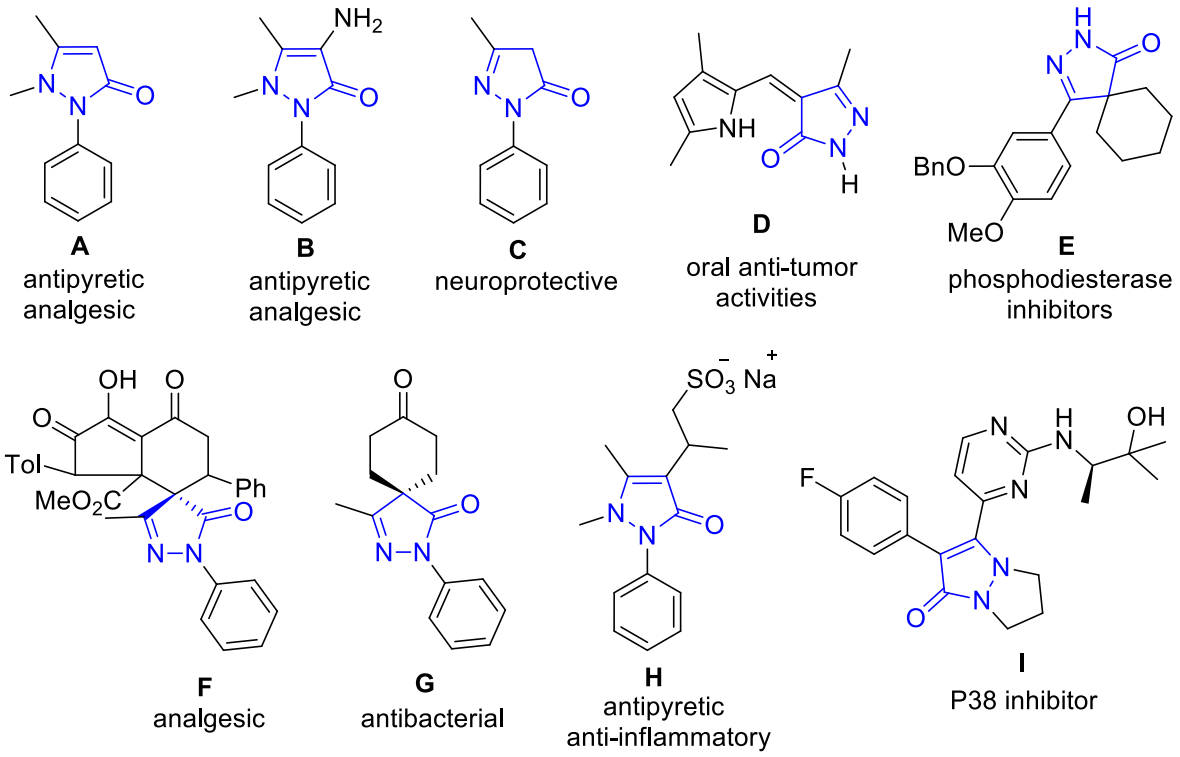


Figure 1: Bioactive molecules bearing pyrazolone moiety.

Besides these, pyrazolones are widely used as dyes for various applications in the food, textile, photographic, and cosmetics industries.[25] Pyrazolones were also applied as the solvent for extraction of metal ions,[26] for analytical purpose,[27] in the preparation of azo colourants,[28] ligands in complexes with catalytic activity,[29] and the synthesis of rare earth metal complexes with interesting photophysical properties.[30] Pyrazolones were used in vinyl polymerization of norbornene;[31] in polymeric membrane electrode for lanthanoid ion-selective solvent polymeric membrane electrode;[27] and thermal oxidative degradation of polypropylene.[31] They were also used in the study of photochromism phenomena.[32,33,34] As a consequence of this, derivatization of other complex molecules from pyrazolone structure in an aqueous medium for providing enhanced reactivity and activities has emerged. Dihydropyrano[2,3-*c*]pyrazole and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] are the type of those compounds which are synthesized from pyrazolone over the last decades and holds huge potential in the field of medicinal chemistry because of their wide-ranging biological activities such as- anti-bacterial (**J**),[35] anti-HIV,[36] insecticidal, anti-infective,[37] anti-platelet, anti-fungal (**M**),[38,39] anti-cancer (**N**),[40,41] anti-microbial (**K**),[42] antioxidant activity (**O**),[43] molluscicidal agent (**P**),[44] analgesics,[45] anti-inflammatory (**Q**)[46,47] and it also serves as potential inhibitors of human Chk1 kinase (**L**) (Figure 2).[48,49]

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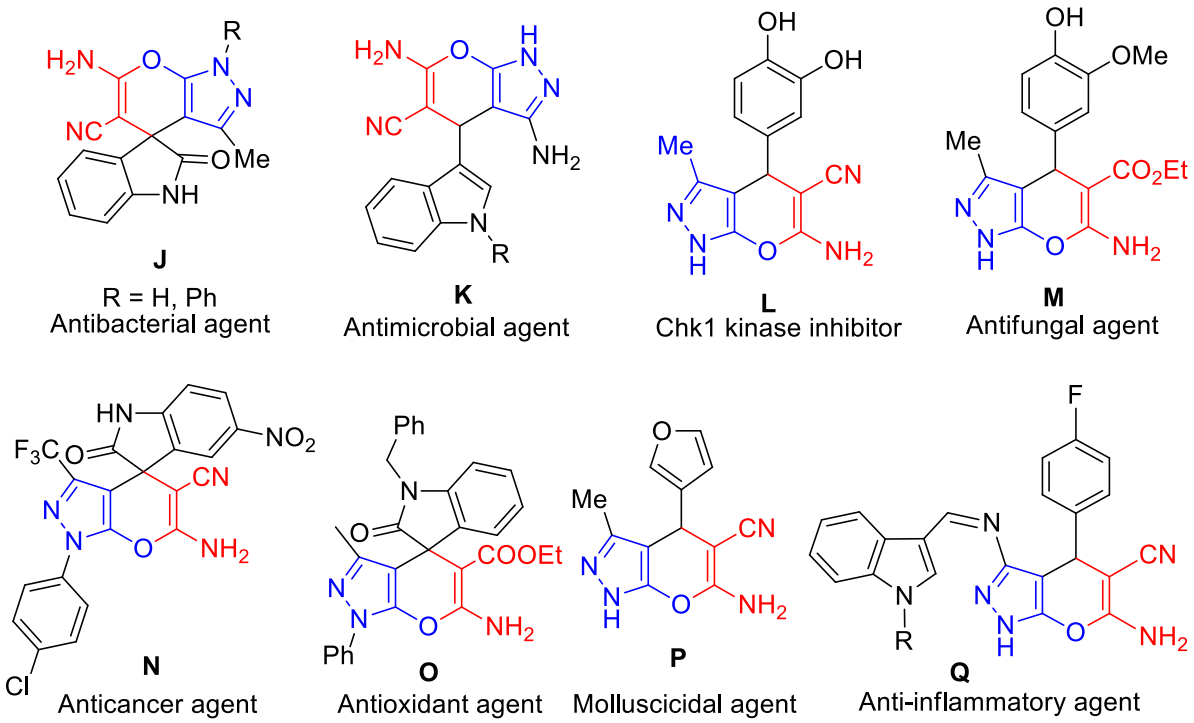


Figure 2: Medicinally privileged dihydropyrano[2,3-*c*]pyrazoles and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles.

In view of these importances, a vast array of synthetic approaches has been reported over the last decades for the synthesis of dihydropyrano[2,3-*c*]pyrazole and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives employing conventional as well as a green method involving two-component, three-component, four-component reactions. In 2013, a review article systematized the literature data on the synthesis of pyrano[2,3-*c*]pyrazole starting from 1905.[50] In 2018, another review article summarized the synthetic methods for the pyrano[2,3-*c*]pyrazoles.[51] However, still there are a lot of publications that are untouched and a surge of investigation is required for the synthesis and medicinal aspects of these heterocycles. Therefore, we have emphasized the synthetic pathways of pyrano[2,3-*c*]pyrazoles mainly on the utilization of an aqueous medium. The foremost aim of this review is to summarize the up to date advances in the applications of pyrazolone as starting material as well as *in situ* generated synthon in multicomponent reactions (MCRs) for the synthesis of dihydropyrano[2,3-*c*]pyrazoles and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives in the aqueous medium. To furnish a complete and understandable overview, the article is classified according to catalyst-free, base-catalyzed, acid-catalyzed, nanoparticle catalyzed, salt catalyzed synthesis.

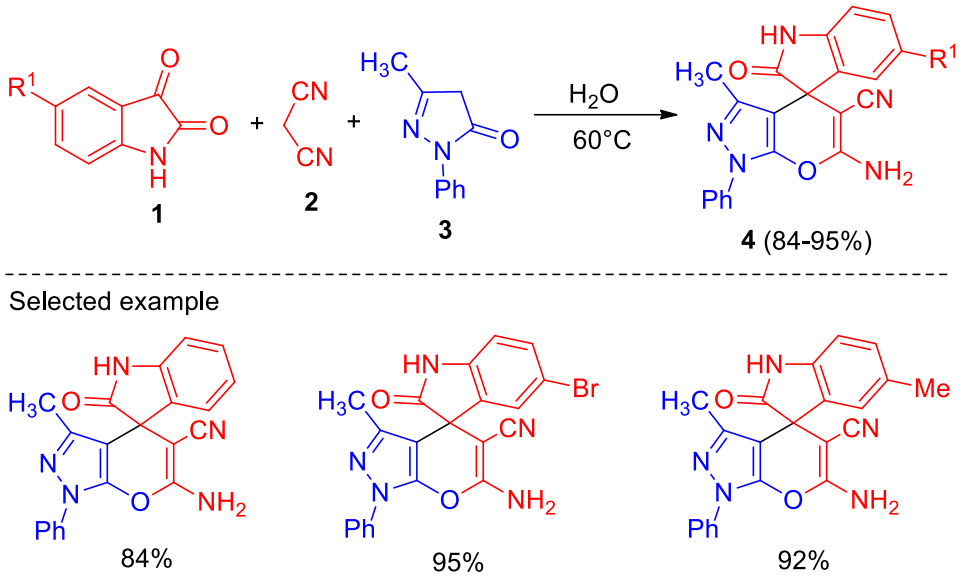
2. Synthesis of Dihydropyrano[2,3-*c*]pyrazoles and Spiro-pyrano[2,3-*c*]pyrazoles in the Aqueous Medium

2.1 Catalyst free synthesis

From the viewpoint of green chemistry, the design and development of an efficient, clean, and novel reaction procedure for the synthesis of diverse structural scaffolds under the catalyst-free condition with maximum yield and minimum cost by using inexpensive, non-toxic solvents or starting materials has reached an exceptional level in the last decades. Based on that in 2011, Zhao *et al.* reported a non-catalytic method for the preparation of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] derivatives **4** in 84-95% yield by the three-component reaction of substituted isatin **1**, malononitrile **2,** and 3-methyl-1-phenyl-1*H*-pyrazole-5(4*H*)-one **3**

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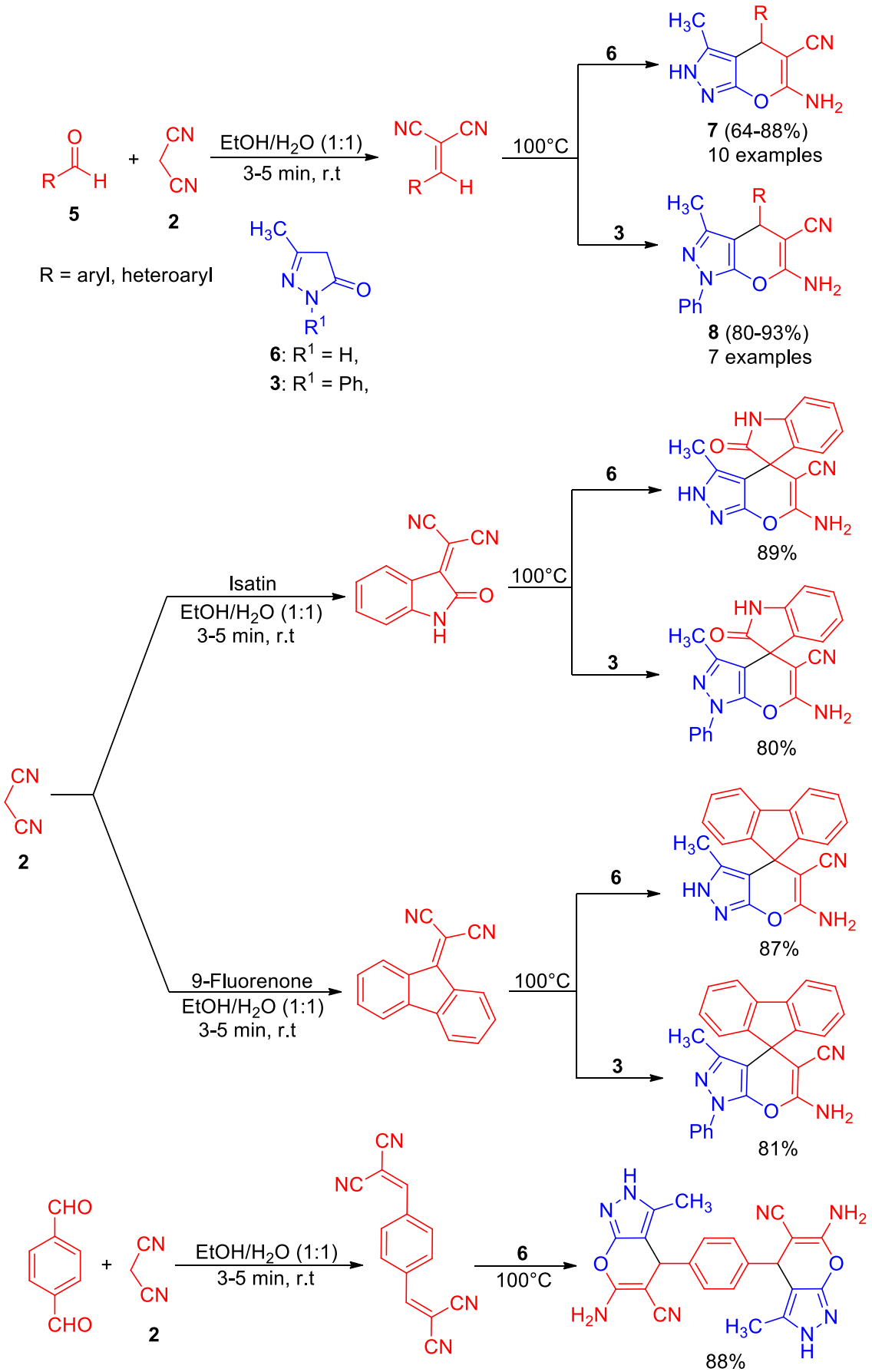
using water as a reaction medium (Scheme 1).[52] The reaction was carried out at different reaction condition by changing the temperature of the model reaction from 20°C to 90°C and it was found that by increasing the reaction temperature, the yield of the product was increased and it was excellent at 60°C which indicates the best condition for the reaction. The methodology has several benefits such as mild reaction conditions, shorter reaction time, simple work-up procedure, eco-friendly and environmental friendliness.



Scheme 1: Catalyst-free synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] **4** in aqueous medium.

In 2012, Mandha and his co-worker described another catalyst-free protocol for the four-component synthesis of pyrano[2,3-*c*]pyrazole derivatives in good yield *via* the one-pot reaction of several aromatic aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate in presence of aqueous ethanol as a reaction media at a temperature ranging from 25°C to 100°C (Scheme 2).[53] But upon replacing the hydrazine hydrate with phenylhydrazine, the same four-component reaction strategy to accomplish the pyrano[2,3-*c*]pyrazole derivatives **8** was not observed. However, the preparation of 3-methyl-1-phenyl-1*H*-pyrazole-5(4*H*)-one **3** from an initial condensation of ethyl acetoacetate and phenylhydrazine and its treatment with aldehyde **5** and malononitrile **2**, was found to lead to the desired product in very good yield. Similarly, the preparation of 3-methyl-1*H*-pyrazol-5(4*H*)-one **6** alone also results in a better yield of product **7** as compared to the corresponding one-pot four-component reaction. Furthermore, the reaction of substituted isatin, or 9-fluorenone, or dialdehyde terephthalaldehyde with malononitrile, and pyrazolone under the same reaction afforded the corresponding product- spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles], spiro[fluorine-9,4-pyrano[2,3-*c*]pyrazole], and 4,4′-(1,4-phenylene)bis(6-amino-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) in high yield respectively.

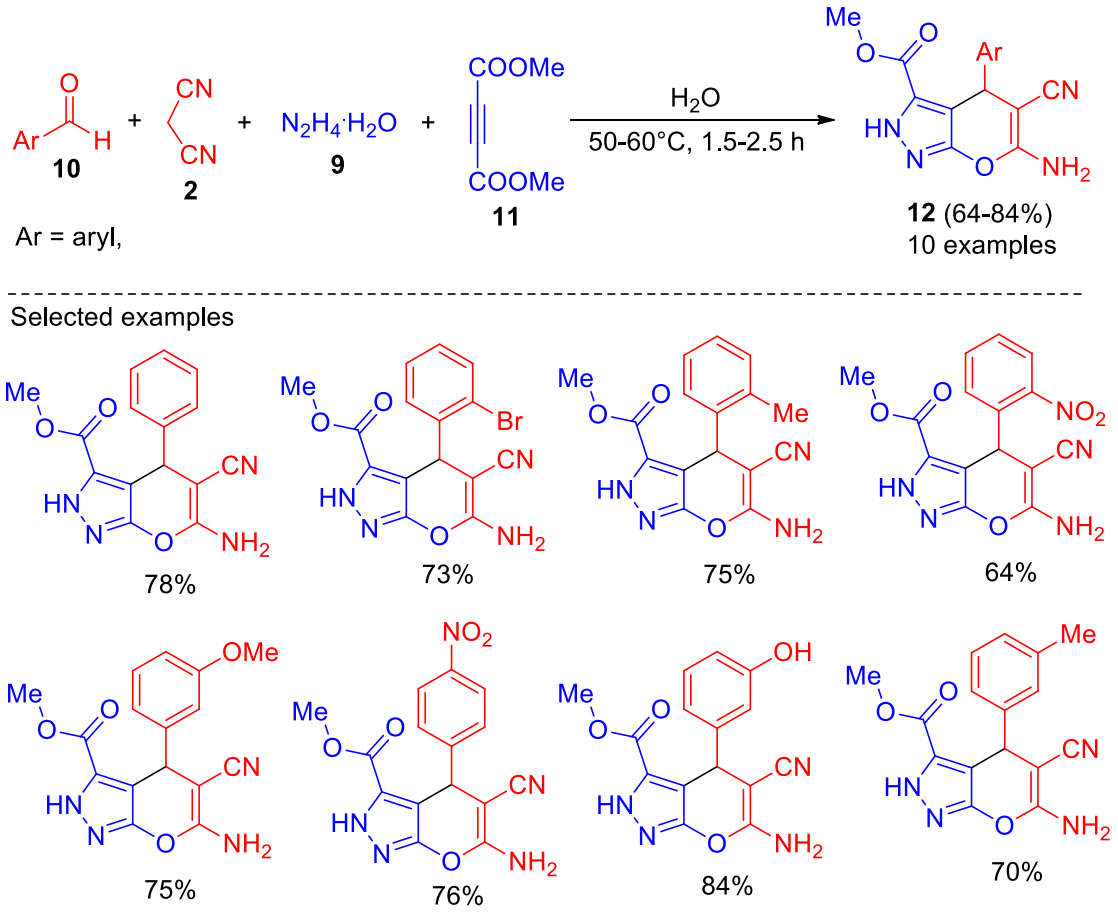
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Scheme 2: Three-component catalyst-free synthesis of dihydro- and spiro-pyrano[2,3-*c*]pyrazole derivatives.

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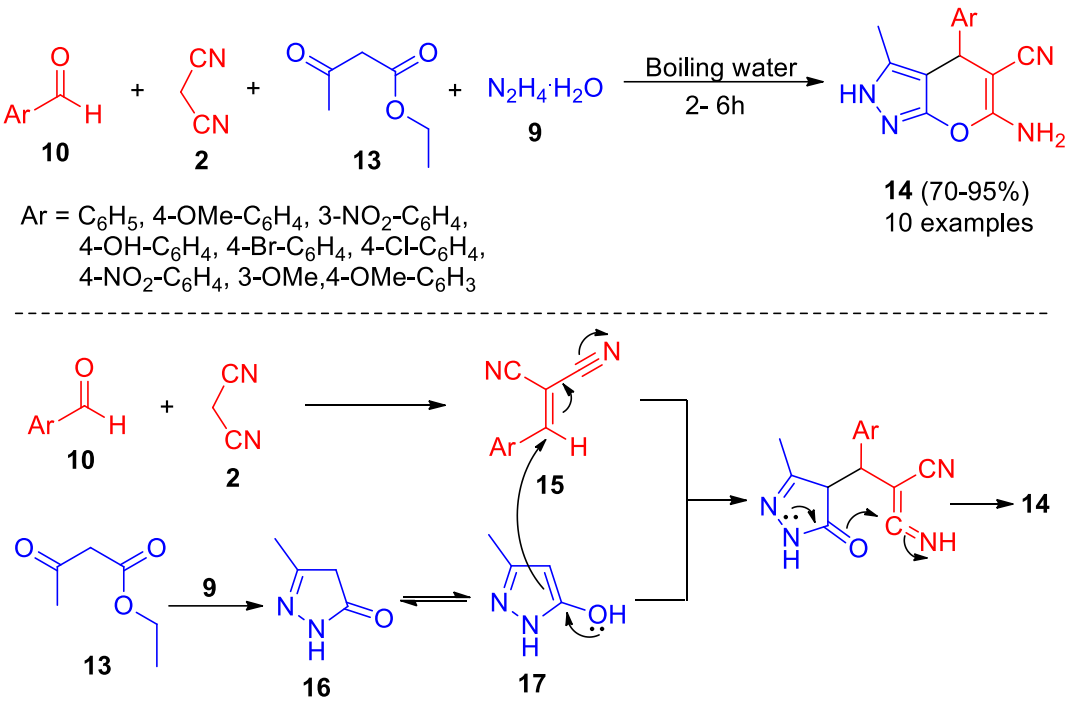
A very efficient and simple strategy for the one-pot synthesis of several dihydropyrano[2,3-*c*]pyrazole derivatives **12** in 64-84% yield from *in situ* generated pyrazolone has been developed by Zonouz *et al.* in 2012. The synthesis involves the four-component condensation reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and dimethyl acetylene dicarboxylate **11** in presence of water at 55°C–60°C for 1.5-2.5 hours without employing any other catalyst or additives (Scheme 3).[54] Isolation of product by simple work-up procedure and use of water makes this protocol very convenient in terms of synthetic efficiency as well as from a green chemistry point of view.



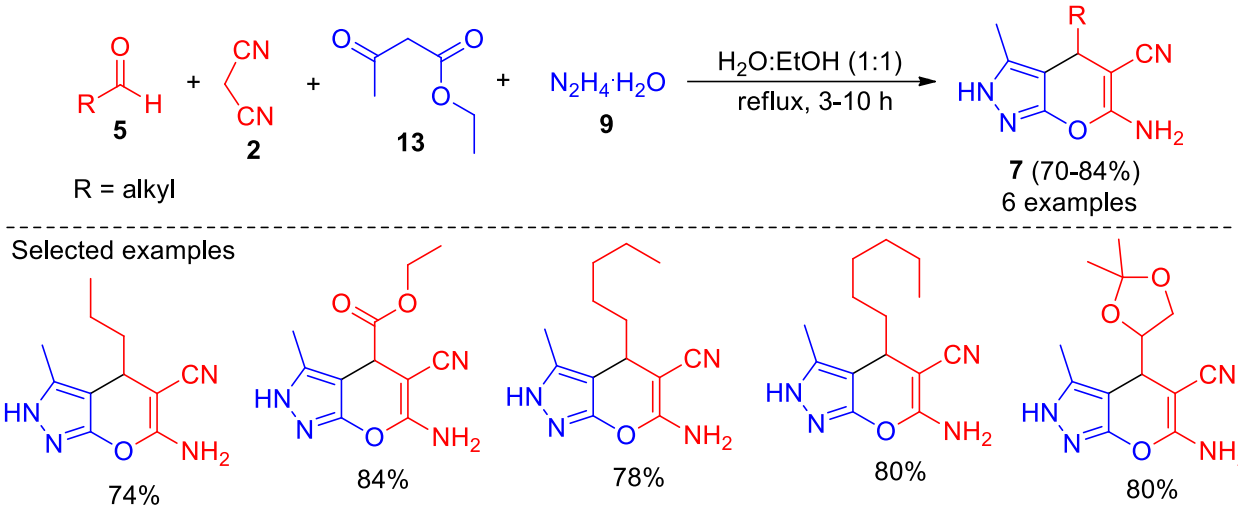
Scheme 3: Water mediated synthesis of dihydropyrano[2,3-*c*]pyrazoles **12** from *in situ* generated pyrazolone.

Another achievement has been gained by Bihani *et al.* reported that the practical catalyst-free four-component condensation reaction of several aromatic aldehydes **10**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** refluxed in water afforded the corresponding dihydropyrano[2,3-*c*]pyrazole derivatives **14** in good to excellent yield after 2-6 hours (Scheme 4).[55] The reaction can proceed through the initial formation of pyrazolone **16** from the condensation of ethyl acetoacetate **13** and hydrazine hydrate **9** which undergo tautomerization to give the intermediate **17**. The intermediate **17** then undergo Michael addition with the *in situ* generated α-cyanocinnamonitrile **15**, followed by intramolecular cyclization, that results in the formation of the desired product **14**. They also develop another catalyst-free synthetic method for the preparation of alkyl-substituted dihydropyrano[2,3-*c*]pyrazole derivatives **7** from aliphatic aldehyde **5**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** in presence of aqueous ethanol as the solvent under reflux condition The product was formed in 70-84% yield within 3-10 hours (Scheme 5).

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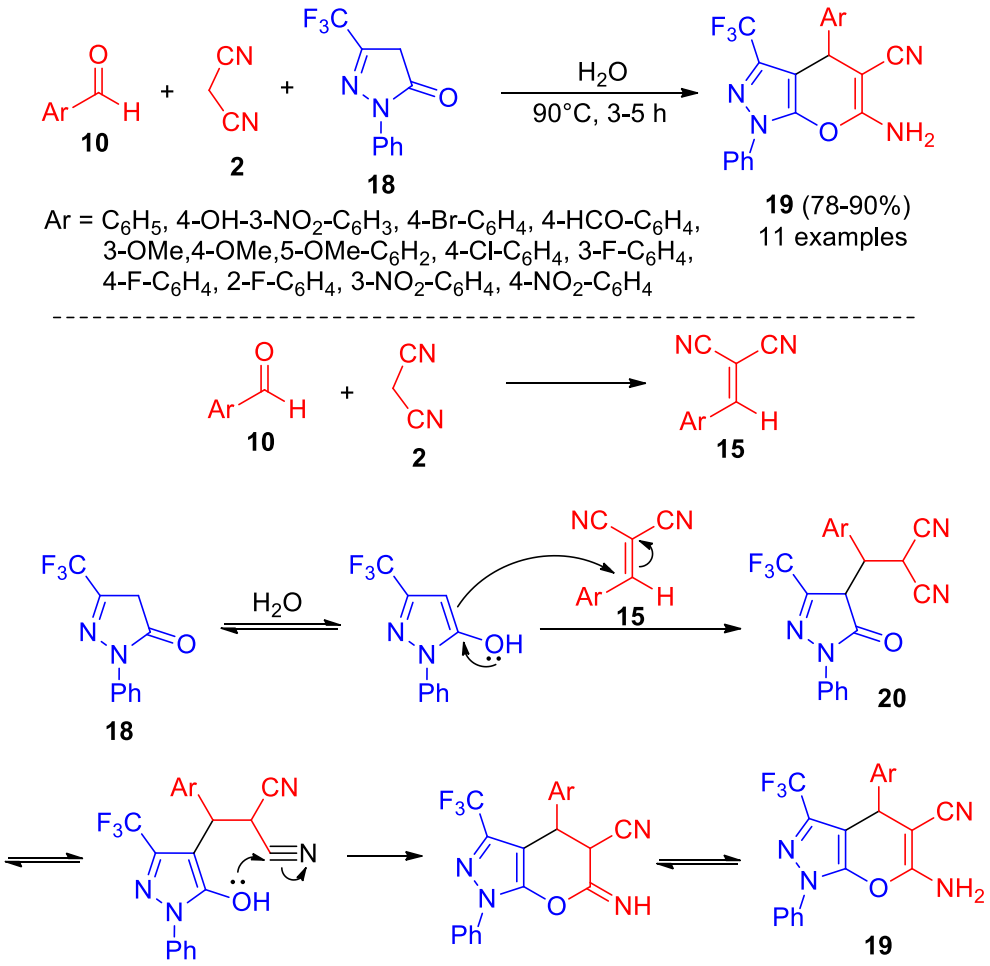
Scheme 4: Synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives **14** in boiling water.



Scheme 5: Synthesis of alkyl-substituted dihydropyrano[2,3-*c*]pyrazoles **7** in aqueous ethanol.

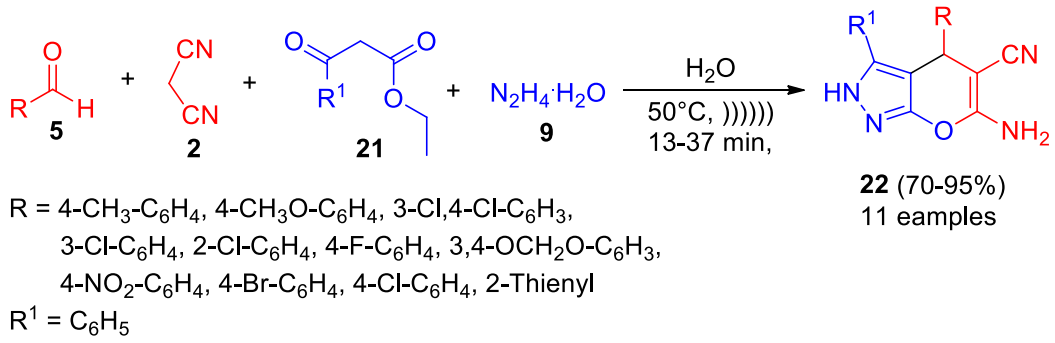
Chenxia *et al.*[56] reported that the one-pot three-component reaction of various substituted aldehyde **10**, malononitrile **2**, and 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one **18** under aqueous medium without using any catalyst afforded the dihydropyrano[2,3-*c*]pyrazole derivatives **19** at 90°C in 3-5 hours (Scheme 6). By applying this atom economical procedure, a total of 11 derivatives were synthesized in 78-90% yield. The plausible mechanism for this transformation involves the initial Knoevenagel condensation reaction between aryl aldehyde **10** and malononitrile **2**, which result in the formation of α-cyanocinnamonitrile **15**, that can then experiences nucleophilic attack from the pyrazolone **18** to produce the intermediate **20**. In the final step, the intermediate **20** undergo intramolecular cyclization followed by subsequent isomerization to form the desired product **19**.

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Scheme 6: Preparation of dihydropyrano[2,3-*c*]pyrazoles **19** from trifluoromethyl pyrazolones.

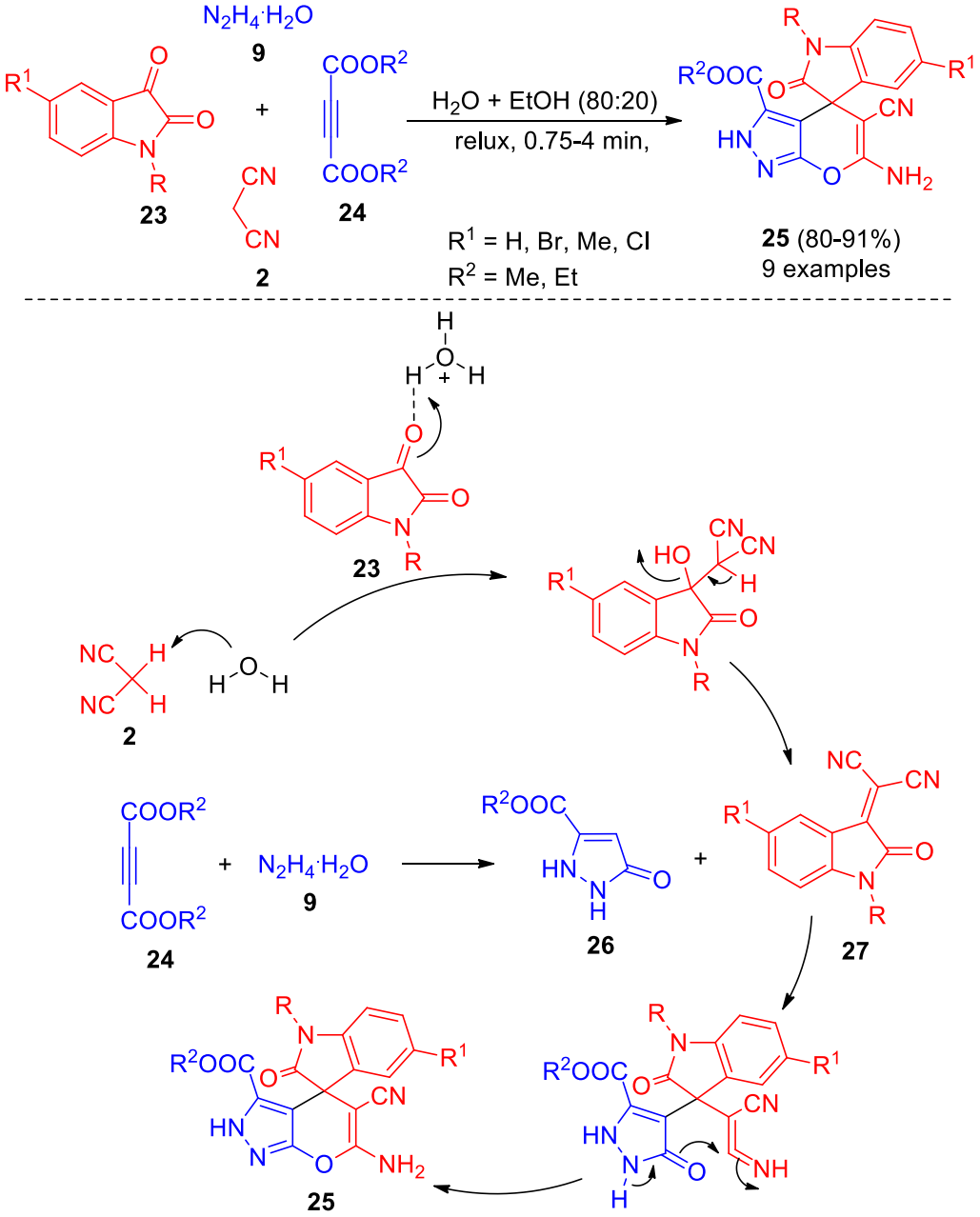
In 2013, the research group of Zou developed an ultrasound irradiated catalyst-free one-pot procedure for the construction of dihydropyrano[2,3-*c*]pyrazole derivatives **22** in 70-95% yield by the reaction of several substituted aldehyde **5**, malononitrile **2**, hydrazine hydrate **9**, and ethyl-3-oxo-3-alkylpropanoate **21** in water medium in 13-37 minutes (Scheme 7).[57] The reaction was initially carried out in different solvents including ethanol, methanol, acetonitrile, THF, dioxane, and water under ultrasound irradiation as well as under high stirring conditions. However, the best results were obtained when water was used as a reaction medium under ultrasound irradiation as compared to conventional stirring conditions. Also, the reaction temperature was reduced when the reaction was performed in the ultrasound irradiation. By applying this methodology, 11 compounds were synthesized in good to excellent yield.



Scheme 7: Ultrasound-assisted synthesis of dihydropyrano[2,3-*c*]pyrazoles **22**.

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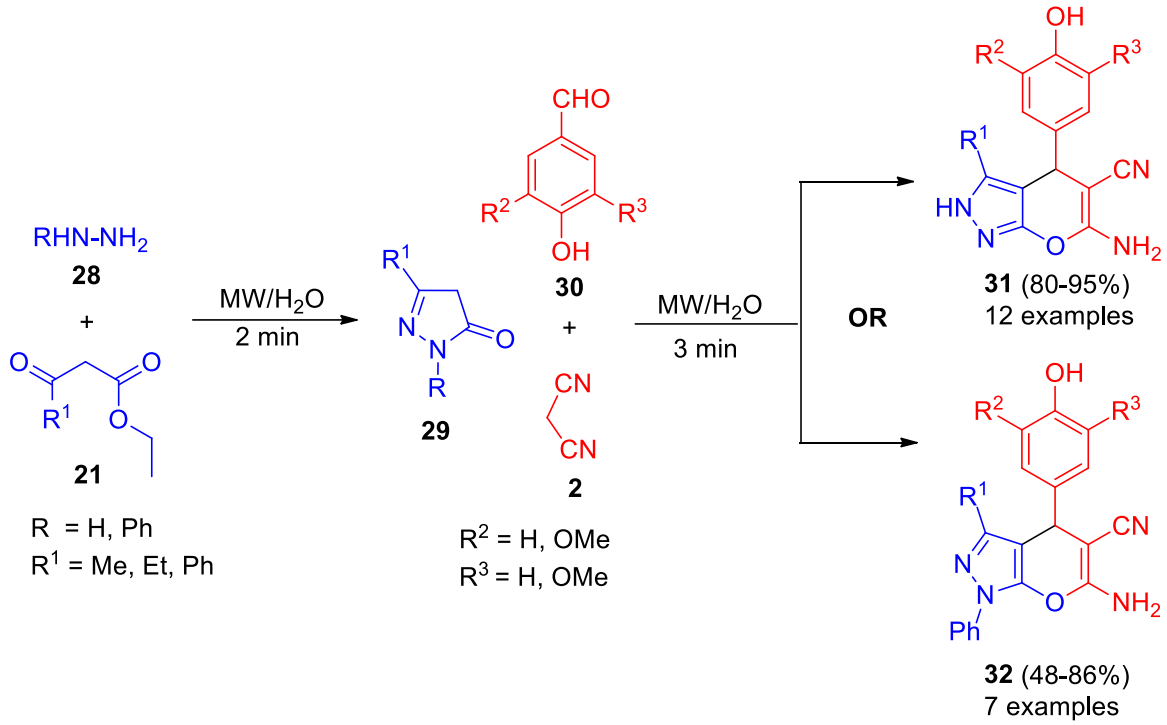
A simple straightforward catalyst-free procedure for the one-pot four-component reaction of substituted isatin **23**, malononitrile **2**, hydrazine hydrate **9,** and dialkyl acetylene dicarboxylate **24** for the construction of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] derivatives **25** in 80-91% yield by using aqueous ethanolic solution under reflux condition within 4 minutes has been accomplished by Pore *et al.* (Scheme 8).[58] The mechanistic reaction pathway for this transformation starts with the *in situ* formation of pyrazolone **26** from the exothermic reaction of hydrazine hydrate **9** and dialkyl acetylene dicarboxylate **24**. On the other hand, the presence of water in the reaction mixture leads to the generation of carbanion of malononitrile as well as activation of the carbonyl carbon of **23**, thereby facilitates the Knoevenagel condensation of **23** with malononitrile **2**, and generates the intermediate **27**. The 1,2-nucleophilic addition of pyrazolone **26** to intermediate **27**, followed by subsequent ring closure yield the final product **25**.



Scheme 8: Four-component synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **25**.

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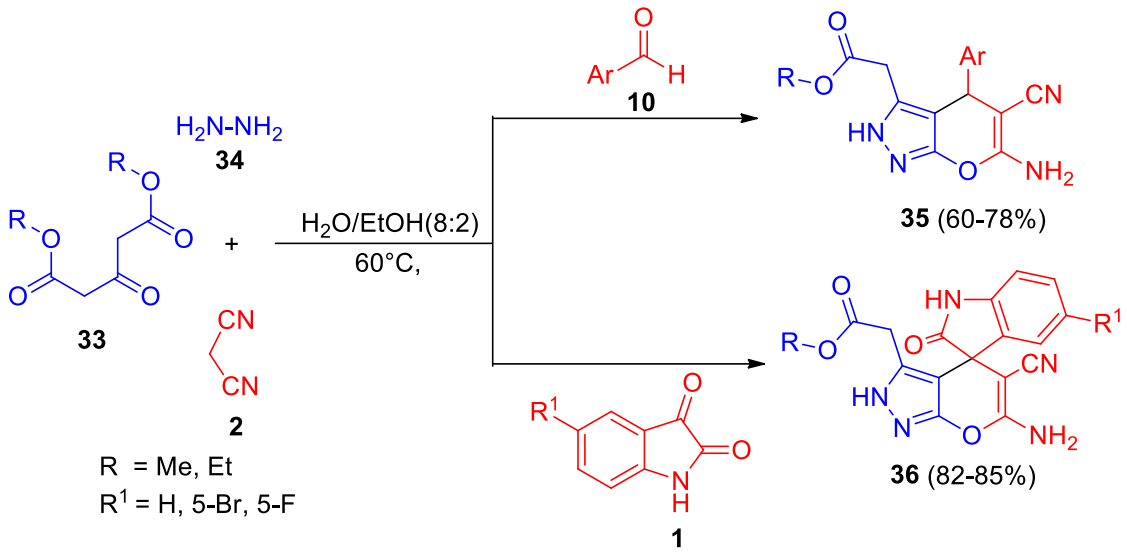
In 2014, Yang *et al*.[59] demonstrated a microwave-assisted one-pot strategy for the synthesis of dihydropyrano[2,3-*c*]pyrazoles **31** and **32** from aromatic aldehydes **30**, malononitrile **2**, and pyrazolone **29** in a water medium (Scheme 9). They firstly prepared the pyrazolone **29** from the reaction of ethyl acetoacetate **21** and hydrazines **28** under microwave oven (300 W) at 80°C in 2 min. After that, malononitrile **2** and aromatic aldehydes **30** were added swiftly with pyrazolone **29** and irradiated successively at 80°C for 3 min. Total 19 compounds were obtained by this method and the yield of the corresponding product **31** and **32** were high ranging from 80-95% and 48-86% respectively.



Scheme 9: Microwave-assisted synthesis of dihydropyrano[2,3-*c*]pyrazoles **31** & **32**.

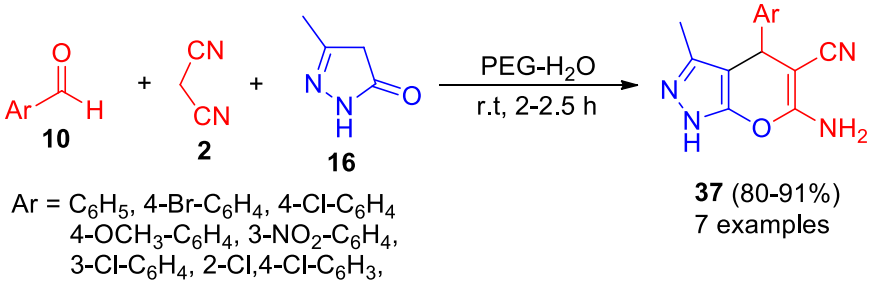
An efficient, regio, and chemoselective one-pot four-component reaction for the construction of dihydropyrano[2,3-*c*]pyrazole derivatives **35** & spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] **36** has been developed by Koohshari and his group. The catalyst-free domino treatment of various substituted aryl aldehyde **10** or substituted isatin **1**, malononitrile **2**, hydrazine **34,** and dialkyl-3-oxopentanedioate **33** in presence of aqueous ethanolic solution at 60°C afforded the corresponding product **35** and **36** in good yield after 12 hours (Scheme 10).[60]

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Scheme 10: Domino reaction in aqueous ethanol to access dihydropyrano[2,3-*c*]pyrazoles **35** and spiro-pyrano[2,3-*c*]pyrazoles **36**.

Recently, the combination of PEG and water as a sustainable reaction medium for promoting the multicomponent synthesis of dihydropyrano[2,3-*c*]pyrazoles has been established by Survase *et al.*[61] The synthesis of several derivatives of dihydropyrano[2,3-*c*]pyrazoles **37** from aldehydes **10**, malononitrile **2**, and pyrazolone **16** was first carried out by employing different solvent system including toluene, DMF, DMSO, water, PEG-600 and in different ratio of PEG-water solvent system at room temperature. From the optimized reaction condition, it was found that the PEG-water solvent system was the best choice of reaction medium for the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives, and products were obtained in good to excellent yield ranging from 80-91% (Scheme 11).

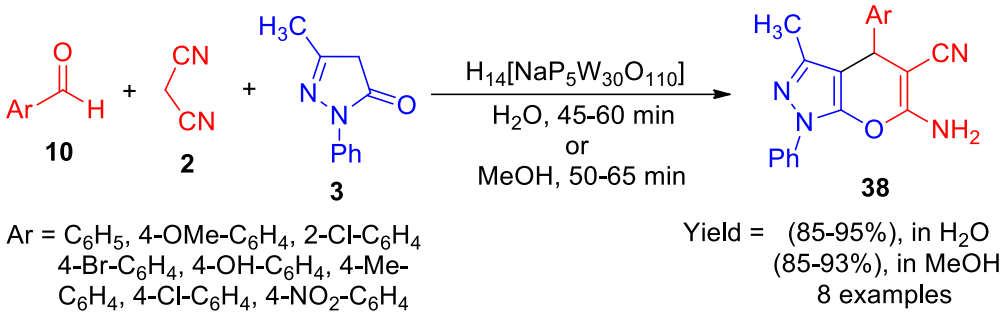


Scheme 11: PEG-H_2O promoted one-pot synthesis of dihydropyrano[2,3-*c*]pyrazoles **37**.

2.2 Acid-catalyzed synthesis

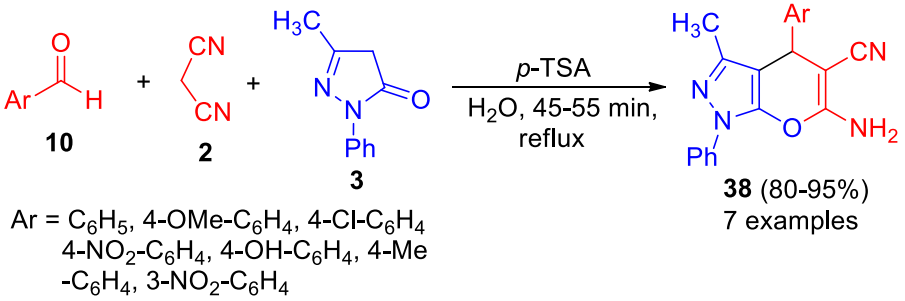
In 2010, Heravi *et al*[62]. reported the synthesis of several dihydropyrano[2,3-*c*]pyrazole **38** from the one-pot condensation reaction of aromatic aldehydes **10**, malononitrile **2,** and pyrazolone **3** by using preyssler type heteropolyacid $H_{14}[NaP_5W_{30}O_{110}]$ as a reusable green solid acid catalyst in aqueous medium under reflux condition. The reaction was also carried out in presence of methanol as the solvent (**Scheme 12**). By using water as the solvent, the product could be isolated in 80-95% yield within 45-60 minutes whereas the reaction in presence of methanol proceeded after 50-65 minutes, and the desired product obtained in 84-93% yield. Due to the utilization of inexpensive, reusable, non-toxic, highly hydrolytic, heterogeneous, thermally stable, and an environmentally benign solid acid catalyst, the methodology offers significant advantages and high product substrate scope.

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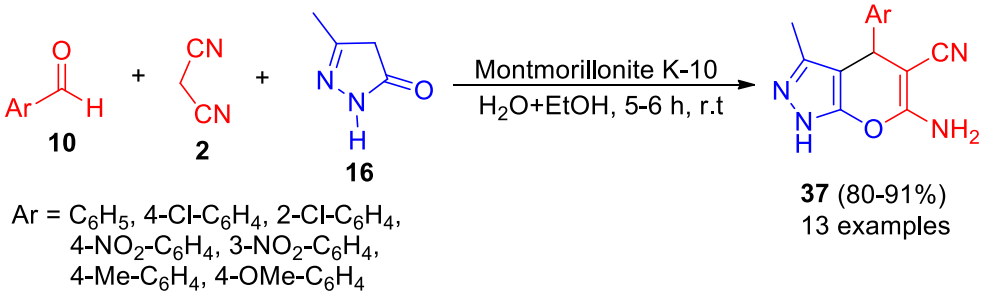
Scheme 12: Acid-catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **38** in water as well as in methanol.

The same group has also developed another acid-catalyzed one-pot methodology for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives **38** *via* the reaction of substituted aldehydes **10**, malononitrile **2,** and pyrazolone **3** in presence of *p*-toluene sulfonic acid (*p*-TSA) as a catalyst in an aqueous medium at reflux temperature for 45-55 minutes. Initial optimization for the reported methodology under a different solvent system like- water, ethanol, dichloromethane, chloroform, and also under solvent-free condition revealed that the reaction performed in presence of water afforded the desired product in 80-95% yield (Scheme 13).[63]



Scheme 13: Three-component p-TSA catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **38**.

Reddy and co-workers described that the synthesis of pyrano[2,3-*c*]pyrazole derivatives **37** in 80-91% yield proceeded through the three-component reaction of aldehydes **10**, malononitrile **2,** and pyrazolone **16** by using montmorillonite K-10 as a reusable green acid catalyst in aqueous ethanol medium at room temperature for 5-6 hours (Scheme 14).[64] By applying this eco-friendly, column chromatography-free methodology 13 derivatives were synthesized in good to excellent yield.

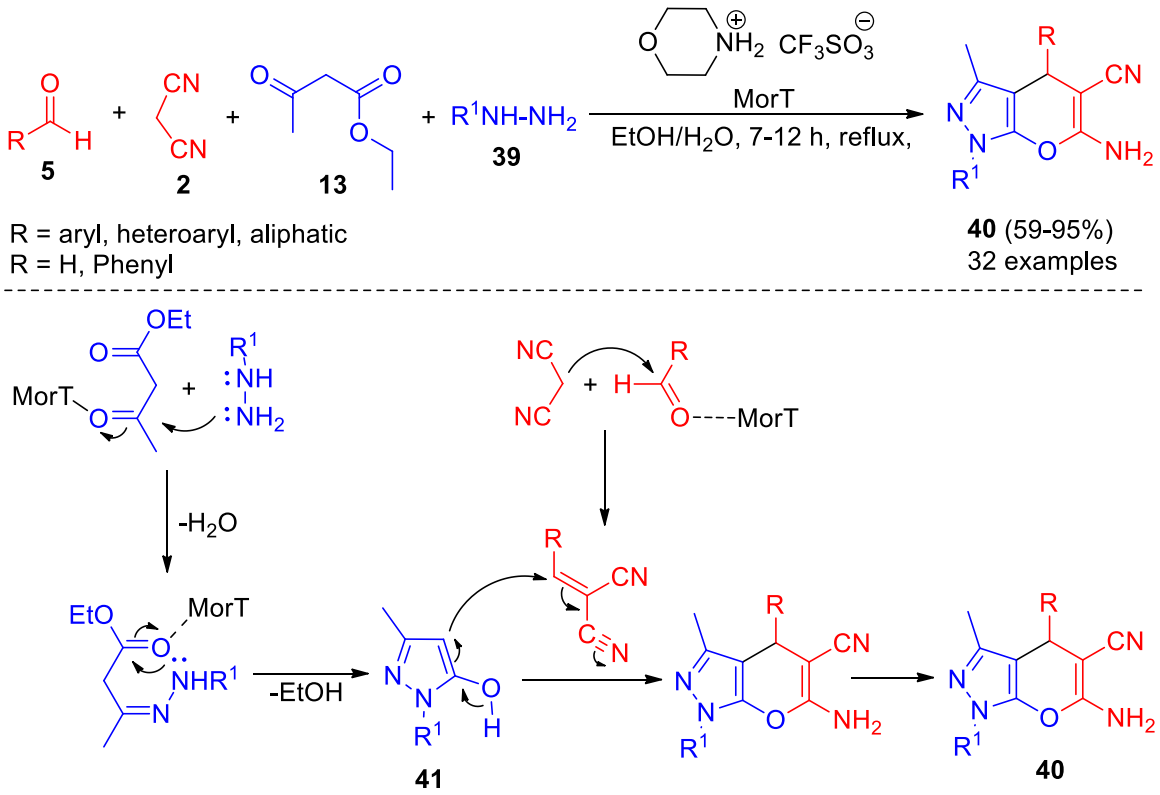


Scheme 14: K-10 catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **37**.

In 2016, Zhou *et al.*[65] demonstrated morpholine triflate (MorT) as a Lewis acid catalyst in one-pot four-component synthesis of pyrano[2,3-c]pyrazole derivatives **37** from several aldehydes **5**, malononitrile **2**,

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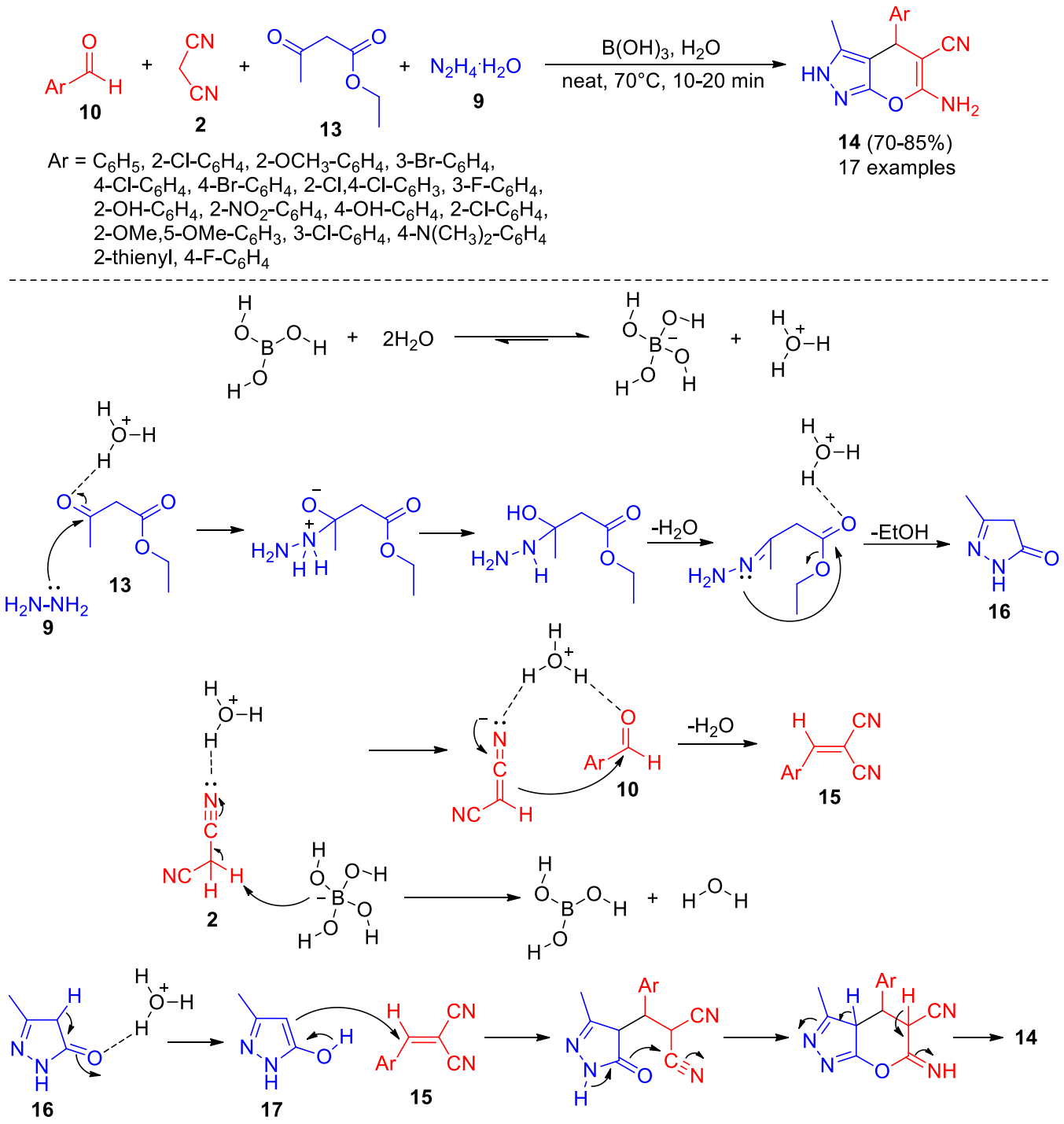
hydrazine **39** and ethyl acetoacetate **13** in aqueous ethanolic solution under refluxing condition for 7-12 hours. For optimizing reaction condition, the reaction was performed in presence of different ammonium triflates and different solvent system such as MeOH, EtOH, DMF, THF, H_2O, and EtOH/H_2O. However, the reaction in presence of aqueous ethanol afforded the product in the highest yield. The mechanism suggested by authors for this transformation involves the *in situ* formation of pyrazolone **41** from ethyl acetoacetate **13** and hydrazine **39** activated by MorT. Then Knoevenagel condensation reaction between aldehyde **5** with malononitrile **2** took place in presence of the catalyst to form α-cyanocinnamonitrile that can undergo Michael addition with pyrazolone **41** resulting in the formation of the final product **40**, after cyclization and tautomerization (Scheme 15).



Scheme 15: Morpholine triflate mediated construction of dihydropyrano[2,3-*c*]pyrazoles **40**.

Treatment of several substituted aryl aldehydes **10**, malononitrile **2**, hydrazine hydrate **9**, and ethyl acetoacetate **13** in presence of an aqueous solution of boric acid as a green catalytic system was found to lead to the formation of pyrano[2,3-*c*]pyrazole derivatives **14** in 70-85% after 10-20 minutes at 70°C (Scheme 16).[66] The interaction of $B(OH)_3$ with water released the H^+ in an aqueous solution that could effectively catalyze the reaction. Initially, the ethyl acetoacetate **13** was activated by H^+ and then hydrazine **9** attacked the carbonyl group of the activated ethyl acetoacetate and removed one molecule of H_2O. Then, another NH_2 group of hydrazine attacked the next carbonyl group of ethyl acetoacetate to give 5-methyl-2,4-dihydro-pyrazol-3-one **16** after removing one molecule of EtOH. In the subsequent step, the reaction of an activated aromatic aldehyde with malononitrile afforded the arylidene malononitrile **15**, which can then undergo tandem Michael addition-cyclization reaction with 5-methyl-2,4-dihydro-pyrazol-3-one **16** and yielded the final product **14.** By applying this tandem one-pot four-component protocol total of 17 compounds were synthesized in the highest yield.

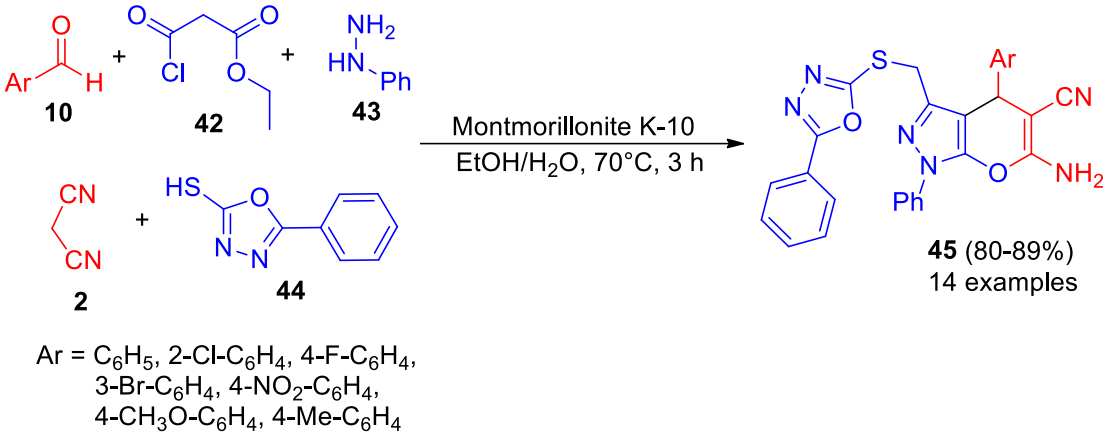
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Scheme 16: Boric acid catalyzed four-component synthesis of dihydropyrano[2,3-*c*]pyrazoles **14**.

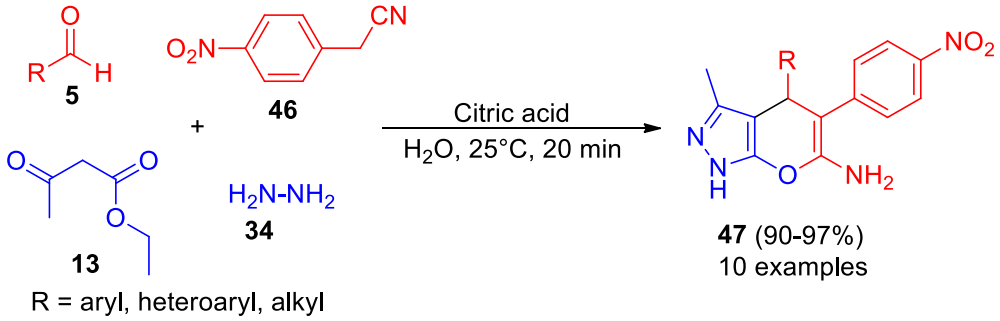
A multicomponent domino procedure has been developed for the synthesis of several thioethers linked dihydropyrano[2,3-*c*]pyrazole derivatives **45** from the reaction of aldehydes **10**, malononitrile **2**, ethyl 4-chloro-3-oxobutanoate **42**, phenylhydrazine **43**, and 5-phenyl-1,3,4-oxadiazole-2-thiol **44** in presence of Montmorillonite K-10 as a reusable green catalyst in aqueous ethanol under the stirring condition at 70°C for 3 hours (Scheme 17).[67] The reaction was also investigated in solvent-free as well as catalyst-free condition. However, products were obtained in low yield with impurities. With this eco-compatible, operational simplicity, and environmentally friendly approach, 14 compounds in 80-89% yields were obtained.

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Scheme 17: Synthesis of thioether linked dihydropyrano[2,3-*c*]pyrazoles **45** in presence of K-10.

Recently, Govindaraju and their team introduced citric acid as a biodegradable and reusable catalyst that facilitates the one-pot multi-component strategy for the construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **47** in good to excellent yield (90-97%) from simple starting material including several aldehydes **5**, 4-nitrophenylacetonitrile **46**, ethyl acetoacetate **13** and hydrazine **34** in presence of water as green solvent at 25°C (Scheme 18).[68] The methodology offers several benefits like simple workup procedure, mild reaction condition, green catalyst, high yield, and also eco-friendly protocol.

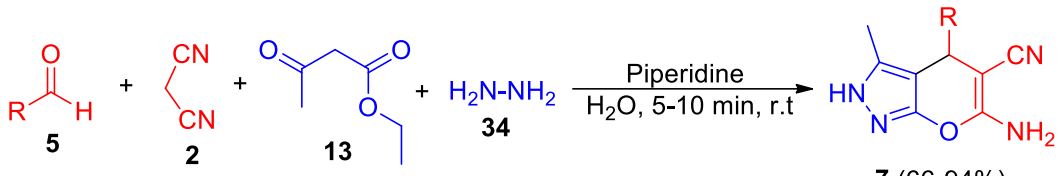


Scheme 18: Citric acid-catalyzed one-pot synthesis of dihydropyrano[2,3-*c*]pyrazoles **47**.

2.3 Base catalyzed synthesis

In 2008 Vasuki *et al.*[69] reported a single step construction of dihydropyrano[2,3-*c*]pyrazole derivatives **7** in good to excellent yield ranging from 66-94% through the four-component reaction of substituted aldehyde **5**, malononitrile **2**, hydrazine **34,** and ethyl acetoacetate **13** by employing piperidine as a base catalyst in aqueous medium at room temperature within 5-10 minutes (Scheme 19). Not only the aromatic aldehydes but also heteroaromatic as well as aliphatic aldehydes were well tolerated by this method and the yields of the products depended on the substitution in different positions of the aldehydes group. All halogenated substrates afforded the final product in quantitative yield.

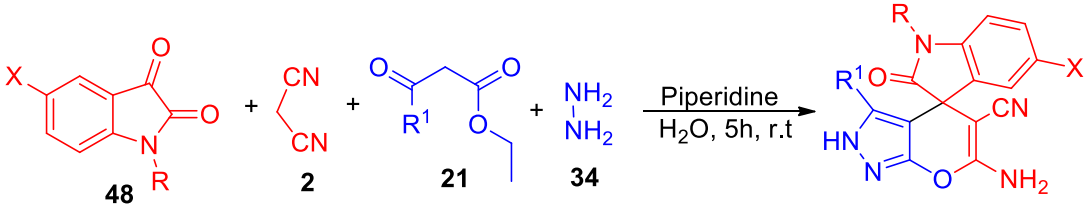
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R = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-O_2N-C_6H_4
4-Cl-C_6H_4, 4-HO-C_6H_4, 2-MeO-C_6H_4, 4-F-C_6H_4,
3-MeO-C_6H_4, 3-O_2N-C_6H_4, 3-MeO,4–MeO-C_6H_3,
3-MeO,5–MeO–C_6H_3, 2-Cl,3-Cl-C_6H_3, 2-Furanyl
2-Cl,4-Cl-C_6H_3, 3-OMe,4-OMe,5-MeO-C_6H_2,
4-Pyridinyl, 2-Thiophenyl, Isopropyl, 3-Pyridinyl,

Scheme 19: Secondary amine catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **7**.

A very simple procedure for the one-pot synthesis of several spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **49** in 80-97% yield *via* the four-component condensation reaction of substituted isatin **48**, malononitrile **2**, β-ketoesters **21,** and hydrazine hydrate **34** in the water at room temperature for 5 hours by using secondary amine piperidine as a base catalyst has been discovered by Ahadi's group in 2010 (Scheme 20).[70] The investigations carried out for the reaction mechanism involving the initial formation of pyrazolone from **21** and **34** that can then react with the Knoevenagel adduct produced from the reaction of isatin **48** and malononitrile **2**, followed by an intramolecular cyclization and tautomerization after which the desired product **49** was obtained.

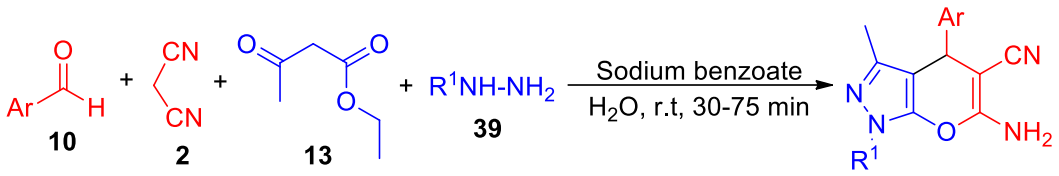


X = H, Br, NO_2
R = H, Me, Et, $PhCH_2$
R^1 = Me, *n*-Pr

Scheme 20: Construction of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] **49** by using piperidine as a base catalyst.

Later, the research group of Kiyani introduced sodium benzoate as an efficient base catalyst that could effectively catalyze the one-pot condensation reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine hydrate **39,** and ethyl acetoacetate **13** in presence water as a solvent at room temperature for 30-75 minutes, leads to the formation of dihydropyrano[2,3-*c*]pyrazole derivatives **50** in 78-94% yield (Scheme 21).[71] Use of water as reaction medium, mild reaction condition, short reaction time, easy isolation, wide substrate scope makes this protocol very significant in terms of synthetic efficiency as well as green chemistry point of view.

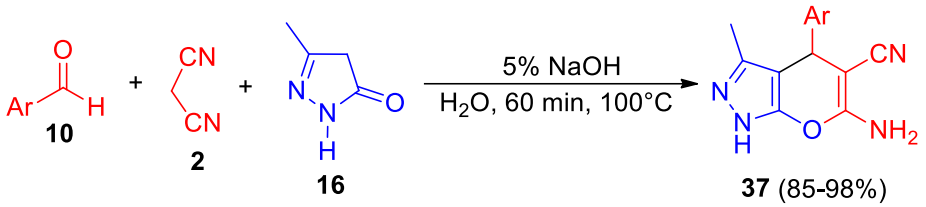
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Ar = C_6H_5, 2-Cl-C_6H_4, 4-F-C_6H_4, 4-OMe-C_6H_4, 2-Cl-C_6H_4
4-NO_2-C_6H_4, 3-Br-C_6H_4, 4-$N(CH_3)_2$-C_6H_4, 4-OH-C_6H_4,
4-Cl-C_6H_4, 3-NO_2-C_6H_4, 2-NO_2-C_6H_4, 4-Me-C_6H_4
R^1 = H, Ph,

Scheme 21: Sodium benzoate as the base catalyst for the synthesis of dihydropyrano[2,3-*c*]pyrazoles **50**.

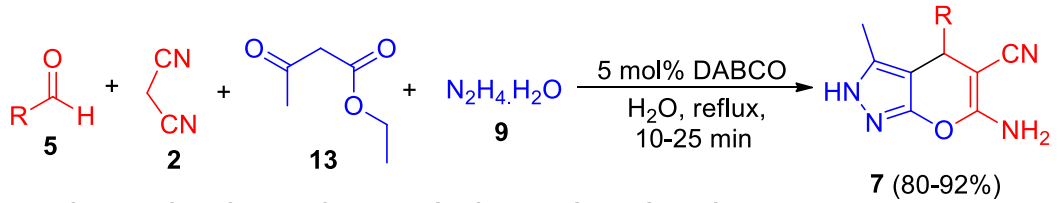
In 2013, Ilovaisky's group reported the "on water" one-pot three-component reaction of aromatic aldehyde **10**, malononitrile **2,** and pyrazolone **16** in presence of sodium hydroxide (NaOH) as a basic catalyst at 100°C for the synthesis of several pyrano[2,3-*c*]pyrazole derivatives **37** in 85-98% yield (Scheme 22).[72] The methodology displays several advantages such as mild reaction conditions, short reaction time, wide substrate scope, high yield of the product, eco-friendly as well as environmentally friendly protocol. By applying this green synthetic protocol, seven compounds possessing electron-rich as well as electron-poor substituents were synthesized in good to excellent yield mainly ranging from 85-98% within a very short reaction time.



Ar = C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4
3-OMe,4-OMe-C_6H_3, 4-F-C_6H_4,
4-NO_2-C_6H_4,4-Me-C_6H_4

Scheme 22: Sodium hydroxide catalyzed three-component synthesis of dihydropyrano[2,3-*c*]pyrazoles **37**.

In 2015, Waghmare and his co-workers reported 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed one-pot construction of dihydropyrano[2,3-*c*]pyrazole derivatives **7** from the four-component reaction of several substituted aldehyde **5**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** in aqueous medium under refluxing condition within 10-25 minutes (Scheme 23).[73] Not only the aryl aldehydes but also heteroaryl aldehydes were well tolerated by this green strategy and a total of 20 compounds were synthesized in good to excellent yield.

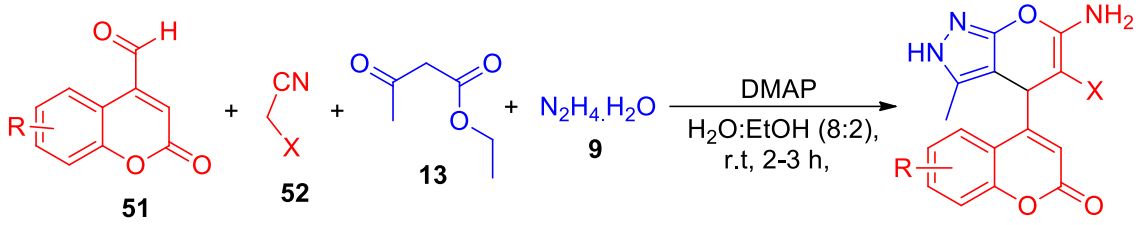


R = C_6H_5, 4-CH_3-C_6H_4, 2-furyl, 3-NO_2-C_6H_4, 4-OH-3-OMe-C_6H_3,
4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-Br-C_6H_4, thienyl,
2-NO_2-C_6H_4, 2-OH-C_6H_4, 3-OH-C_6H_4, 4-OH-C_6H_4, 2-Cl-C_6H_4,
3-Cl-C_6H_4, 3-OMe,4-OMe-C_6H_3, 2-OMe,4-OMe,6-OMe-C_6H_2,
3-OMe,4-OMe,5-OMe-C_6H_2, 1-napthyl

Scheme 23: DABCO catalyzed preparation of dihydropyrano[2,3-*c*]pyrazole **7**.

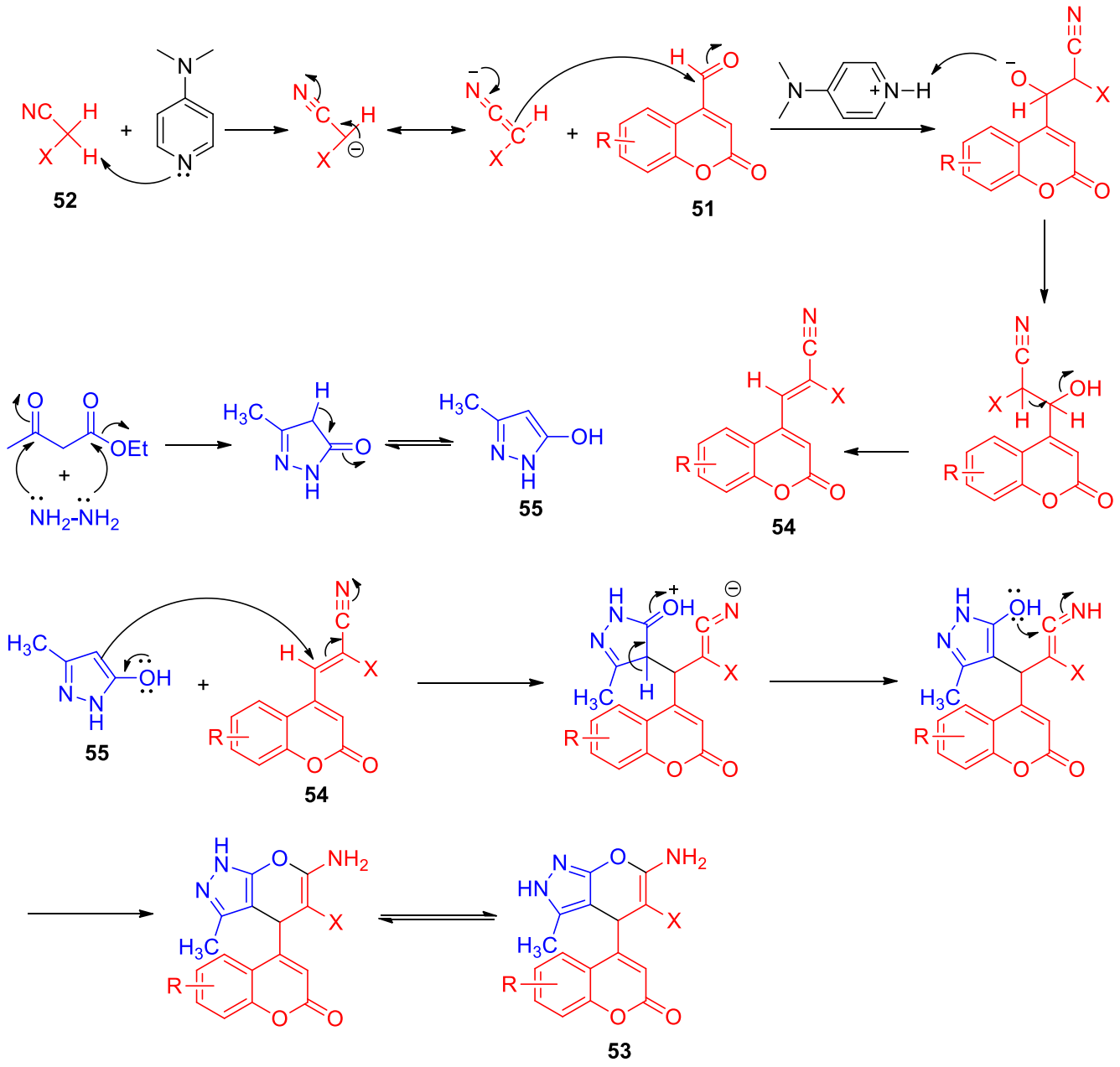
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Another achievement has been gained by Chougala and co-workers in 2016, by applying 4-dimethylaminopyridine (DMAP) as a base catalyst for the construction of several coumarins based dihydropyrano[2,3-*c*]pyrazoles **53** in 82-92% yield from the one-pot reaction of substituted chromene-carbaldehyde **51**, malononitrile **52**, hydrazine hydrate **9** and ethyl acetoacetate **13** in presence aqueous ethanolic solution at room temperature under the stirring condition for 2-3 hours (Scheme 24).[74] A plausible mechanism that explains this transformation starts with the initial formation of coumarin based Knoevenagel product **54** from the DMAP catalyzed reaction of substituted coumarin carbaldehyde **51** and active methylene compound **52** that can then experiences nucleophilic attack from the –OH form of pyrazolone **55** produced *in situ* in the reaction from ethyl acetoacetate and hydrazine. In the next step, intramolecular cyclization and tautomerization yield the corresponding coumarin-based dihydropyrano[2,3-*c*]pyrazoles **53** (Scheme 25).



Scheme 24: Synthesis of dihydropyrano[2,3-*c*]pyrazole **53** from chromene-carbaldehyde.

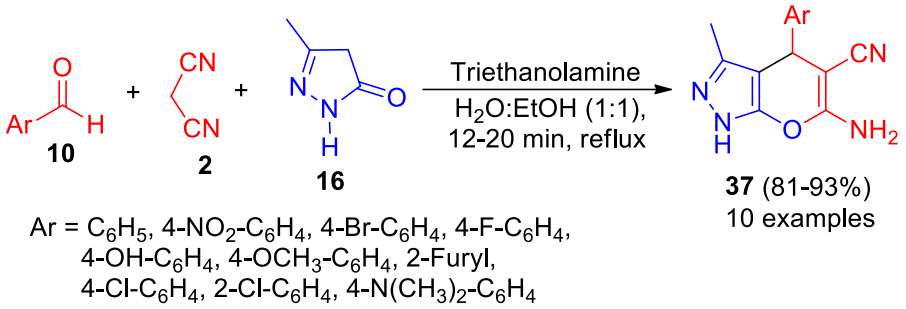
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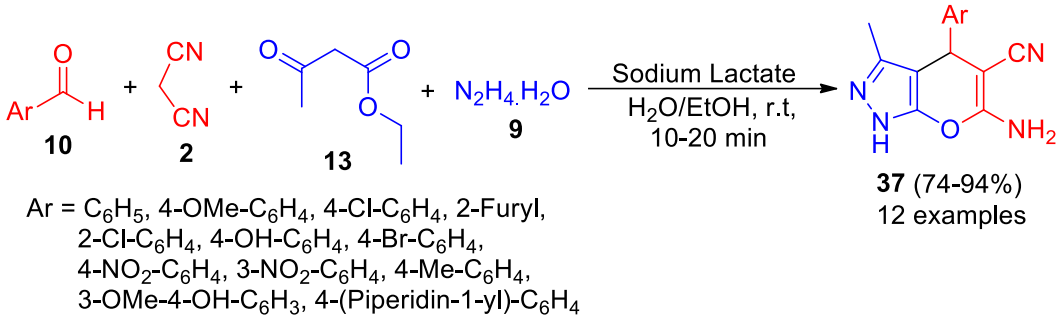
Scheme 25: Plausible mechanism for the formation of **53**.

Jayant P Sonar and his co-workers have demonstrated the triethanolamine catalyzed one-pot synthesis of a series of dihydropyrano[2,3-*c*]pyrazole derivatives **37** in 81-93% yield from the three-component coupling reaction of several substituted aldehyde **10**, malononitrile **2,** and pyrazolone **16** by using the aqueous ethanolic solution as a solvent under refluxing condition for 12-20 minutes (Scheme 26).[75] Aldehydes **10** possessing several electron-withdrawing and electron-donating groups affect the yield of the product and aromatic as well as heteroaromatic aldehydes afforded the product in excellent yield. The same author also reported the utilization of sodium lactate as an efficient base catalyst for the construction of dihydropyrano[2.3-*c*]pyrazoles **37** in aqueous ethanolic solution and the reaction starts with the four component treatment of several substituted aldehydes **10**, malononitrile **2**, ethyl acetoacetate **13** and hydrazine hydrate **9** at room temperature (Scheme 27).[76] The methodology offers several advantages and by using this method 12 compounds were synthesized in 74-94% yield within 10-20 minutes.

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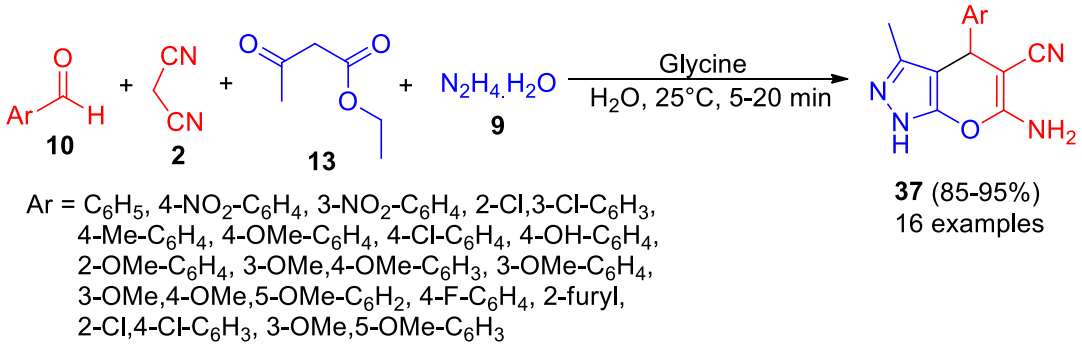
Scheme 26: Rapid access to dihydropyrano[2,3-*c*]pyrazoles **37** in triethanolamine.



Scheme 27: Sodium lactate catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazole **37**.

2.4 Organocatalyzed synthesis

In 2010, the research group of Reddy demonstrated that the utilization of glycine as a non-toxic organocatalyst in the four-component reaction of aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** in presence of water as a solvent at 25°C, afforded the corresponding dihydropyrano[2,3-*c*]pyrazole derivatives **37** in 85-95% yield after 5-20 minutes (Scheme 28).[77] When the reaction was carried out in presence of different solvents like DMF, DCM, EtOH, MeOH; the yield of the product did not increase. However, when the polarity of the solvent system was increased by using water as a solvent the yield of the product increased even though the low amount of the catalyst was used. From the optimization, it was clear that the yield of the product increased as the polarity of the solvent increases. Hence, water was chosen as the best solvent system and the reaction has proceeded very smoothly with all aromatic as well as heteroaromatic aldehydes, and a total of 16 compounds were synthesized.

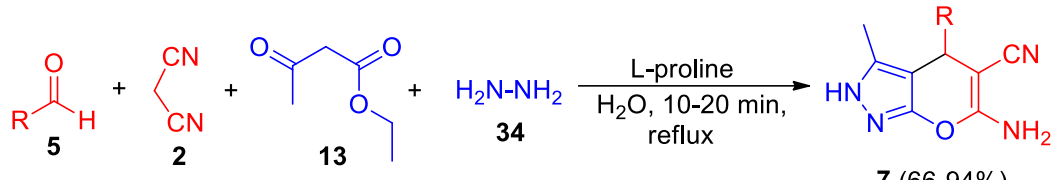


Scheme 28: Glycine as an organocatalyst for the synthesis of dihydropyrano[2,3-*c*]pyrazole **37**.

A very convenient organocatalytic approach for the construction of alkyl and aryl-substituted dihydropyrano[2,3-*c*]pyrazoles **7** in 65-93% yield was developed by Mecadon's group. The methodology involves the four component treatment of aldehyde **5**, malononitrile **2**, hydrazine hydrate **34,** and ethyl

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acetoacetate **13** in a water medium under the influence of 10 mol% of L-proline for 10-20 minutes of reflux. The catalytic activity of L-proline for this transformation was compared by using other catalysts like- γ-alumina, basic alumina, and KF- alumina. When the reaction was carried out in γ-alumina, basic alumina, and KF-alumina under the same reaction condition, the products were obtained in 42-68%, 45-62%, and 30-59% respectively which was comparatively very low in comparison to L-proline due to which L-proline was found to be the best catalyst for this reaction (Scheme 29).[78]

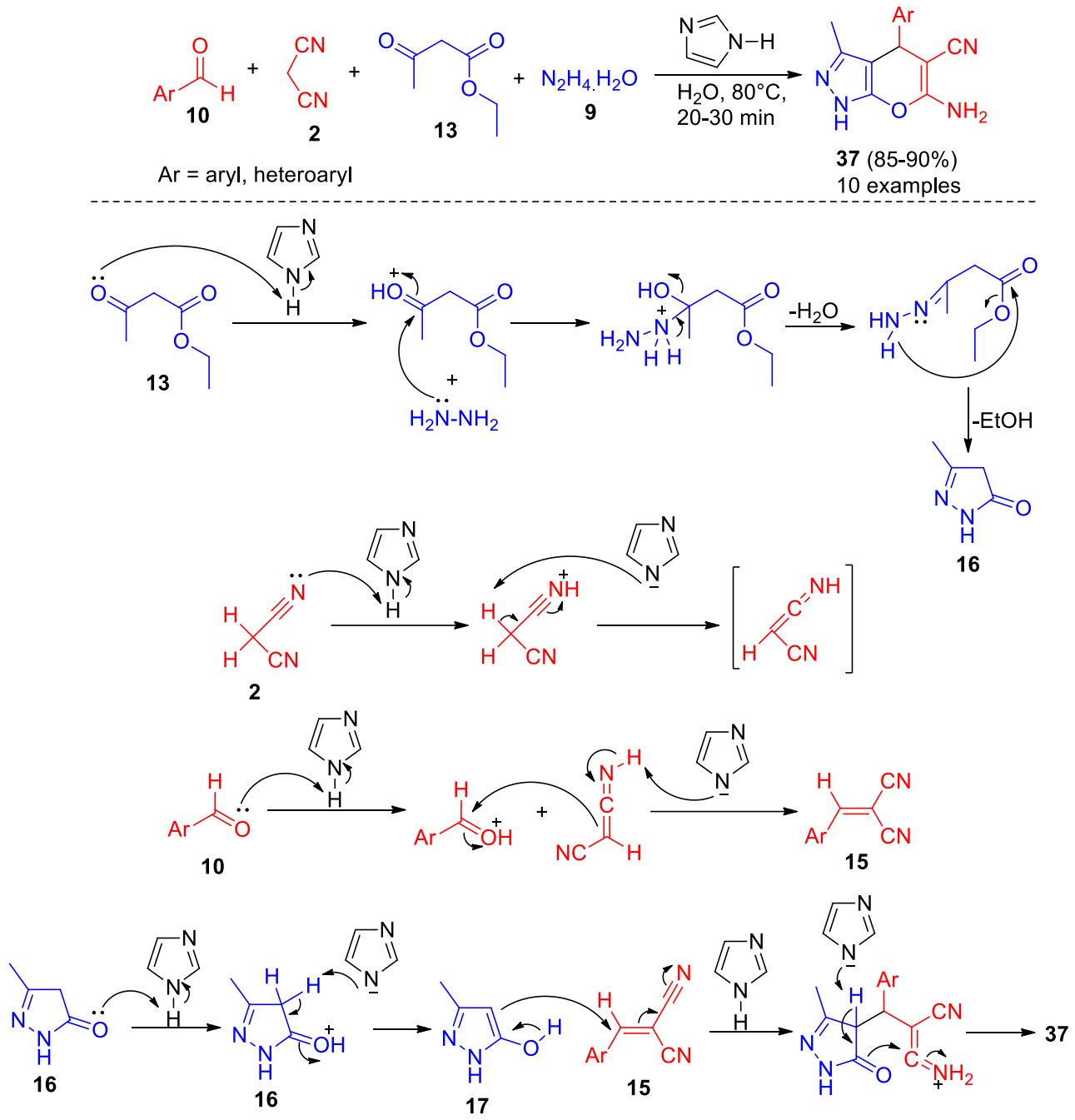


R = C_6H_5, 4-CH_3-C_6H_4, 4-OMe-C_6H_4, 2-OMe,5-OMe-C_6H_3, 4-Cl-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 4-$N(CH_3)_2$-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-HO-C_6H_4, 4-NO_2-C_6H_4, 2-Cl-C_6H_4, 3-OMe-4-HO-C_6H_3, 3-OMe,4-OMe-C_6H_3, 3-OMe,4-OMe,5-OMe-C_6H_2, 1-Naphthyl, 9-Anthranyl

Scheme 29: L-proline catalyzed synthesis of aryl/alkyl-substituted dihydropyrano[2,3-*c*]pyrazoles **7**.

Another successful organocatalytic method for the one-pot construction of dihydropyrano[2,3-*c*]pyrazole derivatives **37** has been accomplished by Siddekha *et al.* in 2011. In this regard, imidazole was introduced as an efficient organocatalyst that effectively catalyzed the four-component reactions of aromatic aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** in presence of an aqueous medium at 80°C for 20-30 minutes (Scheme 30).[79] Several electron-withdrawing and electron-donating groups in aldehydes affect the yield of the product. The electron-withdrawing group increases the yield of the product whereas the electron-donating group decreases the yield. A series of a total of 10 compounds in 85-90% yields were obtained by using this eco-friendly protocol. The mechanism for these transformations starts with the protonation of ethyl acetoacetate **13** by imidazole, followed by an intermolecular attack by hydrazine hydrate **9** and subsequent loss of water, and intramolecular nucleophilic attack by -NH_2 group on the carbonyl carbon afforded the 5-methyl-2,4-dihydro-pyrazol-3-one **16**. Similarly, protonation of aldehyde by imidazole and reaction with 3-imino-acrylonitrile may afford arylidene malononitrile **15**. The next addition of **16** to **15** in the presence of imidazole followed by rearrangement yielded the final product **37**.

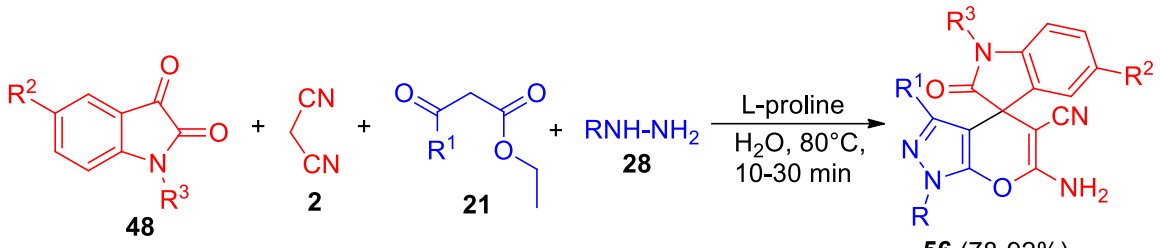
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Scheme 30: Imidazole catalyzed one-pot construction of dihydropyrano[2,3-*c*]pyrazole **37**.

In 2013, Yu *et al.*[80] reported the synthesis of several spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **56** by the reaction of substituted isatin **48**, malononitrile **2**, hydrazine **28,** and β-keto esters **21** in the presence of secondary amine L-proline as an organocatalyst in the water at 80°C for 10-30 minutes. All halogenated and alkyl substitutes on isatin rings smoothly worked under the optimized reaction condition and result in the formation of the product in 78-92% yield (Scheme 31).

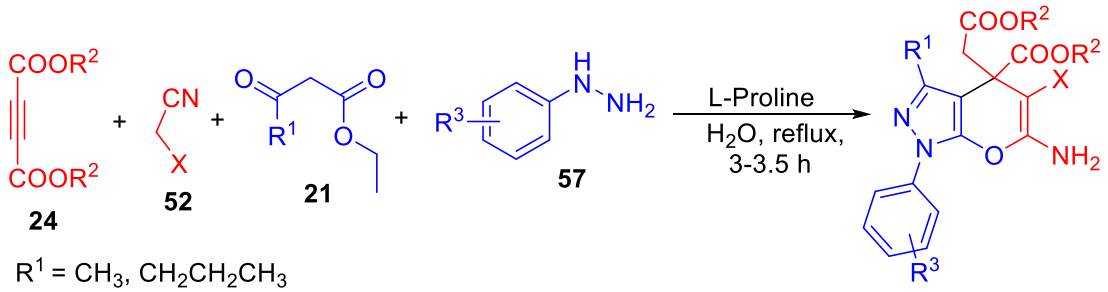
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R = H, OMe-Ph;
R^1 = Me, Ph;
R^2 = 5-H, 5-F, 5-Cl, 5-Br, 5-Me, 4-Br, 5-NO_2;
R^3 = H, Et, n-Pr,

Scheme 31: L-proline catalyzed four-component synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] **56**.

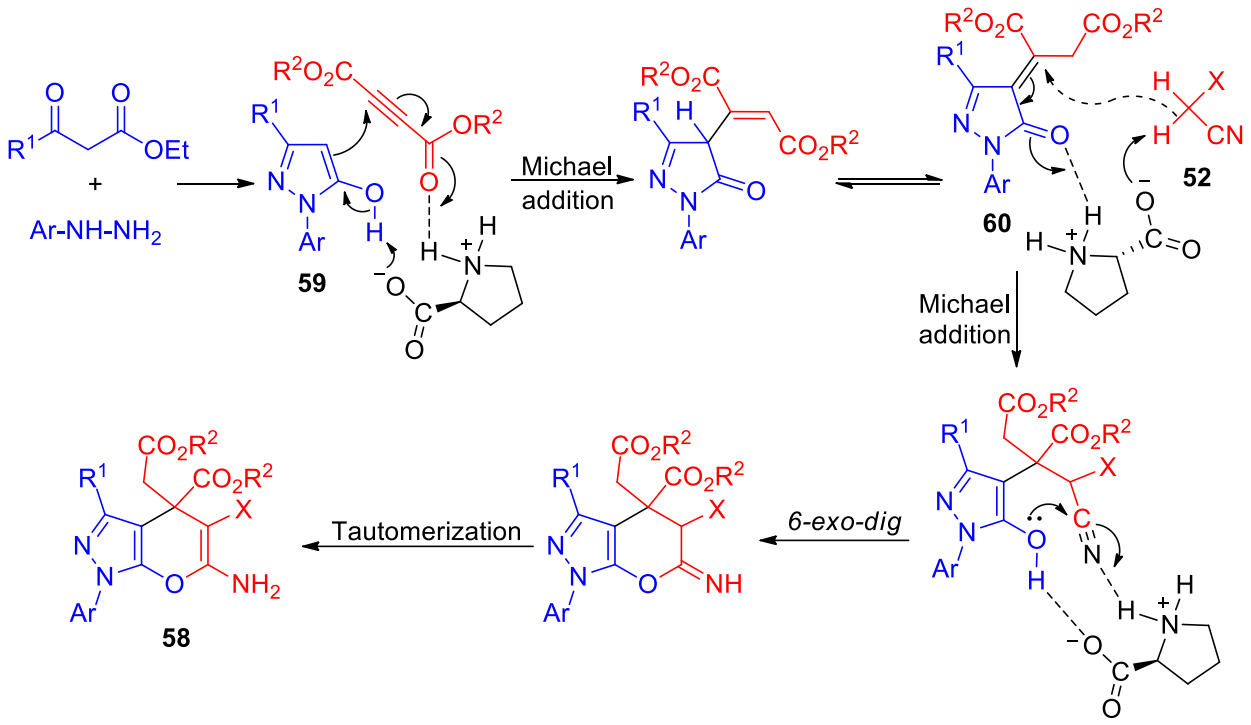
The research group of Prasanna L-proline catalyzed one-pot reaction of dialkyl acetylene dicarboxylates **24**, malononitrile **52**, β-ketoesters **21**, and hydrazines **57** by using water as a solvent for the construction of a series of dihydropyrano[2,3-*c*]pyrazole derivatives **58** under refluxing condition (Scheme 32).[81] This "on water" chemodivergent reaction proceeded through the initial formation of pyrazolone **59** from hydrazine and β-ketoesters that can undergo Michael addition with acetylene dicarboxylates **24** under the influence of L-proline followed by a subsequent [1,3] hydrogen shift, afforded the intermediate **60**. In the next step, a second Michael addition between the enone moiety of intermediate **60** and malononitrile **52** was taken place, which after a *6-exo-dig* annulation step with concomitant tautomerization yields the final product **58** (Scheme 33).



R^1 = CH_3, $CH_2CH_2CH_3$
R^2 = CH_3, CH_2CH_3
R^3 = H, 2,5-$(CH_3)_2$, 4-Cl, 4-F
X = CN, CO_2Et

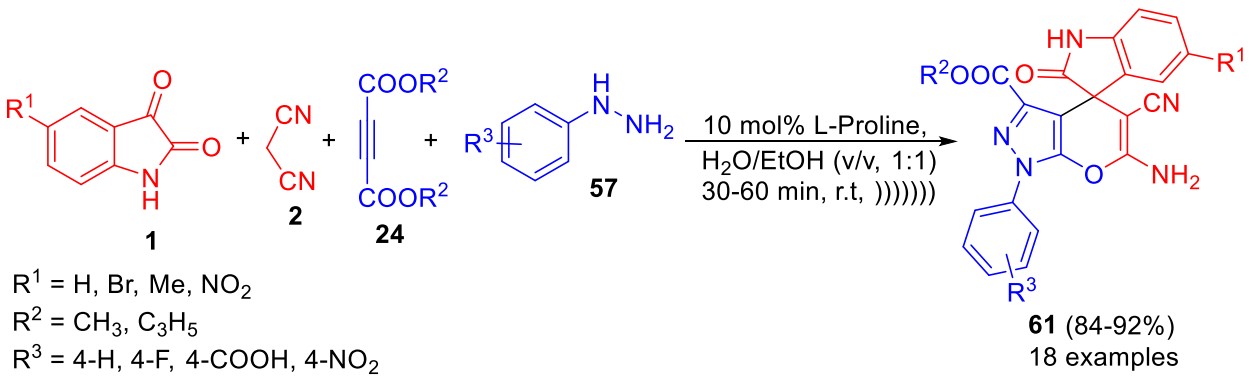
Scheme 32: L-proline as organocatalyst in water to access dihydropyrano[2,3-*c*]pyrazole **58**.

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Scheme 33: Proposed mechanism for the formation of dihydropyrano[2,3-*c*]pyrazole **58**.

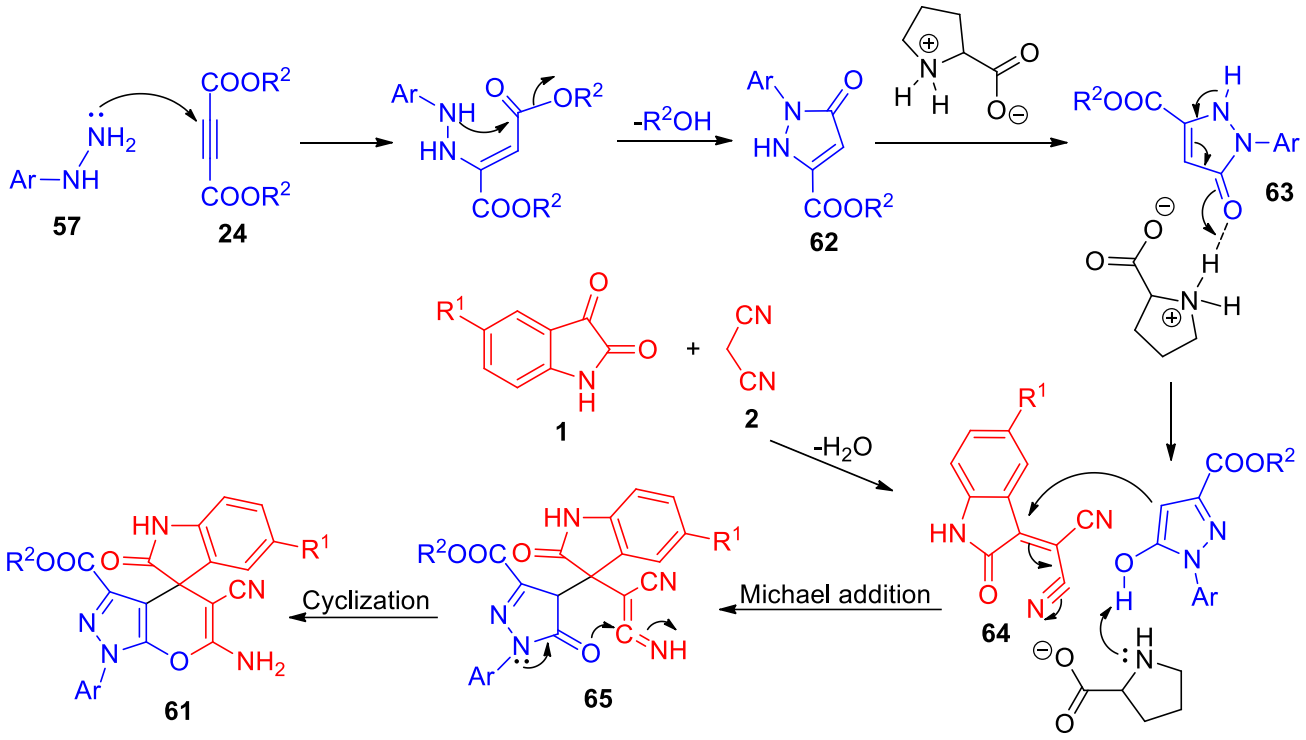
Wang Liju *et al.,*(2014) developed an ultrasound-assisted methodology for the four-component reaction of substituted isatin **1**, malononitrile **2**, dialkyl acetylene dicarboxylates **24,** and substituted hydrazine **57** by using L-proline as a catalyst in an aqueous ethanolic medium (v/v, 1:1), was found to leads to the formation of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] **61** in 84-92% yield at room temperature (Scheme 34).[82] A plausible mechanism that explains the formation of **61** begins with the initial formation of pyrazolone derivatives **62** from the exothermic reaction of **57** with **24** that can then produces the enolate intermediate **63** in presence of L-proline. Then, the Michael addition reaction between the intermediate **63** with Knoevenagel product **64** that was generated from substituted isatin **1** and malononitrile **2** in presence of L-proline, was took place, leads to the intermediate **65**. In the final step, a subsequent cyclization and tautomerization afforded the final product **61** from intermediate **65** (Scheme 35).



R^1 = H, Br, Me, NO_2
R^2 = CH_3, C_3H_5
R^3 = 4-H, 4-F, 4-COOH, 4-NO_2

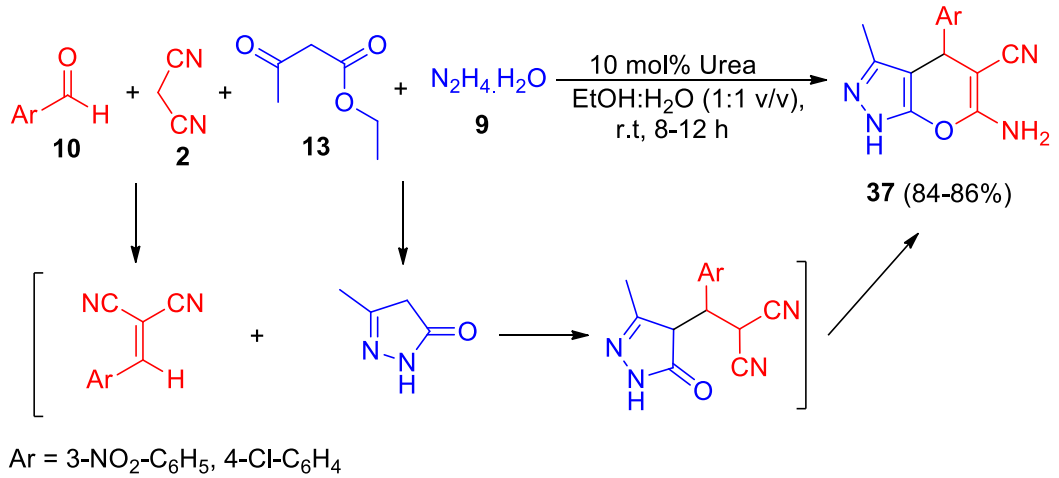
Scheme 34: Ultrasound-assisted L-proline catalyzed synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] **61**.

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Scheme 35: The suggested mechanism that explains the formation of **61**.

Brahmachari and Banerjee established the four component preparation of dihydropyrano[2,3-*c*]pyrazole derivatives **37** from the *in situ* generated pyrazolone and arylidene malononitrile by employing one-pot reaction of several substituted aryl aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** with urea as an organocatalyst in aqueous ethanolic solution at room temperature for 8-12 hours (Scheme 36).[83] The methodology exhibit a vast array of benefits in terms of environmentally friendly synthesis as well as large-scale industrial synthesis.

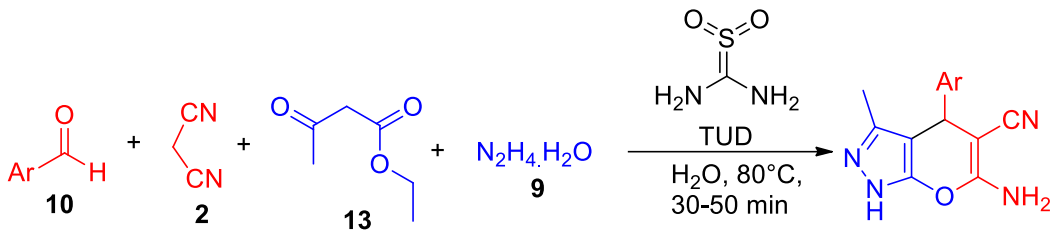


Scheme 36: Urea catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **37** from *in situ* generated pyrazolone.

In 2015, Vekariya *et al.*[84] reported the one-pot construction of dihydropyrano[2,3-*c*]pyrazole derivatives **37** from the four component condensation reaction of various derivatives of aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** by employing thiourea dioxide (TUD) as an organocatalyst in presence of water as solvent at 80°C within 30-50 minutes (Scheme 37). By introducing TUD as an inexpensive,

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non-volatile, reusable catalysts, a total of 24 compounds were synthesized and the products were formed by a simple workup procedure in 86-96% yield. All substituted aryl and heteroaryl aldehydes were smoothly providing the reaction and the rate of the reactions were depends on the substitutions.



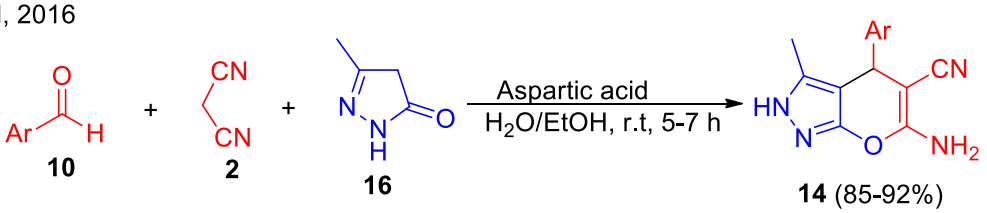
Ar = C_6H_5, 4-OH-C_6H_4, 4-N(Me)$_2$-C_6H_4, 2-OH–5-Br-C_6H_4, 2-OH-C_6H_4, 4-OMe-C_6H_4, 3-NO_2-C_6H_4, 4-CN-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 2-OH–5-NO_2-C_6H_3, 3-OMe,5-OMe,4-OH-C_6H_2, 3-OMe,4-OMe,5-OMe–C_6H_2, 4-NO_2-C_6H_4, 3-OH-C_6H_4, 2-Br-C_6H_4, 2-furayl, 4-F-C_6H_4, 2-OMe-C_6H_4, 2-Thienyl, 4-Br-C_6H_5, 3-OMe,4-OMe-C_6H_3, 2-NO_2-C_6H_4,

Scheme 37: Thiourea dioxide catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **37**.

In 2017, Ahad and Farooqui demonstrated that the multicomponent domino reaction of aldehydes **10**, malononitrile **2,** and pyrazolone **16** in presence of aspartic acid as an efficient organocatalyst in aqueous ethanol afforded the dihydropyrano[2,3-*c*]pyrazole derivatives **14** in 84-91% yield at room temperature (Scheme 38a).[85] In 2019, Khandebharad *et al.* has synthesized several dihydropyrano[2,3-*c*]pyrazole derivatives **37** in good to excellent yield from the four-component reaction of aldehydes **10**, malononitrile **2**, ethyl acetoacetate **13**, and hydrazine hydrate **9** by using sodium gluconate as recyclable organocatalyst in presence of water as a reaction medium under reflux of 15-45 minutes (Scheme 38b).[86] All aryl, as well as heteroaryl aldehydes with electron-withdrawing and electron releasing group on the different position, were smoothly worked under the optimized reaction condition and a total of 13 compounds were synthesized in 85-92% yield. In the same year, several novel dihydropyrano[2,3-*c*]pyrazole derivatives **67** in 80-90% yield has been synthesized by Chate *et al.* from the reaction of aldehydes **10**, malononitrile **2**, ethyl acetoacetate **13,** and isoniazid **66** in the presence of 2-aminoethanesulfonic acid (taurine) as a bio-organic catalyst in water medium at 70°C (Scheme 38c).[87] Another achievement has also been gained by Valiey *et al.* in 2019, who synthesized and fully characterized the melamine modified chitosan (Cs-Pr-Me) materials as a reusable bifunctional organocatalyst, and then the efficacy of the catalyst was tested by applying it in the four-component reaction of aldehydes **10**, malononitrile **2**, hydrazine hydrate **39** and ethyl acetoacetate **13** in the aqueous ethanolic solution as the solvent under reflux condition. Under this condition, several dihydropyrano[2,3-*c*]pyrazole derivatives **50** was prepared within 25 to 50 minutes and the prepared catalyst was found to be very effective for this transformation. A total of 32 compounds were synthesized by this methodology in 70-92% yields (Scheme 38d).[88]

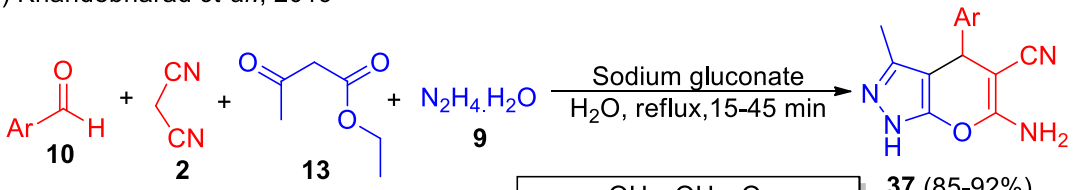
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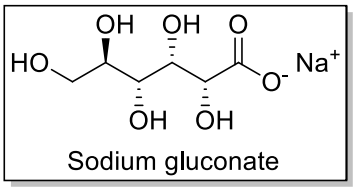
a) Ahad, 2016



Ar = C_6H_5, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 3-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 2-Cl-C_6H_4, 4-CH_3-C_6H_4

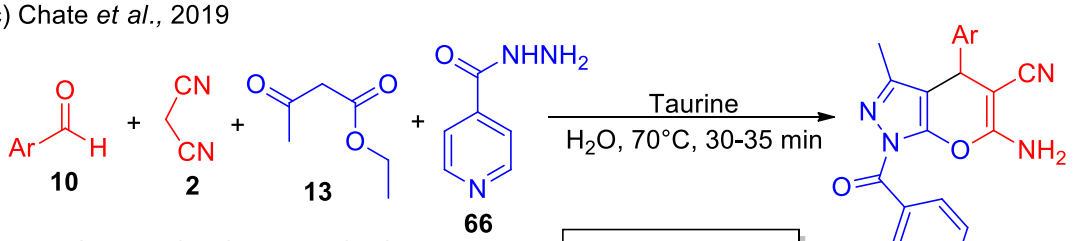
b) Khandebharad *et al*., 2019

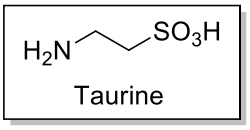




Ar = C_6H_5, 4-OCH_3-C_6H_4, 2-OCH_3- 4-OH-C_6H_3, 2-OCH_3-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 2-Cl-C_6H_4, CH_3, 4-Cl-C_6H_4, 4-$N(CH_3)_2$-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4

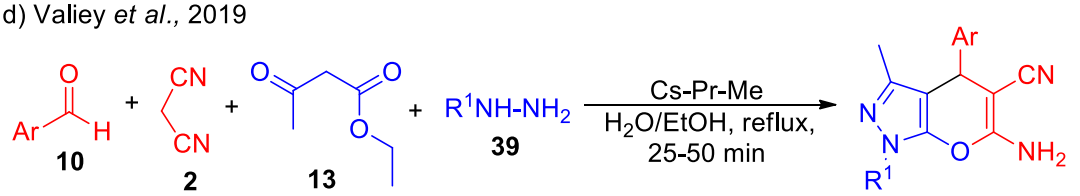
c) Chate *et al*., 2019





Ar = C_6H_5, 4-OH-C_6H_4, 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-OH-3-OCH_3-C_6H_3, 1-Indolyl, 2-OCH_3-1-Naphthyl, 2-Cl,6-Cl-C_6H_3, 3-OCH_3,4-OCH_3,5-$OCH_3C_6H_2$,

d) Valiey *et al*., 2019



Ar = C_6H_5, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-$N(CH_3)_2$-C_6H_4, 4-NO_2-C_6H_4, 2-Cl,4-Cl-C_6H_3, 4-F-C_6H_4, 2-Cl-C_6H_4, 2-NO_2-C_6H_4, 4-OH-C_6H_4, 4-CN-C_6H_4, 2-OH-C_6H_4,3-Br-C_6H_4, 2-OCH_3-C_6H_4, 3-OH-C_6H_4, 4-Br-2-OH-C_6H_3, 4-Pyridyl, 2-Furyl,

R^1 = H, Ph,

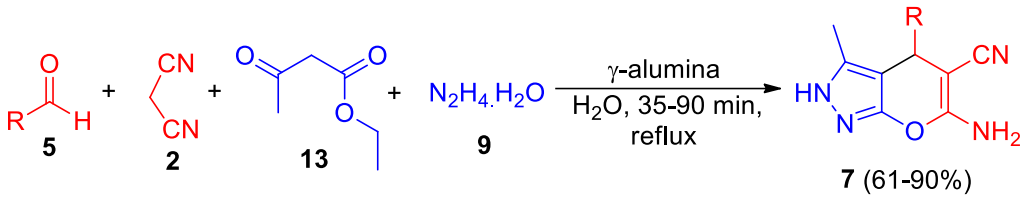
Scheme 38: Synthesis of several dihydropyrano[2,3-*c*]pyrazoles by using different types of organocatalyst.

2.5 Nanoparticle catalyzed synthesis

Mecadon *et al.*[89] described the utilization of γ-alumina as an efficient recyclable catalyst in the four-component reaction of aromatic aldehyde **5**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13**

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for the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives **7** in presence of water as a solvent under refluxing condition within 35-90 minutes (Scheme 39). All aliphatic and aromatic aldehydes were smoothly undergoing the reaction and the yield of the product ranges from 61-90%. The reaction was also performed in presence of other catalysts like KF-alumina, basic alumina and it was found that the rate of the reaction was faster and the yield of the product was increases when γ-alumina was used as a catalyst. The orders of catalytic activity of the tested catalyst for this transformation are as follows- γ-alumina > KF-alumina > basic alumina**.**

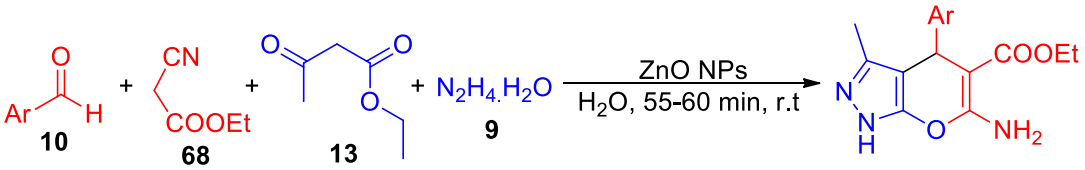


7 (61-90%)
20 examples

R = C_6H_5, 4-CH_3-C_6H_4, 4-OMe-C_6H_4, 3-OMe,4-OMe-C_6H_3, 4-NO_2-C_6H_4, 4-N(CH_3)$_2$-C_6H_4, 4-HO-C_6H_4, 2-NO_2-C_6H_4, 3-Br-C_6H_4, 3-OMe,4-OMe,5-OMe-C_6H_2, 3-NO_2-C_6H_4, 3-OMe-4-HO-C_6H_3, 2-OMe,5-OMe-C_6H_3, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 1-Naphthyl, 9-Anthranyl, Butyryl, Propionyl

Scheme 39: γ-alumina mediated synthesis of dihydropyrano[2,3-*c*]pyrazole **7**.

Sachdeva and Saroj in 2013 reported the preparation of pyrano[2,3-*c*]pyrazole derivatives **69** employing a four-component condensation reaction of aromatic aldehyde **10**, ethyl cyanoacetate **68**, hydrazine hydrate **9,** and ethyl acetoacetate **13** under the influence of zinc oxide nanoparticle (ZnO NPs) as a catalyst in aqueous medium at room temperature (Scheme 40).[90] The reaction was also carried out in heating condition. However, the yield of the product was not much increased as compared to the yield of the product obtained at room temperature. By applying this method, 10 compounds were synthesized in 85-90% yield and the catalyst was reused up to 3 cycles with negligible loss in catalytic property.



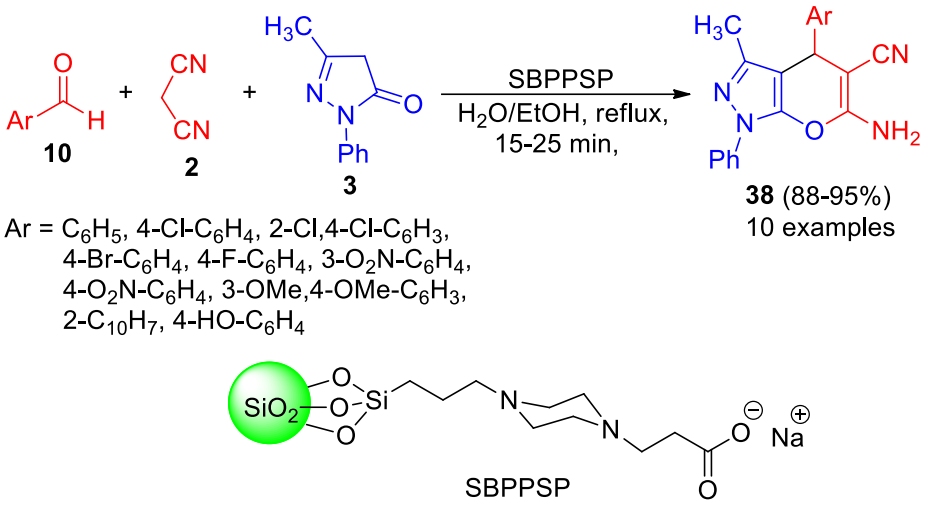
69 (85-90%)
10 examples

Ar = C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 2-thiophene, 4-OCH_3-C_6H_4, 3-OCH_3-C_6H_4, 2-furyl,

Scheme 40: Zinc catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **69**.

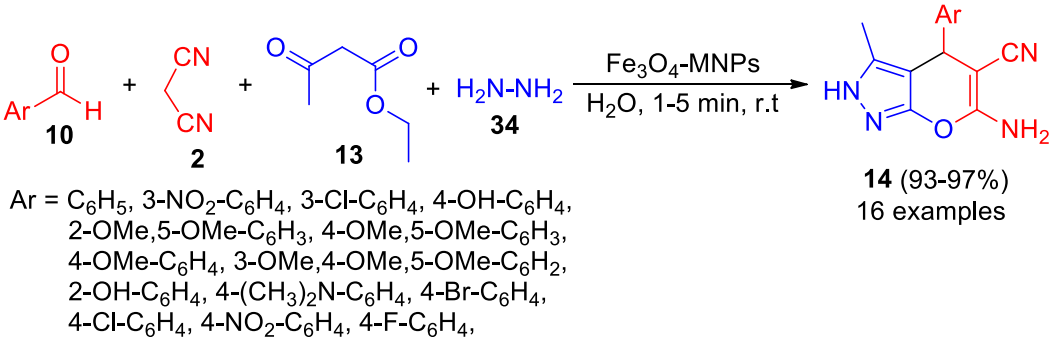
In 2013, the research group of Niknam reported the three-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives **38** from the one-pot reaction of aromatic aldehyde **10**, malononitrile **2,** and pyrazolone **3** by introducing silica bonded *N*-propylpiperazine sodium *n*-propionate (SBPPSP) as an efficient heterogeneous catalyst and aqueous ethanol as a solvent under refluxing condition within very short reaction time (Scheme 41).[91] The simple work-up procedure, mild reaction condition, reusability of the catalyst, wide substrate scope, environmentally as well as eco-friendly nature is the advantage of this method and by using this economically viable method, 10 compounds were synthesized and all the halogenated substrate afforded the product in high yield.

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Scheme 41: Magnetic nanoparticle catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles **38**.

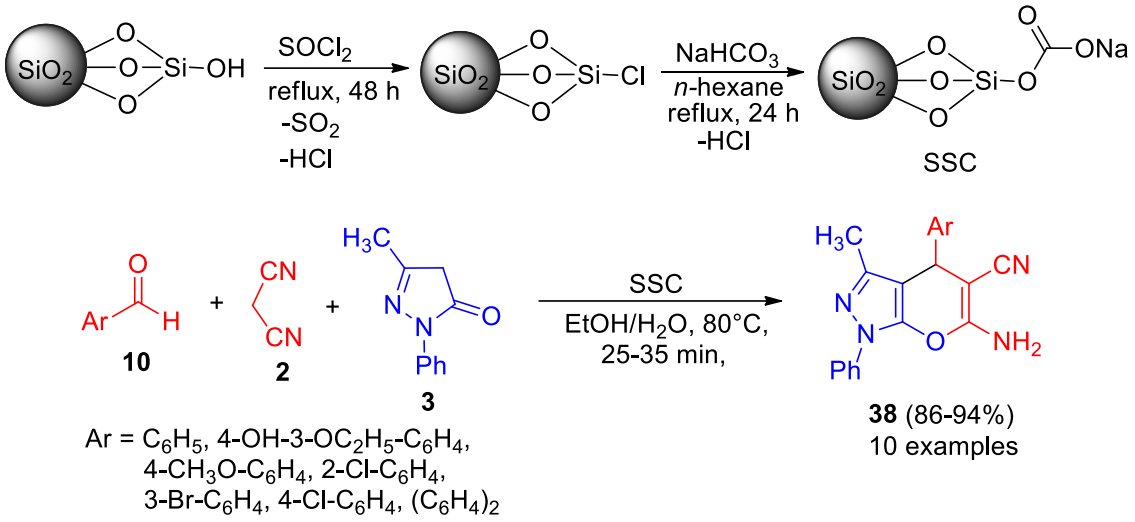
A very simple straightforward method for the construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **14** in 93-97% yield has been developed by Mahmoud *et al.* in 2014 by introducing magnetic Fe_3O_4 nanoparticles catalyzed one-pot four-component reaction of aryl aldehyde **10**, malononitrile **2**, hydrazine **34** and ethyl acetoacetate **13** in water as a solvent at room temperature (Scheme 42).[92] The effect of a catalyst on the reaction was also examined by using three types of the catalyst including Fe_3O_4, and Fe_3O_4 nanoparticle. However, the best yield of the product was obtained in presence of Fe_3O_4 NPs due to the greater diffusion of Fe_3O_4 nanoparticles in the reaction mixture and the catalyst could be easily recovered by using an external magnetic field and the possibility of recyclability was examined for the reaction. From the experiment, it was found that the catalyst could be very efficient for further reaction, leads to a similar yield to the fresh one and the methodology also displays flexibility in tuning the molecular complexity and diversity in a single step.



Scheme 42: Iron oxide nanoparticle catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazole **14** in water.

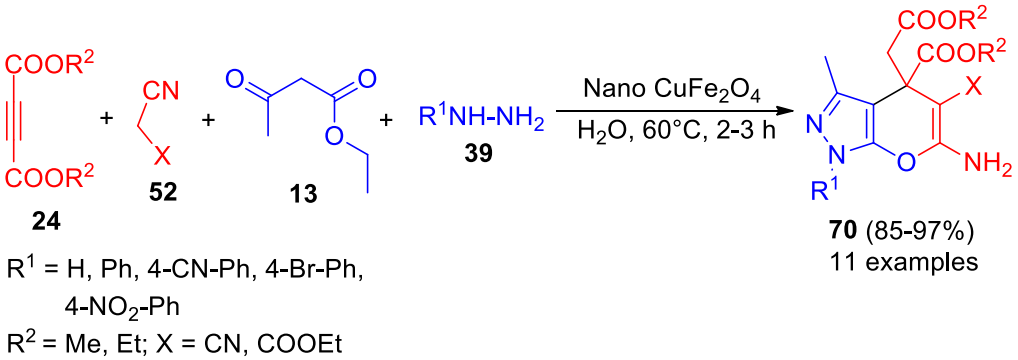
The synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives **38** can also be obtained *via* the three-component reaction of aromatic aldehyde **10**, malononitrile **2,** and pyrazolone **3** using silica sodium carbonate (SSC) as a novel catalyst in aqueous ethanolic solution at 80°C for 25-35 minutes (Scheme 43).[93] The catalyst was prepared from the reaction of silica chloride with sodium hydrogen carbonate and it was fully characterized by FT-IR, XRD, XRF, TG-DTA analysis. The efficacy of the catalyst was found to be very high in this reaction and the catalyst could be recovered simply from the reaction mixture. By applying this simple, mild protocol 10 compounds were synthesized with several electron-poor and electron-rich groups in 86-94% yield.

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Scheme 43: Preparation of SSC and its application in the synthesis of pyrano[2,3-*c*]pyrazole **38**.

In 2014, Pradhan *et al.*[94] reported a one-pot four-component condensation reaction of dialkyl acetylene dicarboxylates **24**, malononitrile/ethyl cyanoacetate **52**, ethyl acetoacetate **13**, and substituted hydrazine **39** for the preparation of a series of dihydropyrano[2,3-*c*]pyrazole derivatives **70** in 85-97% yield by introducing nanocrystalline $CuFe_2O_4$ as an efficient catalyst in presence of water that served as a reaction medium at 60°C for 2-3 hours (Scheme 44). The reaction was carried out in presence of different solvents as well as a catalytic system. However, $CuFe_2O_4$ was found to be the best catalyst, and water was chosen as the best solvent for this methodology. By using water as the solvent, the protocol worked well for a vast array of substrate scope and a total of 11 compounds were synthesized in good to excellent yield. The several advantages displayed by this methodology include mild reaction condition, short reaction time, eco-friendly, easily recoverable and reusable catalyst, environmentally friendly protocol, broad substrate scope, simple workup procedure etc.

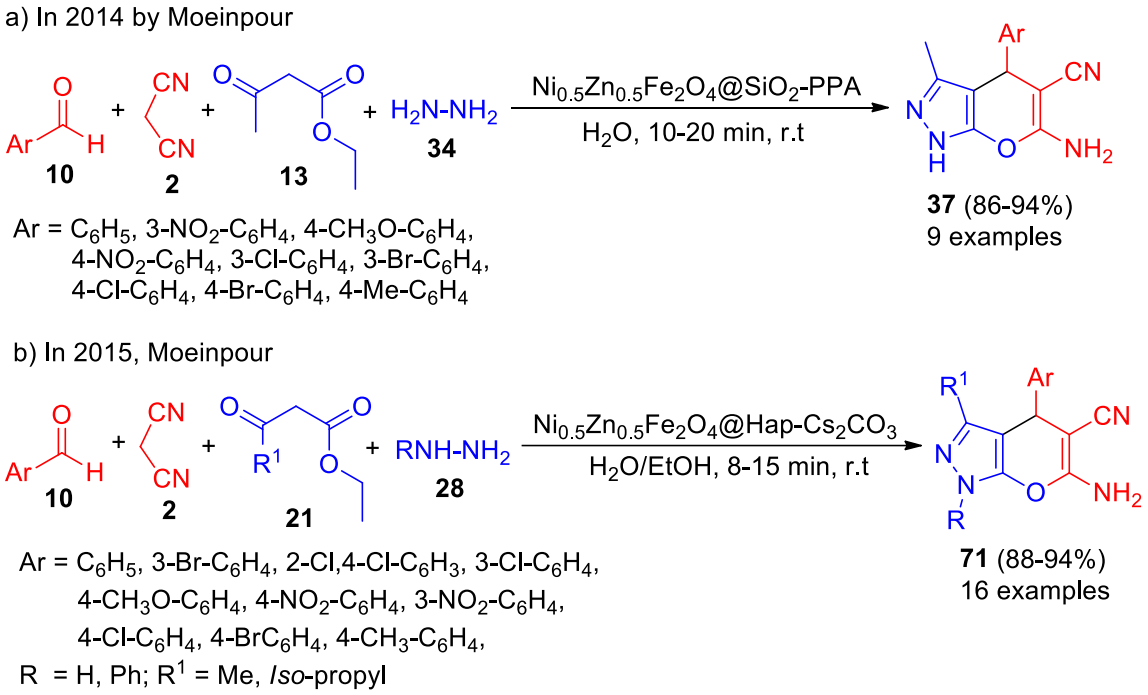


Scheme 44: Synthesis of dihydropyrano[2,3-*c*]pyrazole **70** using nano $CuFe_2O_4$ in water.

Moeinpour and Khojastehnezhad have demonstrated a polyphosphoric acid-functionalized silica-coated nanocatalyst, namely [$Ni_{0.5}Zn_{0.5}Fe_2O_4$@SiO_2–PPA] for the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives **37** proceeding through the four component one-pot reaction of aryl aldehyde **10**, malononitrile **2**, hydrazine **34,** and ethyl acetoacetate **13** using water as a solvent at room temperature (Scheme 45a).[95] They also synthesized cesium carbonate supported on hydroxyapatite-coated $Ni_{0.5}Zn_{0.5}Fe_2O_4$ magnetic nanoparticles $Ni_{0.5}Zn_{0.5}Fe_2O_4$@Hap-Cs_2CO_3 and the catalytic activity of the catalyst was tested in the one-pot reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine **28,** and ethyl acetoacetate **21** in aqueous

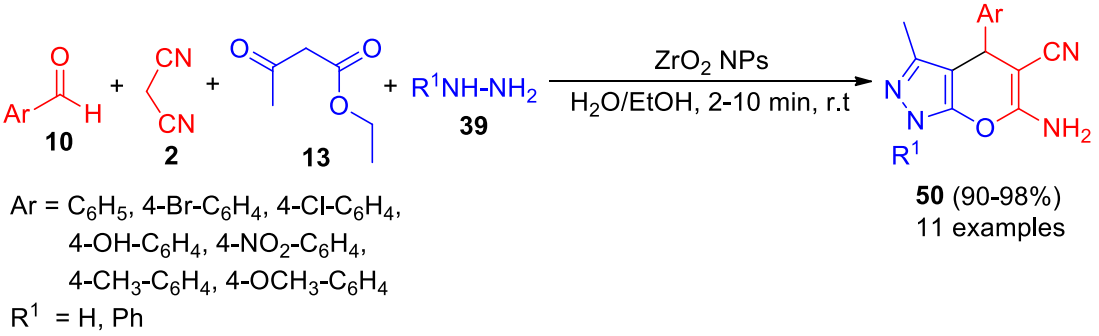
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ethanolic solution at room temperature. It was found that the synthesized catalyst could effectively catalyze the reaction in a very short time and results in the formation of several dihydropyrano[2,3-*c*]pyrazole derivatives **71** in 88-94% yield (Scheme 45b).[96]



Scheme 45: Construction of dihydropyrano[2,3-*c*]pyrazoles **37** and **71** using two different nanocatalysts.

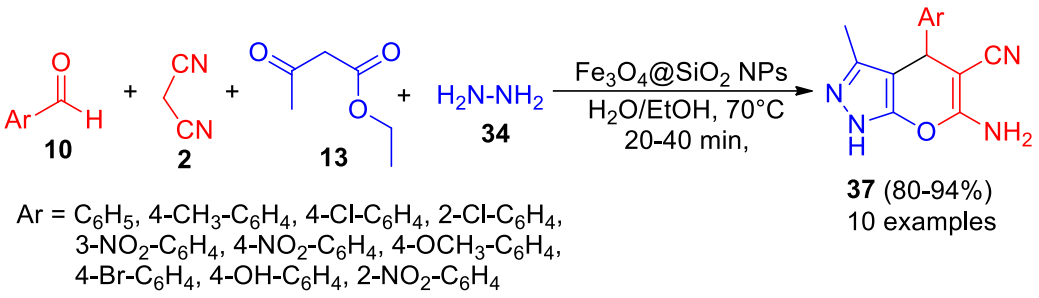
In 2015, Saha *et al.*[97] reported the use of ZrO_2 nanoparticle as a heterogeneous and reusable catalyst in the one-pot reaction of various derivatives of aryl aldehyde **10**, malononitrile **2**, hydrazines **39,** and ethyl acetoacetate **13** by introducing aqueous ethanolic solution as a solvent for the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives **50** at room temperature within 2-10 minutes (Scheme 46). To compare the catalytic activity of ZrO_2 in this transformation, the reaction was performed in presence of other catalysts like Et_3N, L-proline, piperidine, meglumine, γ-alumina; but most of the reaction required a higher temperature and not environmentally friendly, also the yield of the product was not satisfactory due to which the utilization of ZrO_2 provides best alternatives to the reported catalytic system in terms of product yield, reaction time as well as green chemistry point of view.



Scheme 46: Zirconium oxide catalyzed preparation of dihydropyrano[2,3-*c*]pyrazoles **50**.

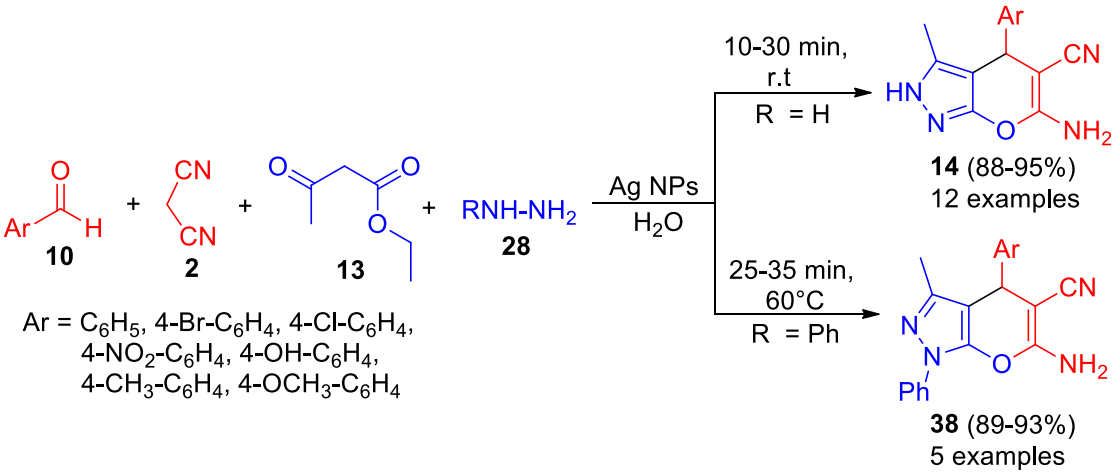
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In 2015, the research group of Soleimani's prepared magnetic Fe_3O_4@SiO_2 core-shell nanoparticle as a heterogeneous catalyst and fully characterized by FT-IR, powder X-ray diffraction, dynamic light scattering, and transmission electron microscopy. The catalytic activity of the prepared catalyst was tested for the four-component reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine **34,** and ethyl acetoacetate **13** using the aqueous ethanolic solution as a solvent at 70°C and was found to be very efficient that leads to the construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **37** in 80-94% yield. All electron-withdrawing group, as well as the electron-donating group on different positions of the aromatic ring, were successfully transformed into the corresponding product in a very short reaction time (Scheme 47).[98]



Scheme 47: Synthesis of dihydropyrano[2,3-*c*]pyrazoles **37** developed by Ebrahim.

At the same time, Yadav and Khurana described the synthesis of silver nanoparticle from water extract of Cinnamomum Tamala leaf, and the synthesized silver nanoparticle was utilized as a catalyst for the formation of pyrano[2,3-*c*]pyrazole derivatives **14** from the four-component reaction of aryl aldehyde **10**, malononitrile **2**, hydrazine **28** and ethyl acetoacetate **13** in aqueous medium at room temperature for 10-30 minutes (Scheme 48).[99] By using this green method, twelve compounds were synthesized in high yield ranging from 88-95%. They also synthesized several dihydropyrano[2,3-*c*]pyrazole derivatives **38** in 89-93% by using phenylhydrazine **28a** (R = Ph) instead of hydrazine hydrate **28b** (R = H) at 60°C within 25-35 minutes.

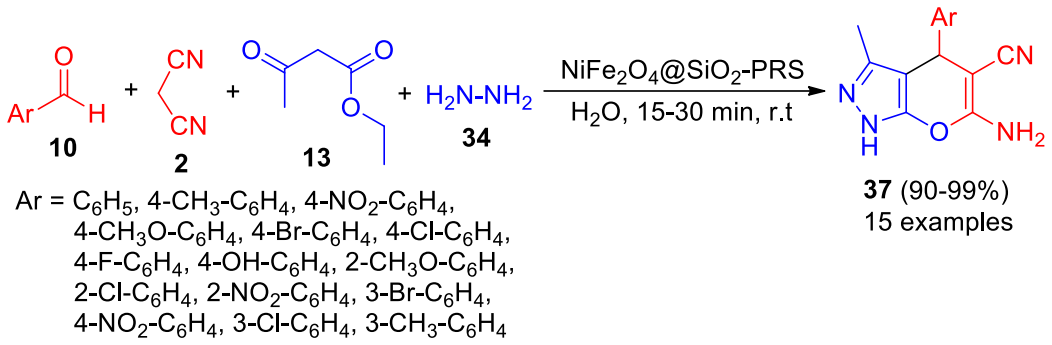


Scheme 48: Silver NPs catalyzed one-pot construction of dihydropyrano[2,3-*c*]pyrazoles **14** & **38**.

A simple and highly efficient methodology that described the construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **37** from *in situ* generated pyrazolone was introduced by Javad *et al.* in 2016. Preyssler-heteropoly acid ($H_{14}NaP_5W_{30}O_{120}$) supported silica-coated $NiFe_2O_4$ magnetic nanoparticles ($NiFe_2O_4$@SiO_2-Preyssler, shortened as NFS-PRS) was prepared in this regard and the catalytic activity was tested by

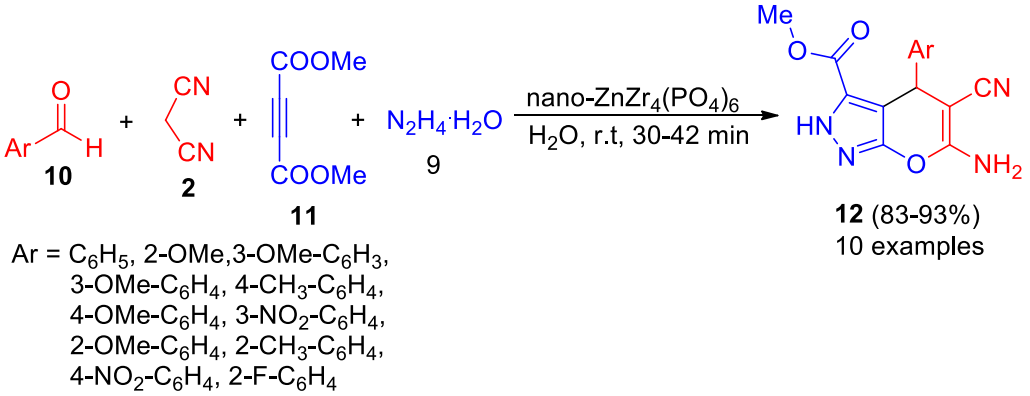
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employing it in the reaction of aldehydes **10**, malononitrile **2**, ethyl acetoacetate **13,** and hydrazine hydrate **34** under the influence of water as solvent at room temperature (Scheme 49).[100] The prepared catalyst was found to be very suitable for the construction of 25 derivatives of pyrano[2,3-*c*]pyrazole in high yield.



Scheme 49: Heteropoly acid-functionalized NPs in the preparation of dihydropyrano[2,3-*c*]pyrazoles **37**.

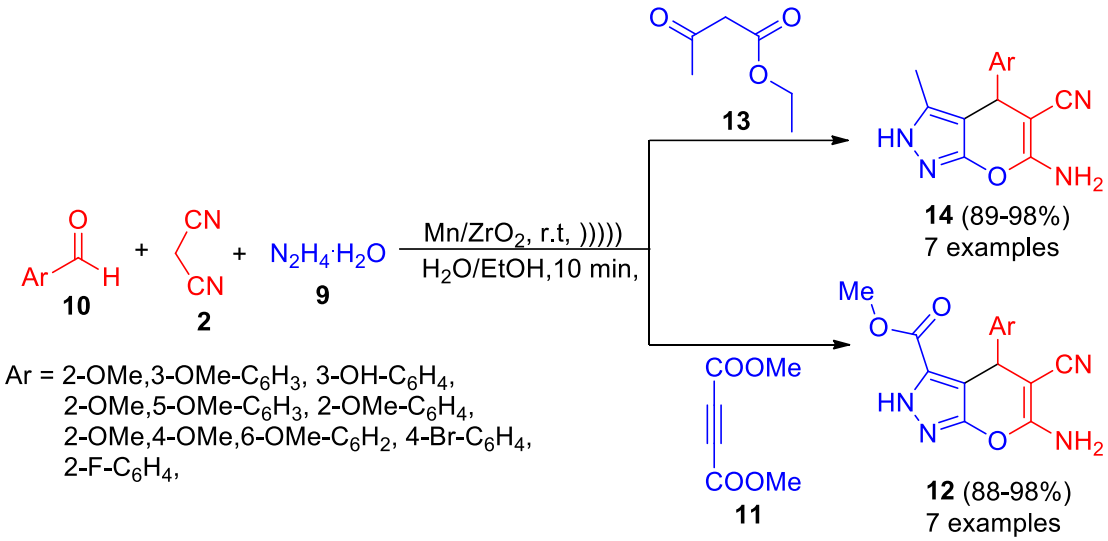
A very efficient procedure for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives **12** in 83-93% yield from the one-pot condensation reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and dimethyl acetylenedicarboxylate **11** by using nanocrystalline $ZnZr_4(PO_4)_6$ ceramics as an efficient heterogeneous catalyst in aqueous medium at room temperature for 30-42 minutes has been discovered by Javad's group (Scheme 50).[101]



Scheme 50: Construction of several dihydropyrano[2,3-*c*]pyrazoles **12** by using nano-$ZnZr_4(PO_4)_6$.

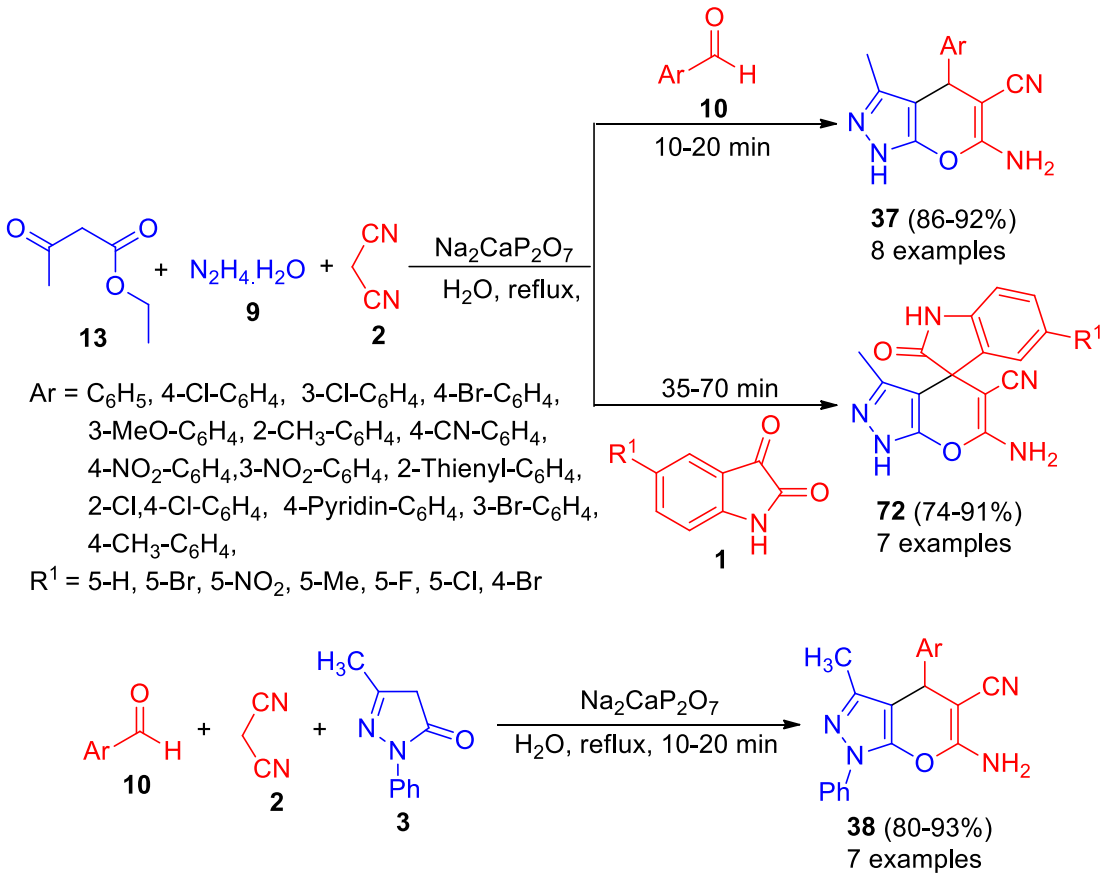
In 2016, Maddila *et al.* reported an ultrasound-assisted one-pot four-component reaction of aryl aldehyde **10**, malononitrile **2**, hydrazine hydrate **9**, and ethyl acetoacetate **13** or dimethyl acetylenedicarboxylate **11** for the construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **14** & **12** in presence of manganese doped zirconia (Mn/ZrO_2) as a catalyst and aqueous ethanolic solution as a solvent at room temperature (Scheme 51).[102] Under the standard reaction conditions, a variety of aryl aldehydes bearing both electron-releasing and electron-withdrawing groups are worked well and have apparently no obvious effect on the product yields as well as on the reaction time, and afforded the pyrano[2,3-c]pyrazole derivatives in good to excellent yield.

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Scheme 51: Ultrasound-assisted synthesis of dihydropyrano[2,3-*c*]pyrazoles **14** & **12**.

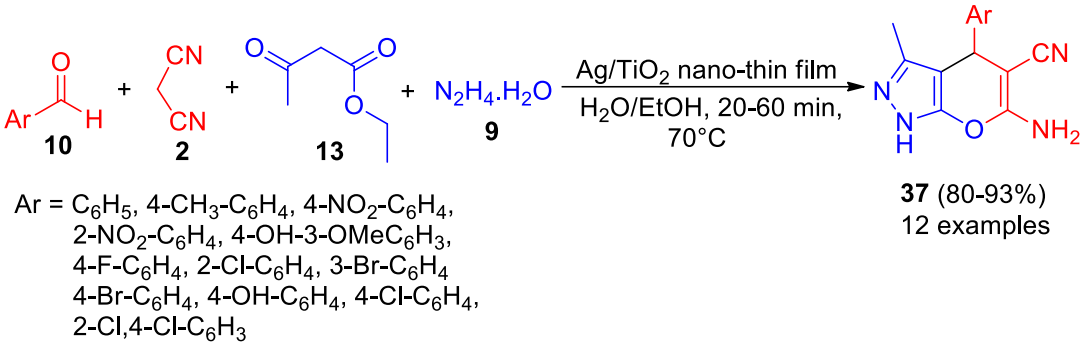
A nano-structured diphosphate ($Na_2CaP_2O_7$) as an efficient catalyst has been synthesized by Maleki *et al.* and applied in the synthesis of several dihydropyrano[2,3-*c*]pyrazole derivatives **37** in 86-92% yield within 10-20 minutes and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **72** in 74-91% yield after 35-70 minutes from the reaction of substituted aldehyde **10**/isatin **1**, malononitrile **2**, ethyl acetoacetate **13** and hydrazine hydrate **9** in presence of water as reaction medium under reflux condition (Scheme 52).[103] They also developed the three-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives **38** in 80-93% yield by the reaction of aldehydes **10**, malononitrile **2,** and pyrazolone **3** under the same reaction condition for 10-20 minutes.



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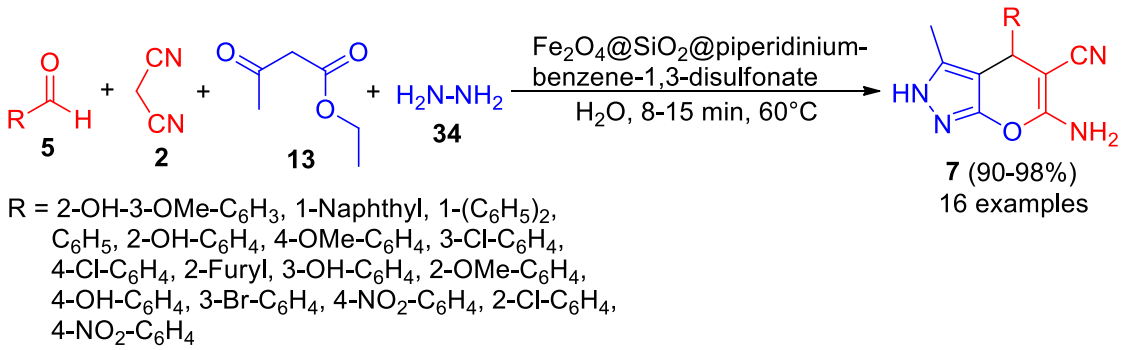
Scheme 52: Nanostructured diphosphate catalyzed synthesis of several pyrano[2,3-*c*]pyrazoles **37**, **72** & **38**.

In 2017, Fatahpour *et al.* reported the successful application of Ag/TiO_2 nano-thin films as an eco-compatible, robust, and reusable heterogeneous catalyst for the one-pot preparation of several pyrano[2,3-*c*]pyrazole derivatives **37** *via* the one-pot four-component condensation reaction of several aromatic aldehydes **10**, malononitrile **2**, hydrazine hydrate **9** and ethyl acetoacetate **13** using the aqueous ethanolic solution as a solvent at 70°C (Scheme 53).[104] The products could be obtained by a simple work-up procedure without using any chromatographic technique in high yield within a very short reaction time.



Scheme 53: Nano-thin films catalyzed preparation of dihydropyrano[2,3-*c*]pyrazoles **37**.

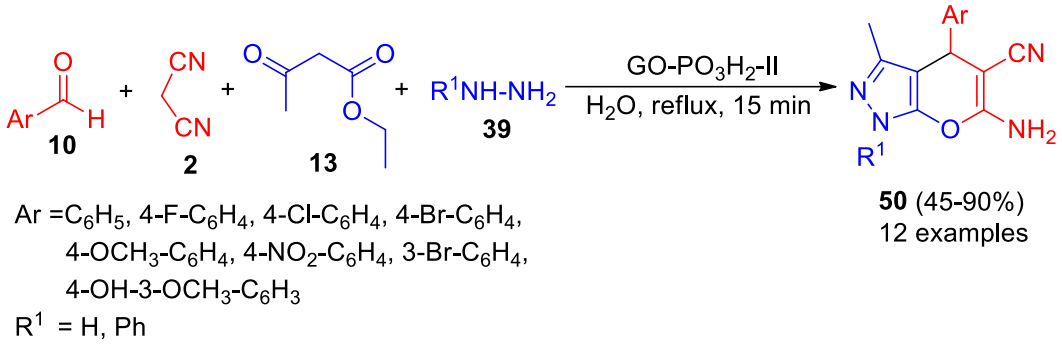
In the same year, Ghorbani-Vaghei and his co-workers developed a novel magnetic Fe_3O_4@SiO_2 nanoparticle supported ionic liquid (Fe_3O_4@SiO_2@piperidinium benzene-1,3-disulfonate) catalyzed condensation reaction of various derivatives of aryl/heteroaryl aldehyde **5**, malononitrile **2**, hydrazine hydrate **34,** and ethyl acetoacetate **13** by using water as a solvent for the one-pot construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **7** under heating condition (Scheme 54).[105] The catalyst was firstly prepared and fully characterized and then its effectiveness was established by applying it in the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives. By applying this method, 16 compounds possessing various substituents were synthesized in good to excellent yield ranging from 90-98%.



Scheme 54: Ionic liquid functionalized MNPs for the construction of dihydropyrano[2,3-*c*]pyrazoles **7**.

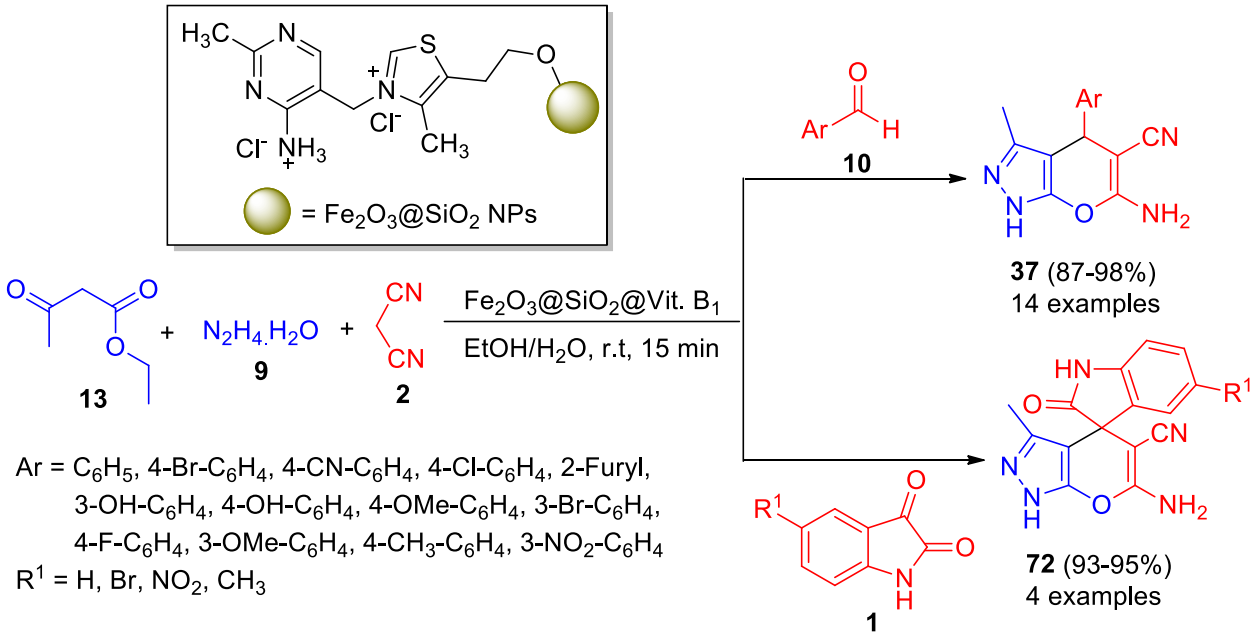
Another achievement has been gained by Zakeri *et al.* in the same year by developing phosphoric acid-functionalized graphene oxide (GO-PO_3H_2-II) as a carbon-based heterogeneous nanocatalyst that could effectively catalyze the four-component reaction of several substituted aryl aldehyde **10**, malononitrile **2**, hydrazine **39,** and ethyl acetoacetate **13** using water as a solvent under refluxing condition and leads to the construction of dihydropyrano[2,3-*c*]pyrazole derivatives **50** in 45-90% yield (Scheme 55).[106]

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Scheme 55: Preparation of dihydropyrano[2,3-*c*]pyrazole **50** in presence of carbon-based nanocatalyst.

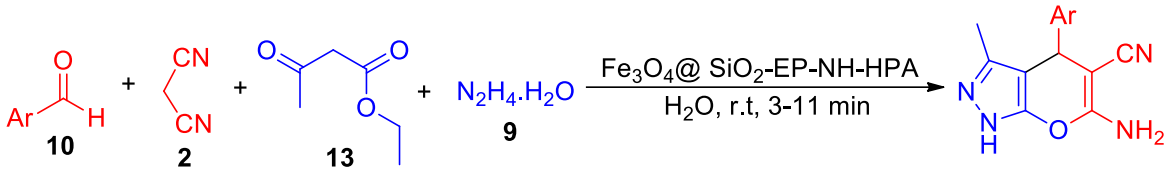
In 2018, Rahman and his group has reported the synthesis of vitamin B_1 functionalized Fe_2O_3@SiO_2 nanoparticle as an efficient, heterogeneous organo-nanocatalyst that could be applied in the reaction of aryl aldehyde **10** or substituted isatin **1**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** by using the aqueous ethanolic solution as a solvent for the one-pot construction of various dihydropyrano[2,3-*c*]pyrazole derivatives **37** & spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole derivatives **72** under the stirring condition at room temperature (Scheme 56).[107]



Scheme 56: Vitamin B_1 functionalized MNPs for the construction of pyrano[2,3-*c*]pyrazole **37** & **72**.

In 2020, Mohtasham and Gholizadeh demonstrated the extraction of natural mesoporous silica from horsetail plant as support for the preparation of $H_3PW_{12}O_{40}$ immobilized on aminated epibromohydrin functionalized Fe_3O_4@SiO_2 nanoparticles (Fe_3O_4@ SiO_2-EP-NH-HPA) that could be applied as a heterogeneous nanocatalyst in the one-pot four-component construction of several dihydropyrano[2,3-*c*]pyrazole derivatives **37** from the reaction of aryl/heteroaryl aldehyde **10**, malononitrile **2**, hydrazine hydrate **9** and ethyl acetoacetate **13** by using water as a solvent at room temperature (Scheme 57).[108] By applying this operational simplicity, eco-friendly, non-toxic, environmentally friendly protocol, twenty compounds possessing both electron-withdrawing groups as well as electron-donating groups were synthesized in 89-98% yield.

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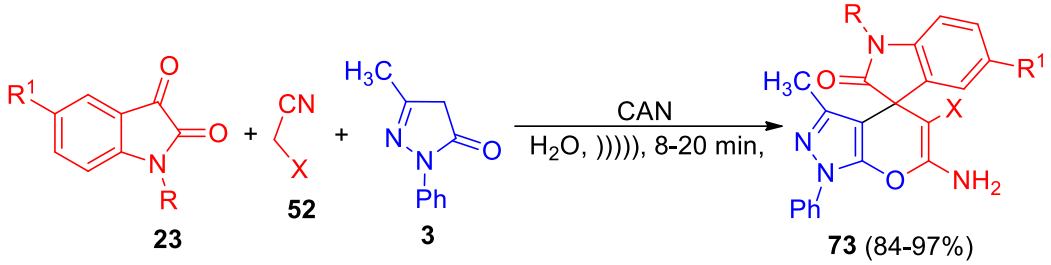
Ar = C_6H_5, 4-Cl-C_6H_4, 2-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-CH_3-C_6H_4, 4-N(CH_3)$_2$-C_6H_4, 2-OH-C_6H_4, 4-OCH_3-C_6H_4, 2-OCH_3-C_6H_4, 3-NO_2-C_6H_4, 4-OH-C_6H_4, 3-OH-C_6H_4, 3-OH,4-OH-C_6H_3, 3-CH_3-C_6H_4, 3-Br-2-OH-C_6H_3, 4-CN-C_6H_4, 1-Naphthyl, 2-Thienyl, 4-Br-C_6H_4, 3-Br-C_6H_4

37 (89-98%)
20 examples

Scheme 57: Heteropoly acid-functionalized NPs in the synthesis of dihydropyrano[2,3-*c*]pyrazole **37**.

2.6 Salt catalyzed synthesis

In 2013, Dandia and co-workers have demonstrated an ultrasound-assisted one-pot synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **73** in 84-97% yield from the three-component reaction of substituted isatin **23**, malononitrile/ethyl cyanoacetate **52,** and pyrazolone **3** by using cerium ammonium nitrate (CAN) as a catalyst in an aqueous medium for 8-20 minutes (Scheme 58).[109] Substituents on the C-5 position of isatin affect the yield of the product and this environmentally friendly protocol lead to the construction of a total of 12 compounds by simple workup procedure in high yield.

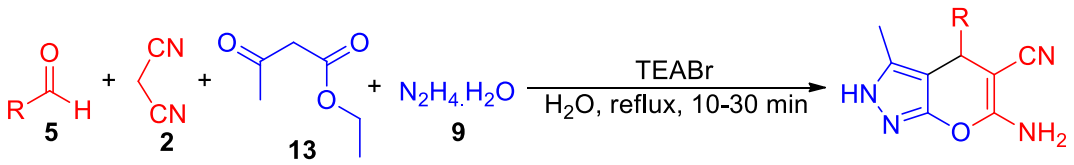


73 (84-97%)
12 examples

R = H, C_2H_5, CH_2-CH=CH_2, CH_2-C_6H_5,
R^1 = 5-H, 5-Br, 5-Me, 5-Cl, 5-Me, 5,7-Me_2
X = CN, COOEt

Scheme 58: Ultrasound-assisted salt catalyzed synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazoles] **73**.

In the same year, Kumar *et al.* reported another salt catalyzed one-pot reaction of aldehyde **5**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** by using tetraethylammonium bromide (TEABr) as a catalyst and water as a solvent under reflux condition for the preparation of dihydropyrano[2,3-*c*]pyrazole derivatives **7** in 68-90% yield (Scheme 59).[110]



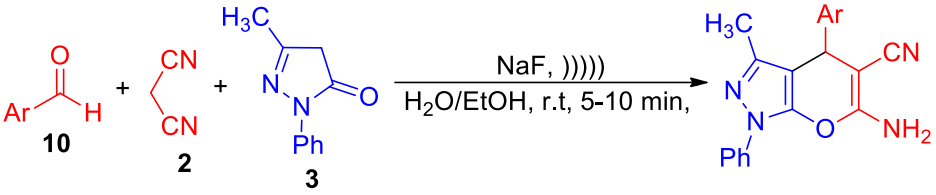
R = C_6H_5, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 4-CN-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_5, 2-F,4-F-C_6H_3, n-Propyl, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 2-Thienyl, 3-F-C_6H_4, 3-CF_3-C_6H_4, 2-CH_3,5-$CH_3C_6H_3$, 2-Furyl, Styryl

7 (68-90%)
16 examples

Scheme 59: Salt catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazole **7**.

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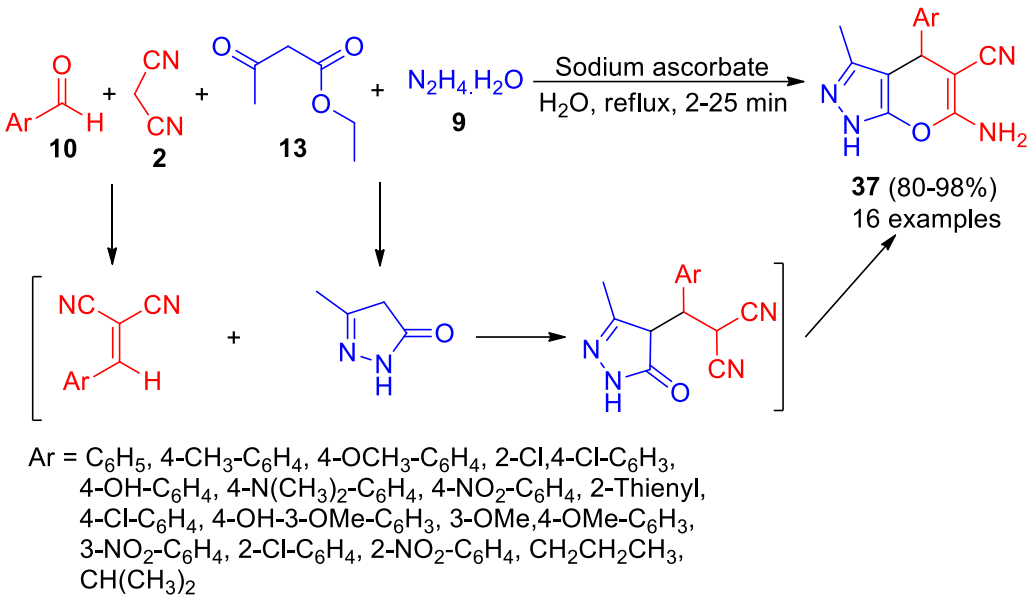
The research group of Konakanchi developed a one-pot four-component strategy for the construction of pyrano[2,3-*c*]pyrazole derivatives **38** in 88-98% yield *via* ultrasound-assisted condensation reaction of several substituted aromatic aldehyde **10**, malononitrile **2,** and pyrazolone **3** by using sodium fluoride (NaF) as a catalyst in aqueous methanol at room temperature for 5-10 minutes (Scheme 60).[111] The reaction can proceed through the Knoevenagel condensation of aldehydes and malononitrile, Michael's addition of pyrazolone with Knoevenagel product followed by cyclization and tautomerization reaction.



Scheme 60: Ultrasound-assisted synthesis of dihydropyrano[2,3-*c*]pyrazole **38** in presence of NaF.

Recently, Kiyani and his groups discovered the utilization of sodium ascorbate as an efficient, environmentally benign heterogeneous catalyst for the one-pot four-component cyclo condensation reactions of several aldehydes **10**, malononitrile **2**, hydrazine hydrate **9**, and ethyl acetoacetate **13** in presence of water as a reaction medium under reflux of 2-25 minutes and the catalytic activity of the reported catalyst was found to be very successful in the transformation of the reactant into the corresponding dihydropyrano[2,3-*c*]pyrazole derivatives **37**. The methodology displays several advantages like- use of readily available reactants, operational simplicity, easy isolation of product, green reaction media, use of inexpensive and non-toxic catalyst, eco-friendly protocol, etc (Scheme 61).[112] The reaction mechanism for this transformation begins with the initial formation of pyrazolone from the reaction of hydrazine hydrate and ethyl acetoacetate that can then undergoes Michael addition with the *in situ* generated arylidene malononitrile from the Knoevenagel condensation reaction of aldehydes with malononitrile under the influence of sodium benzoate. In the final step, an intramolecular cyclization followed by tautomerization afforded the desired product.

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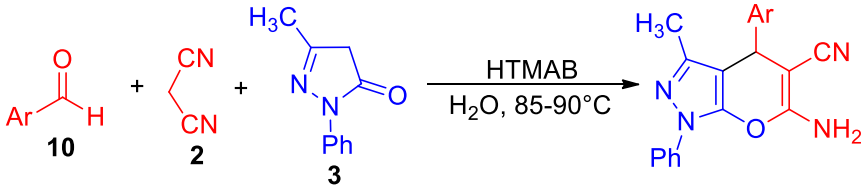
Scheme 61: Synthesis of pyrano[2,3-*c*]pyrazole **37** using sodium ascorbate from *in situ* generated pyrazolone.

2.7 Phase Transfer Catalyst (PTC) mediated synthesis

In 2005, Tong-Shou Jin *et al.* reported the synthesis of several dihydropyrano[2,3-*c*]pyrazole derivatives **38** *via* the three-component reaction of aromatic aldehyde **10**, malononitrile **2,** and pyrazolone **3** by using hexadecyltrimethylammonium bromide (HTMAB) as a phase transfer catalyst (PTC) in aqueous medium at 85-90°C in 79-92% yield. All aromatic aldehydes bearing electron-poor or electron-rich substituents on different positions of the ring are well reacted under the optimization condition and smoothly provide the corresponding product **38** in good to excellent yield. However, the reaction cannot proceed in the case with aliphatic aldehydes due to the low activity in comparison to highly reactive aromatic aldehydes (Scheme 62a).[113] Also, the treatment of aromatic aldehydes **10**, malononitrile **2,** and pyrazolone **3** in presence of *p*-dodecylbenesulfonic acid (DBSA) in an aqueous medium at 60°C afforded the desired dihydropyrano[2,3-*c*]pyrazolone **38** in 82-94% yield. It is pertinent to note that all aromatic aldehydes were well tolerated by this method in the successful transformation to corresponding product **38**. However, aldehyde possessing dimethylamino group on the 4-position of the aromatic ring were failed to give the desired product **38** and the starting material was recovered after the completion of the reaction under the same reaction condition. This is due to the presence of a strong electron-donating dimethylamino group and the subsequent formation of a quinoid structure that decreases the reactivity of the aldehydes group (Scheme 62b).[114]

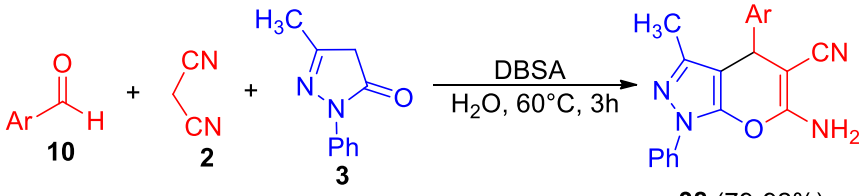
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a) Jin *et al.*, 2005

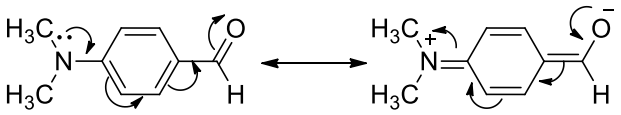


Ar = C_6H_5, 4-$(CH_3)_2$N-C_6H_4, 2-Cl-C_6H_4, 3,4-$(OCH_2O)C_6H_3$, 2-Cl,4-Cl-C_6H_3, 3-Cl-C_6H_4, 4-HO-C_6H_4, 4-OMeC_6H_4, 3-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-CH_3-C_6H_4

b) Jin *et al.*, 2006



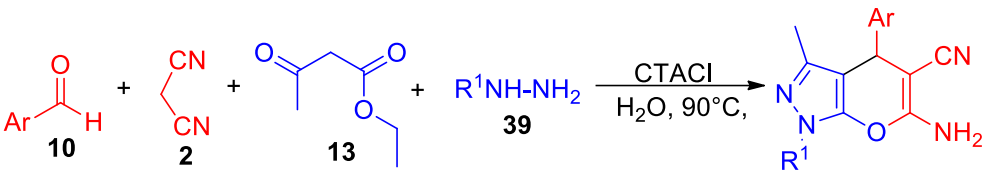
Ar = C_6H_5, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-CH_3-C_6H_4, 2-Cl,4-Cl-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-HO-C_6H_4, 3,4-$(OCH_2O)C_6H_3$, 4-Cl-C_6H_4, 4-CH_3O-C_6H_4,



Quinoid structure

Scheme 62: Three-component synthesis of pyrano[2,3-*c*]pyrazole **38** using different PTC.

In 2013, Wu *et al.* demonstrated the synthesis of several dihydropyrano[2,3-*c*]pyrazole derivatives **50** by a one-pot four-component reaction of aromatic aldehyde **10**, malononitrile **2**, different hydrazines **39,** and ethyl acetoacetate **13** by using cetyltrimethylammonium chloride (CTACl) as a phase transfer catalyst (PTC) and water as a solvent at room temperature under an open atmosphere with vigorous stirring for 10 min and then the mixture was allowed to heat to 90°C with vigorous stirring for 4 hours (Scheme 63).[115] The product was formed as a solid which was purified by simple column chromatography over silica gel (100–200 mesh).



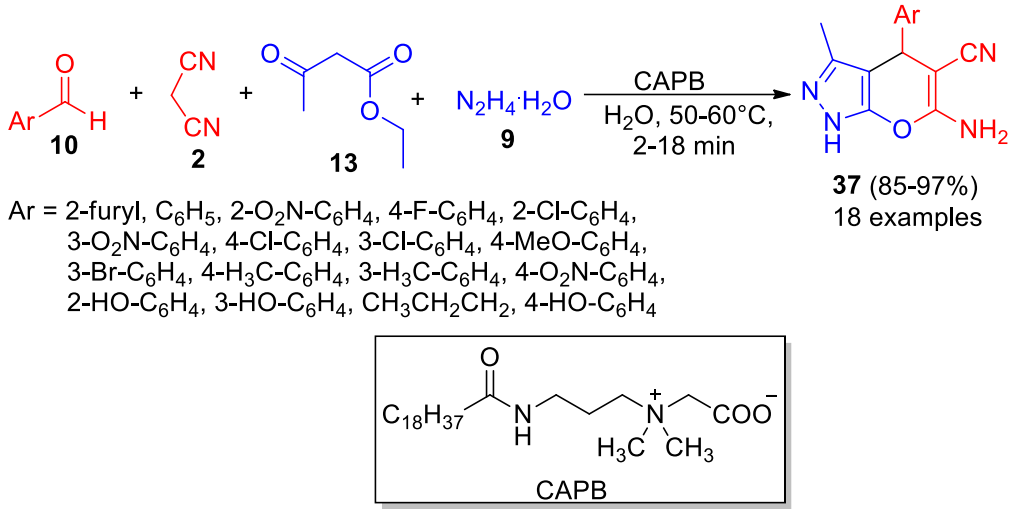
Ar = C_6H_5, 4-CH_3-C_6H_4, 4-N$(CH_3)_2$-C_6H_4, 4-Br-C_6H_4, 4-OCH_3-C_6H_4, 3-Cl,4-Cl-C_6H_3, 2-Cl,4-Cl-C_6H_3, 4-F-C_6H_4, 4-CF_3-C_6H_4, 4-OH-C_6H_4, 3-NO_2-C_6H_4,
R^1 = H, Ph,

Scheme 63: Rapid access to dihydropyrano[2,3-*c*]pyrazole **50** in presence of CTACl as PTC.

In 2014, Tamaddon and Alizadeh reported the synthesis of several dihydropyrano[2,3-*c*]pyrazole derivatives **37** through the one-pot four-component condensation reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** under the influence of surfactant

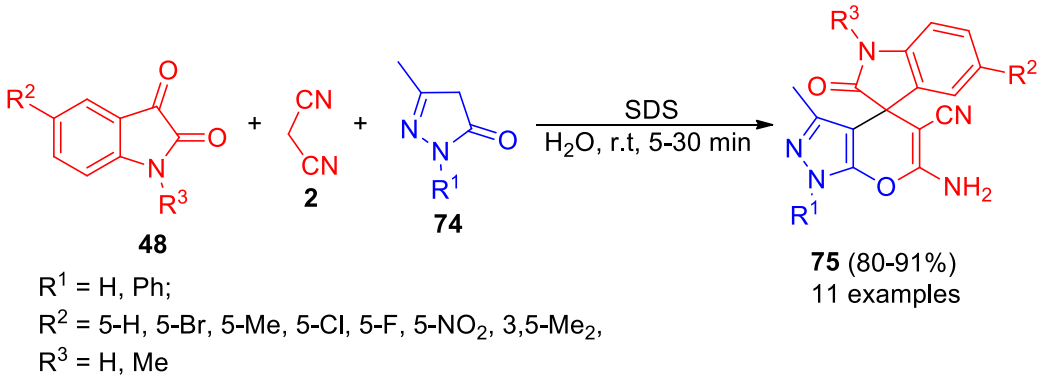
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Cocamidopropyl betaine (CAPB) as a catalyst in aqueous medium at 50-60°C (Scheme 64).[116] The high reaction rate, short reaction time, and increase in the product yield can be achieved by using CAPB as the catalyst and it is mainly due to the formation of high performance viscoelastic worm-like micelles that increase the polarity and viscosity of water to provide a suitable medium for the reaction.



Scheme 64: Construction of dihydropyrano[2,3-*c*]pyrazole **37** using surfactant CAPB as a catalyst.

Devi and co-workers developed a sodium dodecyl sulfate (SDS) catalyzed one-pot three-component condensation reaction of substituted isatin **48**, malononitrile **2,** and pyrazolone **74** for the preparation of various spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **75** by employing water as a solvent and the reaction has completed within 15-30 minutes at room temperature (Scheme 65).[117]

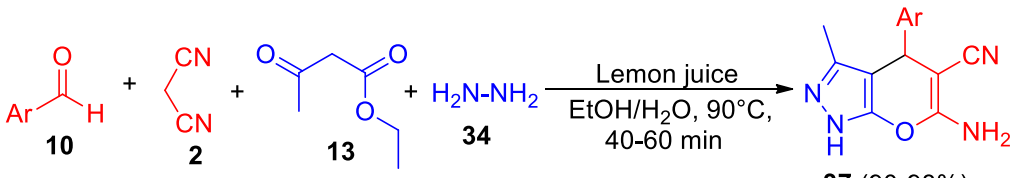


Scheme 65: Sodium dodecyl sulfate catalyzed synthesis of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] **75**.

2.8 Nature derived catalyst mediated synthesis

In 2016, Vekariya and his group reported the use of fruit juice of Citrus Limon (lemon juice) as the biodegradable and renewable natural catalyst that could effectively catalyze the one-pot reaction of several derivatives of aldehyde **10**, malononitrile **2**, ethyl acetoacetate **13**, and hydrazine hydrate **34** by using the aqueous ethanolic solution as a solvent at 90°C, lead to the construction of dihydropyrano[2,3-*c*]pyrazole derivatives **37** in 90-98% yield (Scheme 66).[118] The catalytic activity of lemon juice is mainly due to the presence of citric and ascorbic acids, thereby which it acts as an acid catalyst in this transformation.

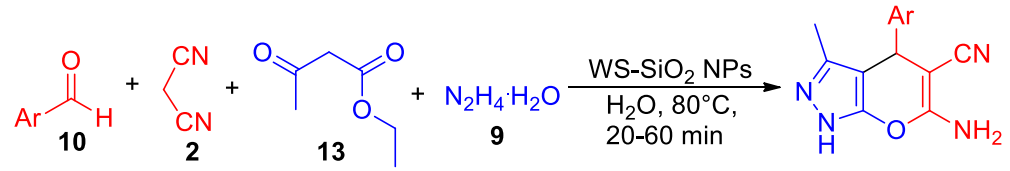
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Ar = C_6H_5, 2-OH-C_6H_4, 4-OH-C_6H_4, 2-OH-5-Br-C_6H_3, 3-OMe,4-OMe-C_6H_3, 3-OMe,4-OMe,5-OMe-C_6H_2, 4-NO_2-C_6H_4, 3-OH-C_6H_4, 2-Cl-C_6H_4, 4-OMe-C_6H_4, 4-CN-C_6H_4, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 3-NO_2-C_6H_4, 3-OMe,5-OMe-4-OH-C_6H_2, 2-furayl, 4-$N(Me)_2$-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 2-OH-5-NO_2-C_6H_3

Scheme 66: Lemon juice as a natural catalyst for the preparation of dihydropyrano[2,3-*c*]pyrazole **37**.

In 2017, Patel *et al.*[119] derived nano-silica from agricultural waste wheat straw and it can be applied as a heterogeneous catalyst for the one-pot preparation of several dihydropyrano[2,3-*c*]pyrazole derivatives **37** from the four-component reaction of aromatic aldehyde **10**, malononitrile **2**, hydrazine hydrate **9** and ethyl acetoacetate **13** by using water as a solvent at 80°C (Scheme 67). The catalytic activity of the prepared catalyst was compared with other catalysts and it was found to be very superior to the reported catalyst for this transformation. By applying this catalytic system, 11 compounds were synthesized within a very short reaction time in good to excellent yield ranging from 87-94%.

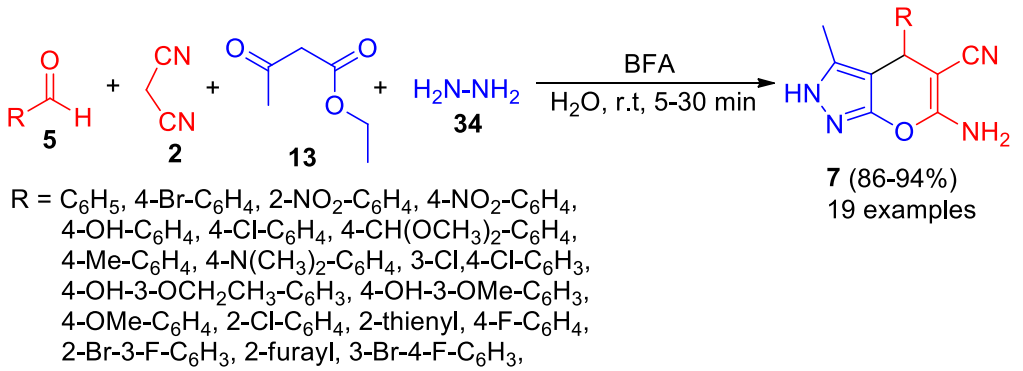


Ar = C_6H_5, 4-OH-C_6H_4, 2-OH-C_6H_4, 4-$N(Me)_2$-C_6H_4, 3-NO_2-C_6H_4, 4-OMe-C_6H_4,4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CH_3-C_6H_4, 4-CN-C_6H_4, 4-NO_2-C_6H_4

Scheme 67: Nano-silica derived from wheat straw in the synthesis of dihydropyrano[2,3-*c*]pyrazole **37**.

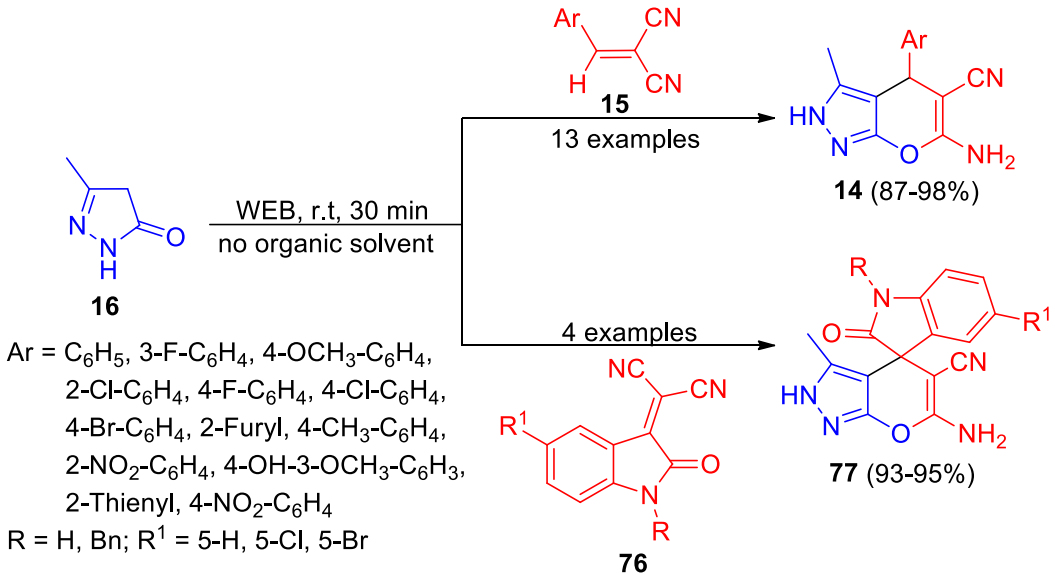
In the same year, the research group of Sachin has developed another nature-derived catalyst for the construction of dihydropyrano[2,3-*c*]pyrazole derivatives **7** from the *in situ* generated pyrazolone by employing water as a reaction medium. The synthesis was carried out *via* the one-pot reaction of several derivatives of aryl/heteroaryl aldehyde **5**, malononitrile **2**, hydrazine hydrate **34,** and ethyl acetoacetate **13** in an aqueous medium at room temperature under the influence of bael fruit ash (BFA) as a natural catalyst (Scheme 68).[120] The presence of metal oxides having active M^{2+}, oxide, and hydroxides provides several Lewis basic sites (O^{2-} and OH) along with Lewis acid sites (M^{2+}) that activate the reactants towards the completion of the reaction.

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Scheme 68: Preparation of dihydropyrano[2,3-*c*]pyrazole **7** by using bael fruit ash as a natural catalyst.

Recently our group also synthesized a series of dihydropyrano[2,3-*c*]pyrazole derivatives **14** and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] **77** from the two-component reaction of arylidene malononitrile **15** /or 2-(2-oxoindolin-3-ylidene)malononitrile **76** and pyrazolone **16** by using water extract of banana peels (WEB) as nature-derived reaction medium at room temperature for 30 minutes. Although this is not included in the multicomponent reaction. However, several advantages such as mild reaction conditions, environmentally friendly nature, operational simplicity, low cost, an excellent yield of the product make this methodology very attractive for future application in organic synthesis (Scheme 69).[121] In this reaction WEB plays an important role both as the catalyst as well as a solvent without using any other ligand, base, metal additives, acid, etc.

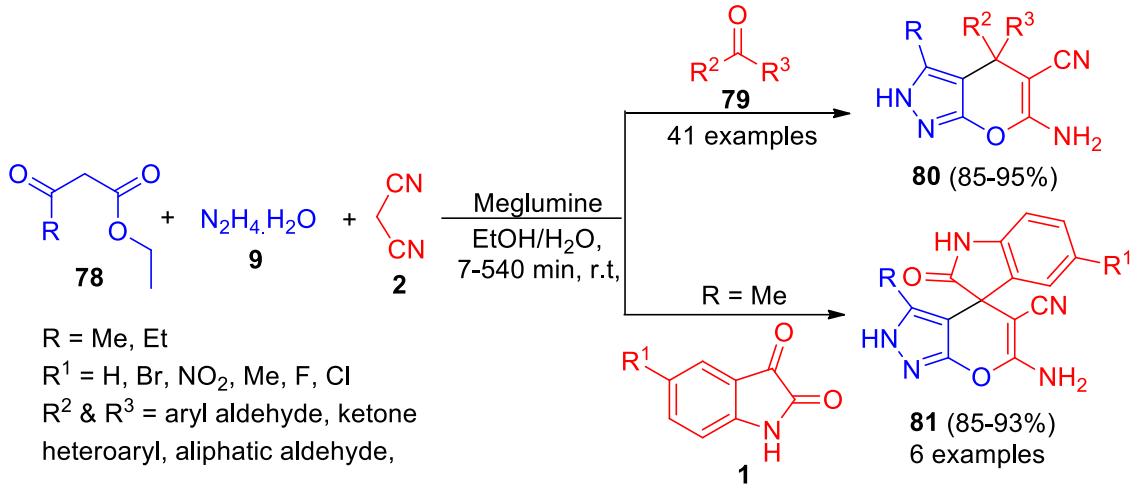


Scheme 69: WEB in the synthesis of dihydropyrano[2,3-*c*]pyrazole **14** and spiro-pyrano[2,3-*c*]pyrazoles **77**.

2.9 Other synthetic approaches

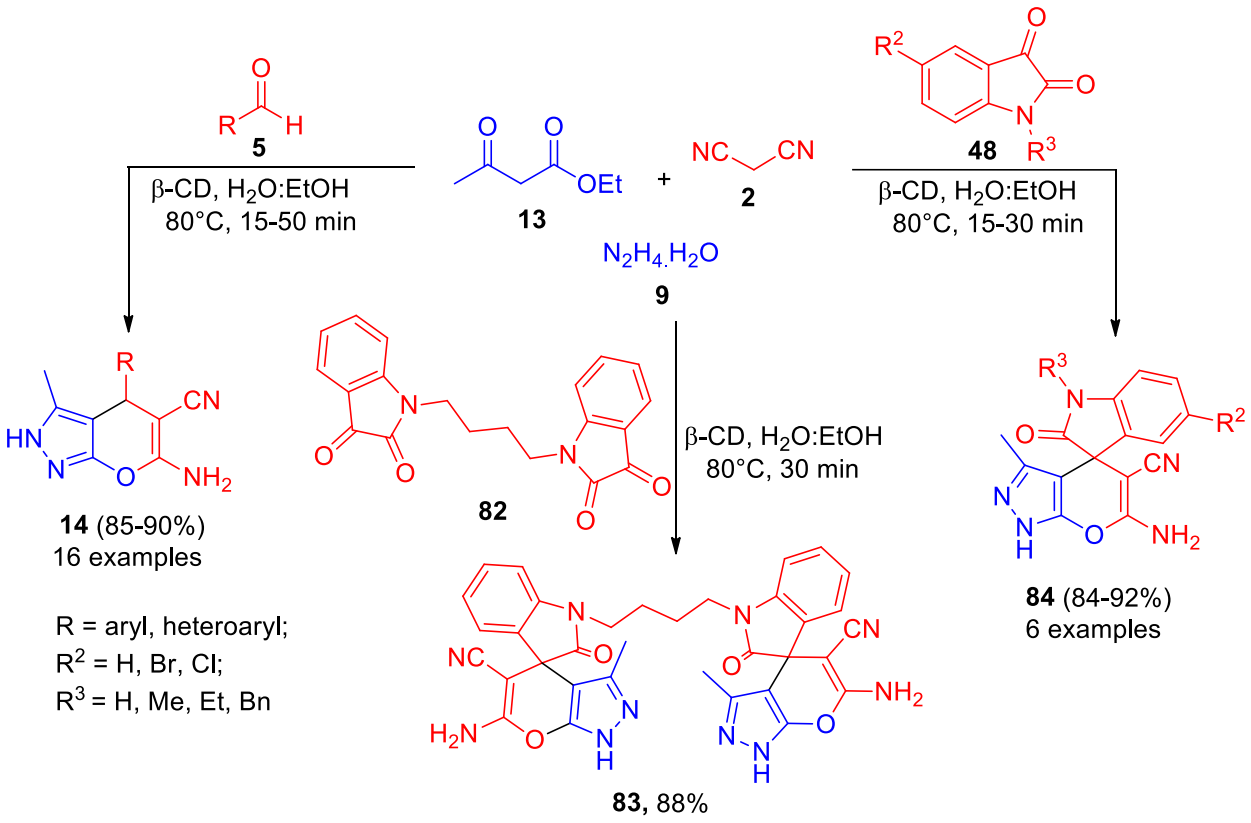
A one-pot four-component condensation reaction of different carbonyl compound **79**/substituted isatin **1**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **78** by introducing bio-based catalyst meglumine in aqueous ethanolic solution at room temperature yield the dihydropyrano[2,3-*c*]pyrazole derivatives **80** and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **81** (Scheme 70).[122] All aromatic, heteroaromatic as well as aliphatic aldehydes, ketones were smoothly undergoing the reaction in the successful transformation to the corresponding product.

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Scheme 70: Synthesis of dihydro- and spiro-pyrano[2,3-*c*]pyrazoles in presence of meglumine.

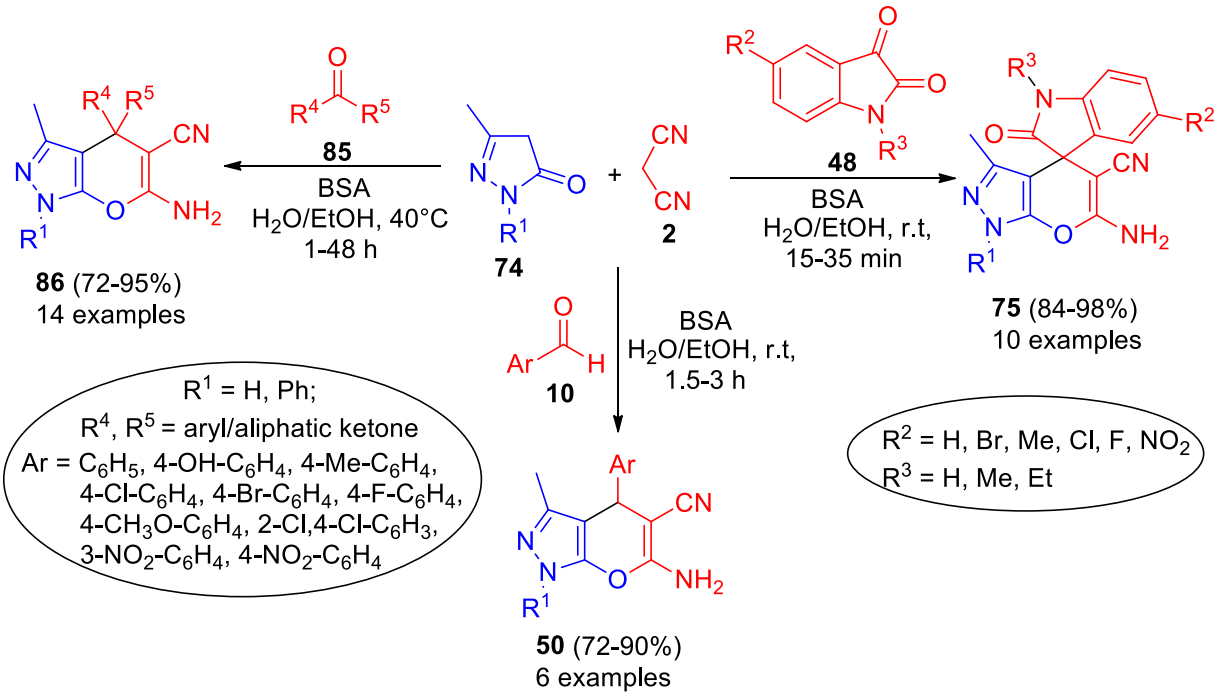
In 2015, the research group of Tayade described a one-pot green methodology for the construction of several substituted dihydropyrano[2,3-*c*]pyrazole derivatives **14**, spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **83** & **84** in good to excellent yield *via* the four-component reaction of aldehyde **5/**substituted isatin **48** or 1,1-(butane-1,4-diyl)bis(indoline-2,3-dione**)** **82**, malononitrile **2**, hydrazine hydrate **9** and ethyl acetoacetate **13** under the influence of supramolecular β-cyclodextrin (β-CD) as an efficient, biodegradable, reusable catalyst in aqueous ethanol (9:1) at 80°C for 15-30 minutes (Scheme 71).[123] Various substitution at the C-5 position in isatin as well as substitution in aldehyde gave the corresponding dihydropyrano[2,3-*c*]pyrazoles **14** & spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] **84** in 85-90%, 84-92% yield respectively.



Scheme 71: Synthesis of various substituted pyrano[2,3-*c*]pyrazole **14**, **83**, **84** by using β-cyclodextrin (β-CD).

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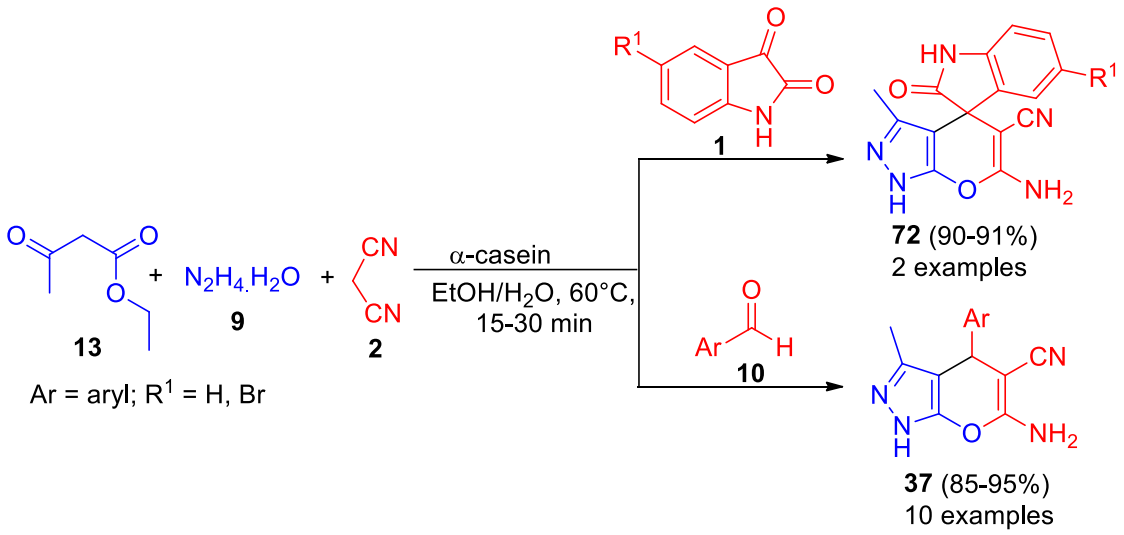
In 2016, Dalal *et al.* demonstrated Bovine serum albumin (BSA) as a biocatalyst for the synthesis of several ketones derived dihydropyrano[2,3-*c*]pyrazole **86**, dihydropyrano[2,3-*c*]pyrazole derivatives **50**, and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **75** in good to excellent yield from the three-component condensation reaction of ketone **85**, aldehydes **10** or isatin **48**, malononitrile **2** and pyrazolone **74** using aqueous ethanol as a solvent (Scheme 72).[124] The catalytic activity of BSA was found to be very efficient for the successful conversion of aldehydes, ketones, and isatins possessing various electron-withdrawing as well as the electron-donating group to the desired product. The utilization of BSA as an efficient catalyst provides an alternate route to metal catalysts as well as finding further applications in the field of synthetic organic chemistry and biocatalysis.



Scheme 72: BSA catalyzed synthesis of different pyrano[2,3-*c*]pyrazole **86**, **50** & **75**.

The use of α-casein as an efficient catalyst for the construction of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives **72** and dihydropyrano[2,3-*c*]pyrazole derivatives **37** through the four-component reaction of aromatic aldehyde **10** or substituted isatin **1**, malononitrile **2**, hydrazine hydrate **9,** and ethyl acetoacetate **13** in presence of aqueous ethanolic solution at 60°C has been developed by Milani *et al.* in 2019 (Scheme 73).[125] The catalytic activity of α-casein was found to be very efficient that lead to the construction of a total of 12 compounds in very high yield and the product could be achieved by a simple work-up procedure without using any other purification techniques.

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Scheme 73: Access to spiro-pyrano[2,3-*c*]pyrazole] **72** & dihydropyrano[2,3-*c*]pyrazole **37** using α-casein.

Conclusions

Because of the marvelous application in synthetic organic chemistry, material science, medicinal and pharmaceutical chemistry, food industry, textile industry, cosmetics products, chemical industry; the exploitation of pyrazolone in organic synthesis has rapidly increased continuously. Tremendous efforts have been devoted over the last decades for the construction of dihydropyrano[2,3-*c*]pyrazole and spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives based on pyrazolone *via* several sequential strategies including base-catalyzed, acid-catalyzed, nano catalyzed, and organocatalyzed multicomponent reactions. Development of catalytic synthetic processes by environmentally benign reaction media instead of hazardous materials, volatile organic solvents, and reagents in order to control the production of dangerous byproducts that can affect human health and the environment has been the foremost goal for synthetic chemist in industry and academia. In this regard, the use of water as a replacement of organic solvents in the development of the organic synthetic procedure has received substantial attention due to their abundantly available, non-hazardous, non-flammable, unique redox stability, and cheap nature. Furthermore, the utilization of water in synthetic processes sometimes leads to different modes of reactivity or selectivity which are often difficult to achieve with organic solvents. Given the importance of both topics in organic synthesis, we have summarizes the up to date advances for the synthesis of dihydropyrano[2,3-*c*]pyrazoles and spiro-pyrano[2,3-*c*]pyrazoles based on pyrazolone *via* multicomponent reactions in the aqueous medium. Although remarkable results are obtained, various simple, effective, and concise methodologies are still highly desired and it is significant to expand the scope of the reactions and mildness of the conditions for the synthesis of pyrano[2,3-*c*]pyrazole derivatives. We hope the reviewed methodology has been beneficial for researchers working in this field and is projected to encompass vital applications to the amalgamation of complex natural products and the design of new pharmaceutical compounds that will be of industrial interest in application to many branches of chemistry.

Acknowledgements

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The author thanks the Central University of Gujarat, Gandhinagar-382030, Gujarat, India, and UGC for the Non-NET fellowship.

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