

# Green approaches-synthesis of dihydropyrano [2,3-c] pyrazole by using eco-friendly catalyst: review

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**Abstract:** Magnetized dextrin, Nanoeggshell, ZN(ANA)Cl<sub>2</sub>, Molecular sieves, SO<sub>3</sub>H carbon powder, PTSA these novel naturally based catalyst are applied for the synthesis of dihydropyrano (2,3-c) pyrazole. Impelementation of green chemistry principle was evaluated for the synthesis of dihydropyrano(2,3-c) pyrazole derivative. Dihydropyrano(2,3-c) derivatives are synthesized by multicomponent condensation reactions by using components like aldehyde, hydrazinehydrate, ethylacetoacetate, malanonitrite. The principle affairs these procedure are mild condition, short reaction time, easy work up, high yield. Reusability of catalysts and the absence of toxic organic solvent. Selected synthesized derivatives were used for Anti-inflammatory, Antidepressant, Antipyretic, Antifungal, Analgesic, Anti-HIV, Antimicrobial, Anticancer activity against four human cancer cell lines viz. melanoma cancer cell line(SK-MEL-2), breast cancer cell line (MDA-MB-231), Leukemia cancer cell line (K-562) and cervical cancer cell line (HeLa). ADME study of synthesized anticancer agent indicates good oral drug-like behaviour and nontoxic nature.

**Keywords:** dihydropyrano(2,3-c)pyrazole, Magnetized dextrin, Nanoeggshell, ZN(ANA)Cl<sub>2</sub>, Molecular sieves, SO<sub>3</sub>H carbon powder, PTSA, Green chemistry, Multicomponent reaction.

## INTRODUCTION:

In the second half of the twentieth century, rapid advances in science and technology resulted created in tremendous economic development and an improvement in living standards in industrialized countries. However, such economic development has resulted in significant environmental deterioration, as seen by increased climate change, the creation of ozone holes, and the buildup of non-destructive organic contaminants throughout the biosphere. The newly scenario necessitated the pursuit of a solution that would strike a balance between the utilization of natural resources, economic expansion, and environmental preservation.

As a result of such thoughts throughout the previous two decades, public awareness of the need for environmental protection has grown, prompting a focus on "green and viable technologies."

Green chemistry, also known as sustainable chemistry, refers to chemical products and processes that limit or eliminate the usage and manufacture of harmful compounds. It entails decreasing or eliminating the use of dangerous compounds in chemical processes, as well as reducing harmful and toxic intermediates and products, as a new area of chemistry using ecological approaches. Each reaction must have three green components in order to be labelled "green": solvent, reagent/catalyst, and energy consumption. Green chemistry is based on twelve principles that can be used to create or recreate molecules, materials, reactions, and processes that are safer for human health and the environment. Green chemistry processes have been developed in a variety of areas, including organic, inorganic, biochemical, polymeric, toxicological, environmental, physical, and technological chemistry.

Green chemistry's fundamental principles apply to a wide range of synthetic organic synthesis processes, including reducing byproduct/waste generation, reducing the use of hazardous chemicals/raw materials and increasing the use of safer or more environmentally friendly solvents and (bio) catalysts, renewable raw materials, and how to improve energy efficiency[1,2].

The goals of green chemistry in environmental protection and economic profit are achieved through several dominant directions such as catalysis, biocatalysts, the use of alternative renewable raw materials (biomass), alternative reaction media (water, ionic liquids, supercritical fluids), alternative reaction conditions (microwave activation, Mechanochemistry and ultrasound) as well as new photocatalytic reaction[1,3,4].

The most important principle of green chemistry is that designing of biocompatible catalyst and eliminate the generation and the formation of toxic byproduct. Dihydropyran pyrazole is a fused heterocycle contain pyrazole and pyran as basic rings. Dihydropyran pyrazole is structural units of several biologically active compound and plays important role in medicinal chemistry. for instance, Anti-inflammatory, Antidepressant, Antipyretic, Antifungal, Analgesic, Anti-HIV, Antimicrobial, Anticancer. A no of different methods were developed for the synthesis of dihydropyrans pyrazole via three or four component reaction by using different catalyst. For example, ambrelyst, L-proline, sodium benzoate, trimethylamine,  $\beta$ -cyclodextrins, morpholine, piperidine, cetyltriethyl ammonium chloride, cerium ammonium trinitrate. These methods have suffered from some drawback like high reaction time, low yield, use of toxic and expensive catalyst. By considering this problem it is necessary to synthesize the dihydropyran pyrazole with utilization of eco-friendly catalyst so as to enhance the yield, reduce reaction time, eliminate use of toxic catalyst [5].

Multicomponent reaction (MCR) is a new approach to organic synthesis in which three or more than three components react sequentially in one pot, resulting in selectively the desired product while decreasing waste. For the synthesis of these heterocyclic

organic molecules, various ecologically friendly conditions have been created. Water is becoming a competitive reaction media in green organic synthesis, alongside other organic media such as ionic liquid, ethanol, and PEGs, due to benefits such as rapid reaction rate, isolation by simple filtration, and consideration of its green credentials [13]. So MCRs are indeed cost-effective, time saving, and environmentally benign as compared to step-by-step reactions of traditional organic synthesis one-pot without isolating the intermediate from three or more substrates [15] in achieving the desired final/target product [14]. As a result, MCRs have become a very valuable tool in drug development, and when combined with environmentally friendly solvents and a reusable catalyst, chemists have a lot of options for avoiding environmental damage. Hence, MCRs become a very useful tool in the drug discovery along with the environmentally benign solvents and a reusable catalyst creates a great scope for the chemists to prevent the environmental contamination. Majority of MCRs require a multifunctional catalyst to control the selectivity in the sequential reactions. At present, catalyzed MCRs are in common practice to synthesize a variety of heterocycles and heteroatomic organic compounds.

### Magnetized Dextrin Nano catalyst for the Synthesis of Dihydropyrano[2,3-c]pyrazole.

#### 1. Introduction :

Dextrin is a water-soluble polymer produced from starch and glycogen hydrolysis. This low molecular weight biopolymer, which has valuable qualities like biodegradability, natural origins, good availability, and strong reactivity, could be a promising material to use in the production of environmentally friendly catalysts[6].

#### 2. Structure:

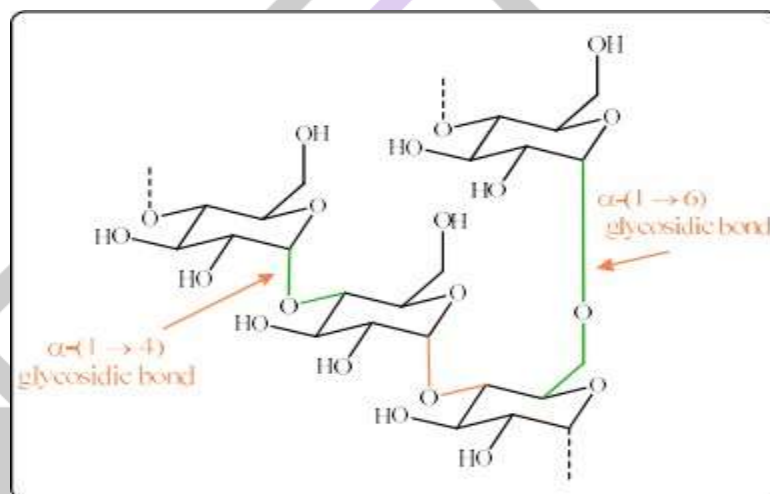
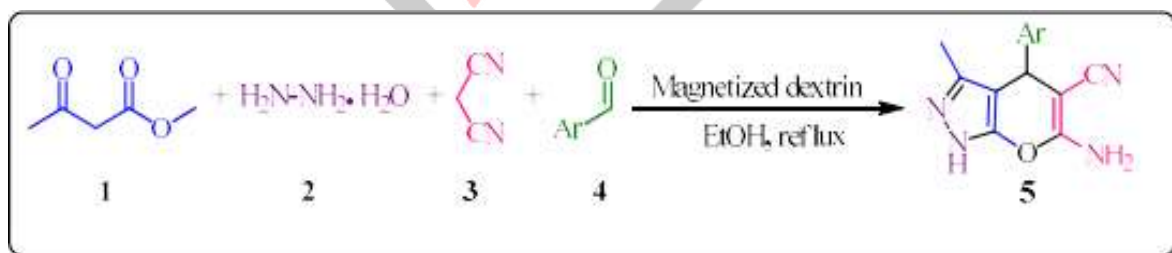


Figure No.1 Structure of Magnetized Dextrin[6].

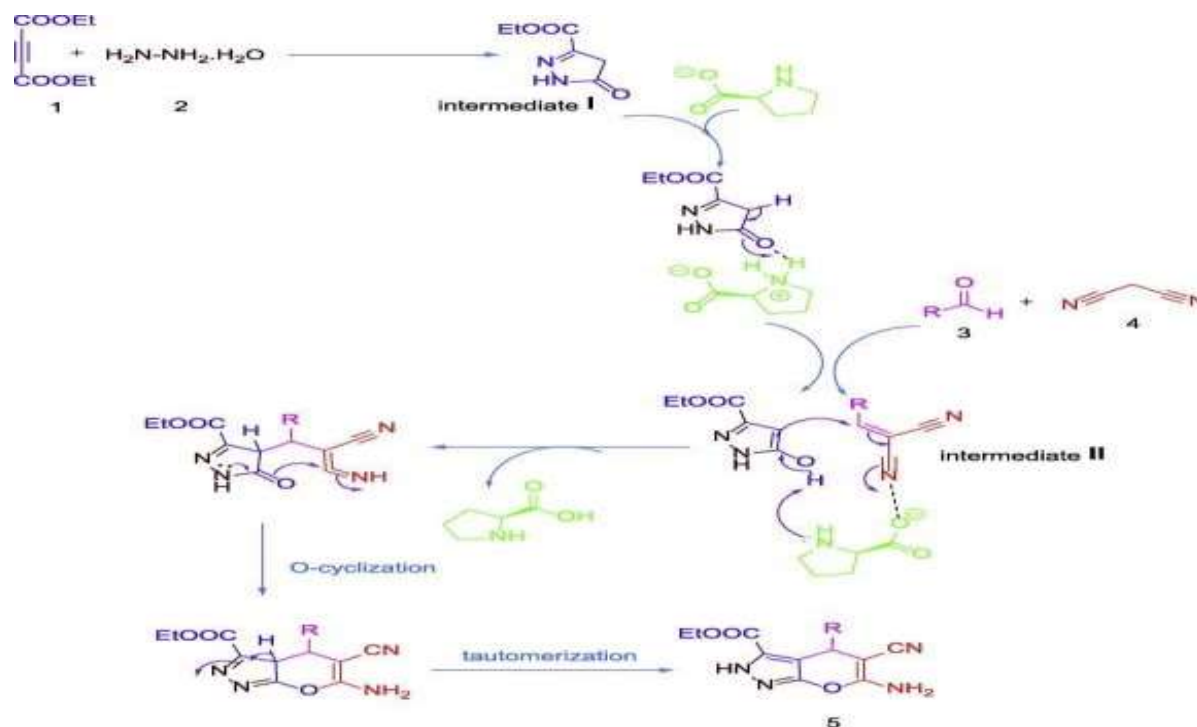
#### 3. Synthetic Pathway



Scheme 1. The synthesis of dihydropyrano[2,3-c]pyrazoles derivatives Magnetized dextrin[6].

#### 4. Mechanism:

Synthesis of Pyranopyrazole (4) which involves a domino Michael addition-tautomerism-O-cyclization sequence of reactions. The reaction may proceed via forming chelation between ethylacetoacetate (1) and hydrazinehydrate(2) to form intermediate(I) and which then reacts with alkylidenemalononitrile (B) (Knoevenagel condensed product of an aldehyde with malononitrile) to give intermediate (II) (Michael adduct). The Michael adduct then undergoes O-cyclization to give Pyranopyrazoles (4) [6].



Scheme 2. Mechanism for synthesis of DHPPs[7].

### 5. Preparation of magnetized dextrin:

First, 2 mmol  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and 1 mmol  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  were dissolved in 100 mL of distilled water, then the aqueous solution of 0.35 g dextrin in 25 mL distilled water was added to the solution. The temperature of resulting mixture was raised to  $90^\circ\text{C}$  and stirred under nitrogen atmosphere for one hour. Later,  $\text{NH}_4\text{OH}$  (25%) was added dropwise over 15 min to the stirring above suspension. The reaction continued for about one hour. Finally, the black crude precipitate was collected by magnet and washed several times with distilled water and ethanol to remove non-reactive materials, and then dried at room temperature for 6 hours to obtain magnetized dextrin nanocomposite[6].

### 6. General Procedure for the Synthesis of dihydropyran[2,3-c]pyrazole Derivatives :

The mixture of hydrazinehydrate (2 mmol), ethyl acetoacetate (2 mmol), malononitrile (1 mmol) and aromatic aldehydes (1 mmol) were mixed together in the presence of 0.015 g of magnetized dextrin in ethanol and refluxed for appropriate time. The reaction progress was monitored by thin layer chromatography (TLC). Finally, after completion of the reaction, the catalyst was separated from the reaction mixture through an external magnet and high pure product was obtained by recrystallization of the crude precipitate in ethanol[6].

### Nano-eggshell/Ti(IV) natural based catalyst for synthesis of dihydropyran[2,3-c]pyrazole Derivatives. 1.Introduction :

The eggshell is represented 11 % of the total weight of the egg and composed predominantly of calcium carbonate (94%), organic materials (4%), calcium phosphate (1%), and magnesium carbonate (1%)[7,8].

### 2. Structure of Ti (IV) :

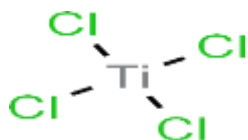
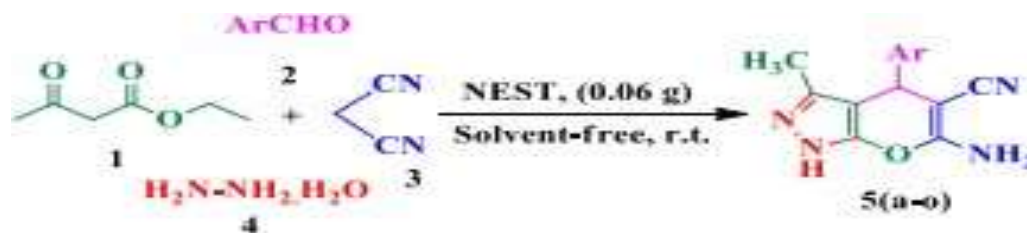


Fig. No:2 Structure of Titanium tetrachloride [7].

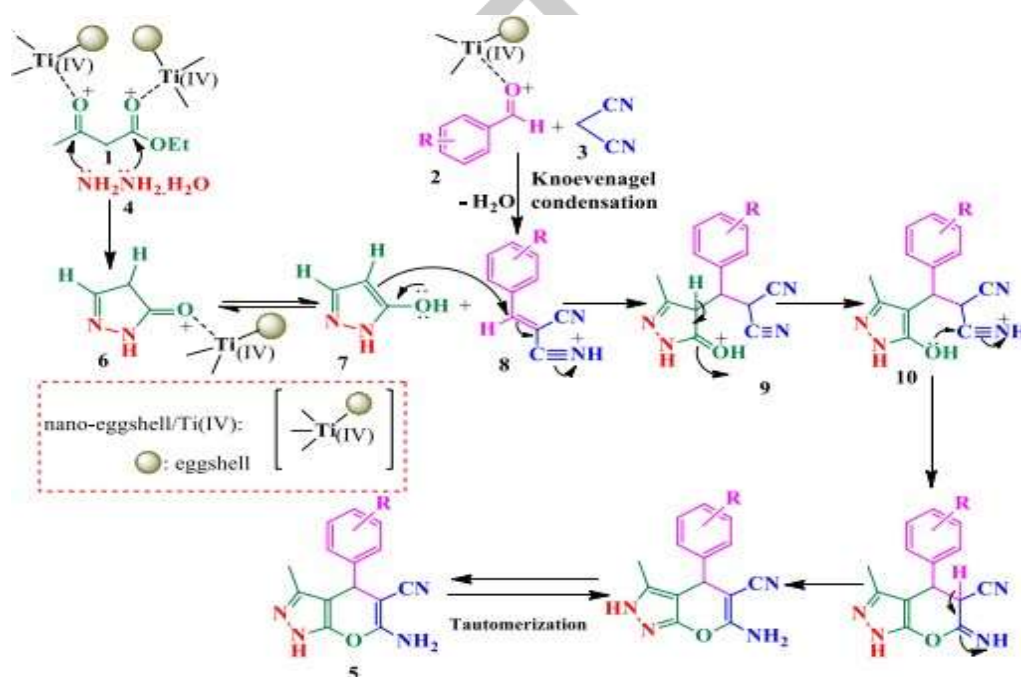
### 3. Synthetic Pathway:



**Scheme 3.** Synthesis of dihydropyrano(2,3-c)pyrazole catalyzed by eggshell/Ti(IV) [7].

### 4. Mechanism :

Initially, the condensation of hydrazine hydrate (4) and ethylacetoacetate (1) was formed intermediate (6) in the presence of NEST as a Lewis acid. The Knoevenagel condensation of malononitrile (3) with aromatic aldehyde (2) was produced the intermediate (8). Michael addition reaction of the intermediate (8) and (7) were generated intermediate (10), followed by intramolecular cyclization and tautomerization have given the DHPPs (5)[7].



**Scheme 4.** Mechanism for synthesis of DHPPs[7].

### 5. Preparation of NEST :

The eggshell was first boiled in boiling water for 30 minutes before being dried in a 150°C oven and powdered. In 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, 1 g of manufactured nano-eggshell powder was agitated for 30 minutes. The titanium tetrachloride (4.36 mL) was carefully added to the mixture, drop by drop. After 30 minutes of stirring at room temperature, the resultant product was filtered and washed three times with dichloromethane. Finally, the NEST was dried for 3 hours at room temperature[7].

### 6. General Procedure for the synthesis of DHPPs :

In a 100 mL round bottom flask, a mixture of aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (2 mmol), ethyl acetoacetate (1 mmol) and NEST (0.06 g) was stirred at room temperature. Progress of the reaction was monitored by TLC (n-hexane:EtOAc, 4:1). After completion of the reaction, the mixture was dissolved in acetone. Then, the catalyst was filtered off and the obtained solution was poured into cold water. The obtained solid product was filtered and purified by recrystallization from ethanol and water (4:1). The obtained

NEST catalyst was then washed with EtOH, dried and reused directly for four times in other fresh reactions with negligible decreasing of the yields[7].

### 7. Reusability of NEST :

The NEST was isolated by filtering the reaction mixture with acetone. The catalyst was recovered and dried at room temperature after being washed with dichloromethane. It was discovered that the nanocatalyst may be reused at least four times before losing significant catalytic activity[7].

No. of Runs	Yield
1	90
2	88
3	86
4	85

### Zn(ANA)Cl<sub>2</sub> complex as efficient catalyst for the synthesis of dihydropyrano[2,3-c]pyrazole Derivatives.

#### 1. Introduction :

Zinc is one of the highly abundant, cheaper and low toxic metals of the periodic table. Many other metals are more difficult to separate/extract in high purity from their respective minerals. Zinc's biological importance makes it an important trace element for regulating enzyme function in both animals and plants. Furthermore, current 'green chemistry' research is focusing on the use of less expensive and less toxic metals as catalysts or stoichiometric reagents to build environmentally sustainable organic synthesis and pharmaceutical synthesis processes. Following these examples, using zinc-based catalysts (homogeneous/heterogeneous) and reagents to meet the requirements of green chemistry would be a smart choice[9,10].

#### 2. Structure :

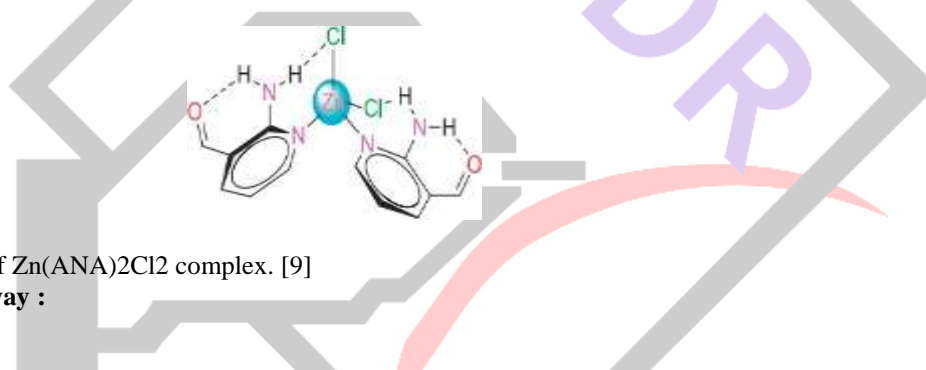
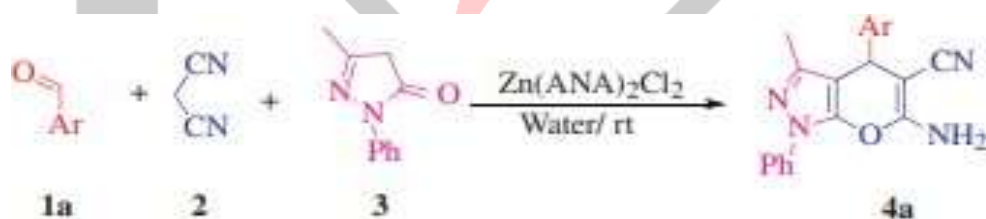


Figure3. Structure of Zn(ANA)<sub>2</sub>Cl<sub>2</sub> complex. [9]

#### 3. Synthetic Pathway :

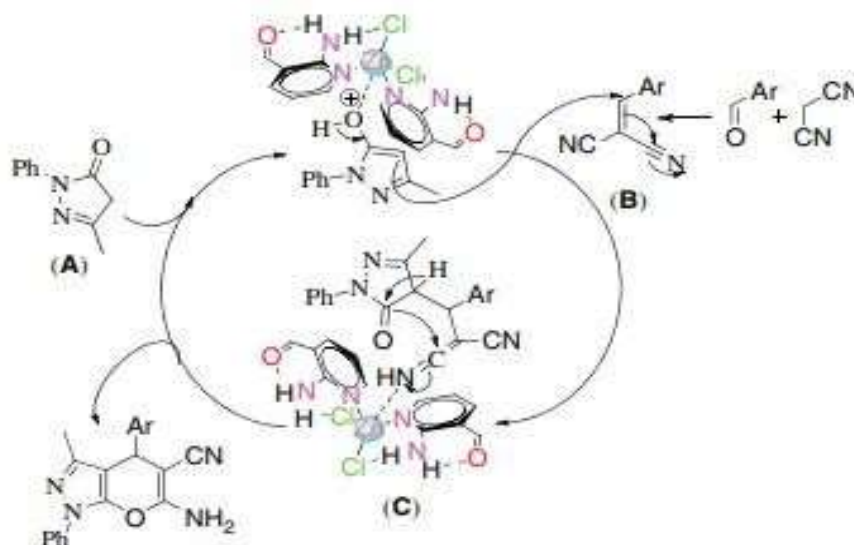


Scheme 5. The synthetic pathway of dihydropyrano(2,3-c)pyrazole catalyzed by using Zn(ANA)Cl<sub>2</sub> complex [9].



#### 4. Mechanism for the formation of pyranopyrazole via catalyzed by Zn(ANA)2Cl2 :

Synthesis of Pyranopyrazole (4) which involves a domino Michael addition-tautomerism-O-cyclization sequence of reactions. The reaction may proceed via forming chelation between phenylmethylpyrazolone and Zn(ANA)2Cl2 complex (A), and which then reacts with alkylidenemalononitrile (B) (Knoevenagel condensed product of an aldehyde with malononitrile) to give intermediate (C) (Michael adduct). The Michael adduct then undergoes O- cyclization to give Pyranopyrazoles (4) [11].



Scheme No 6. Mechanism for synthesis of DHPPs [9].

#### 5. Preparation of Zn(ANA)Cl2 :

The Zn(ANA)2Cl2 complex was prepared on mixing freshly prepared solutions of ANA dissolved in 20 ml ethanol and Zinc chloride tetrahydrate (ZnCl2.4H2O) dissolved in 10 ml ethanol, at reflux temperature for about 3 hr. At the end of the reaction excess ethanol was removed by vacuum and filtered after cooling to obtain pure Zn(ANA)2Cl2 complex [9].

#### 6. General procedure for the synthesis of the dihydropyrano[2,3-c]pyrazoles 4a-1 :

A mixture of aromatic aldehydes (1 mmol), malononitrile (1 mmol) and 3-methyl-1-phenyl-2-pyrazoline-5-one (1 mmol) was stirred with water at room temperature in the presence of 10 mol of Zn(ANA)2Cl2 complex for an appropriate time to produce dihydropyrano[2,3-c]pyrazoles. Reaction progress was monitored by TLC. After completion of the reaction, the product was filtered. The residue was washed with ethyl acetate. The ethyl acetate was evaporated under vacuum and the obtained solid was purified by recrystallization process in ethyl acetate [9].

#### 7. Recyclability studies of the catalyst (Zn(ANA)2Cl2 complex) :

In order to recycle the Zn(ANA)2Cl2, the reaction mixture was filtered and the residue was quenched two times with ethyl acetate to separate the crude product after the first catalytic run. The water layers are dried and reused for the next catalytic runs. It has been noticed that up to four successive catalytic runs yields dihydropyrano[2,3-c]pyrazoles that are almost in the close range (entries 1–4 of Table 2) and there was no considerable agglomeration of Zn(ANA)2Cl2. However, the yields were slowly reduced from the fifth cycle (entry 5 of Table 2) due to increasing the operation time. This is attributed to the decrease of multi-component activity of the catalyst due to the percentage of catalyst and metal deposition, which inhibits the activity of active sites of the catalyst [9].

No. of Runs	Yield
1	86
2	86
3	85
4	85
5	80

#### Molecular sieves : efficient catalyst for synthesis of dihydropyrano[2,3-c]pyrazoles

##### 1. Introduction :

Molecular sieves are a class of porous open-framework solids, which includes aluminosilicates (zeolites), aluminophosphates, and silicoaluminophosphates of diverse structures. Zeolites, the original molecular sieves, are built from corner-sharing SiO<sup>4-</sup> and AlO<sup>5-</sup> tetrahedra and contain regular systems of intracrystalline cavities and channels of molecular dimensions. The net negative charge of the framework, equal to the number of the constituent aluminum atoms, is balanced by exchangeable cations, M<sup>+</sup>, typically sodium, located in the channels which normally also contain water. The name "zeolite" (from the Greek (eo = to boil and XifJoo = stone) was coined by Cronstedt' in 1756 to describe the behavior of the newly discovered mineral stilbite which, when heated, rapidly

loses water and thus seems to boil. The general oxide formula of a zeolite is  $M_x(A1O_2)_y(SiO_2)_z \cdot nH_2O$  where  $y \geq x$ . Aluminate tetrahedra cannot be neighbors in the frameworks of hydrothermally prepared zeolites, i.e. Al-O-Al linkages are forbidden. This requirement is known as the Loewenstein rule. There are at present around 40 identified species of zeolite minerals (with 15 natural and 25 synthetic) and at least 125 synthetic species with a very wide range of aluminum content [15].

## 2. Structure of Molecular Sieves (Zeolite) :

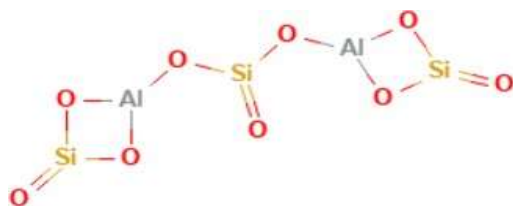
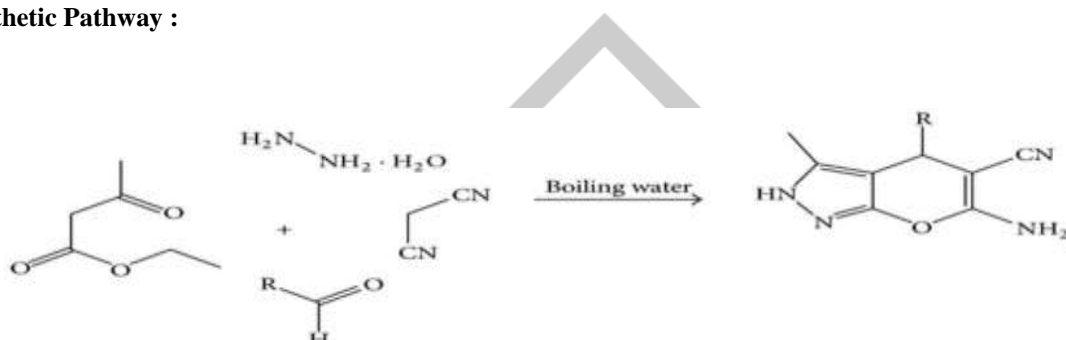


Fig. No 4. Structure of Zeolite

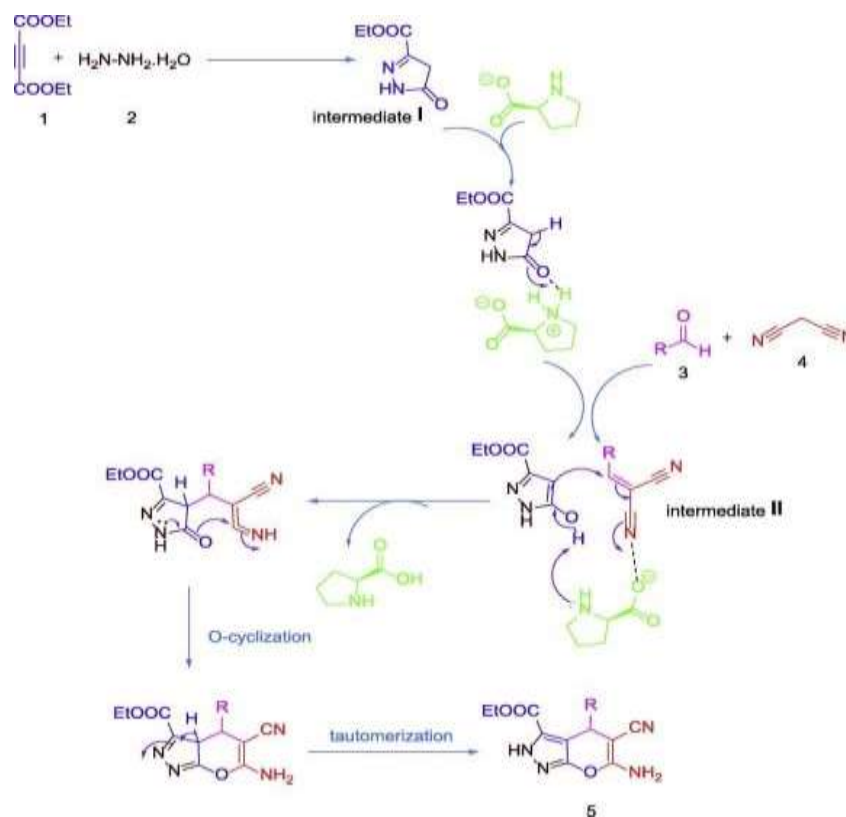
## 3. Synthetic Pathway :



Scheme 7. Synthesis of dihydropyrano(2,3-c)pyrazole catalyzed by Zeolite [16].

## 4. Mechanism for synthesis of pyranopyrazole:

The first step of the reaction is condensation reaction between ethyl acetoacetate and hydrazine hydrate leading to 3-methyl-5-pyrazolone and second step is Knoevenagel condensation between aromatic aldehyde and malanitrile leading to arylidenemalonitriles and which can be easily achieved in ethanol at room temperature without need of any catalyst. Further reaction between 3-methyl-5-pyrazolone and arylidenemalonitriles requires interference of catalyst, since uncatalyzed reaction does not lead to the formation of desired product [16].



Scheme 8. Mechanism for synthesis of DHPPs [16].

#### 5. Preparation of molecular sieves :

Initially Combine aqueous solutions of sodium silicate and sodium aluminate at 80 °C mix/agitate for a time, then "activate" by "baking" at 400 °C. 4A sieves serve as the precursor to 3A and 5A sieves through [cation exchange](#) of [sodium](#) for [potassium](#) (for 3A) or [calcium](#) (for 5A) [16].

#### 6. General procedure:

Initially, ethyl acetoacetate (1mmol) and hydrazine hydrate (1eq) were mixed to form 3-methyl-5-pyrazolone as a white solid. This solid was dissolved in ethanol (10ml) to which p-methyl benzaldehyde (1eq) and malononitrile (1eq) were added. Then the solution was allowed to reflux with MS 4 Å, after 1 h all the starting materials were found to be consumed to form a product [16,17].

#### 7. Recycling and reusability of the catalyst:

Recovered catalyst works with the same efficiency up to 3rd run, (Table 3, Entries, 1, 2, 3) while in the 4th and 5th run product yield gets decreased slightly. The catalyst was recovered simply by extracting the solid mass with ethyl acetate. Loss in the product yield after successive runs may be due to little bit loss of catalyst during each recovery process [16,18].

No. of Runs	Yield
1	90
2	90
3	90
4	88
5	86

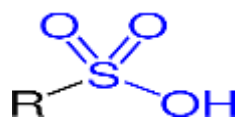
### SO<sub>3</sub>H@carbon powder derived from waste orange peel an efficient nanocatalyst for the synthesis of dihydropyrano[2,3-c]pyrazoles

#### 1. Introduction :

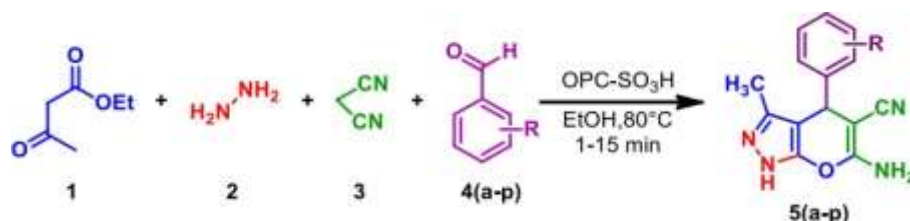
SO<sub>3</sub>H loaded carbon based solid heterogeneous 76 catalyst was studied as an excellent catalyst for the production of 77 biodiesel [18] due to its chemical inertness, good mechanical and thermal stability. Such catalysts 83 were prepared through a simple sulfonation reaction of biomass 84 derived activated carbons obtained from various sources like 85 sucrose [22], glucose [23], starch [24], glycerol [25], rejected tea 86 [26], sewage sludge [27] and coffee residue [28]. Ngaosuwan 87 et al. [19,21,31,32].

#### 2. Structure :



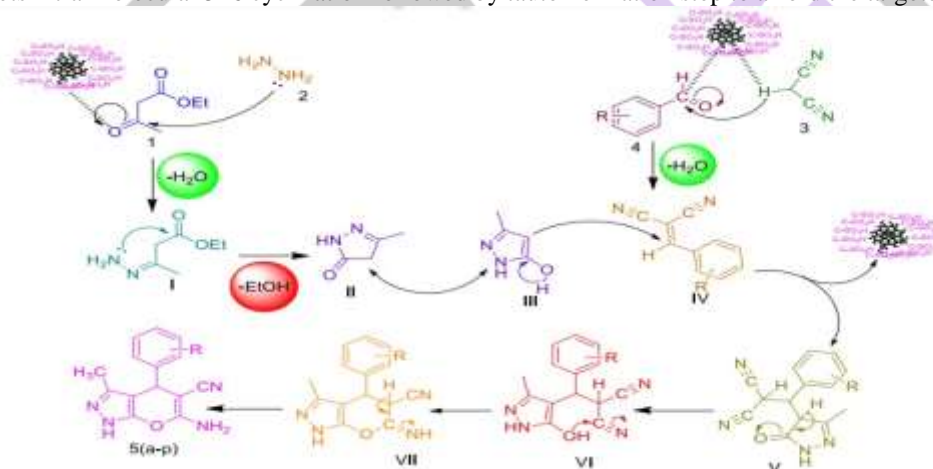
Fig. No 5. Structure of SO<sub>3</sub>H@carbon powder

### 3. Synthetic Pathway :

Scheme 9. Synthesis of dihydropyrano(2,3-c)pyrazole catalyzed by using SO<sub>3</sub>H@carbon powder [29].

### 4. Mechanism :

Initially, a condensation of ethyl acetoacetate 535 with hydrazine hydrate which might have been activated by OPC536 SO<sub>3</sub>H catalyst leads to give the intermediate, 3-methyl-5- 537 pyrazolone (II) which is transformed into III by tautomerization. 538 On the other side, the carbonyl group of aromatic aldehyde was 539 activated by OPC- SO<sub>3</sub>H catalyst and simultaneous activation of 540 active methylene moiety of malononitrile, facilitates the Knoevenagel condensation to form an arylidenemalononitrile (IV). Then 542 the Michael addition of intermediate III to the electron deficient 543 alkene IV leads to the formation of intermediate V. The intermediate 544V then undergoes the nucleophilic attack of OH functionality on 545 the cyano (CN) moiety. Finally, compound VI gets intra-molecular 546 cyclization followed by tautomerization step to afford the targeted 547 products (5a-p) [29].



Scheme 10. Mechanism for synthesis of DHPPs [29].

### 5. Preparation of carbon powder:

The orange peel was sliced into little pieces and washed with deionized water before being dried in the sun for a week. The dried peels were pyrolyzed for about 2 hours at 400 degrees Celsius. Orange peels were carbonized and washed twice with doubly deionized water to ensure uniformity of particle size. The carbon particles were sonicated for 45 minutes at ambient temperature after washing. 5 g fine granular carbonised orange peel powder was mixed with 10 mL pure sulfuric acid in a 100 mL beaker. To aid sulfonation, the carbon powder and sulfuric acid mixture was slowly cooked on a hot plate from 40 to 200 degrees Celsius. The resulting mass was left at room temperature for 1 hours until the foam stopped. After that, the mixture was washed with deionized water for many times and the black crystalline material was again washed with cold water to neutralize the pH level and filtered. The obtained black material was dried at 100 C for 2 h to obtain the orange peel carbonized sulfonic acid (OPC SO<sub>3</sub>H) powder catalyst material (4 g) [29].

### 6. Procedure for the synthesis of dihydropyrano[2,3-c] pyrazole derivatives:

In a 25 mL round bottom flask containing 4 mL of ethanol, a mixture of ethyl acetoacetate (3.0 mmol), hydrazine hydrate x (3.0 mmol) and 20 mg of OPC-SO<sub>3</sub>H powder catalyst was added and stirred at room temperature for about 3 min. To the white colored precipitate, aromatic aldehydes (3.0 mmol) and malononitrile (3.0 mmol) were added and the reaction temperature was elevated to

80 C with stirring around 350–400 rpm for the specified time. After completion of the reaction (as evidenced by TLC), the reaction mixture was cooled to room temperature, and the generated solid was filtered along with the catalyst, washed with deionized water and dried overnight. The product and the catalyst were separated by recrystallization using hot ethanol. The formation of the compounds were confirmed by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, FT-IR and melting points. The carbon catalyst has been recovered successfully by washing with water and ethyl acetate, then dried at 80 C for 3 h and reused [29].

### 7. Reusability of OPC-SO<sub>3</sub>H catalyst:

The efficacy of the recovered OPC-SO<sub>3</sub>H catalyst was examined by the reaction of ethyl acetoacetate (1), hydrazine hydrate (2) and malononitrile (3) with 4-chlorobenzaldehyde (4b), under optimized reaction conditions where, the catalyst could provide 97% to 91% of targeted product 5b without any noticeable loss of its activity even after 7th run. After the 7th run, the activity of recovered OPC-SO<sub>3</sub>H catalyst gradually affected the formation of yield and consumption of time to accomplish the targeted compound 5b. After the 9th run OPC-SO<sub>3</sub>H catalyst activity was more reduced for the formation of product [29].

No of runs	Yield
1	97
2	97
3	95
4	95
5	95
6	93
7	91
8	90
9	83

### Polystyrene supported p- Toluenesulfonic acid as reusable catalyst for the synthesis of dihydropyrano[2,3- c]pyrazoles.

#### 1. Introduction:

P-toluene sulfonic acid (PTSA) or PTsOH or tosylic acid (TSOH) is an organic compound with the formula  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3$ . It is a white solid that is soluble in water, alcohol and other polar organic solvent. The  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2$  group known as the tosyl group and is often abbreviated as TS or TOS.

#### 2. Structure of PS-PTSA(TSOH):

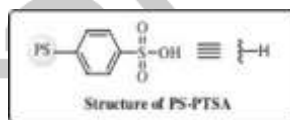
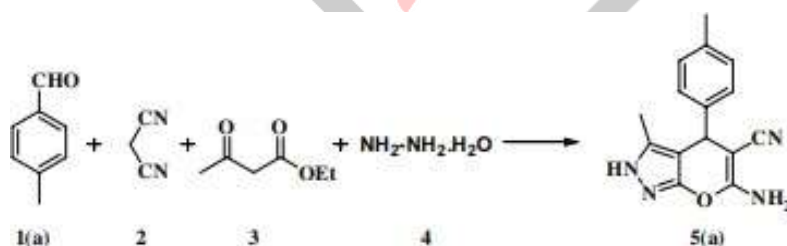


Fig. No 6. Structure of PS-PTSA.

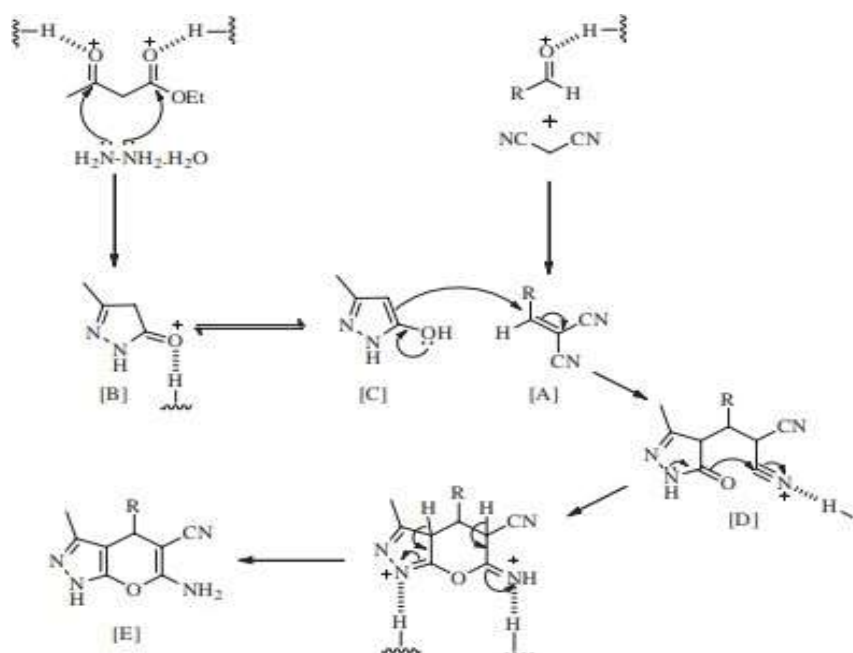
#### 3. Synthetic pathway of dihydropyrano(2,3-c)pyrazole:



Scheme 11. Synthetic pathway of dihydropyrano(2,3-c)pyrazole by using PS-PTSA [30].

#### 4. Mechanism:

Initial formation of arylidenemalononitrile [A] by the Knoevenagel condensation between PS-PTSA activated carbonyl group of aldehyde and malononitrile and pyrazolone [C] by the nucleophilic attack of  $-\text{NH}_2$  groups of hydrazine on PS-PTSA activated carbonyl groups of ethyl acetoacetate. Finally, Michael addition of pyrazolone [C] to arylidenemalononitrile [A] leads to formation of intermediates [D], which on further intramolecular cyclization yield pyranopyrazole [E] [30].



Scheme 12. Mechanism for synthesis of DHPPs [30].

### 5. Preparation of P-Toluene Sulfonic Acid :

To 500 ml a round bottom flask, fitted with a dean stark, which is connected with reflux condenser, 100 ml of toluene and 20 ml of concentrated sulfuric acid ( $d = 1,84$ ) are placed. The lower part of the dean stark trap additionally is filled with toluene. The reaction flask is heated with reflux for 5-6 h at  $160^{\circ}\text{C}$  [30].

### 6. General Procedure :

A mixture of aldehyde 1 (2 mmol), malononitrile 2 (2 mmol), ethyl acetoacetate 3 (2 mmol), hydrazine hydrate 4 (2 mmol), and PS-PTSA (20 mg) in water (10 mL) was stirred vigorously at reflux. Progress of the reaction was monitored by TLC (ethyl acetate:n-hexane, 2:8). After completion of the reaction (Table 3), the reaction mixture was cooled to RT and ethyl acetate (30 ml) was added and filtered to recover the catalyst. Thus, obtained portion of organic layer (ethyl acetate) was dried over  $\text{Na}_2\text{SO}_4$  and concentrated on rotary evaporator under reduced pressure to achieve the desired product. This crude product (5a) was purified by recrystallization from 10% aqueous ethanol as a solvent [30].

### 7. The reusability of polystyrene-supported catalyst:PTSA :

The reusability of polystyrene-supported catalysts was also tested for the synthesis of 5a under the optimal conditions of the respective polystyrene-supported catalysts. After the process, the recovered polystyrene-supported crude catalyst was washed with diethyl ether to get pure catalyst, dried in an oven, and reused directly for subsequent catalytic cycles. Up to five runs, the catalysts were shown to maintain their activity with no noticeable decline in yield (Figure 1). The progressive decline in catalytic activity could be owing to residues from the reaction blocking some active sites on the catalyst surface [30].

No of runs	Yield
1	94
2	94
3	93
4	90
5	88

**Conclusion:** Green, retrievable and cost effective catalysts such as Magnetized dextrin, Nanoeggshell,  $\text{Zn}(\text{ANA})\text{Cl}_2$ , Molecular sieves,  $\text{SO}_3\text{H}$  carbon powder, PTSA are used for the synthesis of dihydropyridone (2,3-c) pyrazole by multicomponent reactions. This procedure has advantages such as high efficiency products, mild reaction condition and easy separation of products from the reaction mixture.

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