

Magnetically Recyclable Nano-FDP: A Novel, Efficient Nano-Organocatalyst for the One-Pot Multi-Component Synthesis of Pyran Derivatives in Water Under Ultrasound Irradiation

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Abstract Highly stable, super-paramagnetic nanoparticle supported L-proline catalyst (nano-FDP) which shows extra-ordinary catalytic activity was synthesized for the first time from economical and easily available starting materials. Characterization of the synthesized catalyst was done by FT-IR, EDX, SEM and TEM analysis. Application of this for synthesis of pyran derivatives under ultrasonication at room temperature showed excellent results. Use of water as a solvent which is nature's own reaction medium, shorter reaction time, high yield of the desired product, recovery of the catalyst by external magnetic field, and its reusability in further runsare the added advantages of this methodology.

Graphical Abstract



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Amarta Kumar Pal amartya_pal22@yahoo.com **Keywords** Novel synthesis of nano-FDP · Magnetically separable nano-organocatalyst · One-pot multi-component reaction · Pyrano-pyrazolone derivatives

1 Introduction

Catalysis has emerged as an essential avenue in modern chemistry because it signifies an innovative way to meet the challenges of energy and sustainability. Existence of a catalyst is primarily required in both modern organic syntheses as well as in chemical industries. Green catalysis is a small chapter of green chemistry but probably the most imperative one [1].One of the most important characteristic that a catalyst should possess in order to become green is recyclability. Homogeneous catalysts despite having many advantages like: high TON (Turn Over Number), extraordinary selectivity etc. cannot fulfil this criterion because of its difficulty in isolation. However the use of heterogeneous catalyst or catalysts can emerge as a tremendous remedy to solve these problems [2, 3].

Nanoparticles as heterogeneous catalysts recently gained lots of attention as green catalyst [4, 5]. However, to separate particles with diameters less than 100 nm from reaction mixture is quite tedious, but magnetic nanoparticles due to their paramagnetic nature can be easily separated [6, 7] by attaching an external magnet. Among several magnetic nanoparticles, Fe_3O_4 nanoparticles are comprehensively studied because of the low cost of starting materials, simple synthetic procedure and relatively higher paramagnetic nature [8].

Since last few decades proline received tremendous priorities in organic synthesis as homogeneous catalyst, because of its high efficiency, environmentally benign behaviour and availability in both enantiomeric forms. But

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major drawbacks of using proline as catalyst are its separation and reusability. In order to overcome these problems we thought of implementing L-proline on Fe_3O_4 nanoparticles which would make it a merger of homogeneous and heterogeneous catalyst thereby increasing its greenness and resolving above mentioned complications.

Because of the mounting environmental concern on ecological safety and global warming chemists throughout the world are developing new methodologies which are efficient and eco-friendly. So, focus on "green chemistry" using environmentally benign conditions and reagents are of utmost importance for the synthesis of widely used organic compounds. Keeping in mind the principles of "green chemistry" it is appealing to carry out reactions in nature's own reaction medium, i.e. water rather than using organic solvents which are harmful. Unique structure and physiochemical properties of water lead to particular interactions like H-bonding, hydrophobic interaction, trans-phase interaction and polarity which influence the rate of reaction and shows additive outcomes. In addition to the above evidences organic reactions using water as a solvent provides certain other advantages like insolubility of the desired product, easy work up procedures which simplifies their isolation [9]. Multi-component reactions (MCRs) [10] have emerged as convergent chemical processes that involve the well defined condensation of more than two reactants to form desired products with very high atom efficiency. This strategy of MCR offers significant environment friendly features in true sense like reduction in number of steps, energy consumption and waste production [11].

Ultrasonication activates organic reactions due to cavitational collapse. Cavitation produce high temperature and pressure inside the bubbles, leading to blustery flow of the liquid and improved mass transfer [12]. Compared with traditional methods, this method provides higher yield and selectivity, with milder reaction condition and shorter reaction time [13].

Pyran is an important class of heterocyclic compound which is of significant importance in pharmaceutical industry and also in medical world owing to its promising medicinal and biological activities (Fig. 1) like anti-tumour, anti-cancer, anti-microbial, anti-oxidant, anti-proliferative, anti-inflammatory, anti-HIV, anti-tumour, analgesics etc. [14–30]. On continuing our exploration for synthesis and application of different nanoparticles in multi-component reactions [31], we herein report a novel method for synthesis of nano-Fe₃O₄-DOPA-L-proline (nano-FDP) which shows extraordinary catalytic activity in one-pot, multi-component synthesis of pyran derivatives under ultrasonic irradiation.

2 Experimental

2.1 Design and Synthesis of Nano-FDP

Recently, organocatalyst have been extensively used in organic synthesis, but still there is a lack of using it under sustainable condition. Though proline is an efficient catalyst for many organic transformations but its recovery from reaction mixture is very difficult, so we planed to attach proline with magnetic nanoparticles for making it easily recyclable. Dopamine a cheap and stable molecule under ambient condition contains phenolic –OH and aliphatic amine group. The phenolic –OH group strongly co-ordinates to ferrite molecule by chelating effect and the amine functionality binds with the carbonyl group of L-proline via amide bond formation thereby keeping the secondary amine site of L-proline free for catalysis.

Nano-FDP was synthesized by a simple, cost effective and efficient method as shown in Scheme 1. Elaborate synthesis paper is described in supporting information.

2.2 Catalyst Characterization

2.2.1 FT-IR

Comparative FT-IR spectra of nano-FDP, Fe₃O₄-DOPA and Fe₃O₄ NPs is shown in Fig. 2. Prominent peak at around 591–611 cm^{-1} which appears in all the three spectra is due to Fe-O vibration. Peaks at 1630 and 1400 cm⁻¹ in the spectrum of Fe₃O₄-DOPA are due to primary -NH₂ bending, and -C-N stretching of dopamine moiety, indicating the successful attachment of dopamine molecule on Fe₃O₄ NPs. These peaks are also present in the spectrum of nano-FDP in almost the same region, but peak at 1465 cm⁻¹ has become more prominent and sharp which indicates the secondary -N-H stretching of amide linkage. The prominent peak at 1685 cm⁻¹ in the spectrum of nano-FDP is the characteristic peak of carbonyl group which arises due to the stretching of amide carbonyl bond indicating the successful attachment of L-proline with dopamine via amide bond formation. The peak at around 3430 cm^{-1} in the spectrum of Fe₃O₄ NPs is because of -OH stretching vibration of Fe₃O₄ NPs [32] this is also present in the other two spectra at 3415 and 3465 cm^{-1} . If we observe carefully, peak at around 3465 cm^{-1} in the spectrum of nano-FDP is very sharp indicating the -N-H stretching of L-proline moiety.





Fig. 1 Structures of some biologically and medicinally active pyran derivatives

2.2.2 EDX and SEM

In order to determine elemental composition of nano-FDP, EDX analysis was performed. The analysis confirmed the presence of carbon, nitrogen, iron and oxygen (shown in Fig. 3). SEM images of Fe_3O_4 NPs, and nano-FDP are shown in Fig. 4. According to SEM images nano-FDP possess spherical shape.

2.2.3 TEM

Particle size of nano-FDP was examined by TEM analysis. The typical TEM images of nano-FDP (Fig. 5) revealed that, the size of the nanoparticles are in the range of 5-20 nm which is same as that of typical diameter of Fe₃O₄ NPs. From TEM images, it is also evident that, black spots are consistently scattered throughout the sample and this can be attributed to the presence of Fe₃O₄ nanoparticles. The corresponding SAED (Selected Area Electron Diffraction) pattern showed spotty diffraction proving the crystalline behaviour of the sample. The width of the L-proline attached dopamine coating is around 4 nm which is clearly visible in the TEM image of freshly prepared nano-FDP. Width of the coating and even the crystalline property of the catalyst is retained after five time of consecutive uses, which is clearly evident from the 'after use TEM images' and SAED patterns of nano-FDP.



Fig. 2 Comparative FT-IR of Fe₃O₄ NPs (top), nano-FDP (middle) and Fe₃O₄-DOPA (bottom)

Fig. 3 EDX of nano-FDP





Fig. 5 a TEM of Fe_3O_4 NPs, **b** TEM of nano-FDP before use at 50 nm, **c** TEM of nano-FDP before use at 10 nm showing uniform coating, **d** SAED of a fraction of nano-FDP before use, **e** TEM image

of nano-FDP after use at 50 nm, f TEM image of nano-FDP after use at 5 nm showing the uniform coating, g SAED of nano-FDP after use



Fig. 6 a Powder XRD of Fe₃O₄ NPs. b Powder XRD of nano-FDP

2.2.4 Powder XRD

Figure 6 represents the XRD-diffraction patterns of the prepared Fe₃O₄ MNPs and nano-FDP. In both the spectra prominent peaks at almost same region were observed, which indicates that crystalline spinal ferrite core structure is preserved in the final catalyst. The XRD patterns shows six characteristic peaks at $2\theta = 30.29^{\circ}$, 35.59° , 43.25° , 53.84° , 57.16° , 62.79° which corresponds to the indices (2 2 0), (3 1 1), (4 0 0), (3 3 1), (4 2 2), (3 3 3), (5 1 1) and (4 4 0) respectively [33].

2.2.5 VSM

Magnetic behaviour of synthesized nano-FDP was studied by Vibrating Sample Magnetometer (VSM), Fig. 7 shows the magnetization curve for nano-FDP. The saturation magnetization value of nano-FDP was found to be 59.89 emu/g, which is slightly lower than that of bare Fe_3O_4NPs (67.22 emu/g) [34] because of coating.



Scheme 2 Synthesis of pyran derivatives



Fig. 7 VSM of nano-FDP

3 Results and Discussions

In order to scrutinize the catalytic activity of nano-FDP, we employed it in four component reaction of ethylacetoacete (11), hydrazine hydrate (10), aldehyde (8) and malononitrile (9) for synthesizing pyran derivatives (12a). Primarily, ethylacetoacetate (1 mmol) and hydrazine hydrate (1.5 mmol) were mixed together, which immediately leads to the formation of white precipitate of 3-methyl-1*H*pyrazol-5(4*H*)-one (15a) to which 4-cholorobenzaldehyde (1 mmol), and malononitrile (1 mmol) along with nano-FDP were added and ultrasonicated in presence of various solvents. Scheme 2 (SI-pg-3).Water was chosen as desired solvent because it was giving excellent yield, its cheap, easily available and it is nature's medium for reaction.

After selection of the solvent, we did comparison of catalytic activity of nano-FDP with other catalysts. The model reaction was then refluxed, as well as ultrsonicated in water (10 ml) in presence of various homogeneous and heterogeneous catalysts like Et_3N , morpholine, $FeCl_2$, $FeCl_3$ glutathione, L-proline, Ni NPs, Pd NPs, Fe_3O_4 NPs, Fe_3O_4 @DOPA NPs, SiO_2 NPs, and Fe_3O_4 -DOPA-L-proline (nano- FDP) nanoparticles (Table 1). From Table 1, it

Table 1 Catalyst

standardization

Sl. no. Catalyst^a Conventional heating (100 °C) Ultrasonication (r.t) Time (min)^b Yield (%)^c Time (min)^b Yield (%) 1 No catalyst 180 15 30 20 2 10 Et₃N 30 30 36 3 Morpholine 30 10 69 60 4 30 55 10 60 Fecl₂ 5 Fecl₃ 30 62 10 68 5 L-Proline 30 88 10 90 6 Glutathione 30 68 10 72 7 Ni NPs 30 72 10 85 8 Pd NPs 30 70 10 81 9 Fe₃O₄ NPs 30 78 10 85 10 SiO₂ NPs 30 75 10 79 11 Fe₃O₄@DOPA NPs 30 80 10 91 Nano-FDP 11 30 91 10 98

Reaction condition: Ethylacetoacetate (1 mmol), hydrazine hydradate (1.5 mmol), 4-Cl C_6H_5 (1 mmol), malononitrile (1 mmol), 5 ml water

 $^{\rm a}$ Amount taken for all the solid catalyst was 0.006 g and Et_3N taken 0.01 ml

^b Time is in minutes

^c Yield is in %

is evident that all the catalysts successfully promoted the reaction leading to the formation of the desired product. But, the synthesized nano-FDP was showing the best result (highlighted in bold in table 1). In absence of catalyst after 3 h very less amount of product was formed. Though the reaction was going smoothly in both the conditions i.e. under refluxed and ultrasonication, but we have chosen ultrasonication as our reaction medium because it was found that the desired product formed within very short time interval under ultrasonication with no side products and most importantly without supply of any external thermal energy, i.e. the reaction was carried out at room temperature (Figs. SI-1, SI-2). On discovering this fact we carried a detailed observation of the model reaction in various time scale, and it was found that the complete conversion of the reactants into desired product took place after 10 min of irradiation (Fig. SI-2). Amount of catalyst used also showed significant effect on reaction. 0.006 g of Nano-FDP under ultrasonication at room temperature is the best catalyst loading for getting the optimum yield. Further



Scheme 3 One-pot for component synthesis of pyran derivatives using nano-FDP

increase in the catalyst concentration did not affect product yield (Fig. SI-3). After standardizing all the important reaction parameters, nano-FDP was used for synthesizing a series of pyrano-pyrazoles. Various aromatic aldehydes, active methylene compounds, hydrazine or phenyl hydrazine were used and reacted them under optimum condition (Scheme 3). The position of the phenyl rings didnot have any effect on the overall product yield as shown in Table 2.

Aldehydes with both the electron-withdrawing and electron-donating substituents in the phenyl ring gave excellent yields at room temperature under utrasonication (Table 2). All the products were characterized on the basis of their analytical as well as spectroscopic data.

A plausible mechanism for the synthesis of pyranopyrazolones by using nano-FDPis shown in Scheme 4. According to proposed mechanism, firstly ethyl acetoacetate (11) reacts instantly with hydrazine hydrate (10) or phenyl hydrazine (14) leading to the formation of pyrazolone derivatives (15a,b). Then, in the second step nano-FDP binds with aldehyde forming iminium intermediate (16) which reacts with malononitrile (9) in Knoevengel fashion to give cyano-olefin compound (18). Finally nano-FDP catalyzes the formation of intermediate (19) which undergoes intermolecular cyclization to afford desired product (12 or 13).

Since our main object is to inspect the recovery and reusability of the nano-FDP, we applied external magnetic field for separation. It was our delight that the catalyst get easily separated without any significant loss of its amount. Then, after washing and drying we applied it for another

Entry	Aldehydes	Products	Time (Min.)	Yield (%) ^a	Melting point (°C)	
					Found	Reported
1	4-Cl C ₆ H ₅	12a	10	98	232–234	234–236 [35]
2	4-NO2 C6H5	12b	8	96	254-256	251–253 [27]
3	4-Me C ₆ H ₅	12c	12	90	207-210	206–208 [27]
4	C ₆ H ₅	13a	4	95	168-170	167–169 [<mark>36</mark>]
5	4-Me C ₆ H ₅	13b	6	89	175–178	176–178 [<mark>36</mark>]
6	4-F C ₆ H ₅	13c	3	96	171–173	170–172 [36]
7	4-NO2 C6H5	13d	4	95	188-190	190–192 [<mark>36</mark>]
8	4-Br C ₆ H ₅	13e	2	97	183–186	181–183 [<mark>36</mark>]
9	4-Cl C ₆ H ₅	13f	2	98	174–176	175–177 [<mark>36</mark>]
10	4-CN C ₆ H ₅	13 g	3	97	195–198	195–197 [<mark>36</mark>]
11	3-NO ₂ C ₆ H ₅	13 h	5	96	187-190	189–191 [<mark>36</mark>]
12	2-Cl C ₆ H ₅	13i	6	95	192–194	190–192 [36]

Reaction condition: Ethylacetoacetate (1 mmol), hydrazine hydradate (1.5 mmol), 4-Cl C_6H_5 (1 mmol), malononitrile (1 mmol), 0.006 g nano-FDP, 5 ml water and ultrasonication

^a isolated yield



Table 2 Synthesis of variouspyrano-pyrazolone derivatives









Fig. 8 Catalyst recycling

set of reaction. It was observed that, catalyst can easily be reused for another four runs without considerable loss of catalytic activity (Fig. 8).

4 Conclusion

In conclusion, we have developed an efficient, super-paramagnetic and highly reusable nano-FDP organocatalyst which was synthesized for the first time using dopamine bridge. Said nano-FDP showed excellent catalytic activity for the synthesis of pyrano-pyrazolones in water under ultrasonic irradiation at room temperature. Recovery and reusability of nano-FDP for five consecutive runs made this procedure more economically viable and environment friendly.

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