

MULTICOMPONENT SYNTHESIS OF PYRANOPYRAZOLES USING LANTHANUM FERRITE AS EFFICIENT AND REUSABLE HETEROGENEOUS CATALYST

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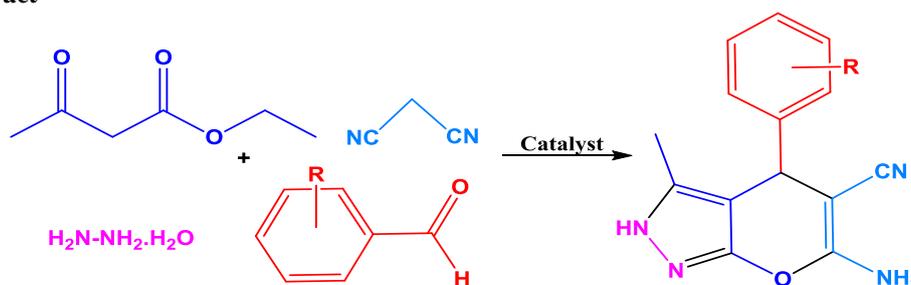
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ABSTRACT

Recent applications of ferrites have received considerable attention in the field of heterogeneous catalyst and actively participated in the development of greener reaction protocols for providing a suitable support. Lanthanum ferrite as efficient and reusable heterogeneous catalyst were found to be efficient for the synthesis of pyranopyrazoles by a four-component reaction of a mixture of hydrazine hydrate, ethyl acetoacetate, aldehydes and malononitrile under solvent free condition. The catalyst was characterized by XRD and FT-IR studies. The advantages of these protocols are its greenness with respect to short reaction time, mild reaction conditions, operational simplicity and high yields. Ferrite catalysts can be easily recovered from reaction systems and reused up to several runs almost without loss of catalytic activity. Synthesized compounds were confirmed by using FT-IR, ^1H & ^{13}C NMR spectroscopic data and melting points compared with reported values.

KEYWORDS: Pyranopyrazoles, lanthanum ferrite, heterogeneous catalyst, multicomponent reaction.

Graphical abstract



INTRODUCTION

The beauty of Multicomponent reactions plays an important role in performing reactions in simple manner in which three or more reactants are combining in a single step to produce target products. Multicomponent reactions fulfil the principles of green chemistry and offer the advantages in terms of experimentally simple to perform, reduced reaction time, high atom efficiency, synthetic efficiency of an ideal organic synthesis and simpler purification techniques.^[1-3] In recent years, the synthesis of heterocyclic compounds using multicomponent protocols develops not only vital part of pharmaceutical groups but also an significant tool in discovery of new drugs.^[4] Developing organic reactions carried out in aqueous media exhibit unique reactivity and selectivity which is another attractive area of green chemistry different from reactions in organic solvents.^[5] Thus the study of multicomponent reactions has involved remarkable attention of scientific community to develop novel and effective protocols.^[6] In modern organic

synthesis utility of heterogeneous solid acid base catalysts has received notable gaining significant attention in pharmaceutical, agrochemical and veterinary products to improve faster rates of reactions, reusability of catalyst and good yields of products. The major goal of green chemistry is to minimizing purification steps, less use of highly hazardous chemicals and easy recycling and recovery of catalyst.^[7] Heterogeneous catalyst is more effective than homogenous catalyst in terms of operational simplicity, high selectivity and reusability.^[8]

In recent years, pyranopyrazoles are an essential class of heterocyclic compounds in which the skeleton is a cyclic pyran that is substituted by pyrazole in the orto position and plays important role in the prominent utilization and applications in pharmaceutical ingredients, biodegradable agrochemicals,^[9-12] antibacterial, antifungal,^[13,14] antitubercular,^[15] antimalarial,^[16] antitumor,^[17] antioxidant,^[18] antihypertensive,^[19]

hypnotic^[20] and vasodilator.^[21] Magnetoplumbite ferrites are used as catalysts in many multi-component reactions carried out in one-pot synthesis. Ferrites are mixed metal oxides with iron (III) oxides as a main component. The catalyst achieves an enhancement in catalytic activity due to easy catalyst separation and recycling over conventional method.^[22] The procedure involves four component reactions of aldehydes; ethyl acetoacetate, malononitrile and hydrazine hydrate for the synthesis of Pyranopyrazoles derivatives. Solvent free reactions were useful to be effective methods for many organic transformations instead of using various organic solvents.^[23, 24] Various catalysts with different conditions are employed for the synthesis of pyranopyrazoles including organocatalyst (MDOs),^[25] imidazole,^[26] per-6-amino- β -cyclodextrin,^[27] D,L-Proline,^[28] disulfonic acid imidazolium chloroaluminate {[Dsim]AlCl₄},^[29] gamma-Alumina,^[30] magnetic Fe₃O₄ nanoparticles,^[31] and isonicotinic acid.^[32] Some of these procedures have drawbacks as the use of hazardous organic solvents, separation of catalyst, long reaction time, expensive and tedious work-up procedure.

In view of the significance associated with this class of reaction here we report synthesis of pyranopyrazoles derivatives by condensation of aldehyde, ethylacetoacetate, hydrazine hydrate and malononitrile in presence of reusable lanthanum ferrite as catalyst and reaction mixture was stirred for desired time in ethanol at 60°C temperatures.

EXPERIMENTAL WORK MATERIALS AND METHODS

Analytical grade chemicals were used and distilled prior to use whenever necessary. The solvents obtained from commercial sources were dried using standard methods as and when required. All the metal salts were obtained from SD fine chemicals and were used as received. Melting points were determined on a quality digital melting point apparatus. The IR spectra were recorded on Bruker FT-IR spectrometer. NMR spectra recorded on a Bruker Avance (300 and 400 MHz) spectrometer using CDCl₃ and DMSO-*d*₆ as a solvent. Chemical shifts (ppm) were referenced to the initial standard tetramethylsilane (TMS). The structural and phase purity of as prepared samples were characterized through XRD measurement using Bruker AXS-D8 advanced X-ray powder diffractometer with CuK α line ($\lambda = 1.54056 \text{ \AA}$) in the 2 θ range from 10-90°. Reactions were monitored by thin layer chromatography using silica gel 60F254 aluminium sheets (Merck).

Preparation of Lanthanum ferrite

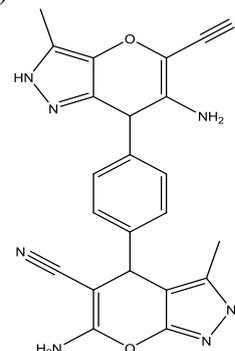
Lanthanum ferrite (LaFe₁₂O₁₉) was prepared by literature method with slight modifications.^[33] The LaFe₁₂O₁₉ partials are synthesised by using solution combustion method. Fe(NO₃)₃·9H₂O and La(NO₃)₂ dissolved in de-ionised water to form an aqueous solution of 0.1 M. An aqueous solution of citric acid was mixed with metal nitrates solution. The molar ratio of solutes in solution

was kept La⁺²:Fe⁺³:C₃H₄(OH)(COOH)₃ = 1:12:19. The pH of solution was adjusted to 7 by adding NH₄OH. It was refluxed at 90°C for 2 hours to allow the carboxyl groups of citric acid to completely chelate metallic ions in the solution. It was heated in microwave for half an hour to obtain the solid precursor. It was calcinated in the muffle furnace at 500°C for 4 hours at a heating rate of 10°C/min and hexaferrite powder was obtained.

General procedure for the synthesis of pyranopyrazoles

A mixture of hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), aldehydes (1 mmol) and malononitrile (2 mmol) and LaFe₁₂O₁₉ (10 wt%) catalyst were placed in 100 mL round bottom flask and reaction mixture was stirred for desired time in ethanol (5 mL) at 60°C temperature. After completion the progress of the reaction was monitored by thin layer chromatography and filtered the mixture for separating catalyst. The recovered catalyst was reused for other uses with no loss in its activity. All of the products were characterised based on their spectroscopic properties by comparison with authentic samples. Purity of compounds was checked by FT-IR, ¹H and ¹³C NMR spectroscopic data, melting points and TLC.

Spectral data of synthesized compound 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-*c*]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-*c*]pyrazole-5-carbonitrile (5a)

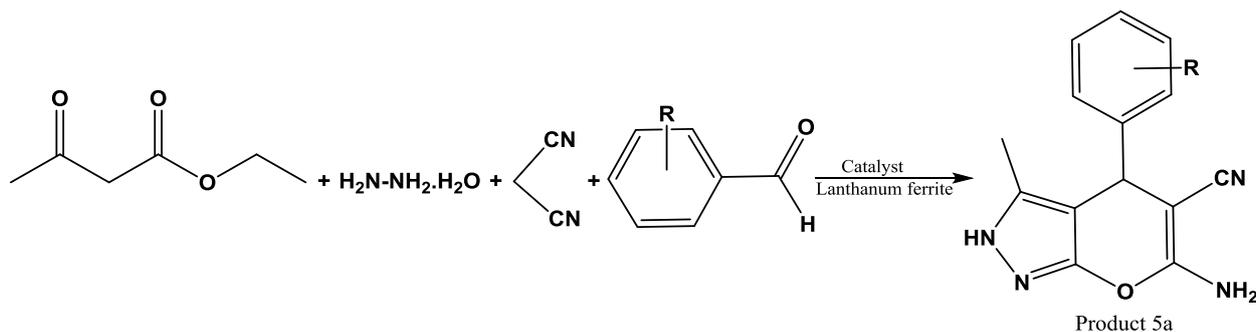


FT-IR (KBr) ν_{max} (cm⁻¹): 746, 1054, 1397, 1487, 1596, 2190, 3227; ¹H-NMR (400 MHz, DMSO-*d*₆, δ , ppm): 1.74 (s, 6H), 4.52 (s, 2H), 6.68 (s, 4H), 7.09 (s, 4H), 11.98 (s, 2H), ¹³C NMR (400 MHz, DMSO-*d*₆, δ , ppm): 9.83, 34.20, 39.80, 40.33, 57.60, 79.27, 97.48, 120.79, 127.66, 135.68, 142.77, 154.90, 160.92; MS: *m/z* 426 (M); *m.p* 265-266 °C (lit. 266-267).

RESULTS AND DISCUSSIONS

To examine the role of catalyst for synthesis of pyranopyrazoles reaction as model reaction of aldehyde, ethylacetoacetate, hydrazine hydrate and malononitrile were allowed to react in presence of lanthanum ferrite (10 wt%) catalyst and reaction mixture was stirred for desired time in ethanol (5 mL) at 60°C temperature (scheme 1). The reaction was completed in 90 minutes to

give compound **5a** was selected as a model reaction to optimize the reaction conditions.



Scheme 1: Pyranopyrazoles synthesis using hydrazine hydrate, ethyl acetoacetate, aldehydes and malononitrile and LaFe₁₂O₁₉ catalyst

In order to establish the optimal condition, the reaction was carried out in absence and presence of varying amount of catalyst in different solvents under different conditions (Table 1). For showing the effect of solvent, the same model reaction was also carried out in different solvents including H₂O, MeOH, EtOH, CH₃CN and CH₂CH₂Cl₂ in the presence of 0.1 mmol of the catalyst.

As shown in table 1, the yield of the reaction in ethanol medium was greater and the reaction time was considerably shorter than the conventional methods. Therefore, our optimized conditions are 0.1 mmol of Lanthanum ferrite catalyst at 90°C under solvent free conditions. All subsequent reactions were carried out using these conditions.

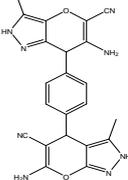
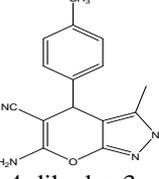
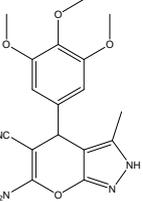
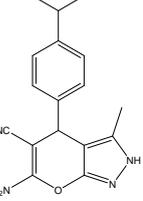
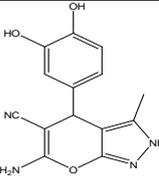
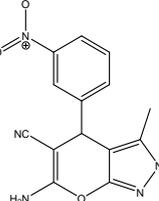
Table 1: Optimization of reaction condition for the synthesis pyranopyrazoles and their effect of solvents in formation (4a)^a

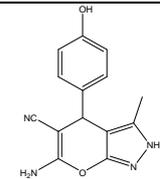
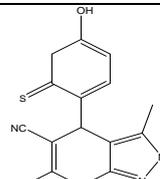
| Entry | Catalyst (wt %) | Condition/ Solvents | Time (min.)/ Yield ^b (%) |
|-------|------------------|---|-------------------------------------|
| 1 | Without catalyst | Reflux/ H ₂ O | 90/87 |
| 2 | 0.1 | Microwave/ CH ₃ CH ₂ OH | 90/94 |
| 3 | 0.1 | Microwave/ CH ₃ OH | 90/90 |
| 4 | 0.1 | Microwave/ CH ₃ CN | 90/86 |
| 5 | 0.1 | Reflux/ ClCH ₂ CH ₂ Cl | 90/88 |
| 6 | 0.1 | Reflux | 90/85 |

^aReactions carried out at 10 mmol scale with molar ratio of aldehyde, ethyl acetoacetate, hydrazine hydrate and malononitrile, ^bisolated yield

We decided to investigate the efficiency of Lanthanum ferrite as a catalyst in the model reaction under solvent-free conditions, which offers eco-friendly, simpler work ups, cleaner products, enhanced selectivity, reduction of by products, and faster reactions. To find the optimum reaction conditions, different parameters were studied for the formation of compound **5a**. The results are summarized in Table 2. It was observed that the reaction was efficiently catalysed by Lanthanum ferrite in ethanol to a high yield of product. Then, the reaction was performed in the presence of various amounts of the catalyst and also in different temperatures under solvent-free conditions. As can be seen, the efficiency of the reaction is affected mainly by the amount of Lanthanum ferrite and reaction temperature. The best result was obtained when the reaction was run at 60 °C in the presence of 1 mmol of Lanthanum ferrite.

Table 2: Synthesis of pyranopyrazoles derivatives in presence of Lanthanum ferrite as a catalyst.

| Sr. No. | Substrate R | Product | Reaction Time (min.) | Yield (%) | M.P. (lit.M.P.)/°C | |
|---------|-----------------------------------|---|----------------------|-----------|--------------------|---------|
| 1. | Terephthaldehyde (5a) |  6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile | 90 | 94 | 195-196 | 196-198 |
| . | p-tolualdehyde (5b) |  6-amino-2,4-dihydro-3-methyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 88 | 175 | 175-176 |
| 3. | 3,4,5-trimethoxybenzaldehyde (1c) |  6-amino-2,4-dihydro-4-(3,4,5-trimethoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 86 | 211 | 210-212 |
| 4. | 4-isopropylbenzaldehyde (5d) |  6-amino-2,4-dihydro-4-(4-isopropylphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 88 | 202 | 201-202 |
| 5. | 3,4 dihydroxybenzaldehyde (5e) |  6-amino-2,4-dihydro-4-(3,4-dihydroxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 89 | 197 | 198-199 |
| 6. | 3-nitrobenzaldehyde (5f) |  6-amino-2,4-dihydro-3-methyl-4-(3-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 90 | 191 | 190-192 |

| | | | | | | |
|----|----------------------------|--|----|----|---------|---------|
| 7. | 4-hydroxybenzaldehyde (5i) |  6-amino-2,4-dihydro-4-(4-hydroxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 88 | 225 | 224-225 |
| 8. | 2-thiophenylaldehyde (5j) |  6-amino-2,4-dihydro-4-(4-hydroxy-6-thioxocyclohexa-1,3-dienyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile | 90 | 87 | 246-247 | 246-248 |

Encouraged by the remarkable results obtained with the above reaction conditions, and to show the generality and scope of this new protocol, a range of pyranopyrazoles were prepared in the presence of Lanthanum ferrite as a catalyst under optimized conditions and the results are shown in Table 2. Most of the reactions proceeded very efficiently and no side-product was observed. Products are observed in high yields over short reaction time.

The catalyst was recovered in ethanol and reused for three more cycles. It is therefore suggested that such reactions for production of the pyranopyrazoles derivatives may be more useful and economical. Further this reaction was tested for synthesis of 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile as a model reaction (Table 3), the plausible mechanism for which has also been proposed in Figure 3.

Table 3: Reusability of catalyst.

| Entry | Catalyst recovery ^a (%) | Yield ^b (%) |
|-------|------------------------------------|------------------------|
| 1 | -- | 94 |
| 2 | 92 | 93 |
| 3 | 89 | 91 |
| 4 | 85 | 87 |

^a catalyst recovered by filtration and washing with ethanol, ^b isolated yield

The X-ray diffraction patterns of Lanthanum ferrite by solution combustion method are shown in Figure 1. This results show that Lanthanum ferrite have a similarity to the data peaks. The indexed XRD peaks and sharp lines are observed due to crystalline natures which are matched with standard JCPDS Card no. 37-1493. The FT-IR spectra of Lanthanum ferrite in the range 450-

4000 cm^{-1} are presented in Fig.4. For comparison of Lanthanum ferrite obtained by solution combustion method attributed to metal oxygen modes of tetrahedral and octahedral sites. From the spectra, it can be seen the absorption bands at around 436, 528, and 698 cm^{-1} corresponds to typical M-O vibrations bands of Lanthanum ferrite (Figure 2).

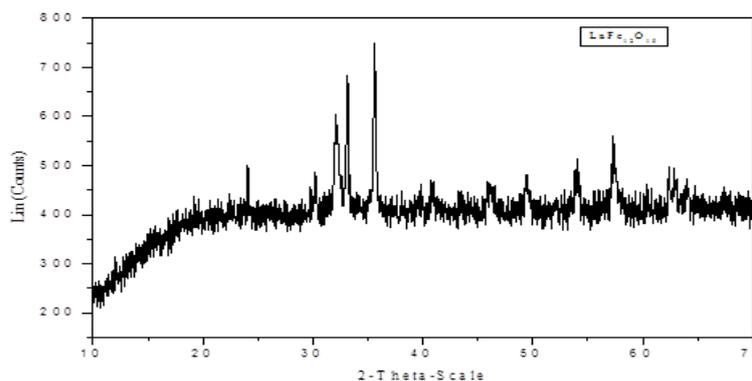


Figure 1: XRD Spectra of Lanthanum ferrite.

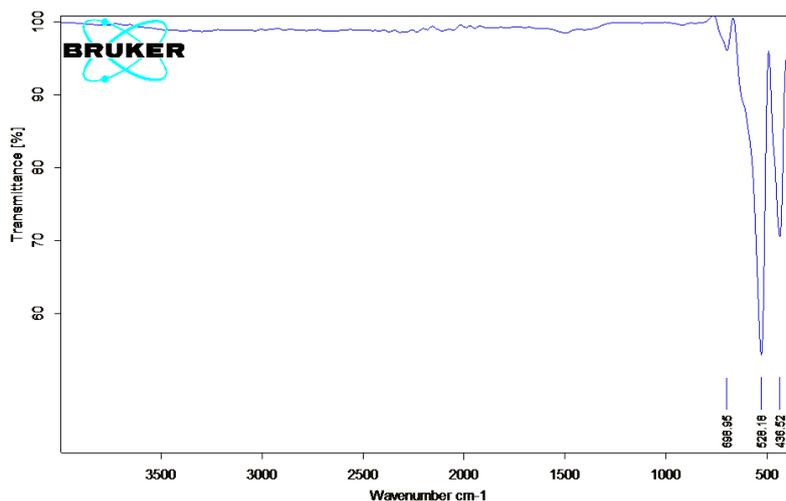
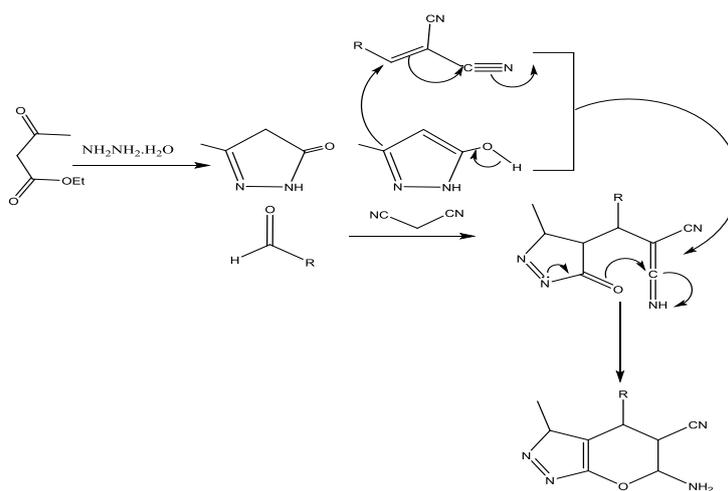


Figure 2: IR spectra for Lanthanum ferrite.



Reaction conditions: Stoichiometric ratio of ethyl acetoacetate, hydrazine hydrate, aldehyde, and malononitrile were refluxed in water

Figure 3: Possible mechanism for the synthesis of derivative of pyranopyrazoles.

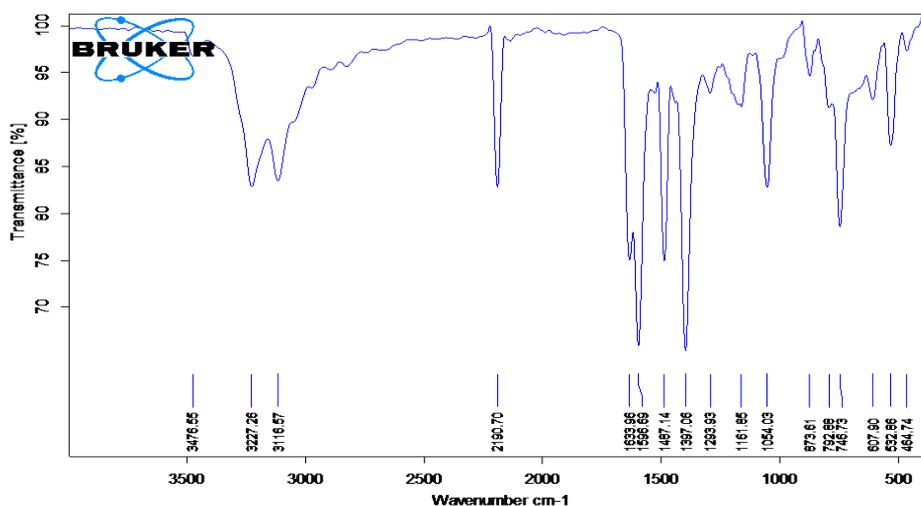


Figure 4: FTIR of 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile.

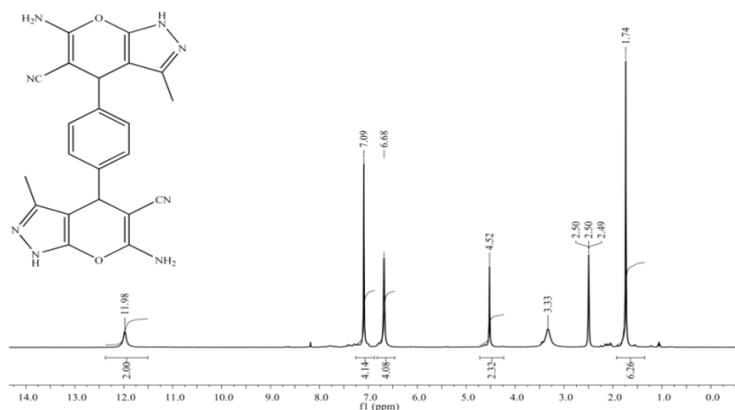


Figure 5: $^1\text{H-NMR}$ of 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile.

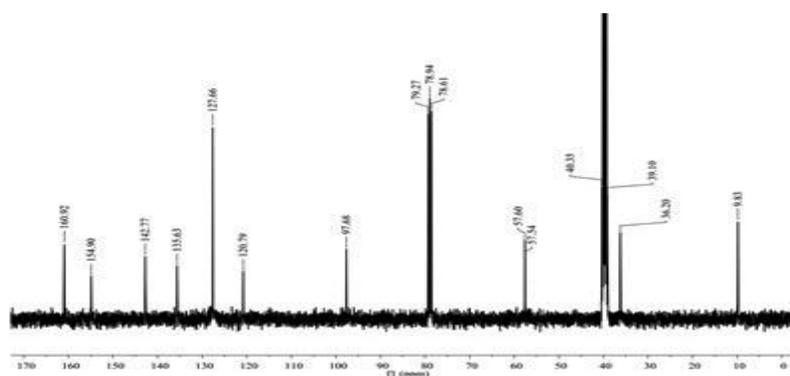


Figure 6: $^{13}\text{C-NMR}$ of 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile.

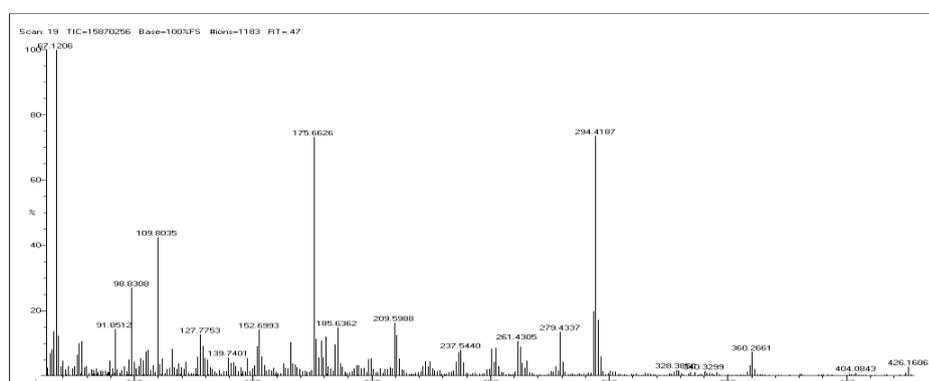


Figure 7: Mass spectra of 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile.

CONCLUSION

The pyranopyrazole derivative 6-amino-7-(4-(6-amino-5-cyano-2,4-dihydro-3-methylpyrano[2,3-c]pyrazol-4-yl)phenyl)-3-methyl-2,7-dihydro-3-methylpyrano[3,2-c]pyrazole-5-carbonitrile was synthesised by a reaction of aryl aldehyde, ethyl acetoacetate, malononitrile and hydrazine hydrate in presence of lanthanum ferrite as a reusable and heterogeneous catalyst. This catalyst is easily

separable and reused without any significant loss of catalytic activity after three runs. The crude product obtained was filtered and recrystallized using chloroform. Purity of the product is checked by melting point and TLC. The structure of synthesised compound is confirmed by FT-IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and mass spectral data. Small amount of catalyst is sufficient to complete the reaction without any side product.

Multicomponent reaction are having great deal of interest because of their greenness, atom economy, environmentally benign conditions, short reaction time, excellent product yield and simple experimental procedure.

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