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ONE POT SYNTHESIS OF 4H-PYRANO [2, 3,-C] PYRAZOLE USING Ni-FERRITE NANOPARTICLES.

Vijay V. Dabholkar*, Swapnil K. Kurade, Keshav S. Badhe.

Organic Research Laboratory, Department of Chemistry,
Guru Nanak college of Arts, Science& Commerce, Sion (E), Mumbai-400 020.
E-mail: vijaydabholkar@gmail.com
swapnilkrd@gmail.com

Abstract
An efficient $NiFe_2O_4$ heterogeneous basic nanocatalyst catalyzed one-pot four component synthesis of '4H-pyrano[2,3,-c]pyrazole' using substituted aromatic aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate at room temperature. Particularly valuable feature of this method includes shorter reaction time, low catalyst loading, use of recyclable heterogeneous $NiFe_2O_4$ catalyst, straightforward procedure and synthesis of product in excellent yield is reported. It combines successfully the synergistic effect of green chemistry with nanocatalysis.

Keywords
Nanocatalyst, One-pot synthesis, Malononitrile, Pyranopyrazole.

1. Introduction

Multicomponent reaction is process in which three or more reactants assembled in single step which covers all portions of reactants to produce product. These reactions are effective in building highly functionalized small organic molecule and complex heterocyclic with high selectivity [I]. In recent years MCR becomes as an important tool in synthetic chemistry because of their high atom economy, energy efficiency, lower cost and simple purification technique. Therefore nowadays, MCR process has become an integral part of pharmaceutical chemistry as well as discovery of new life saving drugs [II]. Hence the development of novel and effective MCR protocols for synthesis of heterocyclic compound has attracted significant interest from heterogeneous catalyst, pharmaceutical group and scientific community across the world [III].

Heterogeneous catalyst always superior to their homogeneous counterpart in view of various aspects such as operational simplicity, high selectivity, reusability, recyclability and environmental compability. In general catalytic property of metal nanoparticle are a function of their size, crystal lattice parameter. The development of new catalyst in nanorange has emerged as a fertile field for innovation and research. Therefore, nanocatalyst is gaining significant attention and becomes a more potential area for synthesis of highly functionalized

pharmaceutically important heterocyclic compound with lower amounts of inexpensive nanocatalyst [IV].

Owning to unique and novel properties like reusability, ability to generate clean product, high surface area and non corrosiveness, recently $NiFe_2O_4$ nano heterogeneous base catalyst is applied as powerful catalyst for several organic transformation these facts encouraged us to use $NiFe_2O_4$ nanocatalyst for the efficient and green synthesis of pyranopyrazoles.

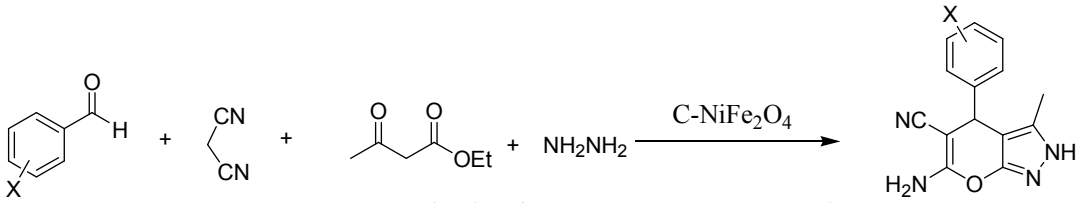
Pyranopyrazoles are very important moiety of organic compound due to their biomedical and pharmaceutical application [V]. In addition to their known herbicidal, fungicidal and bactericidal ability they also exhibit analgesic, anti-inflammatory activity and hypoglycemic agents [VI-VIII]. Furthermore 4H-pyrano[2,3-c]pyrazoles derivative possess biological activities such as insecticidal, antitumor and anticancer properties [IX,X].

On account of these application synthesis of these compound has become an interesting area in synthetic organic chemistry. 6-aminopyrano[2.3-c]pyrazoles were first synthesized by the reaction between 3-methyl-5-pyrazolones with tetracynoethylene [XI], synthesis of these compound from arylidene malononitriles and 3-methyl-5-pyrazolones or 4-arylidene-3-methyl-5-pyrazolones and malononitrile and by the three component condensation of aromatic aldehyde, malononitrile and 3-methyl-5-pyrazolones [XII-XIV]. Sheshtopalov and co workers have developed a chemical [XV] and electrochemical method [XVI] for synthesis of pyranopyrazole via three component condensation of N-methylpiperidone, pyrazoline-5-one and malononitrile. Nonrecyclable catalyst triethylbenzylammonium chloride (TEBA) was used by Shi et al. [XVII] which required longer reaction time. P-dodecylbenzenesulfonic acid (DBSA) catalyzed three components synthesis of pyranozoles also reported .[XVIII] Four component reaction were carried by various researcher using different protocols such as Non-recoverable molecular iodine [XIX], heteropolyacids [XX], use of toxic base such as piperidine [XXI], alumina [XXII] and use of additional microwave or ultrasound irradiation [XXIII,XXIV].

Although reported procedure are effective but many of the existing methodologies suffer from several drawbacks such as longer reaction time, higher temperature, use of toxic bases, tedious process in ionic liquid mediated synthesis, environmentally toxic and expensive catalyst, lack of recyclability, use of microwave oven or sonicator may not be suitable for large scale synthesis .Therefore, recognizing the development of a clean, green and efficient procedures in present work ,we demonstrated $NiFe_2O_4$ nanoparticles as an efficient, green, reusable heterogeneous basic catalyst for scalable synthesis of 4H-pyrano[2,3,-c]pyrazole by four component reaction.

2. Results and Discussion

The reaction between aromatic aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate was chosen as model reaction (Scheme1) for optimization various parameters. Initially, the reaction carried out at room temperature without catalyst, a mixture of product was obtained and reaction was not selective. In order to study the reaction and selectivity, we individually studied the constituent reaction. When the reaction of benzaldehyde and hydrazine hydrate carried out at room temperature without catalyst leads to formation of N,N'-Dibenzylidiene-hydrazine. Similarly, the reaction of ethyl acetoacetate and hydrazine hydrate at room temperature without any catalyst to form pyrazoline. So that, when Equimolar mixture of benzaldehyde, hydrazine hydrate and Ethyl acetoacetate stirred at room temperature, a mixture of product obtained.



Scheme 1: Synthesis of 4H-pyrano[2,3-c]pyrazole

On account of these observation, the following strategy was used to run the reaction. It was noted that catalyst play an important role in reaction of bezaldehyde with malonitrile affords formation of arylidene malonitrile. In other vessel an equimolar mixture of ethyl acetoacetate and hydrazine hydrate was taken which gave pyrazoline rapidly into same vessel when arylidene malonitrile was added followed by C-$NiFe_2O_4$ catalyst which gave 4H-pyrano[2,3-c]pyrazole.

Also the effect of several solvent such as H_2O, Ethanol, Methanol, DMF, DMSO reported in (Table 1) are studied. Initially reaction was carried out under solvent free condition gave low yield of product, which indicate that solvent affect the efficiency of reaction.

The reaction in the protic and aprotic organic solvent had satisfying performance. Hence, in next step we used equivalence of ethanol and DMF solvent system. We were pleased to see that the reaction proceeds smoothly in ethanol:DMF (1:1) solvent system with 80 % yield .

Table 1: Synthesis of 4H-pyrano[2,3-c]pyrazole under different solvent systems at room temperature

Entry	Solvent	Yield of product (%)	Time (min)
1	*H_2O*	*40*	*120*
2	EtOH	*75*	*45*
3	MeOH	*71*	*50*
4	DMF	*70*	*48*
5	EtOH: DMF(1:1)	*80*	*40*
6	EtOH: DMF(2:1)	*70*	*46*
7	EtOH: DMF(1:2)	*74*	*45*
8	DMSO	*62*	*90*
9	Without solvent	*20*	*240*

Reaction conditions: Benzaldehyde(3mmol),Malononitrile(3mmol), Ethyl acetoacetate(3mmol), Hydrazine Hydrate(3mmole) **,** C-$NiFe_2O_4$ (0.03g),ambient temperature (29°C).

In addition to the above, the effect of catalyst concentration was also studied shown in (Table 2). Which indicated that 0.03g of the C-$NiFe_2O_4$ nanocatalyst was sufficient to catalyzed the reaction and increase the quantity of catalyst beyond this did not increase the yield.

Table 2: Effect of different quantity of catalyst on reaction.

Entry	Catalyst quantity (g)	Yield of product (%)
1	0.01	43
2	0.02	60
3	0.03	80
4	0.04	80
5	0.05	80

Reaction conditions: Benzaldehyde(3mmol),Malononitrile (3mmol), Ethyl acetoacetate(3mmol), Hydrazine Hydrate(3mmole) **,** EtOH: DMF(1:1) (5ml), ambient temperature (29°C).

As a heterogeneous catalyst it's reusability is major concern. The reusability and recovery studied using this reaction with benzaldehyde. The $NiFe_2O_4$ nanocatalyst can be recovered from reaction mixture simply by filtration. The catalyst can be recycled several times without loss of it's catalytic activity (Table 3)

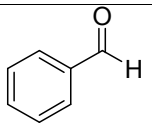
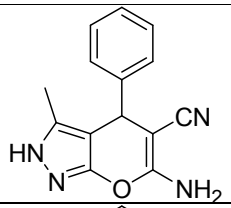
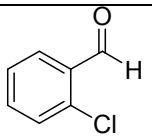
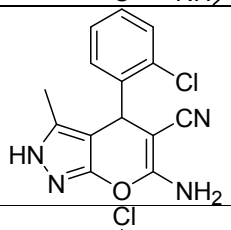
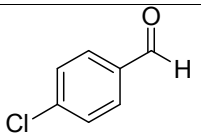
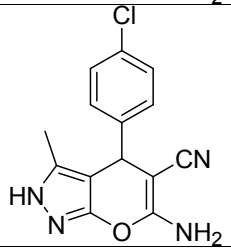
Table 3: Reusability of $NiFe_2O_4$ catalyst

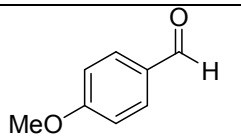
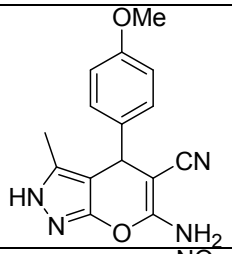
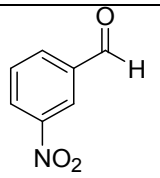
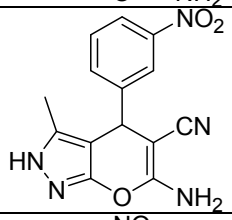
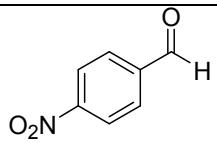
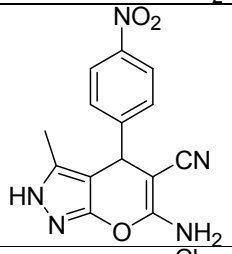
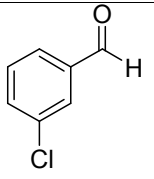
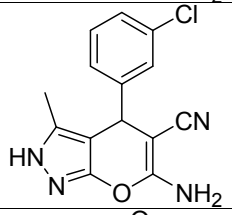
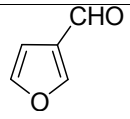
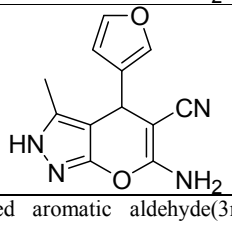
Run	Yield of product (%)
1	78
2	78
3	77
4	76

Reaction conditions: Benzaldehyde(3mmol), Malononitrile (3mmol), Ethyl acetoacetate(3mmol), Hydrazine Hydrate(3mmole) **,** EtOH: DMF(1:1) solvent (5ml), C-$NiFe_2O_4$ (0.03g),ambient temperature (29°C).

After optimizing the reaction conditions, we applied this catalyst for the synthesis of substituted pyranopyarzoles by using substituted aromatic aldehyde with electron donating and electron withdrawing group. To check the feasibility of this protocol whose results are tabulated in (Table 4). Almost, all the employed aldehyde resulted in good to excellent yield of the corresponding product. From (Table 4) revealed that aldehyde having electron withdrawing substituent reacted faster and gave better yield of the product as compared to the aldehyde having electron donating group.

Table 4: Synthesis of substituted 4H-pyrano [2, 3-c]pyrazole using $NiFe_2O_4$ nano particles.

Sr No	Substituted benzaldehyde	Product	Yield (%)	Time (min)	M.P. (^{0}C)	M.P.(^{0}C)
					Found	Reported
1			*80*	40	244-246	243-245[XXV]
2			80	42	243-245	244-246[XXV]
3			79	42	234-236	233-235[XXV]

4			78	50	212-214	211-212[XXV]
5			82	35	233-235	235-236[XXVI]
6			79	38	250-252	249-250[XXVI]
7			78	45	157-159	157-158[XXVII]
8			80	60	241-243	240-244[XXVIII]

Reaction conditions: Substituted aromatic aldehyde(3mmol), Malononitrile (3mmol), Ethyl acetoacetate(3mmol), Hydrazine Hydrate(3mmole) **,** EtOH: DMF(1:1) solvent (5ml), C-$NiFe_2O_4$ (0.03g),ambient temperature (29°C).

3. Characterisation of Catalyst

The structural characterization of $NiFe_2O_4$ nanoparticles were done by X-ray Diffraction using CuKα radiation (λ = 1.54059 Å) at 40 kV and 15 mA shown in Fig 1.

The XRD patterns show the formation of single phase inverse cubic spinal nickel ferrite (the XRD peaks were compared to the standard PDF card number 742081 for inverse cubic nickel ferrite)

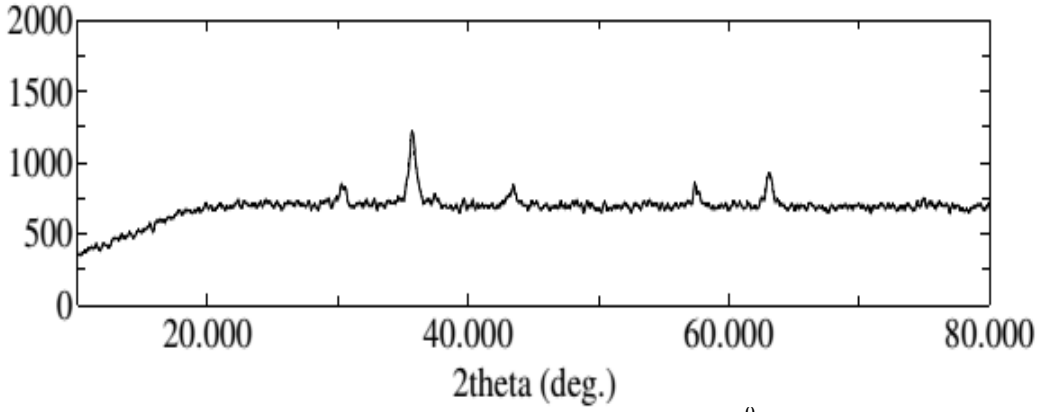


Fig 1. XRD patterns for $NiFe_2O_4$ nanoparticles sintered at 500^0C

Morphological analysis

The morphology of $NiFe_2O_4$ nanoparticles were studied using SEM shown in Fig 2. Most of the particles are found to be spherical in shape.

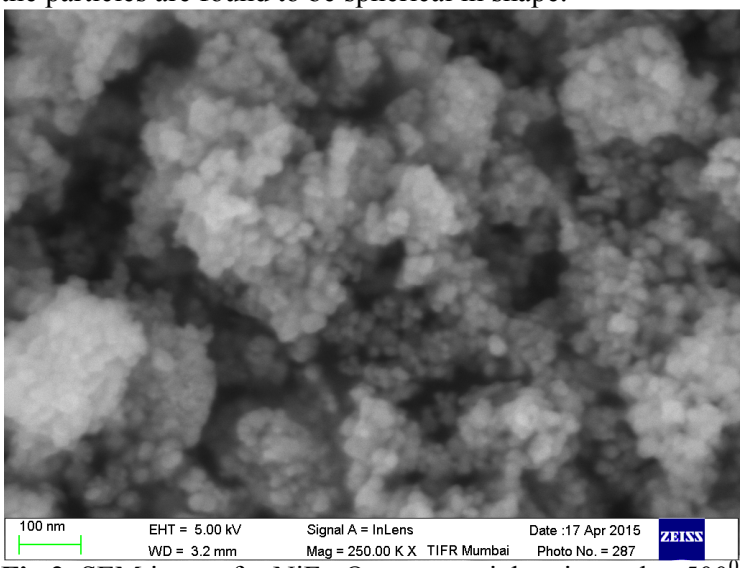


Fig.2. SEM image for $NiFe_2O_4$ nanoparticles sintered at 500^0C.

4. Experimental section

4.1.Chemicals and Analysis.

All chemicals were purchased from S.D.Fine Ltd. Mumbai, India and used without furher purification.Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. FT-IR Spectra were recorded on Bruker Spectrometer in the region of 400-4000cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). Powder X-ray diffraction pattern were collected with monochromatic Cu Kα radiation (λ = 1.54059 Å) at 40 kV and 15 mA using Shimadzu 7000S diffractometer.

4.2. General procedure for synthesis of $NiFe_2O_4$

$NiFe_2O_4$ nanoparticles were synthesized by co-precipitation method[XXIX]. Nickel nitrate, ferric nitrate and sodium hydroxide were used as starting materials. Aqueous solutions of ferric nitrate and nickel nitrate were prepared in de-ionized water, NaOH solution was then added to it slowly and stirred continuously using a magnetic stirrer until a pH reached to 10-11. This solution was then heated at 80^0C for an hour. The obtained precipitate was thoroughly washed with distilled water till pH of filtrate become 7. It was kept overnight for drying. The obtained powder was grounded and calcinied at temperatures 500^0C for 3 h.

4.3. General procedure for synthesis of 4H-pyrano[2,3-c]pyrazole

In 100ml round bottom flask, Ethyl acetoacetate (3mmol) and hydrazine hydrate (3mmol) were taken. To this flask, a mixture of aryl aldehyde (3mmol) and malononitrile (3mmol) in Ethanol:DMF (1:1) (5 ml) followed by catalyst C- $NiFe_2O_4$ (0.03g)stirred at room temperature for appropriate time . The reaction was monitored by TLC. After completion of reaction, reaction mixture heated to evaporate ethanol and reaction mixture filtered. The filtrate was poured in ice-cold water. The precipitate that obtained was filtered off and purified by recrystalliation from hot ethanol. Purity of product checked by using TLC, M.P. and characterized by using ^{1}H-NMR and ^{13}C-NMR.

5. Spectral Data

6-amino-3-methyl-4-phenyl-2,4-dihyropyrano[2,3-c]pyrazole-5-carbonitrile(Sr.No:1): Colorless solid; **IR (KBr) ν_{max}, cm^{-1}:** 3368 (NH_2), 3307 (N-H), 3170 (Ar-H), 2197 (C≡N), 1648 (C=N), 1610 (C=C).**^{1}H NMR spectrum (DMSO, 500 MHz):** δppm = 1.789 (s, 3H, C*H*$_3$), 4.599 (s, 1H, C*H*), 6.864 (s, 2H, N*H*$_2$), 7.169-7.962 (m, 5H, Ar-*H*), 12.094 (s, 1H, N*H*) **^{13}C NMR (500MHz,DMSO-d6)**:δppm=36.370(CH_3),57.329(CH),120.902(CN),126.845-154.885(2xC=C,ArC), 160.987 (C=N)**. MS: *m/z* :** 252.1(M^+).

6-amino-4-(4-chloroyphenyl)-3-methyl-2,4-dihyropyrano[2,3-c]pyrazole-5-carbonitrile(Sr.No:6) : Yellow solid, **IR (KBr) ν_{max}, cm^{-1}:** 3412 (NH_2), 3313 (N-H), 3175(Ar-H), 2185 (C≡N), 1643 (C=N), 1600 (C=C).**^{1}H NMR spectrum (DMSO, 500 MHz):** δppm = 1.800 (s, 3H, -C*H*$_3$), 4.642 (s, 1H, C*H*), 6.926(s, 2H, N*H*$_2$), 7.210-7.393 (m, 4H, Ar-*H*),12.136 (s, 1H, N-*H*).**^{13}CNMR (500MHz, DMSO-d$_6$):**δppm=35.991 (CH_3), 57.203 (CH), 121.092 (CN),128.900-155.138(2xC=C,ArC), 161.334 (C=N)**. MS: m/z:** 286 (M^+).

6. Conclusion

In conclusion, we have demonstrated simple and efficient methodology for the synthesis of 4H-pyrano[2, 3-c] pyrazole in one-pot procedure by using $NiFe_2O_4$ nanocatalyst in good to excellent yield. Easy work-up, purification of compound by non-chromatographic technique, the reusability of the catalyst, low catalyst loading and novelty are the key advantages of this protocol.

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