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RESEARCH ARTICLE

Nano Copper Ferrite Catalysed Improved Procedure for One-Pot Synthesis of Poly Substituted Pyridine Derivatives

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Abstract: The studies on application of magnetically separable substituted nano ferrites towards the multicomponent one-pot synthesis of heterocyclic compounds were thoroughly investigated. The present study gives an efficient method for the one-pot three-component synthesis of poly substituted pyridine derivatives by the cyclo-condensation of aromatic aldehyde, malononitrile and substituted phenols in the presence of magnetically recoverable nano copper ferrite catalyst. This method involves improved advantages like low percentage of catalyst used, lesser reaction times, higher yields, magnetic recoverability and reuse of the catalyst, which makes it an environmentally benign process.

Keywords: Nano copper-ferrite, Magnetically separable catalyst, One-pot multi-component synthesis, Poly substituted pyridines

Introduction

Multi-component reactions [MCRs] play a significant role in the organic synthesis particularly in the synthesis of medicinally potent heterocyclic compounds. It involves a simple workup procedure for the synthesis of medicinally privileged scaffolds by the combination of two or more components in a single step process. Thereby it offers a great advantage over convergent, combinatorial and multistep synthesis[1-3].

The poly substituted pyridine moiety has been identified as key constituent in many naturally occurring and synthetic biological active pharmaceuticals[4]. Among these pyridine derivatives of 2-amino-pyridine-3,5-dicarbonitrile skeleton have great importance as medicinally active compounds like antiprion[5], antibacterial[6], anti-biofilm[6], anti-infective[6], anticancer[7] and anti-hepatitis-B[8]. Penta-substituted pyridine moiety is a medicinally privileged scaffold useful in the potassium channel opening for the treatment of urinary incontinence[9] and the treatment for Creutzfeldt-Jakob disease, Parkinson disease, Hypoxia, Asthma, kidney disease and Epilepsy[10-12]. The importance of this class of compounds can be understood by the number of patents filed in recent years[6-9].

Due to vast range of biologically active poly substituted pyridine frameworks, they attract much attention in their synthesis. A number of procedures were carried out for the synthesis of poly-substituted pyridine derivatives using various synthetic procedures such as Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadiene with 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-one with different types of acetylenic compounds[13], [4+2] cycloaddition of oximinosulphonates[14], Vilsmeier-Haack reaction of α-hydroxy ketene dithioacetals[15], Ruthenium-catalysed cyclo-isomerisation of 3-azadienynes[16] and 6 π-azaelectrocyclization of azatrienes[17] which limit with conventional multi-step process, low yield and challenging work up procedures.

Afterward a first convenient and interesting synthetic methodology reported for the one-pot synthesis of poly-substituted pyridine derivatives by the cyclocondensation of aromatic aldehyde, malononitrile and thiophenol using Et_3N or 1, 4-diazabicyclo[2.2.2]-octane [DABCO] as catalyst[18]. Then a few MCR methods have been reported for the one-pot synthesis of poly substituted pyridine derivatives by the three component condensation of aromatic aldehyde, malononitrile and thiophenol in presence of various catalysts like K_2CO_3 under reflux[19], Ionic liquid 1-*n*-butyl-3-methylimidazolium hydroxide [bmIm] OH[20], Nano crystalline MgO[21], Ammonium hydroxide[22],TBAH [tetra butyl ammonium hydroxide] and Piperdine[23]. The above reported methods have their own importance and merits. But these methods limit in their longer reaction times, low yields, use of toxic chemicals and non-recoverability of the catalyst. Hence there is a necessity to develop newer, greener, effective and environmental friendly methods of synthesis of poly substituted pyridine derivatives. It is further observed that in the above reported methods[18-23] thiophenol has been used as a reactant but substituted phenolic derivatives such as 2-amino-6-phenoxy-pyridine-3, 5-dicarbonitrile derivatives have not been reported.

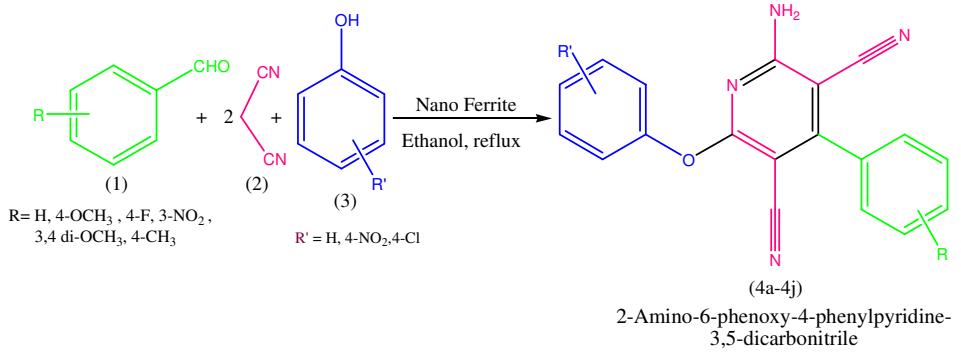
Nano copper ferrite has earlier been used as magnetically separable catalyst for several organic synthetic reactions such as asymmetric hydrosilylation of ketones[24], synthesis of diaryl or aryl alkyl sulfides via cross coupling process under ligand free conditions[25], synthesis of substituted benzoxazoles via Ullmann-type coupling under ligand free conditions[26], cross- coupling of aryl halides with diphenyl diselenide[27], green one-pot three component synthesis of spirooxindoles[28], multicomponent synthesis of 1,4-di substituted 1,2,3-triazoles in tap water[29] and synthesis 1,4 dihydro pyridines involving aromatic aldehyde, ethylacetoacetate and ammonium acetate[30].

As a part of our ongoing research towards the synthesis of biologically active heterocyclic compounds using magnetically separable nano catalysts[31], keeping environmental friendly methods in mind, here we are reporting an efficient improved procedure for one-pot multi-component synthesis of some new poly substituted pyridine derivatives by condensation of aromatic aldehyde, malononitrile and substituted phenols using nano copper ferrite as a catalyst (Scheme 1). This methodology involves high catalytic activity of the catalyst, its magnetic recoverability and reuse for five cycles without any noticeable loss of its catalytic activity.

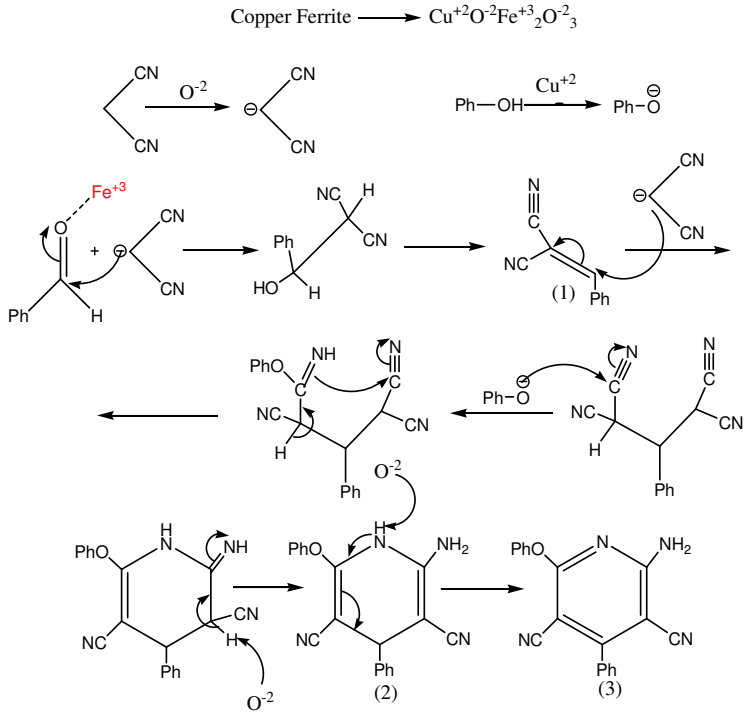
Plausible mechanism for the scheme of the reaction

A plausible mechanism had been proposed for the catalytic activity of the reaction. It can be predicted from the mechanism (Scheme 2) that it follows a base catalyzed pathway. The reaction is initiated by ferrite-mediated Knovenagel condensation of aldehyde and malononitrile, generating cinnamonitrile(1), which reacts with another molecule of malononitrile producing dihydropyridine intermediate (2). Then there are two possibilities to oxidize dihydropyridine to pyridines (3), one is aerobic oxidation of dihydropyridine, which plays a minor role limited by the solubility of oxygen in reaction solvent [ethanol] and the other is an efficient path,

which involves hydrogen transfer from the dihydropyridine intermediate (2) to the Knovenagel intermediate (1). This step causes the involvement of an extra equivalent of aldehyde and malononitrile to get quick good yield of the product[19,22,23].



Scheme 1. Synthesis of substituted pyridine derivatives using aromatic aldehyde, malononitrile and substituted phenols using nano copper ferrite as catalyst



Scheme 2. Plausible mechanism for the formation of pyridine derivatives

Experimental

All chemicals were purchased from commercial sources and liquid aromatic aldehydes and liquid aromatic phenols are purified by distillation prior to use. XRD spectra were recorded on PANalytical-XPert pro diffractometer and the average crystallite size was determined from the corresponding XRD data. The microstructural morphology was studied with a Scanning Electron Microscope (SEM) model JEOL–JSM 6610 LV. FTIR spectra were recorded

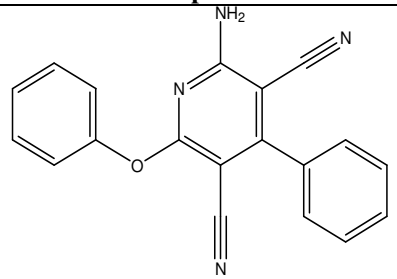
on BRUKER ALPHA FT-IR with Opus 6.1 version. Magnetization M [H] measurements were made using a commercial vibrating sample magnetometer (VSM) model BHV-50 of Riken Denshi Co. Ltd. Japan. Specific surface area (SBET) of samples was determined by BET surface area analyzer (Nova 2000 series, Quanta chrome Instruments, UK). ^{1}H NMR spectra were recorded on the Bruker-Avance 300-MHz spectrometer in $CDCl_3$. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. The mass spectrum was recorded using a Perkin-Elmer PE SCIEX-API 2000, equipped with ESI source used online with a HPLC system after the ultraviolet (UV) detector. Silica gel used for column chromatography was purchased from ACME Chemical Company. All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F_{254} (Merck) and spots were visualized with UV light.

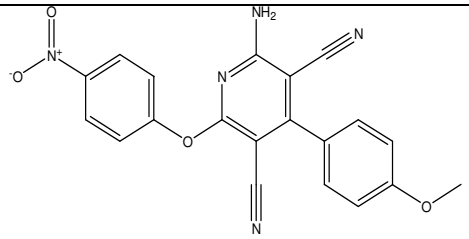
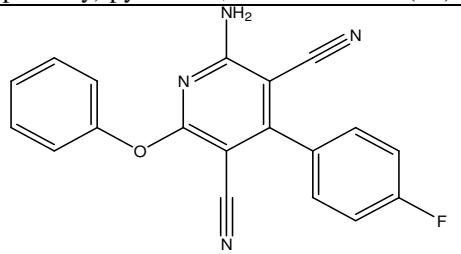
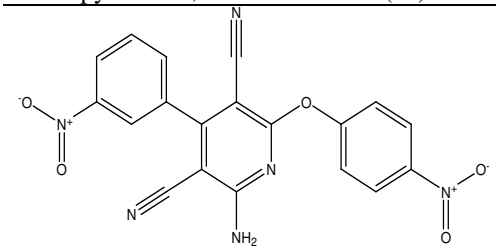
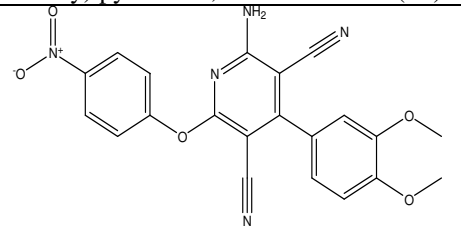
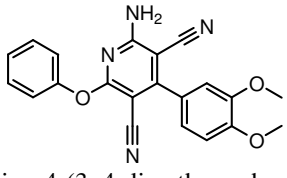
Catalyst preparation and characterization

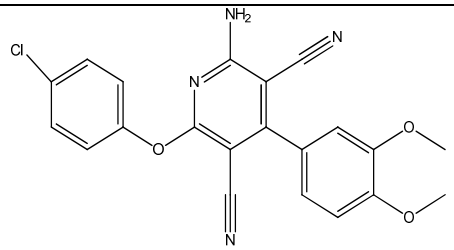
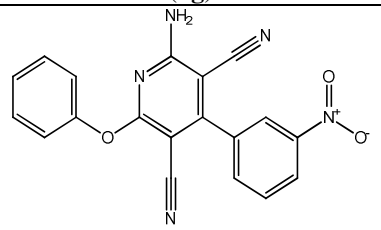
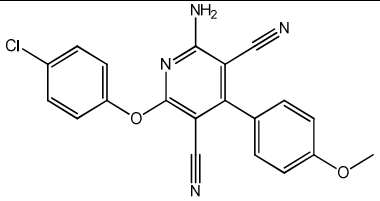
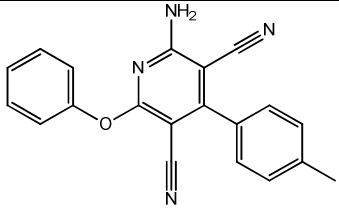
Magnetic spinel nano copper ferrite catalyst with composition $CuFe_2O_4$ was chosen for this study. For the preparation of the catalyst, aqueous solutions of stoichiometric amounts of copper nitrate along with ferric citrate were reacted with citric acid in 1:1 molar ratio. pH of the solution was increased to 7 by addition of ammonia to complete the reaction and ethanediol was added. The solution was evaporated very slowly over a period of ten to twelve hours to dryness. Viscosity and colour changed as the solution turned into a puffy and porous dry gel. As soon as the solvent removal completed, dried precursor underwent a self-ignition reaction to form a very fine powder known as as-synthesized powder. The as synthesized powder, thus obtained was calcined in a muffle furnace at 500 ^oC for 2 hours to remove the residual carbon and furnace cooled. The characteristics of the catalyst were reported by us[31] and the copper ferrite was obtained in nano size (~30 nm), crystalline in nature and having a large surface area of 127 m^2/g.

General procedure for the synthesis of poly substituted pyridine derivatives

The one-pot synthesis of poly substituted pyridine derivatives was carried out in a 250 mL round bottomed flask and fixed with a reflux condenser in an oil bath with temperature control and refluxed. About 500 mg of the catalyst was taken and activated at 500 ^oC for 2 h and cooled to room temperature before the experiment. Aromatic aldehyde (5 mmol) and malononitrile (10 mmol) were mixed together along with the catalyst and 5 mL of ethanol then the contents are stirred for 15 min at 50 ^oC. Afterwards the substituted phenol (5 mmol) was added to the reaction mixture and refluxed. The completion of the reaction was monitored by TLC (*n*-hexane: ethyl acetate 2:1) and the products were isolated by removing the catalyst magnetically from the reaction mixture. All the products were identified by FTIR, ^{1}H NMR and mass spectra of representative compounds and compared.

Compound	Spectral data
 2-Amino-4-(phenyl)-6-phenoxy pyridine-3, 5-dicarbonitrile (**4a**)	Yellow solid; IR (KBr, cm^{-1}) : 3368 (N-H, str), 3077 (Ar-CH, str), 2223 (C-N, str), 1642 (C=C, str), 1591 (C=N, str), 1491 (C-O-C, str) cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) δ=7.26 (s(2H),NH_2), 7.92–7.90 (m(2H),Ar-H), 7.87 (s(1H),Ar-H),7.63 (m(2H),Ar-H), 7.56-7.54 (m(2H),Ar-H), 7.782 (m(1H), Ar-H); Mass: *m/z* 313 (M^++1); $C_{19}H_{12}N_4O$.

 2-Amino-4-(4-methoxyphenyl)-6-(4-nitro-phenoxy) pyridine-3, 5-dicarbonitrile (**4b**)	Yellow solid; IR (KBr, cm^{-1}) : 3371 (N-H, str), 3028 (Ar-CH, str), 2222 (C-N, str), 1572 (C=C, str), 1454 (C=N, str), 1446 (C-O-C, str), cm^{-1}; ^1H NMR ($CDCl_3$,ppm) δ= 7.26 (s(2H),NH_2), 8.17-8.16 (m(2H),Ar-H), 7.92-7.90 (m(2H),Ar-H), 7.023 (m(2H),Ar-H), 6.91-6.90 (m(2H), Ar-H), 3.918 (s(3H), CH_3); Mass: *m/z* 388 (M^++1); $C_{20}H_{13}N_5O_4$.
 2-Amino-4-(4-fluorophenyl)-6-phenoxy pyridine-3, 5- dicarbonitrile (**4c**)	Yellow solid; IR (KBr, cm^{-1}): 3375 (N-H, str), 3042 (Ar-CH, str), 2230 (C-N, str), 1595 (C=C, str), 1509 (C=N, str) 1338 (C-O-C, str) cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ= 7.74(s(2H),NH_2), 7.963(m(2H), Ar-H), 7.26-7.22(m(5H), Ar-H), 7.745(m(2H), Ar-H); Mass: *m/z* 331 (M^++1);$C_{19}H_{11}N_4OF$.
 2-Amino-4-(3-nitrophenyl)-6-(4-nitro-phenoxy) pyridine-3, 5-dicarbonitrile (**4d**)	Yellow solid; IR (KBr, cm^{-1}) : 3371(N-H, str), 3107 (Ar-CH, str), 2226 (C-N, str), 1612 (C=C, str), 1528 (C=N, str), 1383 (C-O-C, str) cm^{-1}; ^1H NMR ($CDCl_3$,ppm) : δ= 7.26(s(2H),NH_2),8.662(s(1H),Ar-H), 8.474-8.32(m(3H),Ar-H),7.8-7.804 (m(4H),Ar-H);Mass: *m/z* 403 (M^++1); $C_{19}H_{10}N_6O_5$
 2-Amino-4-(3, 4-dimethoxyphenyl)-6-(4-nitrophenoxy) pyridine-3, 5-dicarbonitrile (**4e**)	Yellow solid; IR (KBr, cm^{-1}) : 3374 (N-H, str), 3089 (Ar-CH, str), 2222 (C-N, str), 1600 (C=C, str), 1508 (C=N, str), 1339 (C-O-C, str), cm^{-1}; ^1H NMR ($CDCl_3$, ppm) : δ= 3.98 (s(3H), CH_3), 3.94 (s(3H), CH_3) 7.264 (m(2H),NH_2), 7.6875 (s(4H),Ar-H), 6.96–6.95 (m(2H),Ar-H), 7.26-7.20 (s(1H), Ar-H); Mass: *m/z* 418 (M^++1); $C_{21}H_{15}N_5O_5$
 2-Amino-4-(3, 4-dimethoxyphenyl)-6-phenoxy pyridine-3, 5-dicarbonitrile (**4f**)	Yellow solid; IR (KBr, cm^{-1}) : 3374 (N-H, str), 3027 (Ar-CH, str), 2221 (C-N, str), 1600 (C=C, str), 1508 (C=N, str), 1339 (C-O-C, str) cm^{-1}; ^1H NMR ($CDCl_3$, ppm) δ= 3.98 (s(3H), CH3), 3.94(s(3H),CH_3), 7.264 (s(2H),NH_2), 7.68-7.64(m(2H),Ar-H),7.39-7.37(m(3H), Ar-H) 6.97–6.95 (m(2H),Ar-H),7.26 (s(1H), Ar-H); Mass: *m/z* 373 (M^++1);$C_{21}H_{16}N_4O_3$.

 2-Amino-4-(3, 4-dimethoxyphenyl)-6-(4-chlorophenoxy) pyridine-3, 5-dicarbonitrile (**4g**)	Yellow solid; IR (KBr, cm^{-1}): 3374(N-H, str), 3027 (Ar-CH, str), 2222 (C-N, str), 1600 (C=C, str), 1507 (C=N, str), 1372 (C-O-C, str) cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ= 3.99 (s(3H),CH_3), 3.945 (s(3H),CH_3), 7.264 (s(2H),NH_2), 7.68-7.64 (m(2H),Ar-H), 7.39-7.38 (m(2H),Ar-H), 6.97-6.95 (m(2H),Ar-H), 7.26 (s(1H),Ar-H); Mass: *m/z* 408-406 (M^++1); $C_{21}H_{15}N_4O_3Cl$
 2-Amino-4-(3-nitrophenyl)-6-phenoxy pyridine-3, 5-dicarbonitrile (**4h**)	Yellow solid; IR (KBr, cm^{-1}): 3367(N-H, str), 3032 (Ar-CH, str), 2223 (C-N, str), 1613 (C=C, str), 1514 (C=N, str), 1449 (C-O-C, str) cm^{-1}; ^1H NMR ($CDCl_3$, ppm): δ=7.364 (s(2H),NH_2), 8.68-8.64 (m(2H), Ar-H), 8.39-8.38 (m(2H),Ar-H), 7.97–7.75 (m(5H),Ar-H), 8.702 (s(1H),Ar-H); Mass: *m/z* 358 (M^++1); $C_{19}H_{11}N_5O_3$
 2-Amino-4-(3-methoxyphenyl)-6-(4-chlorophenoxy) pyridine-3, 5-dicarbonitrile(**4i**)	Yellow solid; IR (KBr, cm^{-1}) : 3372(N-H, str), 3027 (Ar-CH, str), 2222 (C-N, str), 1564 (C=C, str), 1448 (C=N, str), 1440 (C-O-C, str), cm^{-1}; ^1H NMR ($CDCl_3$, ppm) δ= 7.96 (s(2H), NH_2), 7.96-7.94 (m(2H), Ar-H), 7.92–7.90 (m(2H),Ar-H), 7.783-7.76 (m(2H),Ar-H), 7.32-7.54 (m(2H),Ar-H), 3.918 (s(3H),CH_3); Mass: *m/z* 377.5 (M^++1); $C_{20}H_{13}N_4O_2Cl$.
 2-Amino-4-(p-tolyl)-6-phenoxy pyridine-3, 5-dicarbonitrile(**4j**)	Yellow solid; IR (KBr, cm^{-1}): 3371 (N-H, str), 3014 (Ar-CH, str), 2231 (C-N, str), 1633 (C=C, str), 1416 (C=N, str), 1379 (C-O-C, str) cm^{-1}; ^1H NMR ($CDCl_3$, ppm) δ= 7.768 (s(2H), NH_2), 8.2–7.90 (m(5H), Ar-H), 7.487 (m(2H),Ar-H),7.463 (m(2H),Ar-H),2.582 (s(3H),CH_3); Mass: *m/z* 327 (M^++1); $C_{20}H_{14}N_4O$.

Results and Discussion

Effect of catalysts on the synthesis of pyridine derivatives

As mentioned in introduction part, several catalysts have been reported for the synthesis of poly substituted pyridine derivatives by the cyclocondensation of aromatic aldehyde, malononitrile and thiophenol in presence of various catalysts have been presented in Table 1. The reaction time, temperature of the reaction and yield of the corresponding product in presence of nano copper ferrite catalyst has been presented in Table 2. It is observed from

the literature that the synthesis of substituted pyridines with substituted phenols in presence of nano copper ferrite has not been reported earlier.

Table 1. Effect of catalysts on the synthesis of pyridine derivatives

S.No.	Catalyst	Time min	Temp, ^{0}C	Yield, %	[Ref.]
1	Nano crystalline MgO	120	50	64	[21]
2	K_2CO_3	60	Reflux	80	[19]
3	Piperidine	180	Reflux	49	[23]
4	TBAH (tetra butyl ammonium hydroxide)	60	R.T.	46	[23]
5	Ionic liquid (1-*n*-butyl-3-methylimidazolium hydroxide) (bmIm)OH	70	R.T.	92	[20]
6	Ammonium hydroxide	360	R.T.	52	[22]

Study of catalytic activity on the synthesis of poly substituted pyridine derivatives

Reaction time, temperature and percentage yield of the products formed when malononitrile reacted with Ph-CHO and Ph-OH in presence of copper ferrite catalyst.

Table 2. Reaction conditions and yields for the synthesis of poly substituted pyridine derivatives using nano copper ferrite catalyst

S. No.	R in R-Ph-CHO	R'in R'-Ph-OH	Time, min	Temp, ^{0}C	Product	Yield, %
1	H	H	45	50	(4a)	95
2	4-OMe	4-NO_2	40	50	(4b)	96
3	4-F	H	45	50	(4c)	90
4	3-NO_2	4-NO_2	55	50	(4d)	88
5	3,4-di (OCH_3)	4-NO_2	50	50	(4e)	90
6	3,4-di (OCH_3)	H	55	50	(4f)	92
7	3,4-di (OCH_3)	4-Cl	45	50	(4g)	96
8	3-NO_2	H	60	50	(4h)	86
9	4-Ome	4-Cl	50	50	(4i)	92
10	4-Me	H	45	50	(4j)	96

Effect of solvent on the synthesis of poly substituted pyridine derivatives

Investigation of reaction medium for the process revealed that solvents played an important role in the reaction under investigation. The results are summarized in Table 3. It was found that polar solvents such as CH_3OH, CH_3CN and C_2H_5OH were much better than non-polar solvents. Trace amounts of yield observed when H_2O was used as solvent, presumably due to the aggregation of the hydrophobic catalyst. Although methanol was effective, low yield was obtained when the catalyst was reused. We therefore selected ethanol as solvent. The effect of solvent was checked by the system (4a).

Table 3. Effect of Solvent on the synthesis of poly substituted pyridine derivatives

S.No.	Solvent	Time, min	Temp, ^{0}C	Product	Yield, %
1	H_2O	80	50	(4a)	Trace
2	CH_3CN	65	50	(4a)	45
3	CH_3OH	50	50	(4a)	75
4	C_2H_5OH	45	50	(4a)	95

Effect of temperature on the synthesis of poly substituted pyridine derivatives

The reaction temperature has a notable effect on the proposed reaction. The reaction was examined for temperature effect in presence of ethanol as solvent at different temperatures ranging from r.t. to 50 ^{o}C. The results are reported in Table 4. It is clear that at lower temperatures, even if the time was increased, only low percentage of yields were obtained. Hence, consequently we chose 50 ^{o}C as the optimal temperature for the reaction.

Table 4. Effect of temperature on the synthesis of poly substituted pyridine derivatives

S.No.	Time, min	Temp, ^{o}C	Product	Yield, %
1	120	R.T.	(4a)	30
2	75	40	(4a)	65
3	45	50	(4a)	95

Recycling of the catalyst

Catalyst reusability is of major concern in heterogeneous catalysis. Catalyst recycling was achieved by fixing the catalyst magnetically at the bottom of the flask with a strong magnet, after which the solution was taken off with a pipette, the solid washed thrice with ethyl acetate and the fresh substrate dissolved in the same solvent was introduced into the flask, allowing the reaction to proceed for the next run. The catalyst was consecutively reused five times without any noticeable loss of its catalytic activity. The catalyst is highly magnetic and the saturation magnetization value is found to be 35.56 emu/g, which is much higher than other reported magnetic catalysts. Therefore, it could be easily and almost completely separated by an external magnet which is of a great advantage for a heterogeneous catalyst.

Conclusion

We have reported an efficient and environmentally benign method for the synthesis of poly substituted pyridine derivatives using nano copper ferrite as catalyst. This method offers several advantages including high yield, short reaction times and ease of separation and recyclability of the catalyst.

Acknowledgement

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