

View Article Online View Journal

RSC Advances

This article can be cited before page numbers have been issued, to do this please use: K. I. Sathiyanarayanan and T. R. Mandlimath, *RSC Adv.*, 2015, DOI: 10.1039/C5RA20812B.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/advances

Journal Name

ROYAL SOCIETY

RSC Advances Accepted Manuscript

ARTICLE

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/



Triveni Rajashekhar Mandlimath and Kulathu I. Sathiyanarayanan*

A simple, facile and efficient route was developed for the synthesis of nano ZnAl₂O₄ using ethanolamine. ZnAl₂O₄ nanoparticles were found to be smaller when calcined at 500 °C than at 700 °C. The synthesized nano ZnAl₂O₄ exhibited a high surface area of 147 m²/g with pore volume $0.2 \text{ cm}^3/\text{g}$. ZnAl₂O₄ nanoparticles were found to be spherical in shape with size ranging from 3 - 7 nm. For the first time, we explored the catalytic activity of nano $ZnAl_2O_4$ for the synthesis of propargylamines by A³ coupling of aromatic aldehydes, piperidine and phenyl acetylene. High yields were achieved without any side product. We developed Cu/ nano ZnAl2O4 and utilized it for imidazo[1,2-a]pyridines synthesis by three component coupling of aromatic aldehydes, 2-aminopyridine and phenylacetylene under N2 atmosphere. We achieved good yields, and both nano ZnAl₂O₄ and Cu/ nano ZnAl₂O₄ were recycled for five times successfully. Both the protocols were simple, one pot, solvent-free, economical and involved no additive. They could be an alternative to the existing protocols which involve homogeneous and expensive noble metal catalysts for these reactions.

INTRODUCTION

Multicomponent coupling reactions (MCRs) are the potential tool to synthesize diverse complex organic scaffolds from simple organic moieties via one-pot process. These MCRs have gained extensive interest of researchers because of their uniqueness in yielding high atom economy and often high selectivity. In recent times, intense investigation for the development of eco-friendly solvent free MCRs have been a great concern in order to reduce environmental pollution caused by hazardous organic solvents. Among the MCRs, A³ coupling of (i) aldehyde, alkyne, and amine and (ii) aldehyde, alkyne, and 2-aminopyridine *via* activation of a terminal alkyne C-H bond have been great importance in recent years. The resulting propargylamines and imidazo[1,2-a]pyridines are nitrogen containing compounds with diverse applications:

Propargylamines are the important key components of various natural products,¹ versatile precursors for the synthesis of quinolines,^{2a} indolizines,^{2b}oxazoles,^{2c} pyrroles,2d and pyrrolidines,^{2e} and also potential building blocks for the synthesis of the therapeutic drug molecules such as isosteres, ^{3a} allylamines, ^{3b} β-lactams.^{3c} conformationally restricted peptides, and oxotremorine analogs.^{3d} Recently propargylamine derivatives have attracted attention due to their excellent pharmacological activity. They are strong neuroprotective^{4a, 4b} and anti-apoptotic agents^{4c}. Propargylamine derivative rasagiline is used for treating early Parkinson's disease⁵. Whereas, imidazo[1,2-a]pyridines are the versatile scaffolds mainly occurred in wide range of bioactive molecules and also known for their antiviral,^{6a} antiinflammatory,^{6b,6c} analgesic,^{6c} antipyretic,^{6c} antiulcer^{6d} and antibacterial properties.^{6e} Commercial drugs such as Alpidem

^{a.} Address here.

^{b.} Address here.

^{c.} Address here.

⁺ Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

ARTICLE

Published on 22 December 2015. Downloaded by UNIVERSITY OF NEBRASKA on 29/12/2015 10:29:10.

(anxiolytic agent),^{7a} Zolpidem (insomnia),^{7b}Olprinone (for the treatment of acute Heart failure),^{7c} and Minodronic acid (for the treatment ofosteoporosis)^{7d} contain imidazo[1,2-a]pyridine moiety. In addition to the above applications, imidazo[1,2-a]pyridine derivatives have incurred significant importance as central ligands in the field of electronic devices.⁸

Conventional method of synthesizing propargylamines requires the generation of metallated alkynes utilizing various strong bases such as alkoxides^{9a}, hydroxide,^{9b} LiAlH₄,^{9c} butyl lithium^{9d,9e}, LDA9e and Grignard reagents9f and attack of the generated metallated alkynes to imines. The major drawbacks of this protocol are the need of highly moisture-sensitive reagents in stoichiometric quantity and harsh reaction conditions. In recent years, A³ coupling of aldehydes, amines and alkynes via C-H activation have been developed as alternative to the traditional method, wherein water is the only byproduct. Variety of homogeneous catalysts like Zn(OAc)2,^{10a} AgI,^{10b} AuCl,^{10c} AuI,^{10c} AuCl3,^{10c} AuBr3,^{10c} FeCl3,^{10d} CdI₂,^{10e} InCl₃,^{10f} InBr₃,^{10g} CuCl,^{10h} CuBr,^{10h} CuI,^{10h} NiCl₂,¹⁰ⁱ Hg₂Cl₂,^{10j} Au(III) complexes,¹¹ Ag(I) complexes¹² have been applied. Theses catalysts mostly require hazardous solvents like acetonitrile, toluene, and tedious workup process and often need inert atmosphere. In order to replace the homogeneous catalysts, in recent years, heterogeneous catalysts have been employed: Au nanoparticles,13a Ag nanoparticles,13b Au/CeO2,14 Au/ZrO2,14 Au nanoparticles stabilized on montmorillonite,15 Au and Ag nanoparticles on Egg shell,¹⁶ Ag immobilized on ZnO nanoparticles,17nanocrystallineMgO stabilized Au nanoparticles,18 polystyrene supported NHC-Ag(I) catalyst,¹⁹ Au nanoparticles on $Al_2O_3^{20}$ Cu nanoparticles stabilized on modified montmorillonite.²¹ Although these are heterogeneous in nature, they are expensive and often require toxic toluene, THF solvents, prolonged duration to achieve good yields and metals often lost during the reaction. Ionic liquids immobilized catalysts containing imidazolium molecule with BF4 or PF6 anions have been reported²². These catalysts have serious limitation due to their high cost and disposable problem as they are highly toxic. Metal oxides such as Cu/SiO₂,²³ Cu-Zeolite,²⁴ Zinc titanate nanopowder²⁵ and Co₃O₄²⁶ and copper aluminium based nanocomposites²⁷ have been investigated for propargylamines synthesis. However, most of the catalysts need organic solvent and require long time to achieve high vields.

Various protocols are available in the literature for the synthesis of imidazo[1,2-a]pyridines using Cu-MOF,²⁸ Cu(OTf)₂,²⁹ CuCl,²⁹ InBr₃/Et₃N,³⁰ CuSO₄-glucose,³¹ Iodine,³²CuI/NaHSO₄-SiO₂,³³ CuSO₄/TSOH,³⁴ ZnCl₂/CuCl³⁵ as catalysts. These protocols suffer from serious issues such as need of homogeneous catalysts, long duration and often require additives (like glucose, TsOH and Et₃N) along with metal catalysts.

Considering the biological and therapeutic importance of propargylamines and imidazo[1,2-a]pyridines, and also the inefficiency of existing protocols for their synthesis, in continuation of our previous reports,^{36, 37} herein, we developed a facile synthetic method for nano porous ZnAl₂O₄ with large surface area and employed it as an efficient catalyst for the synthesis of propargylamines. Cu nanoparticles supported on the synthesized nano ZnAl₂O₄ were efficiently used as catalyst for imidazo[1,2-a]pyridines. To the best of our knowledge, this is the

first report for nano ZnAl₂O₄ synthesis using ethanolamine and protocols for the one pot synthesis of propargylamines and imidazo[1,2-a]pyridines using nano ZnAl₂O₄ and Cu/nano ZnAl₂O₄ respectively. The synthetic route of nano ZnAl₂O₄ was very simple. Being solvent free, environmentally friendly, the protocols for A³ coupling reactions utilize low cost reusable catalysts.

Results and discussion

Powder XRD and BET analysis

Figures 1a and 1b display powder XRD patterns of ZnAl₂O₄ calcined at 500 °C (ZAO5) and ZnAl₂O₄ calcined at 700 °C (ZAO7) respectively. Both materials were phase pureand crystallized in face centered cubic phase. All the peaks were indexed based on the standard ICDD data (# 821043). XRD peak broadening of ZAO7 was found to be lesser than that of ZAO5. This indicates the crystallite size of nano ZnAl₂O₄ increased with increase in calcination temperature. The average crystallite size of ZAO5 and ZAO7 determined from Scherrer's formula was 5 nm and 7 nm respectively.XRD pattern (Fig. 2) of Cu/ZAO5 affirmed the presence of copper diffraction peaks ($2\theta = 43.31$ and 50.44) along withZnAl₂O₄ peaks. No other metal oxide peaks were observed in XRD. From the BET method, the specific surface area and pore volume of ZAO5 and ZAO7 were found to be 147 m^2/g , 0.2 cm³/g and 100 m²/g, 0.14 cm³/grespectively. This evidenced decrease in the surface area and pore volume of ZnAl₂O₄ upon increasing the calcination temperature from 500 °C to 700 °C.



Published on 22 December 2015. Downloaded by UNIVERSITY OF NEBRASKA on 29/12/2015 10:29:10.



In the present work, ethanolamine acted as complexing as well as precipitating agent. The gradual addition of ethanolamine led to the formation of the complex with zinc nitrate and aluminium nitrate, which upon calcinations resulted in nanosized particles of ZnAl₂O₄. The evolution of NH₃ and CO₂ gases during calcinations left the pores in the catalysts.In our previous report³⁶, we synthesized ZnAl₂O₄ in the absence of ethanolamine. From the micrographs and powder X-ray analysis, it was identified that the particles were in the range of 5 μ m. Hence, these observations indicated the presence of ethanolamine controlled the ZnAl₂O₄ particle size.

In the case of Cu/ZnAl₂O₄, surface area was found to be 50 m²/g with pore volume 0.07 cm³/g. This confirmed the occupancy of copper over the surface and pores of nano ZnAl₂O₄.

Microscopic and TPD analysis

SEM images of ZAO5 (Fig. 3a) and Cu/ZAO5 (Fig. 3b) showed aggregation of the particles. EDX spectra (supplementary data) affirmed the presence of Zn, Al, O and Zn, Al, Cu and O elements in the catalysts ZAO5 and Cu/ZAO5 respectively. The atomic percentage matched with the theoretical values. EDX spectra of ZAO5 and Cu/ZAO5 showed the absence of C and N peaks, which indicates the absence of ethanolamine.

TEM images of ZAO5 and Cu/ZAO5are shown in Fig. 4a and 4b.The particles were spherical in shape. Crystalline nature and homogeneous distribution of ZAO5 particles were evident from Selected Area Electron Diffraction (SAED) Pattern (Fig. 4a inset). Presence of copper nanoparticles on ZAO5 was identified by TEM-EDX analysis (Supplementary data). Crystalline nature of the Cu/ZAO5 particles was seen from Selected Area Electron Diffraction (SAED) Pattern (Fig. 4b inset). The obtained histogram revealed the narrow size distribution of ZAO5 nanoparticles with 3-7 nm size (Fig. 5).

NH₃-TPD pattern (Fig. 6a) shows two peaks at 194 °C and 367 °C. The ZAO5 possessed medium acidic sites. The total acidity was 5 mmol py/g. CO_2 - TPD pattern (Fig. 6b) exhibited three peaks at 154 °C, 334 °C and 438 °C. The peak at 154 °C was associated with weak basic site (surface hydroxyl group). The peaks at 334 °C and 438 °C were associated with medium (due to

 $M^{n+}-O^{2-}$ pair) and strong (due to isolated O^{2-}) basic sites on the catalyst's surface respectively.³⁸ The total basicity of the catalyst was found to be 2.5 mmol CO_2/g .

XPS analysis was carried out for the sample Cu/ZAO5 to know the oxidation state of copper. Fig. 7 shows the XPS spectrum of



Fig. 3 SEM images of (a) ZAO5 and (b) Cu/ZAO5



Fig. 4 TEM images of (a) ZAO5 and (b) Cu/ZAO5; Inset show respective electron diffraction patterns



Fig. 5 Histogram of ZAO5

Published on 22 December 2015. Downloaded by UNIVERSITY OF NEBRASKA on 29/12/2015 10:29:10.



Fig. 6 NH_3 -TPD (a) and CO_2 -TPD of ZAO5



Fig. 7 XPS spectrum of Cu/ZAO5

Cu/ZAO5. The peaks appeared at 943 eV and 962 eV, characteristic satellite peaks, belong to Cu^{2+} . The peakappeared at 953 eV associated with Cu $2p_{1/2}$.³⁹Thisconfirmed that the copper underwent surface oxidation and that the copper surface was in the form of CuO.

Catalytic role of nano $ZnAl_2O_4$ and $Cu/nano ZnAl_2O_4$ for A^3 coupling reactions

Initially we investigated the catalytic activity of commercial ZnO, Al_2O_3 , bulk ZnAl_2O₄ and synthesized nano ZnAl_2O₄ for the propargylamine synthesis by refluxing benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol) in toluene at 90 °C for 6 h. We found that nano ZnAl_2O₄ gave better yield compared to other catalysts (Table 1).

Due to the smaller surface area and lesser number of active sites, bulk $ZnAl_2O_4$ showed poor yield. In order to optimize the solvent system for the propargylamine synthesis using nano $ZnAl_2O_4$, the reaction was carried out in various solvents including water. It was found to end up with moderate yields. We observed that under neat conditionsnano $ZnAl_2O_4$ resulted in 99.9% yield of propargylamine (Table 2) (Scheme 1).

Table 1. Screening of the catalysts for one-pot synthesis of propargylamines					
Entry	Catalyst	Reaction time (h)	% Yield ^(a)		
1	ZnO	6	50		
2	Al ₂ O ₃	6	45		
3	Bulk ZnAl ₂ O ₄	6	60		
4	Nano ZnAl ₂ O ₄	6	82		

Reaction conditions: Reactants: benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol); solvent: 5 ml toluene, temperature: 90 °C, a GC

Table 2. Effect of solvents on the synthesis of propargylamines

SI. No.	Solvent (5 ml)	Reaction time (h) /Yield (%) ^a
1	Toluene	4/82
2	Ethanol	4/61
3	Tetrahyrofuran	4/50
4	Methanol	4/62
5	Acetonitrile	4/51
6	-	4/99.9

Reaction conditions: Reactants: benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol), temperature: 90 $^{\circ}$ C, a GC



Scheme 1. Nano $\mathsf{ZnAl}_2\mathsf{O}_4\mathsf{catalyzed}$ synthesis of propargylamine derivatives under solvent free conditions

This journal is © The Royal Society of Chemistry 20xx

Page 5 of 10

Published on 22 December 2015. Downloaded by UNIVERSITY OF NEBRASKA on 29/12/2015 10:29:10.

Journal Name

This evidenced the efficiency of nano $ZnAl_2O_4$ under solvent free condition. Further, we explored the catalytic activity of nano $ZnAl_2O_4$ for various benzaldehyde derivatives in order to understand the generality of the catalysts. We found 98-99.9% yield (Table 3).

The plausible mechanism for propargylamine synthesis using nano $ZnAl_2O_4$ (Scheme 2)was proposed based on the literature reports. Iminium ion was formed from aldehyde and

Table 3. One-pot synthesis of propargylamine derivativesusing nano ZnAl₂O₄

Sl. No.	R ₁	Reaction time (h)/yield ^(a)
1	Н	4/ 99.9
2	4 - CH ₃	4/ 99
3	4 - OCH ₃	4/ 99
4	4 - Cl	4/ 99.9
5	4 - F	4/ 99
6	2 - F	4.5/ 98
7	2 - MeO	4.5/ 98
8	2, 4 - Cl	5/ 98
9	3,4 - OCH₃	5/98

Reactants: benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol), solvent free, temperature: 90 $^\circ$ C, 3 GC



Scheme 2. Plausible mechanism for propargylamine synthesis using nano ${\rm ZnAl_2O_4}$ under solvent free conditions

piperidine at room temperature in the initial step. Due to the presence of acidic and basic sites, catalyst nano $ZnAl_2O_4$ involved in the activation of the C–H bond of acetylene forming $ZnAl_2O_4$ – acetylide intermediate in the second step. In the final step, iminium ion reacted with $ZnAl_2O_4$ –acetylide intermediate and resulted propargylamine.

In order to reuse the catalyst, after every cycle the catalyst was recovered by filtration using whatman filter paper, washed with acetone to remove organic moieties and dried at 100 °C. We recycled the catalyst for 5 cycles without significant loss of activity (Fig. 8). Powder XRD pattern of nano $ZnAl_2O_4$, before and after reusability appeared to be the same indicating the re-existence of catalyst without any change (Fig. 9a and 9b).

We compared the activity of nano $ZnAl_2O_4$ with reported catalysts for propargylamines synthesis (Table 4) and understood that most of the reported catalysts are expensive, require solvent and inert atmosphere and also need prolonged reaction time. Nano ZnAl_2O_4 yielded high yield of propargylamine in lesser reaction time under solvent free condition.



Fig. 8 Reusability of ZAO5 for the synthesis of propargylamie



Fig. 9 Powder X-ray diffraction patterns of (a) fresh ZAO5 and (b) reused ZAO5

To understand the scope of the synthesized catalyst nano $ZnAl_2O_4$ for three component coupling reaction, we tested the

catalytic activity of nano $ZnAl_2O_4$ for the coupling reaction between benzaldehyde, 2-aminopyridine and phenylacetylene. But unfortunately no reaction took place (Table 5).

Table 4. Comparison of the activity of the $ZnAl_2O_4$ with other catalysts for the synthesis of propargylamines

SI.	Catalyst	Solvent	Temperature/	Reaction	Yield	Referenc
Ν			reaction	time	(%)	е
0.			condition			
1	NiCl ₂	Toluene	110 °C/Argon	8 h	95	10 (i)
2	Cul	PEG	100	12 h	87	10 (h)
			°C/Nitrogen			
3	SiO₂@Cu	Toluene	110 °C	5 h	94	23
4	InCl₃	Toluene	120 °C/Argon	20 h	90	10 (f)
5	*NAP-	Toluene	100 °C	15 h	98	18
	Mg-					
	Au(0)					
6	Nano	Toluene	130 °C	15 h	87	26
	Co_3O_4					
7	Nano	-	90 °C	4 h	99.9	present
	$ZnAl_2O_4$					work
	* Nana Activa Magnacium Ovida Dlus					

Reactants: benzaldehyde piperidine, phenylacetylene

Table 5 Comparison of the activity of the catalysts for imidazo[1,2-a]pyridine

catalyst	Yield (%)a
ZnAl ₂ O ₄	nil
CuO	61
Cu powder	69
8 wt% Cu/ nano ZnAl₂O₄	90
8 wt% Ni∕ nano ZnAl₂O₄	51
8% Cu-Ni/ nano ZnAl₂O₄	55
	ZnAl ₂ O ₄

Reactants: benzaldehyde (3 mmol), 2-aminopyridine (3 mmol) and phenylacetylene (3 mmol), solvent free, N_2 atmosphere, temperature: 90 °C, ^aGC

Understanding the need of copper and other transition metal catalysts for this reaction, we explored the catalytic activity of various catalysts such as CuO, Cu powder, 8 wt% Cu/ nano ZnAl₂O₄, 8 wt% Ni/ nano ZnAl₂O₄ and 8% Cu-Ni/ nano ZnAl₂O₄ under solvent-free condition as well as with solvent. The catalysts Ni/nano ZnAl₂O₄ and Cu-Ni/ nano ZnAl₂O₄ resulted in moderate yields, whereas, 8 wt% Cu/ nano ZnAl₂O₄ resulted in better yields under solvent-free and in the presence of N₂ atmosphere (Scheme 3). Hence, it was evident that the active site for imidazo[1,2-a]pyridine synthesis was copper and that nano ZnAl₂O₄ acted as support for copper nanoparticles because it provided large surface area and also aggregation of the copper nanoparticles was reduced. We carried out the reaction for other benzaldehyde derivative and 94-89% yields were achieved in 4-6h(Table 6).

Reusability of the catalyst was performed for the coupling between benzaldehyde, 2-aminopyridine and phenylacetylene by recovering the catalyst after every cycle. This was followed by washing with acetone and drying under vacuum. After every cycle, leaching of the metal ion was tested by AAS, and was found to be nil. We successfully recycled the catalyst five times without change in its activity (Fig. 10) and the catalyst was recovered without any change (Figs. 11a and 11b).

The plausible mechanism for imidazo[1,2-a]pyridines synthesis using nano ZnAl₂O₄ (Scheme 4)was proposed on the basis of literature reports. In the initial stage, imine was formed by the condensation of 2-aminopyridine with aldehydes. Formation of propargylamine occurred due to the nucleophilic attack of alkyne to imine. Due to the C-H activation of alkyl triple bond by copper on ZnAl₂O₄,intramolecularnucleophilic attack of nitrogen in pyridine ring to the triple bond either in 5-exo-dig (C-a attack) or 6-endo-dig way (C-b attack) took place. Which was later followed by aromatic isomerization of the cyclic intermediate led to imidazo[1,2-a]pyridines.



3 mmol 3 mmol 3 mmo

Scheme 3 Cu/nano ZnAl $_2O_4$ catalyzed synthesis of imidazo[1,2-a]pyridine derivatives under solvent free condition

Table 6. One-pot synthesis of imidazo[1,2-a]pyridine derivatives					
Sl. No.	R1	Reaction time (h)/yield ^(a)			
1	Н	6/ 90			
2	4 - CH ₃	4/ 89			
3	4 - OCH₃	4/ 89			
4	4 - Cl	4/ 94			
5	4 - F	4/ 94			
6	2 - F	4.3/90			

Reactants: Aldehyde (3 mmol), 2-aminopyridine (3 mmol) and phenylacetylene (3 mmol), solvent free, N_2 atmosphere, temperature: 90 °C, ^aGC



Fig. 10 Reusability of ZAO5 for the synthesis of imidazo[1,2-a]pyridines

This journal is © The Royal Society of Chemistry 20xx



Fig. 11 Powder X-ray diffraction patterns of (a) fresh Cu/ZAO5 and (b) reused Cu/ZAO5



Scheme 4. Plausible mechanism for the synthesis of imidazo[1,2-a]pyridine using Cu/nano ZnAl₂O₄ under solvent free conditions

We compared the activity of Cu/nano ZnAl2O4 with reported catalysts for imidazo[1,2-a]pyridinessynthesis (Table 7). Most of the reported catalysts are expensive, require additive and need prolonged reaction time. Cu/ nano ZnAl2O4 provided good yield of imidazo[1,2-a]pyridinesin lesser reaction time under solvent free condition.

View Article Online DOI: 10.1039/C5RA20812B ARTICLE

RSC Advances Accepted Manuscript

Table 7. Comparison of the activity of the Cu/ZnAl2O4 with other catalysts for the synthesis of propargylamines

SI. No.	Catalyst	Solvent	Temperatur e/reaction condition	Reac tion time	Yield (%)	Referenc e
1	CuCl + Cu(OTf) ₂	Toluene	120°C/ Nitrogen	16 h	93	28
2	InBr3	Toluene	Reflux/ Et ₃ N	12 h	82	30
3	Iodine	Water	60 °C	6 h	85	32
4	CuSO₄/ TSOH	Toluene	110 °C	18 h	60	34
5	Cu/nano ZnAl₂O₄	-	90 °C	6 h	90	Present work

Reactants: Benzaldehyde, 2-aminopyridine and phenylacetylene

EXPERIMENTAL

Materials

 $Zn(NO_3)_2.6H_2O$, $Al(NO_3)_3.9H_2O$ and ethanolamine were purchased from Himedia. Organic chemicals were purchased from Sigma Aldrich. All the chemicals were of high purity and used without further purification.

Synthesis of ZnAl₂O₄ nanoparticles

In a typical synthesis, the aqueous solutions of Zinc nitrate (1 M) and Aluminium nitrate (2 M) were mixed under vigorous stirring. The above homogeneous solution was stirred for 2 h followed by the addition of aqueous solution of ethanolamine (ethanolamine to water volume ratio of 6: 4) drop wise until the white precipitation stopped. The white precipitate was collected by filtration, washed with double distilled water, followed by acetone and it was then dried in oven at 80 °C overnight. The dried precursor was calcined at 300 °C, 500 °C and 700 °C with intermittent grinding.

Synthesis of copper supported on ZnAl₂O₄ nanoparticles

The above synthesized nano ZnAl₂O₄ was dispersed in known amount of copper nitrate solution under vigorous stirring. The stirring was continued for 6 h followed by filtration. The precipitate was washed with water to remove excess of copper nitrate, and was dried with acetone. The above precipitate was dispersed in water using ultrasonication and the dispersion was heated at 60 °C - 70 °C on hot plate under nitrogen atmosphere. To this dispersion, 2 ml of hydrazine hydrate was added drop wise under vigorous stirring under nitrogen atmosphere. Stirring was continued for 2 h. The obtained precipitate was collected by filtration followed by vacuum drying.

General synthetic procedure for ZnAl₂O₄ nanoparticles catalyzed propargylamines

Aldehyde (3 mmol), piperidine (3.3 mmol) and phenyl acetylene (3.6 mmol) were placed in round bottom flask along with nano ZnAl₂O₄ and stirred at 80 °C without solvent. The reaction was monitored by TLC. After completion, the reaction mixture was cooled and extracted with DCM solvent.

General synthetic procedure for Cu/ nano ZnAl₂O₄ catalyzed imidazo[1,2-a]pyridines

This journal is C The Royal Society of Chemistry 20xx

ARTICLE

Aldehyde (3 mmol), 2-aminopyridine (3 mmol) and phenyl acetylene (3 mmol) were placed in round bottom flask along with Cu/nano ZnAl₂O₄. Nitrogen atmosphere was created in round bottom flask and the mixture was stirredat 80 °C without solvent under. The reaction was monitored by TLC. The reaction mixture was cooled and extracted with DCM solvent.

Characterization

Phase purity of the synthesized catalysts was determined by powder X-ray diffraction (XRD) patterns on Bruker X-ray diffractometer (D8 Advanced) with Cu K α radiation ($\lambda = 1.5406$ Å) in the angle range of $2\theta = 10^{\circ}-70^{\circ}$ at room temperature. Specific surface area of the catalysts were measured from Nitrogen adsorption desorption isotherms on Micromeritics ASAP 2020 V3.00 H by Brunauer-Emmett-Teller (BET) method. Scanning Electron Microscopic (SEM) images and Energy Dispersive X-ray Analysis (EDX) data were obtained on JEOL JSM 7001F with BRUKER- QUNTAX Version 1.8.2. Morphology and crystallite size of the catalysts were determined by Transmission Electron microscopic (TEM) on JEOL 3010 instrument with UHR pole piece. Surface acidity of the synthesized nano ZnAl₂O₄ was analyzed by NH₃ temperature-programmed desorption (TPD) technique on Autochem 2910, Micromeritics instrument. 1.0 g of nano ZnAl₂O₄ was preheated in 30 mL high pure Helium flow at 120 °C for 30 min at the heating rate of 10 °C/min. Adsorption of NH₃ was done by passing 10% NH₃ in Helium gas at 30 mL/min flow through the sample for 30 min followed by purging pure Helium at 30 mL/min. NH₃ desorption was studied from 100 °C to 650 °C at 10 °C/min utilizing thermal conductivity detector. CO2 temperature-programmed desorption, TPD technique on the same instrument was used for analyzing surface basicity of nano ZnAl₂O₄. In a typical procedure, dried nano ZnAl₂O₄ powder (1.0 g) was pretreated in 50 mL high pure Helium flow at 200 °C for 30 min. After which, the sample was saturated by CO₂ by passing 10% CO2 in Helium gas with a flow rate of 75 mL/min at 30 °C. The physisorbed CO₂ was removed by flushing Helium at 105 °C over the sample for 2 h. TPD analysis was carried out from 100 °C to 750 °C at the heating rate of 10 °C/min. XPS analysis of Cu/ZAO5 was performed on XM1000 spectrometer at room temperature with Al K radiation (h = 1486.6 eV) as the excitation source. C 1s 284.6 eV signal was referenced for the binding energy values. Concentration of leached metal ions of the catalyst after every cycle of the reaction was tested by Atomic Absorption Spectroscopic technique using Varian AA240 instrument. Organic compounds were confirmed by GC-MS.

Conclusion

In summary, we developed a facile, simple and efficient method for the synthesis of porous nano $ZnAl_2O_4$ with large surface area. The exploration of nano $ZnAl_2O_4$ and Cu/ nano $ZnAl_2O_4$ was found to be efficient catalysts for the synthesis of propargylamines and imidazo[1,2-a]pyridines respectively. The current protocols were simple, solvent- free, and they did not require any additive. Being cheap and reusable, nano $ZnAl_2O_4$ was found to be superior to the existing homogeneous and expensive noble metal catalysts.

Acknowledgement

Triveni Rajashekhar Mandlimath thanks CSIR for providing Senior Research Fellowship. She also thanks B. Uma Mahesh and M. Sathish Kumar for their valuable suggestions. The DST-FIST NMR facility at VIT University is greatly acknowledged (GC-MS). Authors thank Dr.R.Srinivasan, SSL, VIT for language editing.

Notes and references

*Chemistry Division – School of Advanced Sciences VIT University, Vellore – 632014, Tamil Nadu, India

Fax: +914162243092; Tel: +914162244520; Email:sathiya_kuna@hotmail.com

S: Supporting Information

- (a) E. Vedejs, J. W. Grissom, J. K. Preston, J. Org. Chem., 1987, 52, 3488-3489. (b) N. Gommermann, P. Knochel, Chem. Commun., 2004, 20, 2324-2325. (c) Q. Xu, E. Rozners, Org. Lett., 2005, 7, 2821-2824.
- 2 (a) F. Xiao, Y. Chen, Y. Liu, J. Wang, *Tetrahedron*, 2008, 64, 2755-2761. (b) B. Yan, Y. Liu, *Org. Lett.*, 2007, 9, 4321-4326. (c) E. S. Lee, H. S. Yeom, J. H. Hwang, S. Shin, *Eur. J. Org. Chem.*, 2007, 2007, 3503-3507. (d) Y. Yamamoto, H. Hayashi, T. Saigoku, H. Nishiyama, *J. Am. Chem. Soc.*, 2005, 127, 10804-10805. (e) D. F. Harvey, D. M. Sigano, *J. Org. Chem.*, 1996, 61, 2268-2272.
- (a). A. Jenmalm, W. Berts, Y. L. Li, K. Luthman, I. C. Bregh, U. Hacksell, J. Org. Chem., 1994, 59, 1139-1148. (b) Y. Imada, M. Yuasa, I. Nakamura, S. I. Murahashi, J. Org. Chem., 1994, 59, 2282-2284. (c) M. Miura, M. Enna, K. Okuro, M. Nomura, J. Org. Chem., 1995, 60, 4999-5004. (d) Trybulski, J. Eugene, Brabander, J. Herbert, 1994, US5346910.
- 4 (a) C. Binda, F. Hubalek, M. Li, Y. Herzig, J. Sterling, D. E. Edmondson, A. Mattevi, *J. Med. Chem.*, 2004, **47**, 1767-1774. (b) C. W. Olanow, *Neurology*, 2006, **66**, S69-S79. (c) M. Y. Falach, T. Amit, O. B. Am, M. B. H. Youdim, *FASEB J.*, 2003, 17, 2325-2342.
 5 V. Oldfield, G. M. Keating, C. M. Perry, *Drugs*, 2007, **67**, 1725-
- 1747.
- 6 (a) M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. D. Clercq, A. Gueiffier, *Eur. J. Med. Chem.*, 1999, 34, 271-274. (b) K. C. Rupert, J. R. Henry, J. H. Dodd, S. A. Wadsworth, D. E. Cavender, G. C. Olini, B. Fahmy, J. J. Siekierka, *Bioorg. Med. Chem. Lett.*, 2003, 13, 347-350. (c) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, W. Murmann, *J. Med. Chem.*, 1965, 8, 305-312. (d) Y. Kastura, S. Nishino, Y. Inoue, M. Tomoi, H. Takasugi, *Chem. Pharm. Bull.*, 1992, 40, 371-380. (e) Y. Rival, G. Grassy, G. Michel, *Chem. Pharm. Bull.*, 1992, 40, 1170 1176.
- 7 (a) A. N. Jain, J. Med. Chem., 2004, 47, 947-961. (b) N. Hsu, S. K. Jha, T. Coleman, M. G. Frank, Behav. Brain Res., 2009, 201, 233-236. (c) G. Trapani, M. Franco, L. Ricciardi, A. Latrofa, G. Genchi, E. Sanna, F. Tuveri, E. Cagetti, G. Biggio, G. Liso, J. Med. Chem., 1997, 40, 3109-3118. (d) S. M. Hanson, E. V. Morlock, K. A. Satyshur, C. Czajkowski, J. Med. Chem., 2008, 51, 7243-7252.
- 8 S. Takizawa, J. I. Nishida, T. Tsuzuki, S. Tokito, Y. Yamashita, *Chem. Lett.*, 2005, **34**, 1222-1223; b) S. Takizawa, J. I. Nishida, Y. Yamashita, T. Tsuzuki, S. Tokito, *Mol. Cryst. Liq. Cryst.*, 2006, **455**, 381-385; c) S. Takizawa, J. I. Nishida, T. Tsuzuki, S. Tokito, Y. Yamashita, *Inorg. Chem.*, 2007, **46**, 4308- 4319.
- 9 (a) M. E. Jung, A. Huang, Org. Lett., 2000, 2, 2659-2661, (b) S. S. Patil, S. V. Patil, V. D. Bobade, Syn. Lett., 2011, 8, 1157-1159. (c) W. Ryan, C. Ainsworth, J. Org. Chem., 1961, 26, 1547-1550. (d) T. Takahashi, F. Bao, G. Gao, M. Ogasawara, Org. Lett., 2003, 5, 3479-3481. (e) T. Harada, T. Fujiwara, K. Iwazaki, A. Oku, Org.

Published on 22 December 2015. Downloaded by UNIVERSITY OF NEBRASKA on 29/12/2015 10:29:10.

Lett., 2000, **2**, 1855-1857, (f) A. Tuulmets, V. Pallin, J. T. Taul, P. Burk, K. Raie, *J. Phys. Org. Chem.*, 2002, **15**, 701-705.

- 10 (a) E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa, Tetrahedron Lett., 2007, 48, 7184-7190. (b) C. Wei, Z. Li, C. J. Li, Org. Lett., 2003, 5, 4473-4475. (c) C. Wei, C. J. Li, J. Am. Chem. Soc., 2003, 125, 9584-9585. (d) W. W. Chen, R. V. Nguyen, C. J. Li, Tetrahedron Lett., 2009, 50, 2895-2898, (e) D. S. Raghuvanshi, K. N. Singh, Syn. Lett., 2011, 3, 373-377. (f) Y. Zhang, P. Li, M. Wang, L. Wang, J. Org. Chem., 2009, 74, 4364-4367. (g) J. S. Yadav, B. V. S. Reddy, A. V. H. Gopal, K. S. Patil, Tetrahedron Lett., 2009, 50, 3493-3496. (h) Q. Zhang, J. X. Chen, W. X. Gao, J. C. Ding, H. Y. Wu, Appl. Organometal. Chem., 2010, 24, 809-812. (i) S. Samai, G. C. Nandi, M. S. Singh, Tetrahedron Lett., 2010, 51, 5555-5558. (j) Li, P. Hua, Wang, Lei, Chin. J. Chem., 2005, 23, 1076-1080.
- (a) K. K. Y. Kung, V. K. Y. Lo, H. M. Ko, G. L. Li, P. Y. Chan, K. C. Leung, Z. Zhou, M. Z. Wang, C. M. Che, M. K. Wonga, *Adv. Synth. Catal.*, 2013, **355**, 2055-2070. (b) V. K. Y. Lo, K. K. Y. Kung, M. K. Wong, C. M. Che, *J. Organometal. Chem.*, 2009, **694**, 583-591. (c) V. K. Y. Lo, Y. Liu, M. K. Wong, C. M. Che, *Org. Lett.*, 2006, **8**, 1529-1532. (d) G. Villaverde, A. Corma, M. Iglesias, F. Sánchez, *ACS Catal.*, 2012, **2**, 399-406.
- 12 Y. Zhang, A. M. Santos, E. Herdtweck, J. Minkbc, F. E. Kuhn, New J. Chem., 2005, 29, 366-370.
- (a) M. Kidwai, V. Bansal, A. Kumar, S. Mozumdar, *Green Chem.*, 2007, 9, 742-745.
 (b) W. Yan, R. Wang, Z. Xu, J. Xu, L. Lin, Z. Shen, Y. Zhoua, *J. Molecul. Catal. A: Chem.*, 2006, 255, 81-85.
- 14 X. Zhang, A. Corma, Angew. Chem. Int. Ed., 2008, 47, 4358-4361.
- 15 B. J. Borah, S. J. Borah, K. Saikia, D. K. Dutta, *Catal. Sci. Technol.*, 2014, **4**, 4001-4009.
- 16 R. Mallampati, S. Valiyaveettil, ACS Sustain. Chem. Eng., 2014, 2, 855-859.
- 17 F. Movahedi, H. Masrouri, M. Z. Kassaee, J. Molecul. Catal. A: Chem., 2014, 395, 52-57.
- 18 K. Layek, R. Chakravarti, M. L. Kantam, H. Maheswarana, A. Vinu, *Green Chem.*, 2011, **13**, 2878-2887.
- 19 P. Li, L. Wang, Y. Zhang, M. Wang, Tetrahedron Lett., 2008, 49, 6650-6654.
- 20 L. Abahmane, J. M. Kçhler, G. A. Grob, Chem. Eur. J., 2011, 17, 3005-3010.
- 21 B. J. Borah, S. J. Borah, L. Saikia, D. K. Dutta, *Catal. Sci. Technol.*, 2014, 4, 1047-1054.
- 22 J. S. Yadav, B. V. S. Reddy, C. S. Reddy, K. Rajasekhar, J. Org. Chem., 2003, 68, 2525-2527.
- 23 H. Guo, X. Liu, Q. Xie, L. Wang, D. L. Peng, P. S. Branco, M. B. Gawande, *RSC Adv.*, 2013, **3**, 19812-19815.
- 24 M. K. Patil, M. Keller, B. M. Reddy, P. Pale, J. Sommer, Eur. J. Org. Chem., 2008, 2008, 4440-4445.
- 25 C. Mukhopadhyay, S. Rana, Catal. Comm., 2009, 11, 285-289.
- 26 K. D. Bhatte, D. N. Sawant, K. M. Deshmukh, B. M. Bhanage, *Catal. Comm.*, 2011, 16, 114-119.
- 27 J. Dulle, K. Thirunavukkarasu, M. C. M. Hazeleger, D. V. Andreeva, N. R. Shiju, G. Rothenberg, *Green Chem.*, 2013, 15, 1238-1243.
- 28 I. Luz, F. X. L. Xamena, A. Corma, J. Catal., 2012, 285, 285-291.
- 29 N. Chernyak, V. Gevorgyan, Angew. Chem. Int. Ed., 2010, 49, 2743-2746.
- 30 B.V. S. Reddy, P. S. Reddy, Y. J. Reddy, J. S. Yadav, Tetrahedron Lett., 2011, 52, 5789–5793.
- 31 S. K. Guchhait, A. L. Chandgude, G. Priyadarshani, J. Org. Chem., 2012, 77, 4438-4444.
- 32 I. R. Siddiqui, P. Rai, Rahila, A. Srivastava, S. Shamim, *Tetrahedron Lett.*, 2014, 55, 1159-1163.
- 33 S. Mishra, R. Ghosh, Synthesis, 2011, 21, 3463-3470.
- 34 P. Liu, L. Fang, X. Lei, G. Lin, Tetrahedron Lett., 2010, 51, 4605-4608.
- 35 P. Liu, C. L. Deng, X. Lei, G. Lin, Eur. J. Org. Chem., 2011, 7308-7316.

- 36 T. R. Mandlimath, B. Umamahesh, K. I. Sathiyanarayanan, J. Mol. Catal. A: Chem., 2014, **391**, 198-207.
- 37 B. Umamahesh, T. R. Mandlimath, K. I. Sathiyanarayanan, RSC Adv., 2014, 5, 6578-6587.
- 38 Q. Liu, L. Wang, C. Wang, W. Qu, Z. Tian, H. Ma, D. Wang, B. Wang, Z. Xu, Appl. Catal., B, 2013, 136-137, 210-217.
- 39 S. Velu, K. Suzuki, Chinnakonda, S. Gopinath, H. Yoshida, T. Hatoor, *Phys. Chem. Chem. Phys.*, 2002, **4**, 1990-1999.

This journal is C The Royal Society of Chemistry 20xx

RSC Advances Accepted Manuscript



254x190mm (96 x 96 DPI)