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PII:	S0926-860X(17)30242-9
DOI:	http://dx.doi.org/doi:10.1016/j.apcata.2017.05.033
Reference:	APCATA 16255
To appear in:	Applied Catalysis A: General
Received date:	7-4-2017
Revised date:	24-5-2017
Accepted date:	27-5-2017

Please cite this article as: Najrul Hussain, Pranjal Gogoi, Manash R.Das, Pinaki Sengupta, Vladimir E.Fedorov, Igor P.Asanov, Mariia N.Kozlova, Sofya B.Artemkina, Development of novel efficient 2D nanocomposite catalyst towards the three-component coupling reaction for the synthesis of imidazo[1,2-a]pyridines, Applied Catalysis A, Generalhttp://dx.doi.org/10.1016/j.apcata.2017.05.033

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## Development of novel efficient 2D nanocomposite catalyst towards the three-component coupling reaction for the synthesis of imidazo[1,2-*a*]pyridines

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### **Graphical abstract**



### Highlights

- Development of Cu based 2D nanocomposites using graphene and h-BN
- Cu based nanocomposites used for synthesis of imidazo[1,2-a]pyridines
- The catalysts were well characterized before and after performing the reaction
- Comparative study of the catalytic activity of synthesized materials was performed
- CuO/rGO nanocomposite was found to be more efficient and reusable catalyst

#### Abstract

Two dimensional (2D) materials such as graphene and functionalized hexagonal boron nitride (h-BN) supported copper catalysts (CuO/rGO, CuO/h-BN, Cu(0)/rGO, Cu(0)/h-BN, CuS/rGO and CuS/h-BN) were prepared, characterized and evaluated their catalytic activity for the synthesis of imidazo[1,2-*a*]pyridines *via* one pot three component reaction between 2-

aminopyridine, aldehyde and terminal alkynes. The imidazo[1,2-*a*]pyridines are an imperative class of nitrogen ring containing heterocyclic compounds which has wide range of applications in medicinal chemistry and drug molecule production. The reported synthetic protocol provides a rapid access to substituted imidazo[1,2-*a*]pyridines with excellent yields. CuO/rGO nanocomposite material was found to be highly active catalyst for the aforementioned reaction. The advantages of our protocol for the preparation of imidazo[1,2-*a*]pyridines over other previously reported includes shorter reaction times, functional group tolerance, recyclable catalyst and additive-free.

**Keywords**: Two dimensional (2D) material, nanoparticles, nanocomposite, graphene oxide, reduced graphene oxide, functionalized hexagonal boron nitride

### 1. Introduction

Imidazo[1,2-*a*]pyridine is one of the most imperative pyridine fused heterocycle found in various agrochemicals and pharmaceuticals. In pharmaceuticals, they have been used as analgesic, antiviral, anti-inflammatory, antibacterial, antipyretic, anxioselective and hypnoselective agents. They are  $\beta$ -amyloid formation inhibitors and create a novel class of orally active nonpeptide bradykinin B<sub>2</sub> receptor antagonists. Additionally, they are also used as benzodiazepine receptor agonists and calcium channel blockers. Several clinical drugs and agricultural chemicals have this structural unit, such as zolpidem, alpidem, olprinone, minodronic acid etc. [1-5] (Scheme 1).

Considering enormous applications of various imidazo[1,2-*a*]pyridine derivatives in different fields, continuous efforts have been made for their synthesis. Among them some of the important synthetic routes include one pot condensation of 2-aminopyridine, aldehydes and

isonitriles [6,7], coupling reaction of 2-aminopyridines with  $\alpha$ -halocarbonyl compounds [8], one pot three component condensation reaction between 2-aminopyridine, benzyl halide and isocyanides [9], one pot three component coupling of alkynes, aldehyde and 2-aminopyridine [10], Suzuki-cross coupling between arylboronic acid with 3-halo-2-arylimidazo[1,2-a]pyridines [11], tandem cycloisomerization of aryl propargylic alcohols with 2-aminopyridines [12] etc. Among different types of multicomponent reaction strategy, one pot three component coupling reactions of aldehyde, alkynes and 2-aminopyridine is the most convenient and attractive method for the production of imidazo[1,2-a]pyridine derivatives because of shorter reaction time, higher stability, reusability, availability of substrates and inexpensive reagents [13].

Until now, a number of catalyst have been recognized towards one pot three component coupling reaction for the imidazo[1,2-*a*]pyridines synthesis which includes CuI/Cu(OTf)<sub>2</sub> [14], CuCl/Cu(OTf)<sub>2</sub> [10,15], CuSO<sub>4</sub>/TsOH [7], CuSO<sub>4</sub>/glucose [16] etc. However, these are associated with issues like use of homogenous catalyst which results difficulties in separation, need of anhydrous reaction conditions or inert atmosphere, requirement of additives to enhance the reaction yield. The use of easily separable heterogeneous catalyst may replace the homogenous catalyst and without the use of any additive is of great importance in sustainable chemistry. In this regards several efficient heterogeneous catalysts have been developed by many research groups. For example, Luz *et al.* reported Cu-MOFs as heterogeneous catalyst for this three component coupling reaction [17]. Tajbaksh and his co-workers reported Fe<sub>3</sub>O<sub>4</sub> nanoparticles (NPs) supported biimidazole Cu(I) complex as a reusable catalyst for this coupling reaction [18]. Guntreddi *et al.* adapted simple one-pot imidazo[1,2-*a*]pyridines synthesis by using magnetic nano-Fe<sub>3</sub>O<sub>4</sub>–NaHSO<sub>4</sub>·SiO<sub>2</sub> as reusable catalyst [19]. Very recently, Mandlimath and his co-workers developed an efficient copper supported ZnAl<sub>2</sub>O<sub>4</sub> nanocatalyst for the synthesis of imidazo[1,2-*a*]pyridines [20]. These

catalysts are proved to be efficient to yields the desired product but their substrate scope is limited to only 2-aminopyridine or phenylacetylene. Therefore, there is a high requirement for the development of an efficient and reusable catalyst for the synthesis of imidazo[1,2-a]pyridines with wide range of substrates. Here, the reported catalytic system avoids the use of additives, without inert atmosphere and sufficiently reusable towards the synthesis of imidazo[1,2-a]pyridines.

Metal and metal oxide NPs are undeniably one of the most exciting functional materials in catalytic applications due to their different structures and properties. But, due to the strong interactions between the particles they easily undergo aggregation which in turn greatly affects the catalytic activity. To resolve this issue, different type of ligands as well as various stabilizers such as polymers, dendrimers are used to prevent agglomeration of NPs [21-23]. But the use of such kind of capping agents could be ingredient of the catalyst as contamination and therefore may severely limit their catalytic application. This can be easily overcome by using support materials. Furthermore, it is well known that the support plays a crucial role in catalytic activity in case of heterogeneous catalyst. In that case, graphene and functionalized hexagonal boron nitrides (h-BN) are two excellent 2D materials that are used as promising support in the synthesis of metal and metal oxide NPs due to their high thermal conductivity, electric insulation, chemical inertness, great mechanical strength [24,25]. These 2D materials are particularly promising and emerging support for the synthesis of composite nanomaterial for catalytic applications because of their high surface area and good absorption capacities. Metal and metal oxidegraphene nanocomposite materials finds wide range of applications in catalysis which includes oxidation of alcohols, CO oxidation, hydrogenation, Fishcher-Tropsch synthesis and coupling reactions [26]. But surprisingly, as compared to the significant progress of metal/metal oxide-graphene nanocomposite materials in catalysis, the h-BN supported metal/metal oxide NPs have been enduring far behind than that of graphene

based nanocomposite materials. Therefore, we have developed metal and metal oxide NPs on to functionalized h-BN for catalytic application and also report a comparative study of their catalytic performances with graphene supported metal and metal oxide NPs.

In this study we have chosen Cu due to its availability, low cost and environmental compatibility nature [27,28]. In spite of these peculiar advantages of using Cu, there is limited number of reports on Cu based heterogeneous catalyst in organic catalytic reactions and to the best of our knowledge there is no report on Cu based NPs on graphene and h-BN as a catalyst towards the synthesis of imidazo[1,2-*a*]pyridines. Keeping this in mind, we have developed CuO NPs on to rGO sheets as well as on to h-BN sheets by using hydrothermal technique. The use of hydrothermal technique for the synthesis of CuO NPs avoids the use of extra reducing agent and also provides the necessary stability to the composite material for catalytic conversion. We have also reported here the use of other chalcogenide nanocomposite material such as CuS/rGO and CuS/h-BN to investigate the effect of the counterparts of Cu towards the size and shape of the composite materials which will in turn effects the catalytic activity of the materials towards the reaction. Furthermore, we have also developed Cu(0) NPs on to rGO sheets and h-BN sheets and investigated their catalytic activity towards the synthesis of imidazo[1,2-*a*]pyridines.

#### 2. Experimental

#### 2.1. Materials and Methods

Graphite powder (<20 μm, Sigma-Aldrich), potassium permanganate (>99%, E-Merck, India), hydrochloric acid (AR grade, Qualigens, India), sulphuric acid (AR grade, Qualigens, India), H<sub>2</sub>O<sub>2</sub> (30%, Qualigens, India), ascorbic acid (99%, Fisher Scientific, India), Cu(NO)<sub>3</sub>.3H<sub>2</sub>O (99-104%, Sigma-Aldrich), Cu(CH<sub>3</sub>COO)<sub>2</sub>.H<sub>2</sub>O (>99%, E-Merck, India),

Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (Qualigens, 99%) and all substrates for organic reactions were used from Sigma Aldrich, USA.

X-ray diffraction (XRD) analysis were carried out with a scanning rate of 3 deg.min<sup>-1</sup> using ULTIMA IV Rigaku X-ray diffractometer from 5-100° with a Cu K $\alpha$  X-ray source ( $\lambda$  = 1.54056 Å). Transmission electron microscopy (TEM) as well as high resolution transmission electron microscopy (HRTEM) images were taken on a JEOL JEM-2011 electron microscope, Japan functioned at an accelerating voltage of 200 kV. The diffuse reflectance infrared Fourier transform (DRIFT) spectra of samples were taken by using IR Affinity-1, Shimadzu, Japan in the range of 4000-400 cm<sup>-1</sup>. The thermal stability of the synthesized materials were investigated by TA-SDT (model: Q600DT, TA Instruments, USA) at a heating rate of 10 °C rise in temperature per minute. Atomic absorption spectroscopy (AAS) analysis was carried using Perkin Elmer (Model-Analyst-700) spectrometer to determine the metal content of the composite material. X-ray photoelectron spectroscopy (XPS) analysis were done by Specs Phoibos 150 instrument using a monochromatized Al Ka excitation at a pressure ~  $3 \times 10^{-9}$  mBar, pass energy is 20 eV, electron take off angle is 55°, the full width at the half maximum of Au4 $f_{7/2}$  is ~ 0.8 eV). Organic reactions were examined by thin-layer chromatography (TLC) with the help of aluminium-backed silica gel plates; the chromatograms were envisioned with ultraviolet light (254 nm). Column chromatography technique was adapted for the purification of the organic products with the help of silica gel 60 (100-200 mesh). All NMR spectra of the products were recorded by using Bruker Advance DPX 500 MHz NMR spectrometer. Chemical shifts are stated on the  $\delta$  scale in ppm downfield from tetramethylsilane of  $\delta = 0.0$  ppm using the residual solvent signal at  $\delta = 7.26$ ppm (1H) or  $\delta = 77$  ppm (<sup>13</sup>C) as an internal standard.

### 2.2. Synthesis of the graphene oxide (GO)

The detailed synthesis procedure and characterization of GO was reported in our previously published papers [29, 30].

#### 2.3. Synthesis of functionalized hexagonal boron nitride (h-BN)

Functionalized hexagonal boron nitride samples were prepared by treatment with  $H_2O_2$  (30%) as it has been described in our previous work [31]. In the typical procedure 150 mg h-BN was ground by agate mortar and then pestle for 15 min. After that it was put into a cylindrical Teflon autoclaves (rated pressure 2–3 atm). 30 mL 30%  $H_2O_2$  was added to the autoclave and ultrasonicated for 5 min and then thermostated in a water bath for 25–50 h at 100 °C. After the reaction, solid phase of the mixture was decanted by centrifugation, washed with water followed by ethanol and then dried at room temperature.

# 2.4. Synthesis of the CuO NPs onto reduced graphene oxide sheets (CuO/rGO nanocomposite)

20 mL of GO suspension (1 g in 100 mL water) was added to the 100 mL round bottom flask containing 20 mL aqueous solution of Cu(CH<sub>3</sub>COO)<sub>2</sub>.H<sub>2</sub>O (0.2595 g dissolved in 20 mL water). Then the mixture was stirred for 1 h at 25 °C and then transferred the reaction mixture to 50 mL autoclave for hydrothermal treatment at 150 °C for 5 h. Finally the solid product was obtained by centrifugation and then repeatedly washed with ethanol and water. Finally the solid residue was dried in air oven at 70 °C.

# 2.5. Synthesis of CuO NPs onto the functionalized hexagonal boron nitride (CuO/h-BN nanocomposite)

Typically, 20 mL of h-BN-ethanol suspension (20 mg in 40 mL ethanol) was mixed with 20 mL aqueous solution of Cu(CH<sub>3</sub>COO)<sub>2</sub>.H<sub>2</sub>O (0.2595 g dissolved in 20 mL water) and allowed to stir for 1 h. The reaction mixture was transferred to a 50 mL autoclave and subjected to hydrothermal treatment at 150 °C for 5 h. After that the solid product was

obtained by centrifugation and then repeatedly washed with ethanol and water. Finally the solid residue was dried in air oven at 70  $^{\circ}$ C.

# 2.6. Synthesis of the Cu(0) NPs onto reduced graphene oxide sheets (Cu(0)/rGO nanocomposite)

The detailed synthesis method of Cu(0)/rGO nanocomposite material and its characterization was reported in our previously published paper [32].

2.7. Synthesis of Cu(0) NPs onto functionalized hexagonal boron nitride (Cu(0)/h-BN nanocomposite)
Cu(CH<sub>3</sub>COO)<sub>2</sub>.H<sub>2</sub>O (0.8 g) was dissolved in 10 mL water in a round bottom flask. 20 ml of h-BN-ethanol suspension (20 mg in 40 ml ethanol) was added to the above solution and stirred for 1 h followed by addition of ascorbic acid (0.1M, 10 mL) to the reaction mixture and heated to 80 °C for 3 h. The product was treated with H<sub>2</sub>O<sub>2</sub> to remove the unused ascorbic acid and after that the solid product was obtained by centrifuge and repeatedly washed with ethanol and water and then dried at 70 °C in an air oven.

2.8. Synthesis of the CuS NPs onto reduced graphene oxide sheets (CuS/rGO nanocomposite) The detailed synthesis method of CuS/rGO nanocomposite material and its characterization was reported in our previously published paper [33].

2.9. Synthesis of CuS NPs onto functionalized hexagonal boron nitride sheets (CuS/h-BN nanocomposite)

0.164 g Cu(NO)<sub>3</sub>.3H<sub>2</sub>O is dissolved in 20 mL water and then 0.248 g of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added to it. The reaction mixture was mechanically stirred until the colour changed to yellowish green. After that 20 mL of h-BN-ethanol suspension (20 mg in 40 mL ethanol) was added to the above solution and then the whole reaction mixture was heated to 80 °C with vigorous stirring for 4h. Finally, the solid product was collected by centrifuge and washed with ethanol and water and then dried in an air oven at 70 °C.

# 2.10. General experimental procedure for the synthesis of imidazo[1,2-a]pyridines derivatives:

A mixture of aldehyde (1.2 mmol), alkyne (1.2 mmol) and 2-aminopyridine (1 mmol) were taken in a 25 mL round bottom flask. Then a suspension of the nanocomposite material (15 mg in 3 mL DMSO) was added to the above reaction mixture. The whole reaction mixture was ultrasonicated for 2 min followed by heating with continuous stirring at 110 °C for 8 h. The completion of the reaction was monitored by thin-layer chromatography (TLC). The product was extracted with ethyl acetate ( $2 \times 10$  mL) followed by drying over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuum. The crude products were purified by column chromatography with silica gel (60-120 mesh) using EtOAc/hexanes as eluent to get the desired final product. The products were analysed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (Details are shown in the supporting information).

#### **3.** Results and Discussions

#### 3.1. Characterization of all the synthesized nanocomposite materials

The detailed characterization of the Cu(0)/rGO and CuS/rGO nanocomposites were discussed in our previously published paper [32,33]. The formation of CuO and CuS NPs on to the rGO sheets and h-BN surface was first confirmed by X-ray diffraction (XRD) technique as shown in the Fig. 1.The XRD pattern of the CuO/rGO nanocomposite revealed that the peaks at 20 values of about 32.56°, 35.56°, 38.81°, 48.71°, 53.54°, 58.50°, 61.59°, 65.91°, 68.19°, 72.68° and 75.18° corresponding to d – spacing of 2.74, 2.52, 2.31, 1.86, 1.71, 1.58, 1.50, 1.41, 1.37, 1.31 and 1.26 Å are assigned to the (110), (-111), (111), (-202), (020), (202), (-113), (-311), (220), (311) and (-222) crystallographic planes of CuO NPs, respectively [34]. All the diffraction peaks and other lattice parameter found in the XRD are a = 4.68 Å, b = 3.42 Å, c = 5.12 Å with volume cell of 80.90 Å can be indexed in the

monoclinic phase of CuO NPs. These values are good agreement with the respective JCPDS card No 01-070-6830. The average crystallite size of the CuO NPs onto rGO sheets is determined by using Sherrer equation on PDXL software and found to be 2.50 nm. Similar crystallographic planes of CuO NPs in CuO/h-BN nanocomposite material were found (Fig. 1b). The formation of CuS NPs on to the h-BN is also confirmed by XRD analysis as shown in Fig. 1c. Also the formation of Cu(0) NPs on to h-BN was confirmed by XRD as shown in Fig. 1d. The peaks at 43.30°, 50.43° and 74.13° corresponding to *d*- spacing of 2.08, 1.80 and 1.27 Å are assigned to the (111), (200) and (220) planes of cubic Cu(0) NPs (JCPDS card No 00-004-0836). The typical diffraction peak at 26.61° corresponds to the (002) plane of h-BN in these composite materials.

The size, morphologies and microstructures of all the prepared nanocomposites were examined by using TEM and HRTEM techniques. The TEM images of CuO/rGO nanocomposite materials as shown in Fig. 2 revealed that the CuO NPs are uniformly scattered on to the surface of rGO sheets and are spherical in structure. It is observed from the TEM images as shown in the Fig. 2 that the rGO sheets are irregular and folded and CuO NPs are wrapped by those folded sheets, which therefore enables unifrom distribution of particles by preventing from agglomeration [35]. The particle size distribution curve obtained by using Image J Software shows the average particle size of the CuO NPs at around ~ 5 nm (Fig. 2c). The HRTEM image as shown in Fig. 2e clearly shows the interplanar spacing of 0.25 nm which can be indexed with the (-111) plane of cubic CuO NPs. The diffraction dots found in the SAED pattern proves the crystalline nature of the CuO NPs and the crystal lattices corresponding to the (111) and (-202) planes of CuO are clearly visible (Fig. 2f). The TEM image of CuO/h-BN nanocomposite material shows that the CuO nanoparticles are more or less uniformly distributed on to the surface of h-BN sheets (Fig. 3). The average size of the CuO NPs on to h-BN sheets is found to be ~ 9 nm which is larger than that onto rGO sheets.

The average size of Cu(0) NPs onto h-BN sheets is obtained from particle size distribution curve and it is found to be 14 nm (Fig. 4(c)). But some of the Cu(0) NPs are susceptible to undergo agglomeration and also the distribution of the particles are not uniform as compared to CuO NPs onto rGO and h-BN sheets. The morphology of the Cu(0) NPs on the surface of rGO sheets are discussed in our previous publication [29] and found that the size of the Cu(0) NPs is larger onto h-BN sheets than onto the rGO sheets. Further, it is seen from the TEM images of the synthesized CuS/h-BN nanocomposite (Fig. 4(d-f)) that the CuS NPs are very large and undergoes agglomeration and therefore forms a cluster type structure. The details of the surface morphology of the CuS/rGO nanocomposite was given in our previous publication and observed that synthesized CuS/rGO nanocomposite has crystalline structure with an average particle size of about 183 nm [33]. TEM and HRTEM images evident that the particles size and morphology of the Cu NPs are dependent on the support material as well as on the counterparts of Cu. The sizes of the CuO NPs on to rGO sheets are smaller and uniformly dispersed than that of h-BN sheets. It can be seen from the TEM images of all the synthesized copper/h-BN nanocomposite materials that the NPs are distributed in the shape of irregular structures and are prone to agglomeration and as a result of which a broad particle size distribution is observed. The regular and uniform distribution of Cu and CuO NPs onto rGO sheets as compared to functionalized h-BN sheets is because of the presence of adequate number of oxygen containg functional groups present on rGO surface as compared to functionalized h-BN. The presence of various oxygen containing functional groups on rGO sheets can act as active sites for decoration of the NPs with good dispersion than that of functionalized h-BN sheets where only hydroxyl groups are present [36, 37].

The FTIR spectra of GO, h-BN, CuO/rGO and CuO/h-BN are displayed in Fig. 5. The FTIR spectra of h-BN (Fig. 5a) displayed two prominent peaks at 1392 cm<sup>-1</sup> and 813 cm<sup>-1</sup> which are due to the B–N stretching and B–N bending of h-BN, respectively. The intensity of the

peak observed at around 3395 cm<sup>-1</sup> of h-BN which is due to the –OH groups is reduced in the CuO/h-BN nanocomposite material (Fig. 5b) implying that the –OH groups of h-BN served as the active sites for the formation of CuO NPs on to the h-BN surface. Similar observations were found in the FTIR spectral analysis of Cu(0)/h-BN and CuS/h-BN nanocomposite materials (Shown in Fig. S1). As shown in Fig. 5c, the stretching vibrations of O–H, C=O, C–O–C of GO is observed at 3130, 1732, and 1052 cm<sup>-1</sup>, respectively. The peaks at 1224 cm<sup>-1</sup> of GO corresponds to the vibration of carboxyl groups. Moreover, the peaks observed at 1439 cm<sup>-1</sup> and 1585 cm<sup>-1</sup> corresponds to C–O–H bending of phenolic groups and the C=C stretching of aromatic rings. These peak intensities of the oxygen containing functional groups present on GO is decreased in the CuO/rGO nanocomposite material as shown in Fig. 5d, which suggest that the epoxy, carboxyl, hydroxyl and carbonyl groups present in GO are considerably decreased after formation of the CuO NPs on the rGO sheets. This implies that these oxygen containing functional groups served as active sites for decoration of CuO NPs. As a result of which uniform distribution of CuO nanoparticles onto rGO sheets was obtained.

XPS analysis was performed to study the oxidation state of the Cu, CuO and CuS NPs on the rGO and h-BN sheets. The high resolution C1s and O1s XPS spectrum of CuO/rGO nanocomposite is shown in Fig. 6. The C 1s spectrum of CuO/rGO shows the peak at 284.59 eV from sp<sup>2</sup> carbon atoms and the less intense components at 286.92 eV (C–O bonds) and 288.70 eV (carboxyl group). The weak satellite line at 291.01 eV is related to the inelastic energy losses at photoionization process. The O1s spectrum can fit into three components at 529.58 eV from CuO, 531.24 eV from C-O bonds and 532.92 eV from water molecules (shown in Fig. 6). The spectra B1s of CuO/h-BN consists of two components at 189.23 eV and 190.95 eV with the intensity ratio 0.15. The most intense peak at 190.95 eV comes from BN and the weak line corresponds to borides (shown in Fig. 7). The N1s spectrum consists of

<sup>13</sup> 

two components at 396.58 eV and 398.23 eV with the intensity ratio 0.19. The most intense component is related to BN, and the weak component corresponds to the negatively charged nitrogen atoms (possibly nitride of Cu) (Fig. 7). Although, the XRD spectrum of Cu(0)/h-BN shows that Cu is in zero oxidation state, the XPS spectra shows that Cu is also in +2oxidation state in Cu(0)/h-BN nanocomposite material (Fig. S2). This may be due to the fact that Cu(0) is less stable onto h-BN sheets as compared to rGO sheets and it underwent oxidation easily in contact with air. But in case of Cu(0)/rGO nanocomposite, Cu is in purely zero oxidation state and very much stable which is described in our previous publication. This is because rGO sheets are folded and oriented in different directions and it is assumed that the Cu(0) NPs are present inside the folded rGO sheets as well as along the basal plane and the edges of the rGO sheets. The details XPS spectrum analysis of Cu(0)/rGO nanocomposite is discussed in our previously published paper [32]. The S2p XPS spectrum of CuS/h-BN shows two lines at 162.70 eV and 169.33 eV from sulfide and sulfate groups, respectively (Fig. S3). The Cu 2p spectrum has an intense line at 931.52 eV from CuS, the shoulder at 933.54 eV and intensity of the satellite decreases. We can suggest that CuS and copper sulphate contributes to the surface of Cu NPs in this sample. The details discussion of the XPS spectra of the CuS/rGO nanocomposite is given in our previous publication [33].

# 3.2. Catalytic activity of the different Cu based nanocomposites for the synthesis of imidazo[1,2-a]pyridines

The Cu based nanocomposites as described above were applied to the three component coupling reaction. First, all catalysts were easily suspended in the appropriate solvent by ultrasonication. To establish an approximate ranking activity among the synthesized composite materials, different types of substituted 2-aminopyridine, benzaldehyde and phenylacetylene were chosen as a standard benchmark reaction for the synthesis of imidazo[1,2-*a*]pyridines (Table 1). The highest activity was achieved with CuO/rGO

nanocomposite followed by CuO/h-BN, Cu(0)/rGO, Cu(0)/h-BN, CuS/rGO and CuS/h-BN. Although CuO/h-BN nanocomposite material lead to comparatively good yield of the desired product, but the activity sharply decreased in the second run of the reaction. The disrupt change in the activity of reused CuO/h-BN is accompanied by changes in the surface morphology of the material upon reuse which is supported by TEM images (Fig. 9(d-e)). Cu(0)/rGO and Cu(0)/h-BN nanocomposites displayed almost same efficiency but afforded lower yield of the product than that of CuO/rGO and CuO/h-BN nanocomposites. But surprisingly, both the CuS/rGO and CuS/h-BN nanocomposites displayed lowest activity among all the synthesized materials. This poor performance is due to the agglomeration of the CuS NPs onto rGO sheets and h-BN sheets which results lower surface to volume ratio of these two nanocomposites. On the basis of this findings the highest catalytic activity towards the synthesis of imidazo[1,2-*a*]pyridines with the yield of 91-95% is achieved with CuO/rGO nanocomposite. The higher catalytic activity of CuO/rGO nanocomposite is attributed to the enhanced interaction between CuO NPs with the substrates resulting from the uniform distribution of small sized CuO NPs onto rGO sheets.

# 3.3. Reaction optimization for the CuO/rGO nanocomposite catalyst in one pot three component coupling reaction of the synthesis imidazo[1,2-a]pyridines

With the optimized catalyst in hand, further we have performed optimization reaction condition by screening different common solvents as shown in Table 2. At first and foremost, we tried with evergreen solvents H<sub>2</sub>O, but unfortunately our catalytic system was unable to afford the desired product because the catalyst CuO/rGO nanocomposite is not properly dispersed in water. After that we tried with different organic solvents such as THF, DMF, acetonitrile, DMSO, toluene and *N*-methyl-2-pyrrolidone (NMP). Although the solvents DMF and NMP afforded comparatively good yield of the desired product, but significant difference in the catalytic activity of the catalyst is found with toluene under our catalytic

system. DMSO was found to the best solvent for this catalytic system (Entry 7, Table 2). Also we have also optimized the reaction temperature and found 110 °C as optimum temperature for this reaction.

# 3.4. Scope of the CuO/rGO nanocomposite catalyst in one pot three component coupling reaction for the synthesis of imidazo[1,2-a]pyridines

After having the optimized reaction conditions with established catalyst, the versatility and efficiency of the CuO/rGO nanocomposite catalyst is explored for the synthesis of imidazo[1,2-*a*]pyridines using different substituted 2-aminopyridines, aldehydes and alkynes. The results summarised in Table 3 shows that the reactions preceded extraordinarily well in terms of reaction yields and turn over frequency. The turnover frequency (TOF) of the synthesized catalyst is found to be higher than the previously reported TOF data for the imidazo[1,2-a]pyridines synthesis [18]. To investigate the scope and limitation of the established catalytic system CuO/rGO nanocomposite in the aforementioned reaction, various substrates containing electron donating, electron withdrawing and neutral groups were exposed. The benzaldehyde containing electron withdrawing groups such as Cl coupled with both substituted and un-substituted 2-aminopyridines and phenyl acetylenes to give excellent yields of the product (entry 5,6,7, 10, 15 table 3). But electron donating groups on benzaldehyde afforded slightly lower yield of the desired product than that of un-substituted benzaldehyde as well as benzaldehyde containing electron withdrawing groups (entry 3, 11, 12, 13 Table 3). Further, the phenylacetylenes containing electron donating groups such as methyl gave slightly higher yields of the product than that of un-substituted phenylacetylenes. (Entry 2, 8 Table 3). To explore the further scope of the catalyst, we have chosen 2aminopyridines containing different substituent at different positions. Surprisingly, it is found that the effects of electron donating as well as electron withdrawing groups on 2-

aminopyridine ring are not pronounced in this three component coupling reaction under the catalytic system.

The proposed mechanism for the synthesis of imidazo[1,2-*a*]pyridine by CuO NPs based on the previous literature on Cu(II) catalytic system is shown in scheme 2 [38]. First, condensation of 2-aminopyridine and benzaldehyde gives the 2-iminepyridine (2), a Schiff base followed by Cu(II)-mediated aminomethylation of alkyne (1) with the Schiff basecopper complex results the formation of propargylamines (3). Then the cyclization of propargylamines gives intermediate 4 which then went through rearomatization to provide imidazo[1,2-*a*]pyridines.

#### 3.5. Stability and reusability of the nanocomposite catalyst

Since several heterogeneous catalysts suffer from leaching of the active species from the support, and as a result of which the stability and reusability of the catalysts are highly limited. To check whether the active species CuO leached out from the rGO support during the reaction, a hot filtration test was performed. In this typical test, a mixture of 2-aminopyridine, benzaldehyde and phenylacetylene was stirred in presence of the CuO/rGO nanocomposite catalyst under optimized conditions. After continuing the reaction for 3 h, the catalyst was separated and the reaction yield was found to be 49% yield. After that, the filtrate portion was heated further upto 5 h to check the progress of the reaction which shows no further progress of the reaction. This clearly proves that no CuO NPs was leached from the catalyst after performing the reaction. These findings enthused us for subsequent investigation of the reusability of the catalyst. The reusability of the CuO/rGO and CuO/h-

BN nanocomposites were investigated for the three component coupling reaction of 2aminopyridine, 4-chlorobenzaldehyde and phenylacetylene. After accomplishment of the reaction, the catalyst were simply recovered through filtration and washed with first water and then by acetone and dried in air oven. The recovered catalyst was then used for further reaction without any activation of the catalyst. As shown in Fig. 8, CuO/rGO nanocomposite catalyst can be consecutively used for five times without loss of significant activity for the aforementioned reaction. But a significant decrease of the catalytic activity of the CuO/h-BN nanocomposite is found after first cycle of the reaction as shown in the Fig. 8.

Moreover, to confirm the stability of the catalyst, the size and shape, surface morphology and the chemical oxidation state of the CuO/rGO and CuO/h-BN nanocomposites catalyst were investigated by XRD, TEM and XPS after first run of the reaction. The XRD of CuO/rGO nanocomposite as shown in the Fig. 9 revealed that the crystallinity of the nanocomposite remain same after performing the catalytic reaction. The average crystallite size of the CuO NPs for reused catalyst is determined by Sherrer equation using PDXL software in XRD and found to be 2.7 nm which is very close to the CuO NPs in the CuO/rGO composite before the catalytic reaction.

The XPS proved that the oxidation state of the Cu in CuO/rGO nanocomposite after performing the reaction remain same as before the reaction (Fig. 9). The Cu2p spectra in the CuO/rGO have a specific shape for cupric species containing the doublet Cu2p<sub>1/2</sub>, <sub>3/2</sub> with the spin-orbital splitting of 19.80 eV and the maximum of Cu2p<sub>3/2</sub> at 932.91 eV and charge transfer satellites for each component in the doublet. Also the same observation was found in case of reused CuO/rGO after performing the reaction. This confirms that CuO NPs are well decorated onto the surface of rGO sheets and are very stable even after its use as catalyst in the reaction.

Furthermore, TEM images of recycled CuO/rGO nanocomposite catalyst showed preserve of nano structure with uniform distribution of spherical CuO NPs onto rGO sheets as in the fresh catalyst (Fig. 9(b-c)). Particle size distribution plot obtained from TEM measurements showed the average size of the CuO NPs at around  $5 \pm 0.70$  nm which is almost similar to that observed in the fresh catalyst. These results evident that CuO/rGO nanocomposite catalyst is physically as well as chemically stable. However, the TEM image of the CuO/h-BN nanocomposite shows a significant change in the morphology compared with the CuO/rGO nanocomposite ((Fig. 9(d-e)). This is the reason for the rapid decrease in the yield of the coupled product after the first cycle of the CuO/h-BN nanocomposite catalysed reaction. This may be due to the instability of the CuO NPs onto h-BN sheets because of the absence of adequate number of oxygen containing functional groups on h-BN sheets unlike the rGO sheets where the presence of sufficient amount of oxygen containing functional groups can act as anchor for the decoration of NPs.

#### 4. Conclusion

In conclusion, we have developed various two dimensional nanocomposite material of Cu with graphene as well as functionalized hexagonal boron nitride and evaluated their catalytic efficiency towards the synthesis of imidazo[1,2-*a*]pyridines. CuO/rGO nanocomposite was found to be the most efficient catalyst in the three component coupling reaction of various substituted 2-aminopyridine, aryl aldehyde and terminal alkynes. Unlike the previous reports, this protocol avoids the need of anaerobic procedures, uses cost effective two dimensional Cu catalysts and affords excellent yields of expected products with a wide range of functional groups tolerance. The catalyst morphology remains unaltered even after performing the reaction that proves the formation of stable composite materials which is an important parameter in chemical industry. In summarizing, although there have been many

report for the development of metal/metal oxide-graphene nanocomposite materials in different catalysis, the commercial applicability of these catalysts in industrial process is yet to be explored. However, the main issue in industrial applications is the large scale productivity of the catalyst and it mainly depends on its activity as well stability. In that case the present study on developing 2D nanocomposite materials as stable catalyst for the synthesis of industrially important compounds imidazo[1,2-*a*]pyridine derivatives will provide an important platform.

#### Acknowledgements

The authors are grateful to the Department of Science and Technology, New Delhi for the financial support (DST Project No. INT/RUS/RFBR/P-193 & CSIR-NEIST Project No. GPP 301). The authors are also thankful to the Director, CSIR–NEIST, Jorhat, for his interest in this work. VF acknowledges financial support from the Russian Foundation for Basic Research (Project No. RFBR15-53-45041). We are also thankful to SAIF NEHU, Shillong for the TEM and HRTEM facility. NH acknowledges UGC, New Delhi, India for SRF Fellowship grant.

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# Figures



**Fig. 1**. XRD pattern of (a) CuO/rGO, (b) CuO/h-BN, (c) CuS/h-BN, (d) Cu(0)/h-BN nanocomposites



**Fig. 2.** Low magnified TEM images of CuO/rGO nanocomposite (a, b and d), particle size distribution curve (c), high magnified TEM image of a single nanoparticle (e), SAED pattern of CuO NPs (f)



**Fig. 3.** Low magnified TEM images of CuO/h-BN nanocomposite (a,b and d), particle size distribution curve (c), high magnified TEM image of s single particle (e), SAED pattern of CuO NPs (f)



**Fig. 4.** TEM images of Cu(0)/h-BN nanocomposite (a-b) along with particle size distribution curve (c) and TEM images of CuS/h-BN nanocomposite (d-f).



**Fig. 5.** FTIR spectra of (a) h-BN, (b) CuO/h-BN nanocomposite, (c) GO and (d) CuO/rGO nanocomposite



Fig. 6. High resolution C1s and O1s XPS spectra of CuO/rGO nanocomposite



Fig. 7. N1s and B1s XPS spectra of CuO/h-BN nanocomposite



**Fig. 8.** Reusability of the CuO/rGO and CuO/h-BN nanocomposites in imidazo[1,2-a]pyridines synthesis





**Fig. 9.** a) XRD pattern of reused CuO/rGO and CuO/h-BN nanocomposites, (b-c) TEM images of reused CuO/rGO nanocomposite, (d-e) TEM images of reused CuO/h-BN nanocomposite, (f) XPS spectra of CuO/rGO and CuO/h-BN nanocomposites before and after performing reaction.



Scheme 1: Imidazo[1,2-*a*]pyridine-based molecules



Scheme 2: Proposed mechanism for the CuO catalysed imidazo[1,2-a]pyridine synthesis

$\begin{array}{c} & & \\ & & \\ R_1 \end{array} \overset{N}{\longrightarrow} H_2 \\ & & \\ R_2 \end{array} + R_3 \overset{Catalyst, DMSO}{\underset{Reaction condition}{}} \\ & & \\ \end{array} \overset{R_1}{\longrightarrow} \overset{N}{\longrightarrow} R_2 \\ & & \\ R_2 \end{array}$						
Entry	Catalysts	Particle Diameter <sup>b</sup>	$\mathbf{R}_1$	<b>R</b> <sub>2</sub>	<b>R</b> <sub>3</sub>	Yield <sup>c</sup> (%)
1		(1111)	Н	Cl	Н	95
2	CuO/rGO	$5 \pm 1.43$	Н	Н	H	91
3			Me	Н	Me	92
1			Н	Cl	Н	92
2	CuO/h-BN	$9 \pm 1.81$	Н	Н	Н	90
3			Me	Н	Me	91
1			Н	Cl	Η	88
2	Cu(0)/rGO	$12 \pm 4.82$	Н	Н	Η	86
3			Me	Н	Me	89
1			Н	Cl	Η	86
2	Cu(0)/h-BN	$14 \pm 0.48$	Н	Н	Н	81
3			Me	Н	Me	86
1			Н	Cl	Н	62
2	CuS/rGO	183+48.51	Н	Н	Η	59
3			Me	Н	Me	40
1		>> 190	Н	Cl	Η	58
2	CuS/h-BN	(Cluster type	Н	Н	Η	52
3		Structure)	Me	Н	Me	49

# Table 1. Comparison of catalytic activity of different synthesized nanocomposite catalysts <sup>a</sup>

<sup>a</sup> Reaction conditions: **2-aminopyridine** (1 mmol), **aldehyde** (1.2 mmol), **alkyne** (1.2 mmol), **catalyst** (0.015 g), **DMSO** (3 mL,) 110 <sup>0</sup>C, 8 h; <sup>b</sup> Average size of the nanoparticles with standard deviation measured by TEM analysis; <sup>c</sup>Isolated Yield

$ \underbrace{\bigcup_{N}^{NH_2}}_{N} + \underbrace{\bigcup_{+}^{CHO}}_{T} + \underbrace{\underbrace{\bigcup_{-}^{CHO}}_{T}}_{T} \underbrace{\underbrace{\underbrace{\bigcup_{N}^{N}}}_{N}}_{T} \underbrace{\underbrace{\underbrace{\bigcup_{N}^{N}}}_{N}}_{N}}_{T} \underbrace{\underbrace{\underbrace{\bigcup_{N}^{N}}}_{N}}_{N}}_{N}}_{N} \underbrace{\underbrace{\underbrace{\bigcup_{N}^{N}}}_{N}}_{N}}_{N} \underbrace{\underbrace{\underbrace{\bigcup_{N}^{N}}}_{N}}_{N}}_{N}}_{N}}_{N}}_{N}}_{N}}_{N}}_{N} \underbrace{\underbrace{\underbrace{\bigcup_{N}^{N}}}_{N$						
Entry	Solvent	Temperature ( <sup>0</sup> C)	Time (h)	Yield (%) <sup>b</sup>		
1	H <sub>2</sub> O	60	5	No reaction		
2	H <sub>2</sub> O	110	10	No reaction		
3	H <sub>2</sub> O	120	24	No reaction		
4	DMF	60	10	25		
5	DMF	80	6	63		
6	DMF	110	8	85		
7	DMSO	110	6	91		
8	DMSO	110	8	91		
9	DMSO	80	10	70		
10	DMSO	120	10	91		
11	NMP	100	10	60		
12	NMP	120	15	74		
13	Acetonitrile	120	10	49		
14	Toluene	120	20	20		
15	Toluene	140	20	24		
<sup>a</sup> Reaction co	nditions: 2-aminopyridine (	1 mmol), <b>phenylacetylene</b> (1.2 mmo	ol), benzaldehyde (	1.2 mmol), CuO/-rGO		

# Table 2. Effect of solvent, time and temperature on the three component coupling reaction <sup>a</sup>

(0.015 g; 2.8% CuO), Solvent (3 mL,)  $^{b}$  Isolated yield

# Table 3: Substrate scope of the CuO/-rGO nanocomposite catalyst towards one pot three component coupling reaction <sup>a</sup>



Entry	2-Amino- pyridine	Aldehyde 2(a-d)	Alkyne 3(a-c)	Product 4(a-p)	<b>Yield</b> <sup>b</sup> (%)	TOF(h <sup>-1</sup> ) <sup>c</sup>
1	$\frac{I(\mathbf{a} \cdot \mathbf{e})}{1\mathbf{a}}^{N H_2}$	Сно 2а	3a -==		91	29.76
2	19	29		4a	03	32 73
2	14	24	<b>⟨</b> ⟩-== 3b			32.13
3	1a	2b	3a		89	29.76
4	1a	2b	3b		91	32.73
5	1a		3a		95	33.63
6	1a	2c	3b		95	33.63

7	1a	2c	3c		93	32.74
8	NH <sub>2</sub> N 1b	2a	3b		92	32.7
9		2a	3a		91	29.76
10	NH <sub>2</sub> 1d	2c	3a		94	35.72
11	1a	MeO 2d	3a	Generative Ak	88	29.8
12	1a	2d	3c		86	29.7
13	NH <sub>2</sub> N 1e	2b	3a		89	32.74

14	1d	2c	3b	94	33.3
15	1c	2c	3a	93	32.7
16	1c	2b	3a	92	33.1

<sup>a</sup> Reaction conditions: **2-aminopyridine** (1 mmol), **Alkyne** (1.2 mmol), **Aldehyde** (1.2 mmol), CuO/-rGO (0.015 g; 2.8% CuO), DMSO (3 mL), Temperature 110 °C, Time 6 h, <sup>b</sup> Isolated Yield, <sup>c</sup> TOF= mol of product/(mol of CuO × reaction time)]