Copper ferrite nanoparticles: an effective and recoverable nanomagnetic catalyst for the synthesis of *N*, *N*′,*N*″-trisubstituted guanidines from the addition reaction of anilines to carbodiimide

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In this study, copper ferrite ($CuFe_2O_4$) nanoparticles were successfully prepared and employed as an efficient catalyst for the synthesis of guanidine derivatives through the addition of anilines to *N*, *N*-dicyclohexylcarcodiimide under solvent-free conditions. This magnetically retrievable catalyst was well characterised by Fourier transform infrared spectroscopy, X-ray powder diffraction, transmission electron microscopy and field emission scanning electron microscope-energy dispersive X-ray techniques. The catalyst can be readily recovered from the reaction mixture by the use of an external magnet and reused several times without remarkable loss of its catalytic activity.

1. Introduction: Guanidines, as a valuable structural unit, play significant function in a broad scope from supramolecular chemistry to biological and pharmaceutical applications [1–4]. In the field of organic synthesis, they can advantageously serve a diverse range of tasks including superbase catalysts [5], building-blocks for preparation of various *N*-heterocyclic compounds [6–8], as well as expedient ligands to provide a wide variety of metal complexes [9, 10]. Hence, design and development of effective protocols in order to obtain guanidine derivatives has attracted growing interest during the past decades. In this regard, several methods have been introduced on the basis of employing different guanidylating agents and conditions such as urea, thiourea and isothiourea derivatives [11, 12], cyanamides [13, 14], chloroformamidines [15], aminoiminomethanesulfonic acids [16], microwave-assisted and mechanochemical techniques [17–20]. Apart from that, carbodiimide derivatives have been regarded as one of the most prevalent reagents for the construction of guanidine-based scaffolds, chiefly via nucleophilic addition of amines [21]. Generally, proceeding this synthetic method requires a metal-catalised process which mainly involves the use of transition-metal catalysts. Accordingly, numerous reports have been presented about the synthesis of guanidine derivatives through the reaction of aromatic and aliphatic amines with carbodiimides (carbodiimide guanidylation) by means of metal-based catalysis [22–26].

Nowadays, utilisation of heterogeneous catalysts (especially nano-catalysts) seems to be an inevitable necessity in different branches of organic synthesis, either from economical or environmental and green chemistry aspects, which accounts for their notable characteristics particularly recovery and reusability features [27, 28]. Within the past years, a few approaches have been developed in order to achieve substituted guanidines through carbodiimide guanidylation by use of heterogeneous metal catalysis [29–31]. Kantam *et al.* [32] reported an efficient procedure to convert various amines into *N*, *N*′,*N*″-trisubstituted guanidines in the presence of *N*, *N*-dicyclohexylcarcodiimide (DCC) using nanocrystalline ZnO as an appropriate heterogeneous catalyst. Furthermore, Corma and his co-workers [33] employed supported palladium nanoparticles to afford *N*-styrylguanidine derivatives from iodoanilines and carbodiimides. Meanwhile, regarding the significant properties of nano-magnetic heterogeneous catalysts, Heydari and co-workers [34] applied CuO immobilised on γ-Fe_2O_3 nanoparticles (CuO@ γ-Fe_2O_3) to catalyse the guanidylation reaction of amines with carbodiimides. On the other hand, copper ferrite ($CuFe_2O_4$) has been found widespread usage in several scientific fields due to remarkable magnetic and conducting effects, favourable chemical and thermal stability together with beneficial catalytic efficiency [35–37]. From the viewpoint of organic chemistry, $CuFe_2O_4$ nanoparticles with noticeable surface area have been utilised in many organic transformations over the last decade [38–42].

According to the aforementioned points, herein we reported a convenient and advantageous approach for the synthesis of *N*, *N*′, *N*″-trisubstituted guanidines via the addition reaction of different anilines to DCC by using $CuFe_2O_4$ nanoparticles as an efficacious and magnetically recoverable catalyst which successfully led to the formation of the desired products.

2. Experimental

2.1. General: Measurement of melting points was accomplished by an Electrothermal Engineering IA9100 apparatus. Bruker Ultrashield 400 MHz Avance III spectrometer was employed to assign ^1H and ^{13}C NMR spectra. Fourier transform infrared spectroscopy (FTIR) was carried out on a Bruker vector 22 spectrometer through KBr pellets. A Costech-ECS 4010 CHNSO Analyser was employed to estimate the elemental analyses. X-ray powder diffraction (XRD) patterns were analysed by means of Philips PW 1830 X-ray diffractometer within a range of Bragg's angle (0.8–80°) with Cu K_α source ($\lambda = 1.5418$ Å). LEO-1455VP microscope was applied for scanning electron microscope (SEM) analysis (acceleration voltage 10 kV). Transmission electron microscopy (TEM) experiments were screened by a Philips EM 208 electron microscope.

2.2. Preparation of copper ferrite ($CuFe_2O_4$): $CuFe_2O_4$ nanoparticles were obtained by means of co-precipitation synthesis method as reported in the literature [38, 43]. At first, to a solution including $Fe(NO_3)_3.9H_2O$ (3.34 g, 8.2 mmol) and $Cu(NO_3)_2.3H_2O$ (1.0 g, 4.1 mmol) in 75 ml of deionised water, an aqueous solution of sodium hydroxide containing NaOH (3.0 g, 75 mmol) in 15 ml of water was added in a dropwise manner within a period of 10 min at room temperature. Upon the formation of a reddish-black precipitate, the reaction temperature was raised to 90°C for 2 h along with continuous stirring. Afterwards, the reaction mixture was cooled to room temperature and then, the attained magnetic nanoparticles were separated by use of an external magnet. Next, it was washed three times with deionised water (3 × 30 ml) and was dried in an air oven overnight at 80°C. Subsequently, it was allowed to maintain

in a furnace at 700°C for 5 h (heating rate of 20°C min^{-1}), after grinding with a pestle and mortar. Finally, cooling to room temperature resulted in 0.842 g of $CuFe_2O_4$ nanoparticles.

2.3. General procedure for the synthesis of *N*, *N*′,*N*″-trisubstituted guanidine derivatives: In a 25 ml round-bottomed flask, DCC (1.0 mmol, 0.206 g) and $CuFe_2O_4$ (0.0459 g) were added which followed by heating at 80°C for 10 min. Afterwards, aniline (1.2 mmol, 0.11 ml) was added and the mixture was allowed to keep stirring for 3 h. Progress of the reaction was monitored via thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature and after addition of ethyl acetate (10.0 ml), the reaction vessel was exposed to sonication for 2 min. Next, nanomagnetic catalyst was separated from the solution by means of an external magnet. Subsequently, evaporation of the solvent under reduced pressure afforded the product and if needed, purification by several washing with solvent gave the desired compound. All of the products were well-characterised by melting point and NMR spectra and are available upon request from the corresponding author (Fig. 1).

2.4. Characterisation data for prepared compounds:

N-phenyl-*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 1, **2a**): White solid, mp:166–168°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.8 Hz, 2H, Ph-H), 6.93 (t, *J* = 7.6 Hz, 1H, Ph-H), 6.87 (dd, *J* = 8.4, 1.2 Hz, 2H, Ph-H), 3.66 (br s, 2H, NH), 3.43 (br s, 2H, Cy-H), 2.00–2.06 (m, 4H, Cy-H), 1.68–1.73 (m, 4H, Cy-H), 1.59–1.64 (m, 2H, Cy-H), 1.28–1.42 (m, 4H, Cy-H), 1.06–1.22 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.39, 150.03, 129.22, 123.63, 121.31, 50.23, 33.84, 25.69, 24.92.

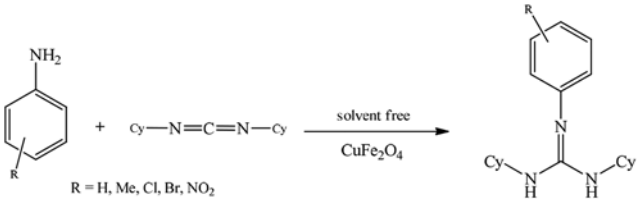
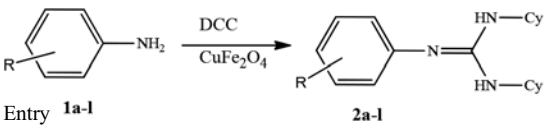


Fig. 1 *Synthesis of N,N′,N″-trisubstituted guanidines using $CuFe_2O_4$ nanoparticles*

Table 1 Synthesis of different *N*, *N*′,*N*″-trisubstituted guanidines using $CuFe_2O_4$ nanoparticles under solvent-free conditions[a]



Entry **1a-l** **2a-l**

	Starting material	Product	Time, h	Yield, %[b]
1	$PhNH_2$	**2a**	3	98
2	4-Cl-$PhNH_2$	**2b**	2	98
3	3-Cl-$PhNH_2$	**3b**	2	97
4	2,4-DiCl-$PhNH_2$	**2d**	2	97
5	4-Me-$PHNH_2$	**2e**	3	97
6	4-MeO-$PhNH_2$	**2f**	2	98
7	4-Br-$PhNH_2$	**2g**	2.5	95
8	3-Br-$PhNH_2$	**2h**	2.5	96
9	2-Br-$PhNH_2$	**2i**	2.5	97
10	4-NO_2-$PhNH_2$	**2j**	5	96
11	3-NO_2-$PhNH_2$	**2k**	5	92
12	2-NO_2-$PhNH_2$	**2l**	5	94

[a]Reaction conditions: DCC (1 mmol), aniline (1.2 mmol), 80°C, solvent free.
[b]Isolated pure yields.

N-p-Chlorophenyl -*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 2, **2b**): White solid, mp:154–156°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.8 Hz, 2H, Ph-H), 6.80 (d, *J* = 8.4 Hz, 2H, Ph-H), 3.62 (br s, 2H, NH), 3.42 (br s, 2H, Cy-H), 1.98–2.02 (m, 4H, Cy-H), 1.59–1.73 (m, 6H, Cy-H), 1.30–1.41 (m, 4H, Cy-H), 1.06–1.21 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.119, 149.17, 129.21, 126.20, 124.94, 50.19, 33.81, 25.65, 24.89.

N-m-Chlorophenyl-*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 3, **2c**): White solid, mp: 132–135°C; Anal.Calcd. for $C_{19}H_{28}ClN_3$ (%): C, 68.35; H, 8.45; N, 12.58. Found (%): C, 68.34; H, 8.51; N, 12.62. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 8.0 Hz, 1H, Ph-H), 6.87–6.91 (m, 2H, Ph-H), 6.75 (ddd, *J* = 8.0, 1.8, 1.0 Hz, 1H, Ph-H), 3.67 (s, 1H, NH), 3.65 (s, 1H, NH), 3.38–3.45 (m, 2H, Cy-H), 1.99–2.03 (m, 4H, Cy-H), 1.59–1.74 (m, 6H, Cy-H), 1.31–1.42 (m, 4H, Cy-H), 1.06–1.23 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.11, 150.05, 134.52, 130.13, 123.78, 121.82, 121.17, 50.22, 33.80, 25.64, 24.90.

N-(2,4-Dichlorophenyl)-*N*′,*N*″-dicyclohexylguanidine (Table 1, entry 4, **2d**): White solid, mp: 132–133°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.4 Hz, 1H, Ph-H), 6.91 (d, *J* = 2.4 Hz, 1H, Ph-H), 6.66 (dd, *J* = 8.4, 2.4 Hz, 1H, Ph-H), 3.70 (br s, 2H, NH), 3.37 (br s, 2H, Cy-H), 1.93–1.97 (m, 4H, Cy-H), 1.54–1.68 (m, 6H, Cy-H), 1.26–1.36 (m, 4H, Cy-H), 1.02–1.15 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.54, 150.35, 132.34, 130.59, 125.31, 123.90, 123.26, 50.16, 33.68, 25.54, 24.83.

N-p-Methylphenyl-*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 5, **2e**): White solid, mp:156–158°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.0 Hz, 2H, Ph-H), 6.76 (d, *J* = 8.0 Hz, 2H, Ph-H), 3.63 (br s, 2H, NH), 3.42 (br s, 2H, Cy-H), 2.29 (s, 3H, Ar-CH_3), 2.00–2.03 (m, 4H, Cy-H), 1.68–1.73 (m, 4H, Cy-H), 1.58–1.63 (m, 2H, Cy-H), 1.31–1.41 (m, 4H, Cy-H), 1.05–1.21 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.14, 147.62, 130.39, 129.82, 123.37, 50.20, 33.87, 25.71, 24.95, 20.76.

N-p-Methoxyphenyl -*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 6, **2f**): White solid, mp: 144–145°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78–6.84 (m, 4H, Ph-H), 3.79 (s, 3H, Ar-OCH_3), 3.61 (br s, 2H, NH), 3.48 (br s, 2H, Cy-H), 2.00–2.01 (m, 4H, Cy-H), 1.69–1.72 (m, 5H, Cy-H), 1.27–1.41 (m, 5H, Cy-H), 1.06–1.21 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.49, 150.48, 143.46, 124.31, 114.59, 55.47, 34.93, 33.85, 25.70, 24.93.

N-p-Bromophenyl-*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 7, **2g**): White solid, mp: 158–160°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.4 Hz, 2H, Ph-H), 6.75 (d, *J* = 8.4 Hz, 2H, Ph-H), 3.66 (br s, 2H, NH), 3.41 (br s, 2H, Cy-H), 1.99–2.01 (m, 4H, Cy-H), 1.69–1.73 (m, 4H, Cy-H), 1.60–1.64 (m, 2H, Cy-H), 1.35–1.38 (m, 3H, Cy-H), 1.27–1.32 (m, 2H, Cy-H), 1.07–1.19 (m, 5H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.08, 142.82, 132.19, 125.41, 113.87, 50.23, 33.81, 25.63, 24.89.

N-m-Bromophenyl -*N*′, *N*″-dicyclohexylguanidine (Table 1, entry 8, **2h**): White solid, mp: 142–145°C; Anal.Calcd. for $C_{19}H_{28}BrN_3$ (%): C, 60.32; H, 7.46; N, 11.11. Found (%): C, 60.33; H, 7.52; N, 11.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (t, *J* = 8.0 Hz, 1H, Ph-H), 7.04–7.06 (m, 2H, Ph-H), 6.79 (d, *J* = 8.0 Hz, 1H, Ph-H), 3.67 (br s, 2H, NH), 3.41 (br s, 2H, Cy-H), 1.99–2.03 (m, 4H, Cy-H), 1.69–1.74 (m, 4H, Cy-H), 1.60–1.64 (m, 2H, Cy-H), 1.31–1.42 (m, 4H, Cy-H), 1.07–1.23 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.28, 150.08, 130.44, 126.71, 124.05, 122.79, 122.27, 50.23, 33.80, 25.64, 24.90.

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N-o-Bromophenyl -*N′, N″*-dicyclohexylguanidine (Table 1, entry 9, **2i**): White solid, mp:128–129°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.46 (dd, J = 8.0, 1.2 Hz, 1H, Ph-H), 7.14 (t, J = 7.2 Hz, 1H, Ph-H), 6.77 (dd, J = 8.0,1.6 Hz, 1H, Ph-H), 6.70 (t, J = 8.0 Hz, 1H, Ph-H), 4.82 (s, 1H, NH), 4.80 (s, 1H, NH), 3.36 (br s, overlapped with the peak of DMSO(HOD), 2H, Cy-H), 1.83–1.85 (m, 4H, Cy-H), 1.59–1.62 (m, 4H, Cy-H), 1.49–1.51 (m, 2H, Cy-H), 1.05–1.25 (m, 10H, Cy-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.35, 149.98, 132.81, 128.46, 124.18, 121.51, 118.67, 49.91, 33.45, 25.78, 25.14.

N-p-Nitrophenyl -*N′, N″*-dicyclohexylguanidine (Table 1, entry 10, **2j**): Yellow solid, mp: 153–155°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J = 9.2 Hz, 2H, Ph-H), 6.91 (d, J = 9.2 Hz, 2H, Ph-H), 3.90 (br s, 2H, NH), 3.44 (br s, 2H, Cy-H), 1.99–2.02 (m, 4H, Cy-H), 1.61–1.75 (m, 6H, Cy-H), 1.31–1.42 (m, 4H, Cy-H), 1.10–1.23 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.47, 150.38, 140.83, 125.61, 122.82, 50.34, 33.65, 25.52, 24.82.

N-m-Nitrophenyl-*N′, N″*-dicyclohexylguanidine (Table 1, entry 11, **2K**): Yellow solid, mp: 170–171°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.76 (m, 2H, Ph-H), 7.37 (t, J = 8.0 Hz, 1H, Ph-H), 7.19 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H, Ph-H), 3.71 (s, 1H, NH), 3.69 (s, 1H, NH), 3.39–3.48 (m, 2H, Cy-H), 2.00–2.04 (m, 4H, Cy-H), 1.60–1.74 (m, 6H, Cy-H), 1.31–1.42 (m, 4H, Cy-H), 1.08–1.23 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.16, 150.33, 149.21,130.22, 129.73, 118.17, 115.77, 50.27, 33.76, 25.58, 24.86.

N-o-Nitrophenyl-*N′, N″*-dicyclohexylguanidine (Table 1, entry 12, **2l**): Yellow solid, mp: 122–124°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, J = 8.0, 1.6 Hz, 1H, Ph-H), 7.41 (t, J = 8.0 Hz, 1H, Ph-H), 6.99 (d, J = 8.4 Hz, 1H, Ph-H), 6.96 (t, J = 8.2 Hz, 1H, Ph-H), 3.65 (s, 1H, NH), 3.63 (s, 1H, NH), 3.37–3.44 (m, 2H, Cy-H), 2.00–2.04 (m, 4H, Cy-H), 1.58–1.73 (m, 6H, Cy-H), 1.29–1.40 (m, 4H, Cy-H), 1.07–1.21 (m, 6H, Cy-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.95, 145.55, 143.72,133.37, 127.06, 125.26, 120.72, 50.39, 33.75, 25.61, 24.90.

3. Results and discussion: The nanomagnetic catalyst was well characterised by FTIR, XRD, TEM and FESEM-EDX techniques. FTIR analysis was applied in order to investigate the presence of characteristic peaks of prepared $CuFe_2O_4$ nanoparticles (Fig. 2). As shown in Fig. 2, a strong absorption band at 598 cm^{-1} is clearly related to the Fe–O stretching vibration (attributed to the tetrahedral sites of copper ferrite). Furthermore, absorption peak at 435 cm^{-1} represents the existence of Cu–O stretching vibration corresponding to octahedral positions of $CuFe_2O_4$. Moreover, the peak appeared at 1545 cm^{-1} as well as, a broad band at 3398 cm^{-1} obviously reveals the bending and stretching vibrations of O–H groups, respectively.

To evaluate the crystalline structure of synthesised $CuFe_2O_4$ nanoparticles, XRD technique was utilised. As can be seen in Fig. 3, all the characteristic reflection peaks emerged at 2θ values: 18.3, 30.1, 35.6, 43.5, 57.9 and 62.4 which are appropriately in accordance with the standard XRD data carts related to copper ferrite crystals with a spinel structure (JCPDS Card No. 034–0425) [43, 44]. Meanwhile, the average crystal size of the $CuFe_2O_4$ was attained about 24 nm according to the Scherrer equation which evidently approves the nano-sized crystallinity of the prepared copper ferrite.

Field emission scanning electron microscope (FESEM) was employed to survey the surface morphology of prepared $CuFe_2O_4$ nanoparticles. As displayed in Fig. 4, FESEM micrographs disclose the spinel structure of copper ferrite. In addition, FESEM analysis indicates that the average particle size is in the range of 15–25 nm. Besides, studying the elemental distribution of $CuFe_2O_4$ was achieved by using energy dispersive X-ray (EDX) spectrum (Fig. 5) which properly reveals the presence of Cu (12.66%), Fe (22.53%) and O (64.80%) elements in the catalyst (calculated Fe/Cu ratio is ∼1.78).

Moreover, TEM image of prepared copper ferrite (Fig. 6) clarifies the tetragonal crystalline structure of $CuFe_2O_4$ nanoparticles with the particle size of 16 nm which is consistent with FESEM results.

3.1. Catalytic effect of $CuFe_2O_4$ nanoparticles in guanidylation reactions of anilines: The catalytic efficiency of $CuFe_2O_4$

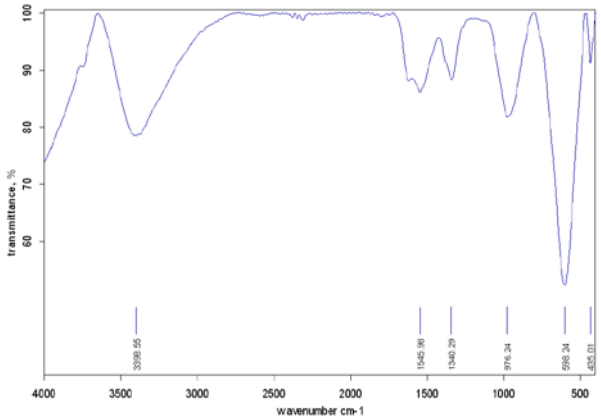


Fig. 2 *FTIR spectrum of $CuFe_2O_4$ nanoparticles*

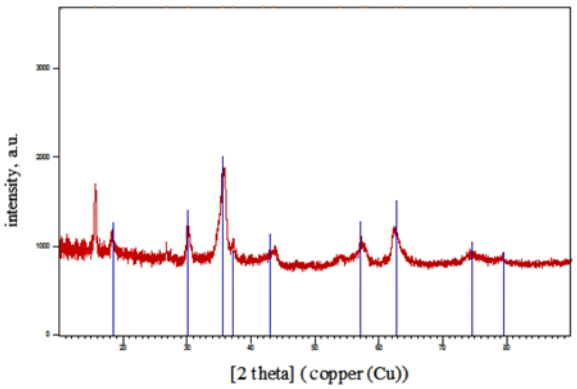


Fig. 3 *XRD pattern of $CuFe_2O_4$ nanoparticles*

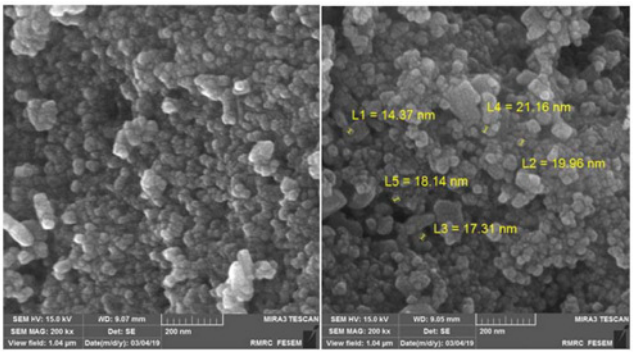


Fig. 4 *FESEM images of copper ferrite nanoparticles*

nanoparticles was studied in guanidylation reactions of various anilines with DCC in order to prepare *N*, *N*′,*N*″-trisubstituted guanidines. In this trend, the reaction of aniline (1.2 mmol) and DCC (1 mmol) in the presence of copper ferrite nanoparticles (catalyst) was elected as model reaction to ascertain the optimum conditions whose results are summarised in Table 2. Firstly, to explore the effect of solvent on progress of our model reaction, a series of solvents comprising ethyl acetate, water, dichloromethane, n-hexane and tetrahydrofuran were examined at 60°C (Table 2, entries 1–5).

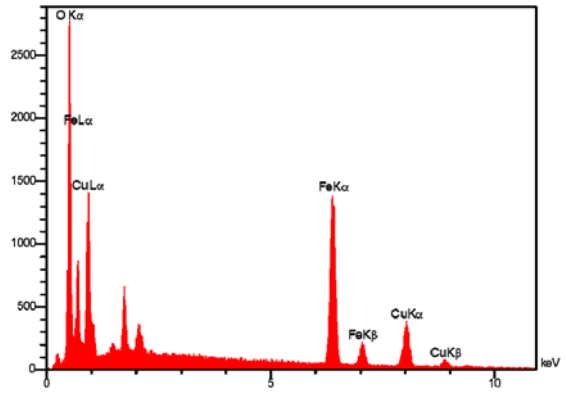


Fig. 5 *EDX analysis of $CuFe_2O_4$ nanoparticles*

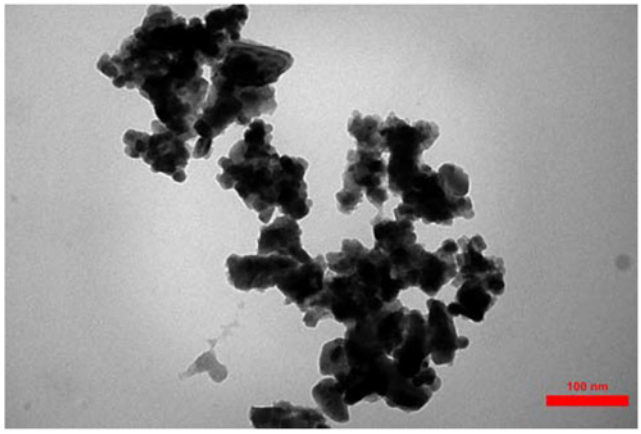


Fig. 6 *TEM image of copper ferrite nanoparticles*

Table 2 Optimisation of reaction conditions for the synthesis of *N*, *N*′,*N*″-trisubstituted guanidines from aniline and DCC[a]

Entry	Solvent	Catalyst, mg	Temperature, °C	Yield, %[b]
1	water	40	60	20
2	dichloromethane	40	60	60
3	ethyl acetate	40	60	50
4	n-hexane	40	60	40
5	THF	40	60	30
6	—	40	60	75
7	—	40	80	98
8	—	40	100	98
9	—	40	r.t.	5
10	—	30	80	55
11	—	50	80	98
12	—	—	80	—

[a]Reaction conditions: DCC (1 mmol), aniline (1.2 mmol), solvent (3 ml), 3 h.
[b]Isolated yields.

Meanwhile, the reaction was assessed under solvent-free condition (Table 2, entry 6). As can be observed from Table 2, the solvent-free condition strikingly afforded the highest yield of the product. In order to investigate the required amount of the catalyst, different quantities of $CuFe_2O_4$ nanoparticles (30, 40 and 50 mg) were tested which accordingly, 40 mg of the catalyst was determined as the optimised amount and increasing the amount of catalyst did not affect the yield (Table 2, entries 7, 10–11). It is worth mentioning that the formation of the corresponding product did not occur in the absence of the catalyst (Table 2, entry 12). Additionally, the optimum temperature of the reaction was analysed by performing at 25°C (room temperature), 60°C, 80°C and 100°C that eventually 80°C was selected as the favourable temperature (Table 2, entries 6–9). As a matter of fact, the product yield considerably was

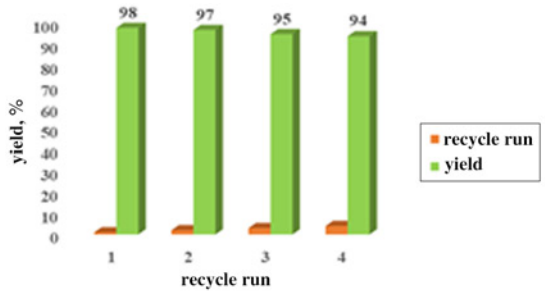
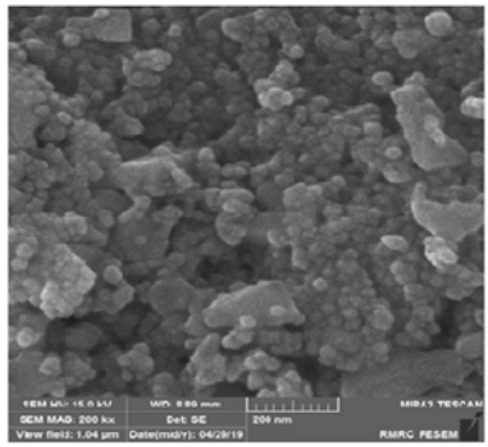
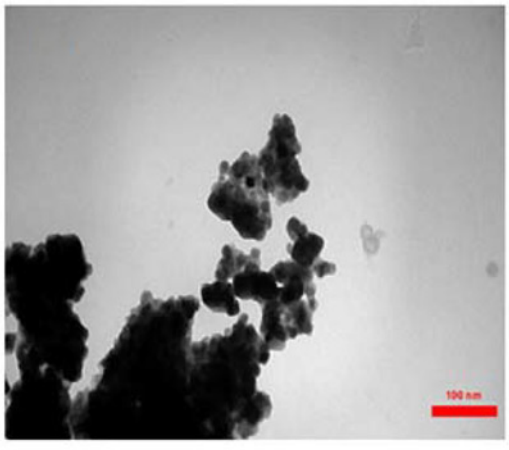


Fig. 7 *Reusability study of the catalyst for the model reaction*



a



b

Fig. 8 *FESEM and TEM images of reused catalyst*
a FESEM image
b TEM image

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impressed by enhancing the temperature to 80°C, whereas raising it to 100°C did not influence the yield.

In the next step, the obtained optimum conditions were exerted for the synthesis of various *N*, *N*′,*N*″-trisubstituted guanidine derivatives (Table 1, entries 1–12). For this purpose, a variety of anilines containing electron-donating and electron-withdrawing groups (Table 1, entries 2–12) were exploited to react with *N*, *N* dicyclohexylcarbodiimide which in all cases afforded the corresponding guanidines in high to excellent yields. Additionally, evaluating the steric effect of diverse ortho, meta and para substituents showed no evident preference for any of these positions. For example, *o*, *m* and *p*-bromo aniline attained the relevant guanidine products in 97, 96 and 95% yield, respectively (Table 1, entries 7–9). Similarly, utilisation of *o*, *m* and *p*-nitro aniline, respectively, resulted in expected *N*, *N*′,*N*″-trisubstituted guanidines in 94, 92 and 96% product yield (Table 1, entries 10–12). Interestingly, 2,4-dichloro aniline unveiled no observable difference in the yield of the product with respect to meta and para monosubstituted aniline (Table 1, entries 2–4).

One of the most important parameters of the heterogeneous catalyst is convenient and effective recovery and reusability of the catalyst which undoubtedly exhibits the efficiency and stability of the catalyst. To estimate the reusability of the catalyst, it was separated after completion of the reaction and was applied for the subsequent run of our model reaction under the same condition. Owing to magnetic character of copper ferrite, it was readily isolated from the reaction mixture (using an external magnet) and reused up to four times with negligible loss of activity in comparison to fresh catalyst (Fig. 7).

As a noteworthy issue, the FESEM and TEM micrographs of the retrieved catalyst did not demonstrate any appreciable change after four-cycle run (Fig. 8).

4. Conclusion: In this work, synthesis of *N*, *N*′,*N*″-trisubstituted guanidines was impressively accomplished by using $CuFe_2O_4$ nanoparticles. This magnetic nano-catalyst exhibited noticeable activity in the reaction of various anilines with DCC in order to achieve guanidine derivatives. Utilising this method, different electron-donating and electron-withdrawing anilines were effectively converted to the corresponding guanidine-containing products with high to excellent yields under solvent-free conditions. Besides, one of the most significant features of this nanomagnetic catalyst is simple and fast separation and recovery process via an external magnet. According to empirical results, the recovered catalyst was suitably reused for next runs up to four times with a small loss in its catalytic effect.

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6 References

[1] Ishikawa T., Kumamoto T.: 'Guanidines in organic synthesis', *Synthesis*, 2006, **2006**, (5), pp. 737–752
[2] Schmuck C., Kuchelmeister H.Y.: 'Guanidinium based anion receptors', in 'Artificial receptors for chemical sensors' (Wiley-VCH, Weinheim, Germany, 2010), pp. 273–317
[3] Berlinck R.G., Trindade-Silva A.E., Santos M.F.: 'The chemistry and biology of organic guanidine derivatives', *Nat. Prod. Rep.*, 2012, **29**, (12), pp. 1382–1406
[4] Alegre-Requena J.V., Marqués-López E., Herrera R.P.: 'Guanidine motif in biologically active peptides', *Aust. J. Chem.*, 2014, **67**, (7), pp. 965–971
[5] Ishikawa T.: 'Superbases for organic synthesis: guanidines, amidines, phosphazenes and related organocatalysts' (John Wiley & Sons, London, UK, 2009)
[6] Evindar G., Batey R.A.: 'Copper-and palladium-catalyzed intramolecular aryl guanidinylation: an efficient method for the synthesis of 2-aminobenzimidazoles', *Org. Lett.*, 2003, **5**, (2), pp. 133–136
[7] Deng X., McAllister H., Mani N.S.: 'Cui-catalyzed amination of arylhalides with guanidines or amidines: A facile synthesis of 1-H-2-substituted benzimidazoles', *J. Org. Chem.*, 2009, **74**, (15), pp. 5742–5745
[8] Zeng F., Alper H.: 'Tandem palladium-catalyzed addition/cyclocarbonylation: an efficient synthesis of 2-heteroquinazolin-4 (3H)-ones', *Org. Lett.*, 2010, **12**, (6), pp. 1188–1191
[9] Coles M.P.: 'Application of neutral amidines and guanidines in coordination chemistry', *Dalton Trans.*, 2006, **8**, pp. 985–1001
[10] Trifonov A.A.: 'Guanidinate and amidopyridinate rare-earth complexes: towards highly reactive alkyl and hydrido species', *Coord. Chem. Rev.*, 2010, **254**, (11–12), pp. 1327–1347
[11] Gers T., Kunce D., Markowski P., *ET AL.*: 'Reagents for efficient conversion of amines to protected guanidines', *Synthesis*, 2004, **2004**, (1), pp. 37–42
[12] Costa M.V., de Sequeira Aguiar L.C., Malta L.F. B., *ET AL.*: 'Simple and efficient methodology to prepare guanidines from 1,3-disubstituted thioureas', *Tetrahedron Lett.*, 2016, **57**, (14), pp. 1585–1588
[13] Larraufie M.H., Ollivier C., Fensterbank L., *ET AL.*: 'Radical synthesis of guanidines from N-acyl cyanamides', *Ang. Chem. Int. Ed.*, 2010, **49**, (12), pp. 2178–2181
[14] Zeng C.J., Chen C.J., Chang C.W., *ET AL.*: 'Copper (i) iodide-catalyzed synthesis of N,N′-disubstituted guanidines from n-substituted cyanamides', *Aust. J. Chem.*, 2014, **67**, (7), pp. 1134–1137
[15] Armitage I., Fu M., Hicks F., *ET AL.*: 'The use of chloroformamidine hydrochloride as a reagent for the synthesis of guanidines from electron deficient aromatic amines', *J. Heterocycl. Chem.*, 2017, **54**, (1), pp. 728–734
[16] Miller A.E., Feeney D.J., Ma Y., *ET AL.*: 'The synthesis of amino-iminoethanenitriles, 5-aminotetrazoles, N-cyanoguanidines, and N-hydroxyguanidines from aminoiminomethanesulfonic acids', *Synth. Commun.*, 1990, **20**, (2), pp. 217–226
[17] Chen C.H., Tung C.L., Sun C.M.: 'Microwave-assisted synthesis of highly functionalized guanidines on soluble polymer support', *Tetrahedron Lett.*, 2012, **53**, (31), pp. 3959–3962
[18] Kukade S.D., Singh S.K., Tekade P.V., *ET AL.*: 'Microwave assisted synthesis, characterization and thermoacoustical study of a β-naphthol-guanidine-formaldehyde copolymer resin', *New J. Chem.*, 2016, **40**, (1), pp. 705–710
[19] Štrukil V.: 'Mechanochemical synthesis of thioureas, ureas and guanidines', *Beilstein J. Org. Chem.*, 2017, **13**, (1), pp. 1828–1849
[20] Đud M., Glasovac Z., Margetić D.: 'The utilization of ball milling in synthesis of aryl guanidines through guanidinylation and N-Boc-deprotection sequence', *Tetrahedron*, 2019, **75**, (1), pp. 109–115
[21] Xu L., Zhang W.X., Xi Z.: 'Mechanistic considerations of the catalytic guanylation reaction of amines with carbodiimides for guanidine synthesis', *Organometallics*, 2015, **34**, (10), pp. 1787–1801
[22] Zhu X., Du Z., Xu F., *ET AL.*: 'Ytterbium triflate: A highly active catalyst for addition of amines to carbodiimides to N,N′,N″-trisubstituted guanidines', *J. Org. Chem.*, 2009, **74**, (16), pp. 6347–6349
[23] Pottabathula S., Royo B.: 'First iron-catalyzed guanylation of amines: a simple and highly efficient protocol to guanidines', *Tetrahedron Lett.*, 2012, **53**, (38), pp. 5156–5158
[24] Tsubokura K., Iwata T., Taichi M., *ET AL.*: 'Direct guanylation of amino groups by cyanamide in water: catalytic generation and activation of unsubstituted carbodiimide by scandium (III) triflate', *Synlett*, 2014, **25**, (9), pp. 1302–1306
[25] Bhattacharjee J., Sachdeva M., Banerjee I., *ET AL.*: 'Zinc catalyzed guanylation reaction of amines with carbodiimides/isocyanate leading to guanidines/urea derivatives formation', *J. Chem. Sci.*, 2016, **128**, (6), pp. 875–881
[26] Harinath A., Bano K., Ahmed S., *ET AL.*: '2-Picolylamino (diphenylphosphinoselenoic) amide supported zinc complexes: efficient catalyst for insertion of N–H bond into carbodiimides, isocyanates, and isothiocyanate', *Phosphorus Sulfur Silicon Relat. Elem.*, 2018, **193**, (1), pp. 23–32
[27] Smith G.V., Notheisz F.: 'Heterogeneous catalysis in organic chemistry' (Academic Press, Cambridge, MA, USA, 1999)
[28] Zecchina A., Bordiga S., Groppo E.: 'Selective nanocatalysts and nanoscience: concepts for heterogeneous and homogeneous catalysis' (Wiley-VCH, Weinheim, Germany, 2011)
[29] Mannepalli L.K., Dupati V., Vallabha S.J., *ET AL.*: 'Synthesis of substituted guanidines using Zn–Al hydrotalcite catalyst', *J. Chem. Sci.*, 2013, **125**, (6), pp. 1339–1345

[30] Shaw J.W., Grayson D.H., Rozas I.: 'Synthesis of guanidines and some of their biological applications', In: 'guanidines as reagents and catalysts I' (Springer, Cham, 2015), pp. 1–51
[31] Yavari I., Sodagar E., Nematpour M., *ET AL.*: 'Nanoparticulate copper (II) oxide catalyzed synthesis of guanidine derivatives and their conversion into functionalized iminoguanidines', *Synlett*, 2015, **26**, (9), pp. 1230–1232
[32] Kantam M.L., Priyadarshini S., Joseph P.A., *ET AL.*: 'Catalytic guanylation of aliphatic, aromatic, heterocyclic primary and secondary amines using nanocrystalline zinc (II) oxide', *Tetrahedron*, 2012, **68**, (29), pp. 5730–5737
[33] Grirrane A., Garcia H., Corma A., *ET AL.*: 'Orthogonal C-N plus C-C tandem reaction of iodoanilines leading to styrylguanidines catalyzed by supported palladium nanoparticles', *Chem.: Eur. J.*, 2012, **18**, (47), pp. 14934–14938
[34] Abbasi S., Saberi D., Heydari A.: 'Copper oxide supported on magnetic nanoparticles (CuO@ γ-Fe_2O_3): an efficient and magnetically separable nanocatalyst for addition of amines to carbodiimides towards synthesis of substituted guanidines', *Appl. Organomet. Chem.*, 2017, **31**, (9), p. e3695
[35] Rani B.J., Saravanakumar B., Ravi G., *ET AL.*: 'Structural, optical and magnetic properties of $CuFe_2O_4$ nanoparticles', *J. Mater. Sci.: Mater. Electron.*, 2018, **29**, (3), pp. 1975–1984
[36] Sharma V.K.: 'Ferrites and ferrates: chemistry and applications in sustainable energy and environmental remediation' (American Chemical Society, Washington, USA, 2016)
[37] Kumar A.S., Thulasiram B., Laxmi S.B., *ET AL.*: 'Magnetic $CuFe_2O_4$ nanoparticles: A retrievable catalyst for oxidative amidation of aldehydes with amine hydrochloride salts', *Tetrahedron*, 2014, **70**, (36), pp. 6059–6067
[38] Baghbanian S.M., Farhang M.: '$Cufe_2o_4$ nanoparticles: a magnetically recoverable and reusable catalyst for the synthesis of quinoline and quinazoline derivatives in aqueous media', *RSC Adv.*, 2014, **4**, (23), pp. 11624–11633
[39] Murthy Y.L.N., Diwakar B.S., Govindh B., *ET AL.*: 'Nano copper ferrite: a reusable catalyst for the synthesis of β, γ-unsaturated ketones', *J. Chem. Sci.*, 2012, **124**, (3), pp. 639–645
[40] Sarode S.A., Bhojane J.M., Nagarkar J.M.: 'An efficient magnetic copper ferrite nanoparticle catalyzed ligand and solvent free synthesis of N-aryl amide from aldoximes and iodobenzene', *RSC Adv.*, 2015, **5**, (127), pp. 105353–105358
[41] Sarode S.A., Jadhav V.G., Nagarkar J.M.: 'Synthesis of 2-aryl quinazolines from (2-aminophenyl) methanol and oxime ether catalyzed by copper ferrite nanoparticles', *Tetrahedron Lett.*, 2017, **58**, (8), pp. 779–784
[42] Cunha I.T., Teixeira I.F., Albuquerque A.S., *ET AL.*: 'Catalytic oxidation of aqueous sulfide in the presence of ferrites (MFe_2O_4, M=Fe, Cu, Co)', *Catal. Today*, 2016, **259**, pp. 222–227
[43] Dandia A., Jain A.K., Sharma S.: '$Cufe_2o_4$ nanoparticles as a highly efficient and magnetically recoverable catalyst for the synthesis of medicinally privileged spiropyrimidine scaffolds', *RSC Adv.*, 2013, **3**, (9), pp. 2924–2934
[44] Lv W.Z., Liu B., Luo Z.K., *ET AL.*: 'XRD studies on the nanosized copper ferrite powders synthesized by sonochemical method', *J. Alloys Compd.*, 2008, **465**, (1–2), pp. 261–264

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