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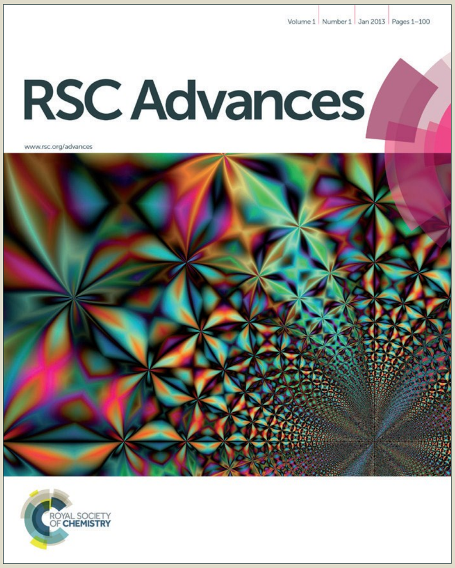

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Journal Name

ARTICLE

Cu-EDTA-modified APTMS-Fe_3O_4@SiO_2 core-shell nanocatalyst: A novel magnetic recoverable catalyst for the Biginelli reaction

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A novel copper-ethylenediamine tetracarboxylate modified core-shell magnetic catalyst has been introduced. The prepared catalyst was fully characterized by various spectroscopic analyses such as XRD, SEM, FT-IR, EDX, ICP, and CHNOS. After characterization, its activity was evaluated as a supported transition metal catalyst in the multi-component Biginelli reaction. The novel catalyst acts as an efficient heterogenized catalyst for synthesis of 3,4-dihydropyrimidin-2(1H)-one/thione derivatives in solvent-free conditions. A wide range of biologically active dihydropyrimidin-2(1H)-one/thiones were synthesized in the presece of the novel catalyst in 10-15 minutes and high yields (85-98% isolated yields). In addition, the reusability of catalyst was tested by an external magnet. Investigation showed that no notable reduction of yields was observed after reusing over ten runs, proving its stability over recycling processes. More importantly, requiring very small amounts (0.35 mol %) of the novel catalyst resulted in the maximum turnover frequency of Biginelly reaction obtained to date (TOF about 1000-1680 h^{-1} and total TOF over 14000 h^{-1}).

Introduction

Because of their outstanding properties, magnetic nanoparticles have received striking interest in various disciplines such as magnetic drug delivery, information storages, ferrofluids, separations, magnetic resonance imaging, and tumor hyperthermia treatment.[1] In catalysis, Magnetic nanoparticles are attractive catalysts since they can be separated from the reaction medium after magnetization by an external magnet. For industrial applications, where the total cost of chemical processes is of most important factors, magnetic separation is an intriguing alternative to filtration or centrifugation because it prevents the loss of catalyst and enhances reusability.[2] Therefore, the development of novel magnetic nanoparticles with tunable catalytic activity is of great significance for both academia and industry.

As a challenging criterion in organic synthesis, pharmaceutical and therapeutic chemicals syntheses have been extensively explored in recent decades.[3] Meanwhile, biologically active 3,4-Dihydropyrimidin-2(1H)-one/thiones (DHPMs) due to important roles in live systems such as calcium channel blocking, anti-inflammation, anti-hypertension, anti-tumor, and acting as neuropeptide antagonists, mitotic Kinesin inhibitors, anti-virals, and others, as reviewed elsewhere have been of the most important synthetic targets.[4] They can be prepared by the three component condensation of an aldehyde, β-ketoester and urea/thiourea in the presence of a strong acid, through the Biginelli reaction.[5] Owing to the considerable attention to DHPMs, the synthetic procedure of Biginelli reaction has been repeatedly modified, thus, to date, marked improvements including the use of Bronsted acid catalysts,[6] Lewis acid catalysts,[7] ionic liquids,[8] magnetic catalysts [9] and magnetic ionic liquids [10] have been reported on it.

Among the aforementioned methods, heterogeneous catalysts play an efficient role in amelioration of the conditions.[11] As examples, the use of Indion-130, Nafion-H, Nafion-NR-50, Amberlyst-70,[12] supported catalysts based on resins, silica gel, alumina or PEG,[13] bioglycerol-based carbon catalyst as one of the carbon-based solid acids [14] has been reported.[15] Most of the reported methods are worthwhile; however, many of them have drawbacks such as: tedious workup of the reaction mixture, difficult separation and recovery of the catalyst, toxic and moisture sensitive reaction conditions, low yields and long reaction times. Therefore, investigations for development of more efficient, simpler and milder catalytic systems are still needed.

With the "greening" of global chemical processes [16] in mind, 'Heterogenization' of homogeneous catalysts is a general trend in catalysis science.[17] As an example, one can find Fe_3O_4@SiO_2 core-shell based heterogenized ionic liquid catalysts such as phosphommolybdic acid [9b] and HSO_4^- immobilized catalysts [10] for the Biginelli reaction. The prepared heterogenized catalysts can now easily separate from the reaction mixture, converting them to the reusable catalysts. The only restriction during heterogenization, is the lower activity/selectivity due to the increasing of mass-diffusion to the catalyst sites.[18] Nowadays, the problem fixed both by the use of porous compounds [19] and the synthesis of "inorganic-organic hybrids" by attachment of organic moieties with pendant attached chains on the

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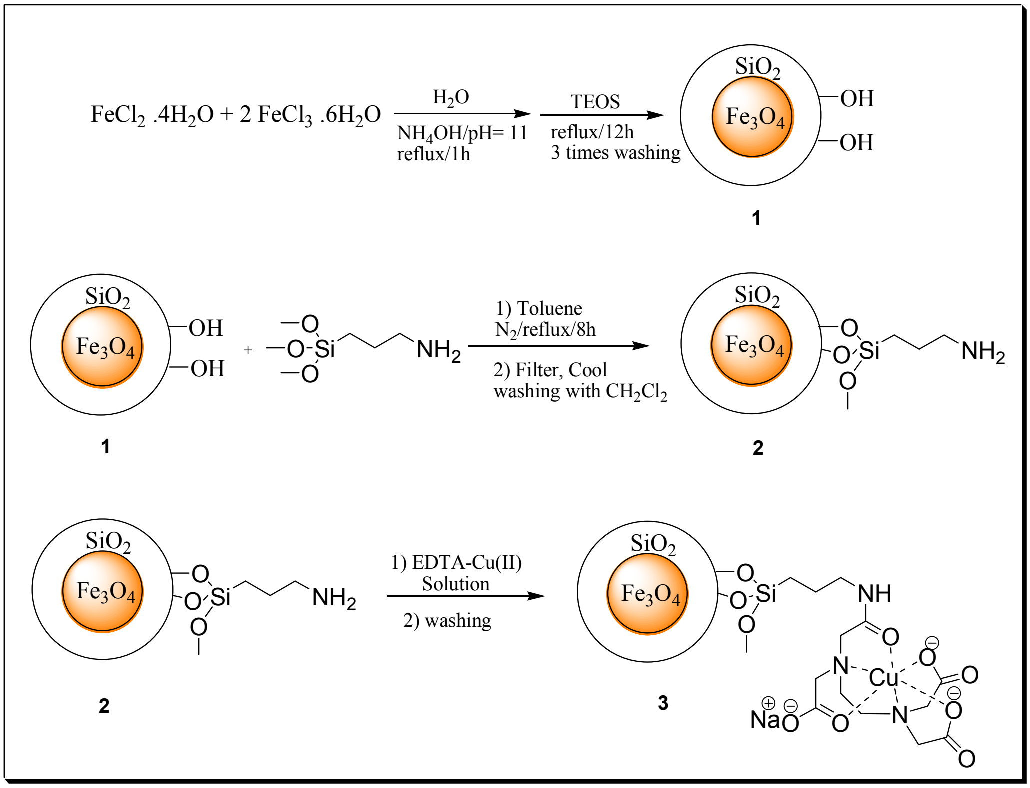
inorganic heterogeneous surfaces.[20] The latter leads to the combination of the two complementary properties: the inorganic properties like mechanical/thermal/structural stability and the properties of organic pendant moieties such as flexibility in solution (like homogeneous catalysts) and therefore, high reactivity of the catalyst.[21] Herein, we report a convenient preparation and structural characterization of an Cu-EDTA-functionalized core-shell magnetic compound as a supported transition metal catalyst in the multi-component Biginelli reaction.

Results and discussion

The catalyst characterization

The core-shell support was prepared according to the previously reported procedure.[22] The prepared nanoparticles of $Fe_3O_4@SiO_2$, **1**, were then functionalized with 3-aminopropyltrimethoxysilane (APTMS) to produce an organic-inorganic hybrid ($Fe_3O_4@SiO_2$-$(CH_2)_3$-NH_2, **2**). Then, the prepared hybrid was affected by basic solution of EDTA-Cu(II) complex. After 24 h stirring at 75 °C, the brown powder washed by deionized water and dichloromethane and dried under vacuum which led to the formation of the EDTA-modified magnetic core-shell compound named as ($Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu, **3**, as illustrated in scheme 1. The prepared ($Fe_3O_4@SiO_2$-$(CH_2)_3$-NH_2, **2**) and ($Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu, **3**) were fully characterized by XRD (Fig. 1a-b), SEM and histogram analyses (Fig. 1c-f), FT-IR (Fig. 2a-b), EDX (Fig. 3) and CHNOS. In addition, the organic loading percent and magnetic properties of **3** were characterized by TGA and VSM analyses, respectively (Fig. 4a and Fig. 4b).



Scheme 1. Preparation of the catalyst

The $Fe_3O_4@SiO_2$ and $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu synthesized were subjected to structural characterization with XRD, Fig. 1a-b. Diffraction peaks related to the (111), (220), (311), (400), (333) and (440) planes were clearly observed. The diffraction peaks are in agreement with that of the cubic structure of Fe_3O_4 (magnetite) with Fd-3m space group (ICDD card No. 75-1372) in both patterns. Also, the broad diffraction peak at 23.5° is the characteristic peak of SiO_2 shell. No other phase was detectable. In addition, there was no copper phase, proving that metallic Cu was not formed. Furthermore, competing two X-ray diffraction patterns proved that no clear loss of crystallinity appeared after the modification of the surface. The measurements were carried out on a Philips X'Pert diffractometer with CuK_α radiation (λ=0.154056 nm).

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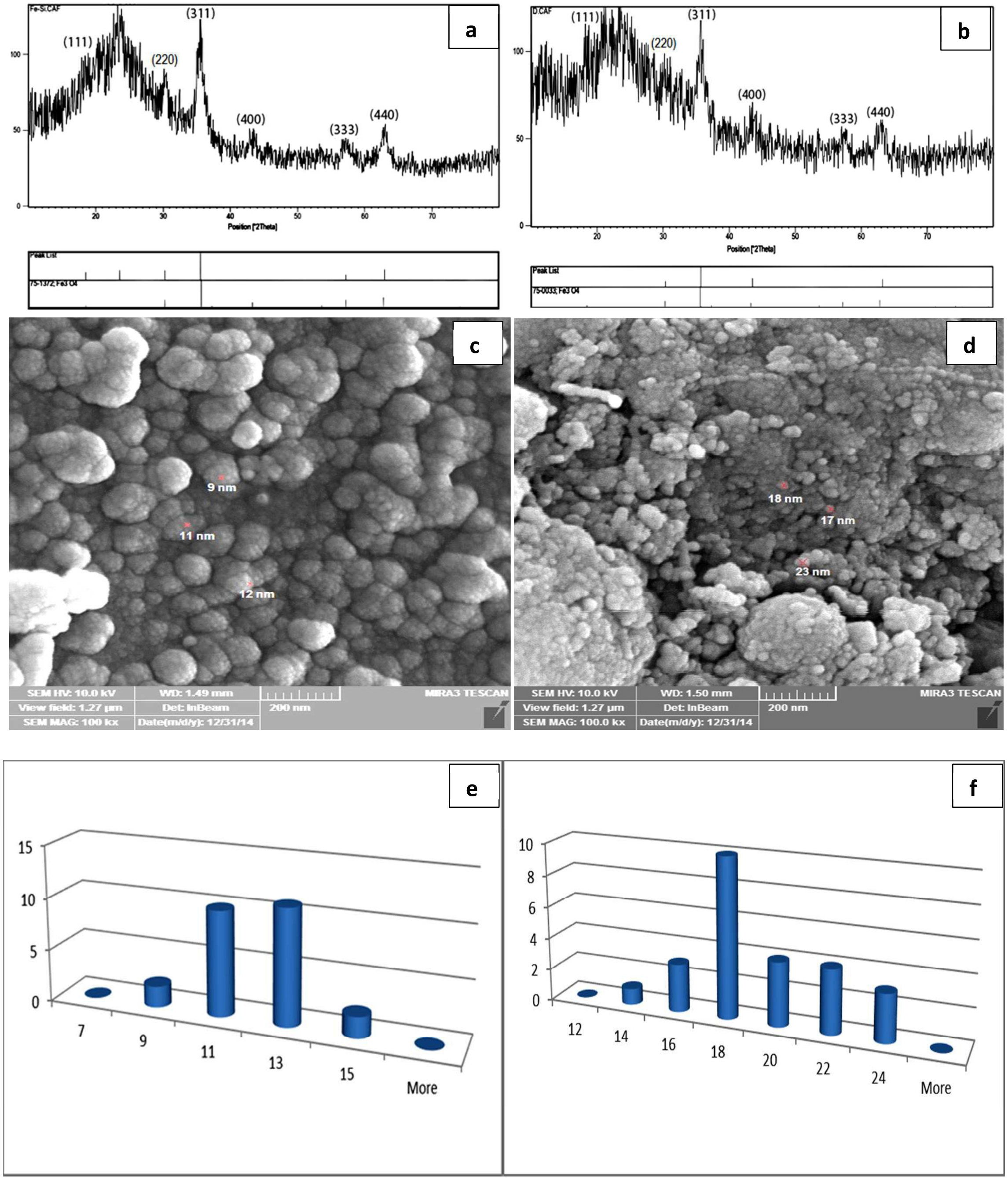

Figure 1. X-ray powder diffraction patterns of the prepared **1** (a) and **3** (b), scanning electron microscopy of **1** (c) and **3** (d), histogram size distribution of **1** (e) and **3** (f).

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The morphologies of prepared compounds were identified by the scanning electron microscopy (Fig. 1c, d). SEM photographs of $Fe_3O_4@SiO_2$ and $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu indicated that both synthetic compounds were present as uniform nanoparticles. Histogram analysis of the SEM images (Fig. 1e, f) showed that the size of the nanoparticles of $Fe_3O_4@SiO_2$ and $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu is about 12 nm and 18 nm, respectively.

The FT-IR spectra of $Fe_3O_4@SiO_2$, $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH_2 and $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu compounds were recorded in the range 400-4000 cm^{-1} (Fig. 2a-b). For $Fe_3O_4@SiO_2$, the H-O-H bending vibrations are observed at about 1000-1650 cm^{-1}, typical of the adsorbed H_2O. In addition, the band at 900-1000 cm^{-1} corresponds to bending vibration of O-H bond. The O-H in plane and out of plane vibrations appear at 1583-1481 and 935-838 cm^{-1}, respectively. The bands at 400-660 cm^{-1}, are corresponding to the stretching of Fe-O bonds in the crystalline lattice of Fe_3O_4. They are characteristically pronounced for all spinel structures and for ferrites in particular. The broader IR absorption band in the 2800–3700 cm^{-1} region is ascribed to Si-OH groups. Stretching vibration modes of Si-O bond are observed at 1120 cm^{-1} and 1180 cm^{-1}. In the FTIR of $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH_2 all of the mentioned bands are present. In addition, a characteristic band due to the stretching of C-H bonds is appeared at 2938 cm^{-1} (red highlighted dotted-line) in which proves the modification of the surface of core-shell $Fe_3O_4@SiO_2$ is successful (Fig. 2a). The FTIR spectrum of the compound named $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu shows all of the mentioned bands. It seems that there is no detectable change associated by introducing EDTA-Cu except the band in 1646 cm^{-1} that shift to 1638 cm^{-1} after modification (Fig. 2b). We consider the new band (1638 cm^{-1}) to the stretching vibration of C=O bond in EDTA modified compound.

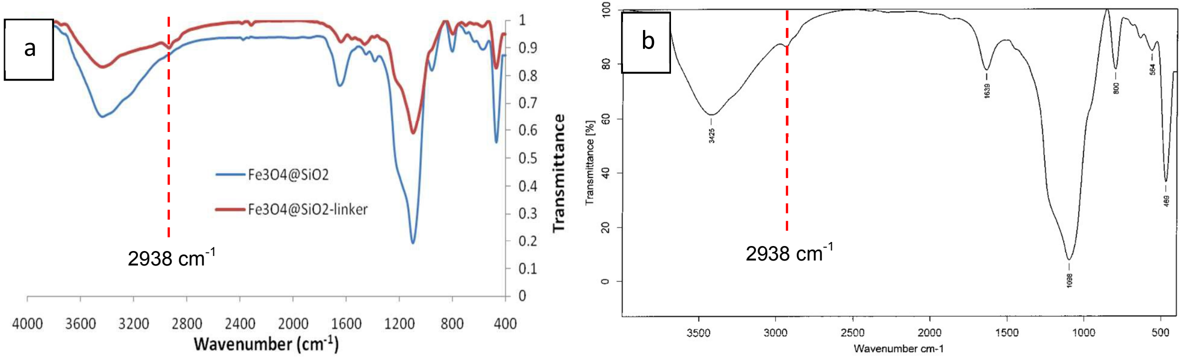
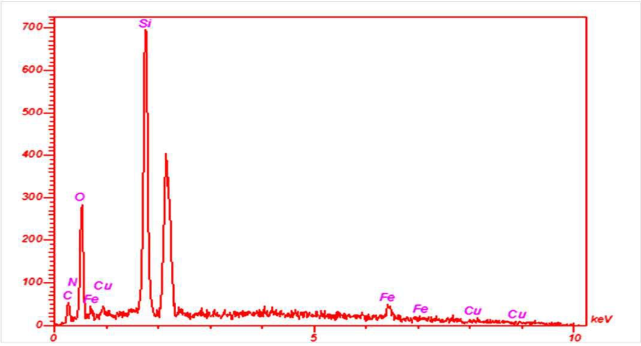


Figure 2. FTIR spectra of the prepared **1** (a, blue-line), **2** (a, red-line) and **3** (b)

The presence of EDTA and more importantly Cu is confirmed by the elemental analysis of the compound **3**. Energy-dispersive X-ray spectroscopy microanalysis (EDAX) was recorded for this compound (Fig. 3). As shown in fig. 3, the compound **3** has carbon, nitrogen, and copper as well as iron and silicon.



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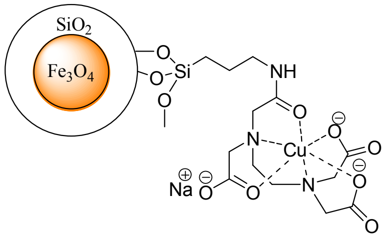
Elt	Line	Int	Kr	W%	A%
C	**Ka**	**30.6**	**0.0144**	**8.81**	**19.81**
N	**Ka**	**3.0**	**0.0221**	**2.72**	**4.53**
O	Ka	99.0	0.0855	41.65	47.48
Si	Ka	426.0	0.1637	25.58	18.87
Fe	Ka	52.7	0.1373	16.62	5.69
Cu	**Ka**	**9.1**	**0.0453**	**4.62**	**3.62**
			0.4689	100.00	100.00

Figure 3. Energy-dispersive X-ray spectroscopy microanalysis (EDAX) of compound **3**

Quantitative elemental analysis of **3**, showed 8.81% C (equal to 7.3 mmol C/g) and 2.72% N (equal to 1.9 mmol N/g). Therefore, the ratio of C/N resulted from EDAX is about 3.84. To characterize more precisely, the ratio of ligand/metal for the complex must be calculated by this method. Calculation of the N/Cu resulted in 2.7. Interestingly, the resulted 2.7 ratio is in agreement with the proposed structure of **3** (scheme 2), in which there are 3 nitrogen atoms for each copper ion.

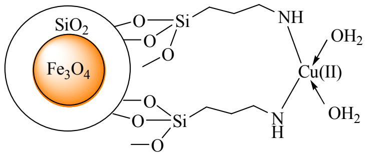


Scheme 2. The proposed structure of **3**

In addition, the C/N ratio of 3.84 is approximately in agreement with this structure because it must have 14 C atoms and 3 N atoms. So, it must have the C/N ratio of 4.6.

The loading of the active site on the magnetic core-shell is determined by considering the presence of 3 N atoms in each active site and is about 0.64 mmol per gram of the catalyst.

There was just one uncertainty on the basis of the results of EDAX analysis. Whether the structure is as illustrated in scheme 2 or the directly complexed Cu-amino groups structure without the presence of EDTA (scheme 3). However, if this was the case, the N/Cu ratio must be 2 instead of calculated 2.7, but the calculated C/N ratio of 3.8 is more near to 4 than 4.6. However, the formation equilibrium constant (K_f) for EDTA-Cu is higher than K_f for a bidentate N-Cu complex, for more exact confirmation of the proposed structure and to rule out the structure shown in scheme 3, the compound **3** was subjected to the elemental CHNOS analysis.



Scheme 3. The ruled out directly complexed Cu-amino structure of **3** without the presence of EDTA

The CHNOS analysis showed 6.23% C, 1.49% N and 1.55% H in the compound **3**. Clearly, it means there are 5.19 mmol C/g and 1.07 mmol N/g in the prepared structure. On the basis of the results, C/N ratio is about 4.8, the number which is more near to 4.6 than 4. Therefore, the presence of EDTA and subsequently the structure proposed in scheme 2 is confirmed. Considering 3 N atoms in each active site, the loading of compound is calculated about 0.35 mmol/g by CHNOS. Since EDAX analyzes a dot- non-uniform region of structure and because in the synthetic procedure, 0.5 mmol EDTA-Cu complex was affected by 1 g of the APTMS-modified core-shell compound, the results obtained from CHNOS must be more realistic than results of EDAX (0.64 mmol/g). So, the loading is considered as is determined by CHNOS (0.35 mmol/g) for the compound **3**.

In contrast to a homogeneous catalyst which has well-defined active sites, the active sites of heterogeneous catalysts have remained obscure. Therefore, many reports are present in the Literature that consider the modification by APTES and APTMS as a continuous and distinct shell around the SiO_2 layer, whereas, others consider just a local functionalization on the surface. Among those which showed local functionalization, many indicated a tri-bridged O-Si bond between the linker and surface of SiO_2 [23] but some others demonstrated a two-bridged O-Si bond between the linker and surface of SiO_2 [24] as did we.

In scheme 2, the sodium comes from EDTA•2Na. XRD spectroscopic analysis rules out the reduction of Cu(II) to metallic Cu. Therefore, it is reasoned that copper was in its +2 oxidation state and must have had a counter ion in the structure of its complex. According to the materials used, there are just two probabilities, the presence of (1) sodium ion (from the EDTA•2Na) and (2) potassium ion (from the K_2CO_3). Based on EDAX spectroscopy, there is no K element in the structure. Hence, sodium must be the counter ion present in the structure of compound **3**. However, the reason that sodium was not observed in EDAX spectrum is that Na element is lighter than being detected by EDAX.

Further quantitative determination of the organic group loaded on the surface of compound **3** was performed by using thermo-gravimetric analysis (TGA) (Fig. 4a). Three weight losing steps were observed in the analysis. First step which is due to the evaporation of adsorbed water appeared at about 108 °C. The peak is followed by a weight loss of 8.0 % at about 261 °C, corresponding to the loss of EDTA-Cu complex. This proves a loading of about 0.32 mmol/g. As the third step, a weight loss of 11.6 % at 408 ^{o}C is observed which is corresponded to the complete loss of organic linker from the surface of compound **3**. The result is in agreement with those of CHNOS analyses.

The magnetic feature of compound **3** is also measured in an applied magnetic field at r.t, with the field sweeping from

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−8000 to +8000 Oersted (Fig. 4b). The ‘retentivity/magnetic saturation’ ratio for the compound is about 0.001, proving that **3** has superparamagnetic nature. Its M (H) hysteresis loop is completely reversible and the mentioned reversibility confirms that no aggregation occurred in the magnetic fields. In addition, the magnetic saturation value of **3** is 5.00 emu/g at r.t. Its high permeability in magnetization as well as good magnetic saturation is sufficient for magnetic separation of it with a conventional magnet.

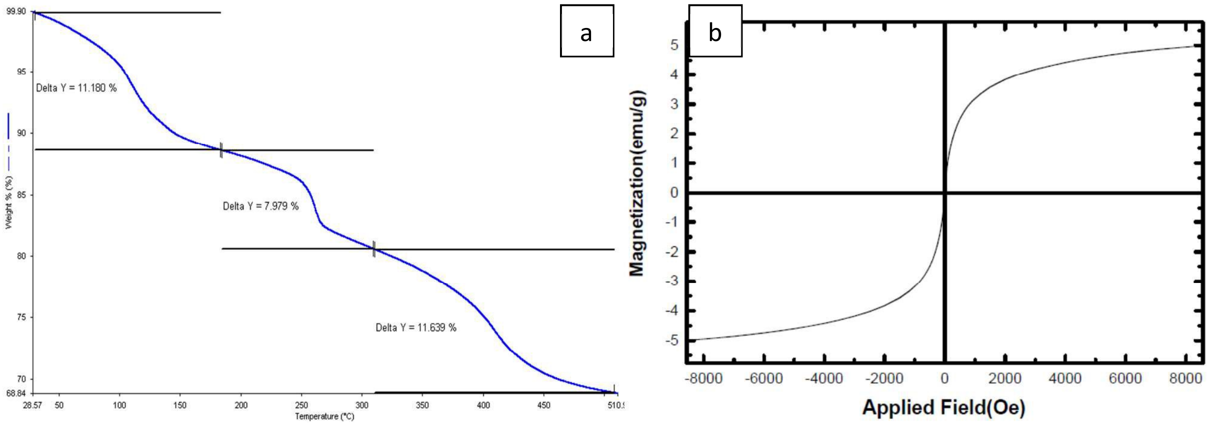

Figure 4. Thermo-gravimetric analysis (a) and vibrating sample magnetometer curve of **3** at r.t (b)

Catalytic activity

After detailed characterization of the prepared compound **3**, its catalytic activity was investigated in the Biginelli reaction for the formation of various dihydropyrimidin-2(1H)-one or thione compounds.

A mixture of benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol) and urea (1.2 mmol) was allowed to react in the presence of catalyst **3** as the model reaction. Systematic screening of the reaction conditions was done precisely in the presence of various catalyst amounts, different times, different solvents and various reaction temperatures (Table 1).

Table 1. Screening the reaction conditions

Entry	Catalyst	Time (min)	Temperature (^{o}C)	Solvent	Yield %
1	3 mg (0.11 mol%)	30	100	ACN	55
2	7 mg (0.25 mol%)	30	100	ACN	72
3	10 mg (0.35 mol%)	30	100	ACN	89
4	15 mg (0.55 mol%)	30	100	ACN	87
5	10 mg (0.35 mol%)	10	100	ACN	78
6	10 mg (0.35 mol%)	15	100	ACN	80
7	10 mg (0.35 mol%)	25	100	ACN	83
8	10 mg (0.35 mol%)	35	100	ACN	81
9	10 mg (0.35 mol%)	10	75	ACN	61
10	10 mg (0.35 mol%)	10	120	ACN	83
11	**10 mg (0.35 mol%)**	**10**	**100**	-	**88**
12	10 mg (0.35 mol%)	10	100	DMF	75
13	10 mg (0.35 mol%)	10	100	EtOH	80
14	10 mg (0.35 mol%)	10	100	DMSO	71
15	10 mg (0.35 mol%)	10	100	NMP	76

Reaction conditions: Benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol)

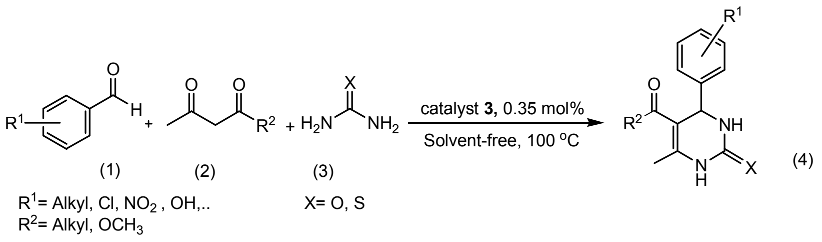

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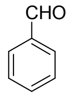
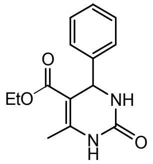
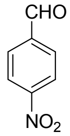
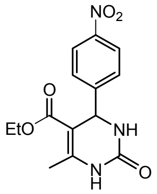
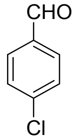
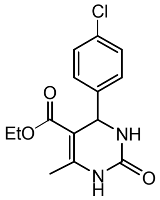
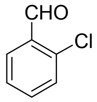
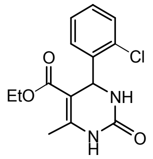
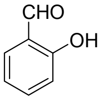
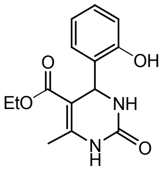
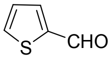
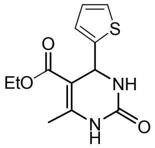
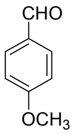
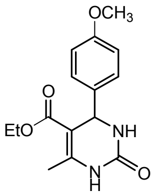
Table 2. The synthesis of various 3,4-dihydropyrimidin-2(1H)-one/thiones in the presence of catalyst **3**.

Entry	Aldehyde	R^2/X	Product	Yields (%)	Time (min)	TON[a]	TOF (h^{-1})[b]	Ref.
4a		OEt/O		88	10	251	1506	[25]
4b		OEt/O		98	10	280	1680	[25]
4c		OEt/O		92	10	262	1572	[26]
4d		OEt/O		85	10	242	1452	[25]
4e		OEt/O		90	10	257	1542	[27]
4f		OEt/O		91	10	260	1560	[28]
4g		OEt/O		95	10	271	1628	[25]

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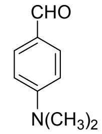
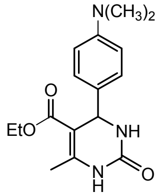
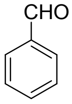
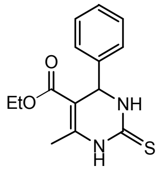
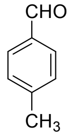
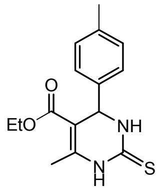
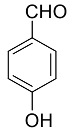
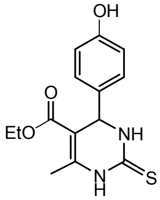
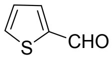
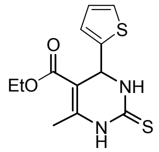
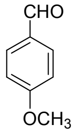
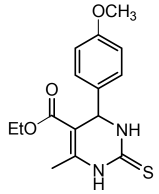
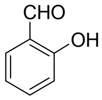
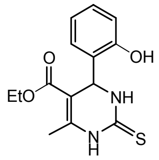
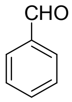
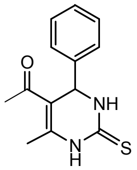
4h		OEt/O		92	10	262	1572	[29]
4i		OEt/S		92	10	262	1572	[30]
4j		OEt/S		89	15	254	1016	[31]
4k		OEt/S		94	10	268	1608	[32]
4l		OEt/S		92	15	262	1048	[33]
4m		OEt/S		88	10	251	1506	[30]
4n		OEt/S		87	15	248	992	[27]
4o		Me/S		85	10	242	1452	[29]

Reaction conditions: Aldehydes (1 mmol), 1,3-dicarbonyl compounds (1 mmol), urea/thiourea (1.2 mmol), free-solvent, 100 °C. Just the isolated yields are reported. a) Number of moles of product produced from 1 mole of catalyst. b) TON per unit of time.

After optimization of reaction conditions, it was proved that the reaction in the presence of 10 mg of the catalyst (0.35 mol%) under solvent-free conditions and at 100 °C resulted in the corresponding product 4a in excellent yield in 10 minutes. On the basis of the optimal conditions established, the Biginelli reaction of various aldehydes, 1,3-dicarbonyl compounds and urea/thiourea in solvent-free conditions were examined. As shown in Table 2 the reactions proceed smoothly and corresponding 3,4-dihydropyrimidin-2(1H)-one/thiones could be obtained in high yields.

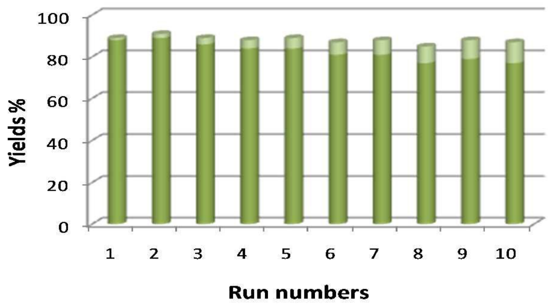


Figure 5. The reusing of catalyst in synthesis of 4a; carried out in 100 °C for 10 minutes.

At the end of the reaction, reusability of the catalyst was evaluated by decanting the vessel using an external magnet and washing the retained catalyst with dichloromethane, drying, and using in a subsequent reaction (Fig. 5). The reaction of benzaldehyde, ethyl acetoacetate and urea resulted in the corresponding 3,4-dihydropyrimidin-2(1H)-one 4a in 88% isolated yield. After ten consecutive reactions, the isolated yield remained similar to the first run and no detectable loss was obtained. The progress was made with 82.6% average yield of the reaction and the total turnover number of up to 14000 h^{-1}.

To check leaching of the catalyst into solution, after 5 minutes from starting, the vessel was magnet decanted and observed that the reaction in the supernatant did not complete even after 6 h. The experiment was repeated and this time instead of 5 minutes, the catalyst was separated after 30 minutes by magnetic decantation and the supernatant was tested by Inductive coupled plasma spectroscopy (ICP-AES). ICP-AES result supported that no detectable amounts of Cu were found in the supernatant proving there is no contribution of homogeneous catalysis (via leached catalyst) in the course of reaction. The novel catalytic procedure in comparison with some other ones is presented in Table 3.

Table 3. Comparison of this work with the previously reported catalysts for Biginelli reaction of 4-nitrobenzadehyde, ethyl acetoacetate and urea

Entry	Catalyst	Time (h)	Yield%	**TOF (h^{-1})**	Ref.
1	$H_5PW_{10}V_2O_{40}$/Pip-SBA-15 (0.6 g, **2 mol%**)	0.75	80	**53**	[25]
2	$H_3PMo_{12}O_{40}$ nanoparticles on Imidazole functionalized Fe_3O_4@SiO_2 (0.03 g, **0.3 mol%**)	0.33	94	**939**	[9b]
3	HSO_4^- imidazole functionalized Fe_3O_4@SiO_2 (0.05 g, **1.1 mol%**)	0.5	97	**176**	[10][a]
4	$NH_4H_2PO_4$/MCM-41 (0.04g, **5 mol%**)	2.5	85	**6.8**	[26]
5	[Et_3NH][HSO_4] (**3 equiv.**)	1.33	76	-	[34]
6	SBSSA (0.05g)	1	93	-	[35]
7	Nano-ZnO (**5 mol%**)	12	65	**1.1**	[36]
8	Fe_3O_4 (**20 mol%**)	0.4	71	**8.9**	[29]
9	Fe_3O_4/PAA-SO_3H (**22.3 mol%**)	1.9	84	**2**	[37]
10	Ce(LS)$_3$ (**20 mol%**)	8	91	**0.6**	[38]
11	**Fe_3O_4@SiO_2-(CH_2)$_3$-NH-EDTA-Cu(II) (0.35 mol%)**	**0.17**	**98**	**1680**	**Current work**

a) Because there was not reaction data of 4-nitrobenzaldehyde, the data of 3-nitrobenzaldehyde is presented here.

Conclusion

In summary, the preparation and characterization of a copper-EDTA-functionalized core-shell magnetic compound as a supported transition metal catalyst in the multi-component Biginelli reaction was described. The novel catalyst acts as a powerful heterogenized catalyst for synthesis of 3,4-dihydropyrimidin-2(1H)-one/thione derivatives in solvent-free conditions. In addition, in competition with other reported catalysts, the new magnetic catalyst has higher activity. Appropriate distance between catalytic active sites (indeed copper ion) from solid surface reduces the steric hindrance and therefore eliminates mass transport limitations. More importantly, the novel catalyst acts its catalytic role in very small amounts (0.35 mol %) and therefore shows the maximum turnover frequency of Biginelly reaction obtained to date (TOF about 1000-1680 h^{-1} and total TOF over 14000 h^{-1}). Reusing the catalyst over ten subsequent reactions was accomplished without notable reduction of yields and proved its stability over recycling processes.

Experimental Section

The Preparation of catalyst

A mixture of $FeCl_2.4H_2O$ (2.5 mmol) and $FeCl_3.6H_2O$ (5 mmol) in de-ionized water (20 mL) was added to a two-necked balloon. After stirring for ten minutes ammonia (25%, 40 mL) was added drop-wise (1mL/min) until the solution pH rise to about 11. Then, TEOS (20 mL) added to above mentioned suspension drop-wise under reflux and stirred for 12 hour. The dark-brown solid was washed with water (3 times) and ethanol (3 times) and oven-dried at 200 ^{o}C to produce $Fe_3O_4@SiO_2$ (compound **1**) as a brown solid. 1 gram of 1 was dispersed in 50 mL toluene and then 3-(trimethoxysilyl)popylamine (20 mmol, 4.5 mL) was added under reflux and inert atmosphere. The mixture stirred for 8 hours and then cooled to r.t, washed with water and dichlomethane and oven-dried at 50 ^{o}C to yield $Fe_3O_4@SiO_2$-Si-$(CH_2)_3$-NH_2 (compound **2**).

A mixture of $CuCl_2$ (anhydrous, 0.5 mmol), EDTA•2Na (0.5 mmol) and K_2CO_3 (1mmol) in water (5 mL) was stirred at r.t for 4 hours resulted in the production of EDTA-Cu(II) complex.

The EDTA-Cu(II) complex solution was added to 1 gram of 2 in water (25 mL) and stirred at 75 ^{o}C for 24 hours. The resulted solid was washed with water and oven-dried at 100 ^{o}C to produce $Fe_3O_4@SiO_2$-$(CH_2)_3$-NH-EDTA-Cu, (compound **3**).

General Procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-one/thiones in the presence of catalyst 3

A mixture of aldehyde (1 mmol), 1,3-dicarbonyl compound (1 mmol), urea/thiourea (1.2 mmol), and catalyst **3** (10 mg, 0.35 mol%) was stirred at 100 ^{o}C in solvent-free conditions. At the end of reaction (determined by TLC), ethanol (10 mL) was added and the catalyst separated by external magnet. The products was obtained and purified via recrystallization from ethanol and chromatographic purification. The structures of products were proved by the comparison of their mp, FTIR and ^{1}HNMR by related literatures.

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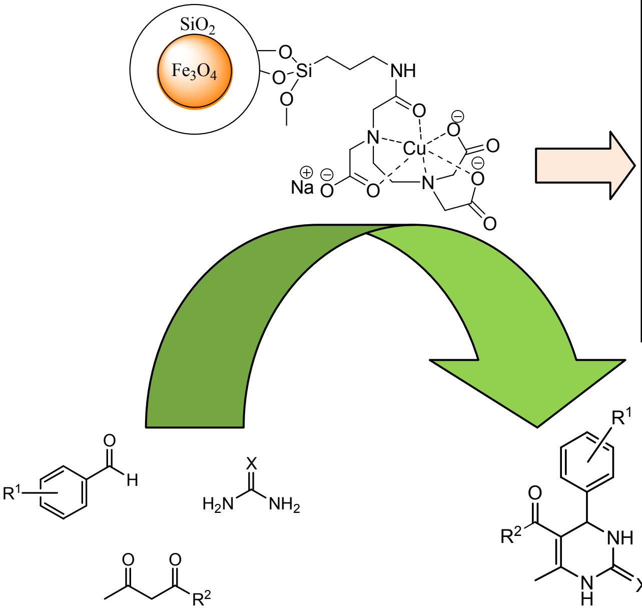

15 examples, 85-98%

Solvent-Free conditions

Catalyst requiring: 0.35 mol%

Turnover Frequency: ~1000-1680 h^{-1}

Average yield in 10 subsequent runs: ~82.6%

Total Turnover Frequency: > 14000 h^{-1}