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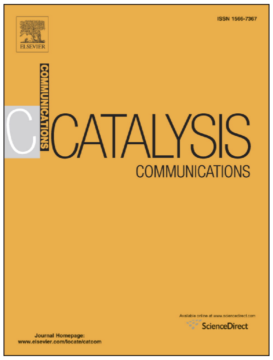

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A Copper(I)-Complexed Magnetic Nanoparticle Catalyst for Enaminone Synthesis

Leila Mohammadi[a,b], Mohammad Ali Zolfigol[b*], Mahsa Ebriminia[a], Kenneth P. Roberts[a], Samira Ansari[c], Tahereh Azadbakht[b] and Syed R. Hussaini[a*]

[a]*Department of Chemistry and Biochemistry, The University of Tulsa, 800 S Tucker Dr, Tulsa, Oklahoma 74104, USA*

[b]*Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran*

[c]*CinnaGen Medical Biotechnology Research Center, Alborz University of Medical Science, Karaj, Iran*

The synthesis of a copper(I)-complexed magnetic nanoparticle catalyst is described. The catalyst was characterized using Fourier transform infrared spectroscopy (FT–IR), energy-dispersive X-ray spectroscopy (XPS), atomic absrobtion spectroscopy (AA), thermogravimetric analysis (TGA), vibrating sample magnetometery (VSM), X-ray photoelectron spectroscopy (XPS), scanning electron miscroscopy (SEM) and transmission electron microscopy (TEM). The catalyst coupled thioamides and diazocarbonyl compounds to produce diverse enaminones. The catalyst reduced the reaction times and temperature and provided enaminones in high yields and selectivity. Moreover, the catalyst can be separated by a magnet and recycled.

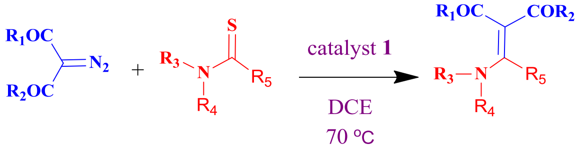
Keywords:

Copper-complexed magnetic nanoparticles

Enaminone

Diazocarbonyl compounds

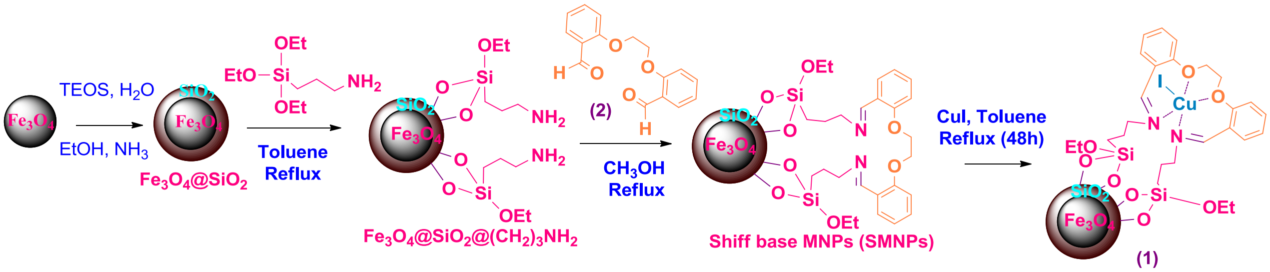
Cross-coupling



Scheme 2. Synthesis of enaminones using catalyst **1**

1. Introduction

Magnetic nanoparticles (MNPs) have been used in many fields such as magnetic recording devices, targeted drug delivery, biomedicine, biosensors, magnetic fluids and bioprobes.[1, 2] The synthesis and applications of MNPs are in great demand because of their recyclability, reusability, high activity and selectivity in chemical processes.[2-5] In continuance of our investigation on the design, synthesis and use of magnetic nano-catalysts,[6, 7] we designed, synthesized and characterized a novel Cu(I) catalyst complexed with magnetic nanoparticles (**1**) (Scheme 1). Next, we tested **1** as a catalyst for the formation of



Scheme 1. Synthesis of catalyst **1.** TEOS = Tetraethyl orthosilicate

enaminones. Enaminone derivatives have great potential as synthetic intermediates because of the existence of three electrophilic and two nucleophilic sites existing within its molecular structure.[8] Enaminones are enamines of a β–ketoester, 1,3-diketone or similar 1,3-difunctional molecules.[9] One reason for their general application is their multipurpose reactivity, as both nucleophiles and electrophiles.[8-10] Furthermore, enaminones are versatile therapeutic pharmacophores.[11]

The enaminone functional group can be found in compounds with anti-inflammatory, anticonvulsive and antibiotic activity.[9, 11] Because of their importance, numerous approaches have been developed for the synthesis of enaminones.[8-13] Some common methods include: the Eschenmoser coupling reaction,[13-15] the imino ester (imidate) approach,[16, 17] amine condensation with dicarbonyl compounds [8, 9, 18, 19] and the metal-catalyzed coupling of α-diazocarbonyl compounds with thioamides.[13,][20]

Although Cu(I)-catalyzed coupling of thioamide and diazo compounds for the formation of enaminones has been reported recently,[21] there are no reports of the use of nanocatalysts in this transformation. In this paper, we address this deficiency and report the use of **1** as an efficient catalyst for the formation of enaminones via the cross-coupling reaction between thioamides and α-diazocarbonyl compounds (Scheme 2). Furthermore, the catalyst can be removed easily by an external magnet. This can be important for industrial applications as the removal of transition metals is one of the biggest costs associated with the production of drugs.[22]

2. Experimental

2.1 *Synthesis of catalyst **1***

$Fe_3O_4@SiO_2(CH_2)_3NH_2$ (Scheme 1) was synthesized according to the literature procedure[7] (experimental details are provided in the supplementary data). 3.00 g of $Fe_3O_4@SiO_2@(CH_2)_3NH_2$ in 50.0 mL of dry methanol was sonicated for 30 min. 1.35 g (5.00 mmol) of 2-[2-(2-formylphenoxy)ethoxy]-benzaldehyde **2** and 20.0 mL toluene were added and the reaction mixture was heated at 70 ^{0}C for five hours. The temperature was lowered to 50 ^{0}C and the reaction was stirred for 43 hours. The reaction was allowed to come to room temperature and the particles were separated using a magnet. The particles were washed three times with dry methanol (30.0 mL × 3), and dried in an oven at 70 ^{0}C for 24 h to provide the MNPs- Schiff base ligand.[7]

Copper(I) iodide (5.00 mmol, 0.950 g) was added to 4.35 g of MNPs- Schiff base ligand and the suspension was refluxed at 110 ^{0}C for 48 hours. The particles were washed with dry methanol and dried for 48 h at 100 ^{0}C in a vacuum oven giving 5.10 g of MNPs-Cu catalyst **1** (0.0918 mmols gm^{-1} of Cu based AAS).

2.2 *General procedure for the synthesis of enaminones*

Thioamide (0.13–0.22 mmol) was dissolved in dry dichloroethane (0.50 mL) and the solution was transferred to a vial containing the diazo compound (1.2–1.6 eq). The well-mixed solution was transferred to a pressure vessel containing the MNPs-Cu catalyst (2.3–3.5 mol% based on Cu). The vials containing the thioamide and the diazo compound were washed with 0.25 mL of dry dichloroethane using the above transfer protocol and the solution was added to the reaction vessel. The mixture was heated in a 70 ^{0}C oil bath for 2–6 hours. An external magnet was used to separate the MNPs-Cu catalyst **1** from the reaction mixture. The crude product was purified using column chromatography (details are provided in the supplementary data).

3. Results and Discussion

3.1 *Characterization of catalyst **1***

The structure of **1** was characterized by FT-IR, EDX, AA, TGA, VSM, XRD, SEM, and TEM. The FT-IR spectra of the blank Fe_3O_4 MNPs, $Fe_3O_4@SiO_2$ core-shell MNPs and the other core-shell surface modified samples showed the absorption band near 630–650 cm^{-1}. This indicates the presence of the Fe–O bond (Fig. 1, supplementary data (SD)). The IR bands near 1105–112 cm^{-1} and 980–993 cm^{-1} show the presence of the Si–O bond. The broad band at 3246 cm^{-1} shows the presence of the NH_2 group. The absorption band appearing at 1634 cm^{-1} in Fig. 1d (SD) is due to the C=N group. The bands appears at 1627 cm^{-1} in Fig. 1e (SD) because of the presence of copper in the structure.[7]

The energy-dispersive X-ray spectroscopy (EDX) of catalyst **1** displayed the presence of carbon (C), nitrogen (N), Iron (Fe), oxygen (O), silicon (Si), copper (Cu) and Iodine (I) (Fig. 2, SI). The atomic absorption spectroscopy (AA) indicated the presence of 1.8% of Cu in catalyst **1**. The TGA of the catalyst showed high thermal stability and negligible organic compound leaching up to 220 °C (Fig. 3, SI). Magnetic measurements of Fe_3O_4 nanoparticles, $Fe_3O_4@SiO_2$ and **1** showed that Fe_3O_4 nanoparticles have the greatest magnetization and **1** has the lowest magnetization (Fig. 4, SD). This supports scheme 1. The surface of coating of Fe_3O_4 nanoparticles increases in each step of scheme 1, which in turn, should result in the reduction of magnetization after each step.

The X-ray photoelectron spectroscopy (XPS) indicated that the copper species on the sample is in +1 oxidation state (Fig.5, SD). Even though Cu metal and Cu(I) spectra are similar, the Cu $2p_{3/2}$ observed at ~932 eV BE and the Auger peak observed at ~916 ev BE confirms that the copper in the catalyst is in the Cu(I) oxidation state.[23] Size, shape and morphology of **1** were also studied by comparing the X-ray diffraction (XRD) pattern of **1** with Fe_3O_4 nanoparticles and $Fe_3O_4@SiO_2$ nanoparticles. The XRD patterns of Fe_3O_4 nanoparticles showed characteristic peaks at 2θ = 30.10°, 35.50°, 43.10°, 53.00°, 57.00°, 62.80°, corresponding to the reflections of (220), (311), (400), (331), (422) and (511). These peaks match with those from the JCPDS card (no. 76-1849) for the spinel cubic structure of Fe_3O_4 (Fig. 6a, SD).[24] All of these peaks are were also found in the XRD spectra of $Fe_3O_4@SiO_2$ and catalyst **1**, which confirms crystalline structures of $Fe_3O_4@SiO_2$ and catalyst **1**. Furthermore, no broad peak pattern was observed between 2θ = 20°–29° which is an indicator of non-crystallinity.[7] Therefore, the spinal cube crystalline nature of Fe_3O_4 is retained during the synthesis of catalyst **1**. By analyzing the SEM and the TEM images (Fig. 1) of catalyst **1**, we found that these particles have various morphologies and they are clearly smaller than a micron in size with some particles as small as 30 nm in length (Fig. 7, SD).

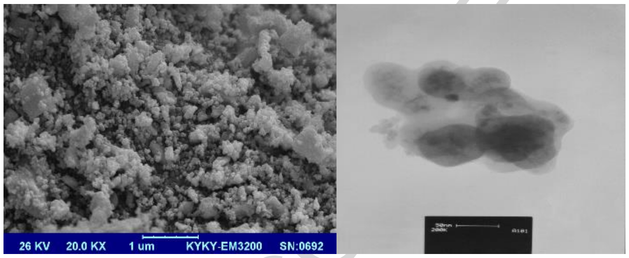


Fig. 1. SEM and TEM images of catalyst **1**

*3.2 Use of catalyst **1** in the synthesis of enaminones*

The coupling of **3** and **4** was selected as a model to optimize the reaction conditions. We chose dichloroethane (DCE) as the solvent because we have previously found it to be the most suitable solvent with the copper(I) catalyst in this transformation.[21] Various amounts of catalyst **1** from room temperature to 70 °C were tested (Table 1). The lowest catalyst loading at 70 °C that gave complete conversion of **3** into **5** was 2.3 mol% of catalyst **1** (Table 1, entry 3). Increasing the catalyst **1** loading to 2.7 mol% did not allow conversion of **3** into **5** at a lower temperature (entry 5, Table 1). The use of even 30 mol% of CuI gave negligible quantities of the product (compare entry 3 with 6, Table 1) and no reaction was observed with just the magnetic part of catalyst **1** (i.e., Fe_3O_4, entry 7, Table 1).

To display the general applicability of this procedure, α-diazocarbonyl compounds were reacted with various thioamides. As shown in Table 2, α-diazoesters (enaminones **6**, **8**, **9**, **11**, **13** & **14**), α-diazoketoesters (enaminones **7**, **10**, **12** & **15**) and α-diazodiketones (enaminones **16** & **17**) all undergo this transformation with 2.3–3.5 mol% of catalyst **1**. Primary (enaminone **11**, Table 2), secondary (enaminones **6–8**, **10** & **12–17**, Table 2) and tertiary (enaminone **9**, Table 2) thioamides can all be converted into the corresponding enaminones with 2.3–3.5 mol% catalyst **1**. A comparison of catalyst **1** with Ru(II)[25] and $(CuOTf)_2$.Tol,[21] which highlights its efficiency is shown for enaminone **7** and **8** (Table 2). Catalyst **1** provided enaminones in less time and in better yields (Table 2). The catalyst also showed excellent diastereoselectivity and provided enaminones as single diastereomers (enaminones **7**, **10**, **12** & **15**). This diastereoselectivity is believed to be due to stronger intramolecular hydrogen bonding between the NH and the ketone carbonyl compared with the hydrogen bonding between the NH and the ester carbonyl. Various other reasons have also been postulated for such selectivity.[13] The stereochemistry of **7**, **10**, and **15** is assigned by comparing with literature values.[25, 26] The stereochemistry of **12** is assigned by comparing the N*H* chemical shifts of **12** with **13** and by comparing the N*H* chemical shift of **14**, **15** and the diketo isomer (two esters of **14** being replaced by two acetyl groups)[27] of **14**. The chemical shift of N*H* hydrogen is significantly downfield in the *E* isomer as a result of stronger H-bonding with the ketone oxygen.[13]

*3.3 Recyclability of catalyst **1** in the synthesis of enaminones*

At the end of each reaction the catalyst could be easily separated from the reaction by an external magnet. After washing with methanol and DCM and drying under a vacuum, the catalyst could be re-used. We also tested the recyclability of catalyst **1** in the coupling reaction of **3** and **4** (Fig. 2) for the synthesis of **5**. Results showed that catalyst **1** could be recycled and reused. Even after five cycles, the catalyst showed robust activity and converted 84% of **3** into enaminone **5** after three hours. There was a loss of catalyst **1** after each cycle (see supplementary data). The loss of the catalyst suggests that the minimal amount of catalyst **1** does remain in the reaction mixture after being separated by an external magnet.

4. Conclusion

In summary, a novel heterogeneous Cu(I) catalyst complexed with magnetic nanoparticles (**1**) was designed, synthesized and characterized by FT-IR, EDX, TGA, DTG, VSM, XRD, SEM, TEM and XPS. Catalytic applications of **1** were studied in the syntheses of enaminones. The catalyst provided enaminones by coupling thioamides and diazo compounds at lower temperature and in less time than literature methods.[21, 25] It is the only example of the use of a magnetic nanoparticle-based catalyst in the synthesis of enaminones from the coupling of thioamides and diazo compounds. The catalyst can be separated easily by a magnet and re-used. The recyclability of the catalyst was shown for the synthesis of enaminones. The ease of separation and reusability of the catalyst can be important for industrial applications, especially where the removal of transition metals is an issue. The catalyst furnishes enaminones as single diastereomers in excellent yields. As such, the catalyst offers many advantages over previously published methods for the synthesis of enaminones.

Acknowledgments

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Supplementary data

Experimental procedures, spectroscopic data and ^{1}H and ^{13}C spectra.

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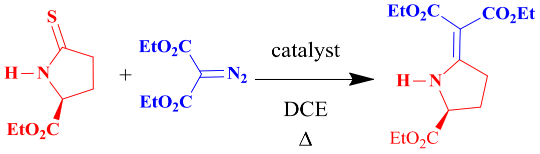
Table 1. Optimization of the reaction conditions for the synthesis of enaminones[a]



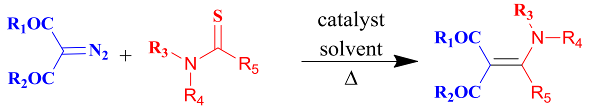
3 4 5

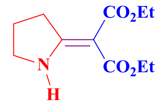
Entry	Catalyst	Temperature	Time	Yield (%)

	loading	(°C)	(hour)	
1	**1**, 0.9 mol%	70	10	20[b]
2	**1**, 1.8 mol%	70	10	50[b]
3	**1**, 2.3 mol%	70	3	100[b] (93%)[c]
4	**1**, 2.7 mol%	r.t.	12	0[b]
5	**1**, 2.7 mol%	50	10	40[b]
6	CuI, 30 mol%	70	3	4[b]
7	Fe_3O_4, 28 mol%	70	3	0[b]

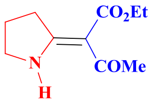
[a] All reactions were performed in an argon atmosphere using a pressure vessel. Reaction conditions: **3** (0.156 mmols), **4** (1.3 eq), DCE 0.75 mL; [b] Percent Conversion of **3** into **5** by ^{1}H NMR. [c] Isolated yield.

Table 2. Enaminone synthesis via catalyst 1 catalyzed coupling reaction between thioamides and α-diazocarbonyl compounds

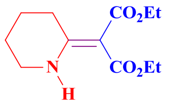




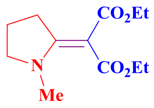
6
(5 h, 70 °C, 92%)



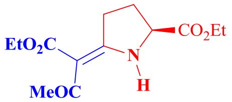
7
(3 h, 70 °C, 91%)
(22 h, 70 °C, 78%)[25]
(22 h, 90 °C, 71%)[25]



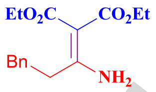
8
(6 h, 70 °C, 86%)
(26 h, 90 °C, 71%)[21]



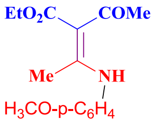
9
(6 h, 70 °C, 65%)



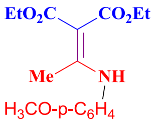
10
(4 h, 70 °C, 89%)



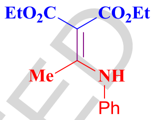
11
(4 h, 70 °C, 84%)



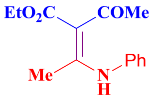
12
(2 h, 70 °C, 93%)



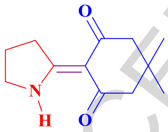
13
(3 h, 70 °C, 92%)



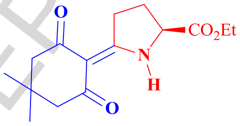
14
(5 h, 70 °C, 90%)



15
(3 h, 70 °C, 91%)



16
(6 h, 70 °C, 82%)



17
(6 h, 70 °C, 90%)

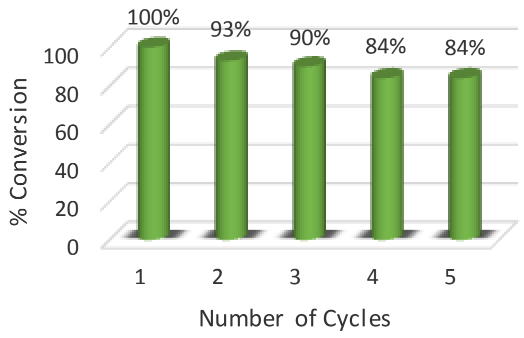
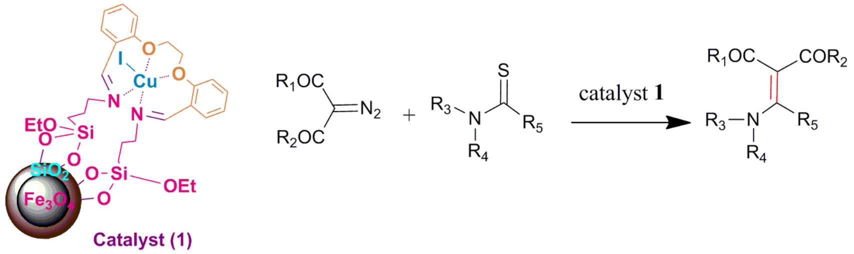


Fig. 2. Recyclability of catalyst **1** in the coupling reaction of **3** and **4** under the optimized reaction conditions. Percent conversion refers to the conversion of **3** into **5** after 3 h as determined by the ^{1}H NMR.

Graphical abstract



Highlight

- A new magnetically recoverable Cu(I)-complexed nanoparticle catalyst is prepared
- The catalyst provides diverse enaminones as single diastereomers in high yields
- The catalyst provides enaminones at lower temperature and in less time than reported methods