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ORIGINAL PAPER

# Wool-$SO_3H$ and nano-$Fe_3O_4$@wool as two green and natural-based renewable catalysts in one-pot isocyanide-based multicomponent reactions

**Ahmad Shaabani**[1] · **Zeinab Hezarkhani**[1] · **Mohammad Tayeb Faroghi**[1]

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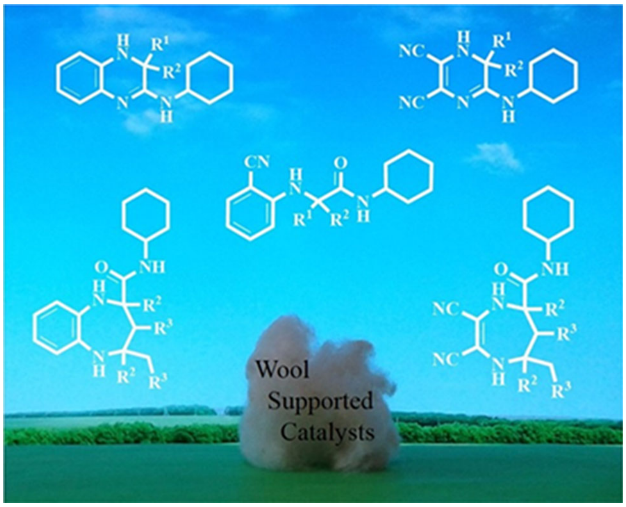
**Abstract** Natural wool sulfonic acid (wool-$SO_3H$) and wool-supported $Fe_3O_4$ nanoparticles (nano-$Fe_3O_4$@wool) with highly loaded $Fe_3O_4$ nanoparticles were simply synthesized and characterized by flame atomic absorption spectroscopy, X-ray diffraction, thermogravimetric analysis, and scanning electron microscopy. The successful synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile, (cyanophenylamino)acetamide, tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide, and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives shows that wool-$SO_3H$ and $Fe_3O_4$@wool nanocomposite have high catalytic activity and can be repetitively used as two biodegradable catalysts.

*Graphical abstract*



**Keywords** Heterogeneous catalysis · Natural wool · Solid acids · Nanostructures · Green chemistry · Multicomponent reactions

## Introduction

Replacement of liquid acids with solid acids is desirable as a “green” approach to process the chemicals in industrial transformations [1]. Recently, sulfated and sulfonated solid acid catalysts were used as important catalysts for various transformations in the fine and industrial production of chemicals [2]. The sulfuric solid acids (R–O–$SO_3H$) are usually prepared from sulfation of supports using chlorosulfonic acid or sulfuric acid in which the –$SO_3H$ group

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✉ Ahmad Shaabani
a-shaabani@sbu.ac.ir

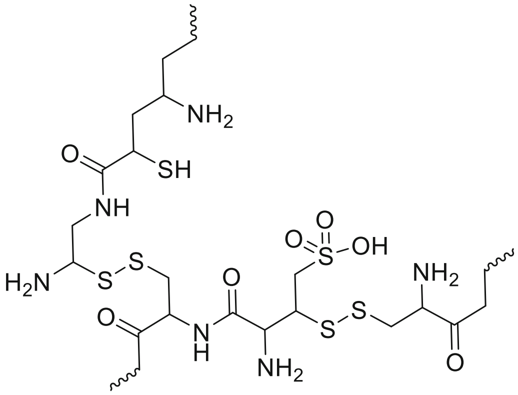
[1] Faculty of Chemistry, Shahid Beheshti University, Tehran, Iran

was chemically bonded or physically adsorbed to the porous organic or inorganic solid surfaces [3–7]. In the case of sulfonic acids (R–$SO_3H$), two procedures for the production of solid acids are reported: (1) the sulfonation of support in a multi-step strategy in which sulfur trioxide ($SO_3$) reacts with functional groups of organic compounds such as phenyl ring in the support to form a sulfur–carbon bond [8–10]; (2) a multi-step strategy that usually involves the loading of the –SH groups on the support and then oxidizing to –$SO_3H$ groups [11, 12].

Wool is a chiral natural biopolymer composed of repetitive units of amino acids cross-linked by S–S bonds [13–15]. Keratin as the main component of wool is insoluble in any solvent, so this biopolymer could be used as natural solid support. The suitable oxidizing agents can attack the disulfide linkages, –S–S–, and they can easily oxidize them to –$SO_3H$ groups in one step [16–18]. When the S–S bonds in keratin are oxidized to the –$SO_3H$ groups, the acidic active sites which were placed on this support may play the role of a solid acid catalyst (Scheme 1). It is important to note, in the case of wool, relatively high sulfonic acid provided on the catalyst (with respect to chemical functionalization of inorganic and organic supports with sulfonic acid groups) combined with its availability, biodegradability, renewability, and being green makes this material attractive as solid acid catalyst [19–22].

In recent decades, composite nanocatalysts, especially supported magnetic metal oxides, have attracted considerable interest of the researchers, because of their potential applications in chemical processes [23, 24]. Simple separation (using an external magnet), availability, high catalytic activity, high chemical stability, reusability, and environmental friendliness are several important advantages of these heterogeneous nanocatalysts. Since unsupported nanoparticles are usually unstable and the coagulation of the nanoparticles during the reaction is frequently unavoidable, the aggregation and agglomeration of $Fe_3O_4$ nanoparticles into less active large particles and bulk $Fe_3O_4$ during the reaction decrease its catalytic activities [23, 24]. As mentioned above, wool contains numerous amino acids units with –NH–CO–, –$NH_2$, and –S–S– functional groups, and the metal oxides nanoparticles uptake by wool fibers can be done by these functional groups; due to the structurally ordered amino acid chains, the aggregation of $Fe_3O_4$ could be prevented.

**Scheme 1**



Polyfunctionalized heterocycles play important roles in the drug discovery process [25, 26]. For example, various types of fused nitrogen-containing heterocycles such as quinoxalinones [27, 28] and benzodiazepines [29, 30] exhibit a wide variety of biological activity. Therefore, it is not surprising that research in the field of synthesis of heterocyclic compounds has received special attention.

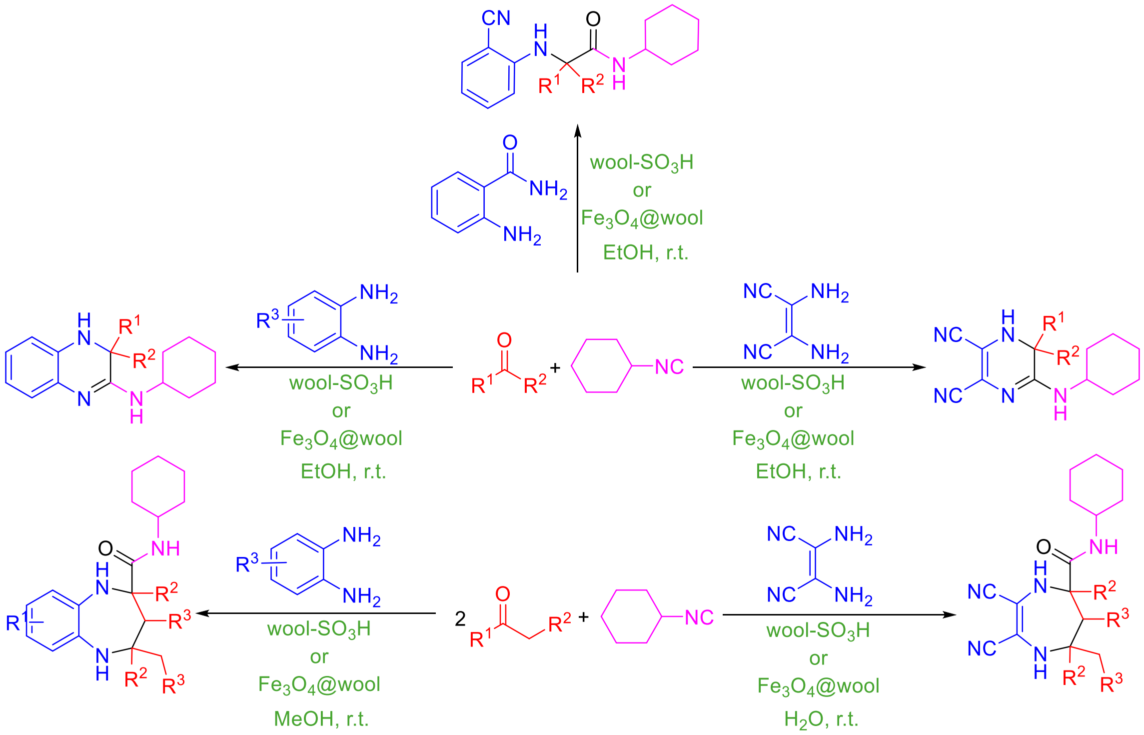
As part of our ongoing program related to developing new methods using solid acids and heterogeneous catalysts in organic compound transformations [3, 4, 31], and based on our previous investigations on multicomponent reaction [32–37], wool-$SO_3H$ and $Fe_3O_4$@wool were synthesized and investigated as catalysts for the synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile, (cyanophenylamino)acetamide, tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide, and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives (Scheme 2).

## Results and discussion

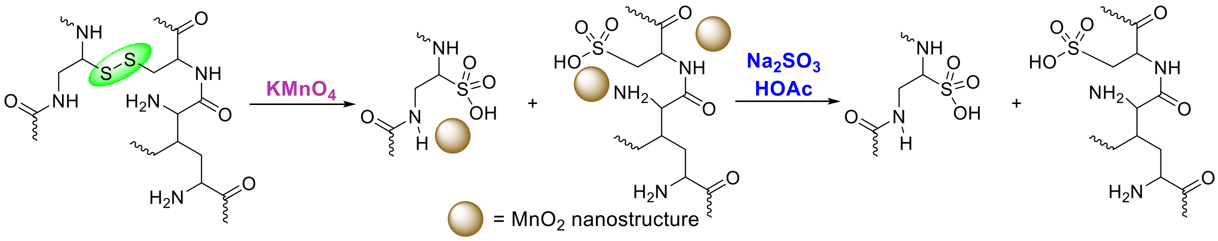
The synthetic route to produce the catalyst was based on the modification of natural wool by oxidation of the –S–S– to –$SO_3H$ groups, using $KMnO_4$ as oxidant and then loading $MnO_2$ on the surface of the modified wool, followed by the removal of $MnO_2$ from the support. The $MnO_2$ was removed from the catalyst by washing with an aqueous solution of $Na_2SO_3$ and acetic acid (Scheme 3). Wool-supported $Fe_3O_4$ nanoparticles were prepared from $FeCl_3$ and $FeCl_2$ solution at pH 11–12 as shown in Scheme 4.

The Fe content of the $Fe_3O_4$@wool catalyst was determined using the FAAS method and the amount of $Fe_3O_4$ was determined to be 15.1 % in this catalyst. The thermal stability of the catalysts was verified by thermogravimetric analysis. Thermogravimetric curves for wool, wool-$SO_3H$, and $Fe_3O_4$@wool are shown in Fig. 1 which revealed that after an initial loss of adsorbed water at 90–236, 90–222, and 90–245 °C, respectively, the main loss of weight occurred. The decomposition step seems to include two stages up to 800 °C. This loss was attributed to the first step of the decomposition reaction at about 236, 222, and 245 °C and the second one at 372, 364, and 383 °C, respectively.

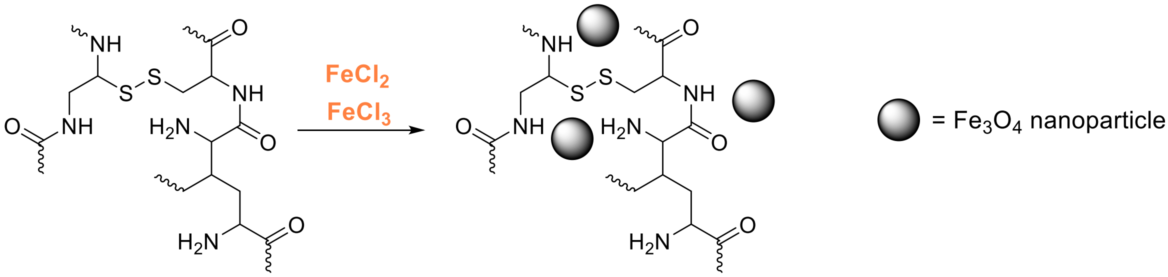
**Scheme 2**



**Scheme 3**



**Scheme 4**



To investigate the structure of the synthesized catalysts, the X-ray diffraction patterns of wool, wool-SO$_3$H, and Fe$_3$O$_4$@wool are depicted in Fig. 2. The diffraction peaks of wool fibers appear as two broad peaks at $2\theta$ values of around 9° and 21°, which are its characteristics (Fig. 2-I). Clearly, the characteristic peaks of wool-SO$_3$H are

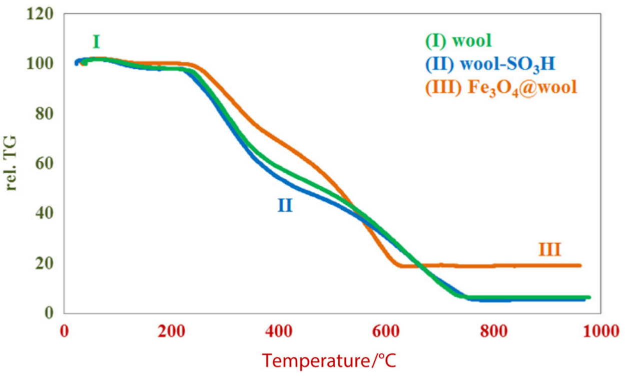


**Fig. 1** TG curves of wool (*I*), wool-SO$_3$H (*II*), and Fe$_3$O$_4$@wool (*III*) in air

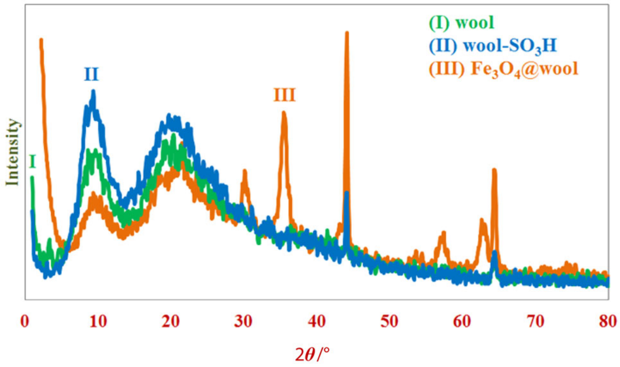


**Fig. 2** XRD patterns of wool (*I*), wool-SO$_3$H (*II*), and Fe$_3$O$_4$@wool (*III*)

observed in the diagram II of Fig. 2, meaning that the morphology of wool after functionalizing with the oxidation of –S–S– to –SO$_3$H groups was retained. To clarify the structure of the inorganic Fe$_3$O$_4$ nanoparticles in the Fe$_3$O$_4$@wool nanocomposite, its XRD pattern was prepared (Fig. 2-III). As seen from Fig. 2-III, the Fe$_3$O$_4$@wool nanocomposite exhibited two main peaks at $2\theta$ values of around 9° and 21° and six main peaks at $2\theta = 30.17°$, 35.53°, 42.88°, 53.61°, 57.20°, and 62.72° which corresponded to the characteristic peaks of wool and Fe$_3$O$_4$ nanoparticles dispersed onto the surface of wool fibers, respectively (Fig. 2).

The morphological characterization of the prepared catalysts was conducted using scanning electron microscope (SEM). According to Fig. 3a, the wool fibers have a length of about 200 μm–2 mm. On comparing Fig. 3b that is related to wool fibers with the SEM image of wool-SO$_3$H (Fig. 3c) confirmed that the catalyst material was formed without a large change in its morphology. The structure and morphology of the obtained Fe$_3$O$_4$@wool nanocomposite were illustrated by SEM (Fig. 3d); the Fe$_3$O$_4$ nanostructures could be observed on the wool fiber surface on which the nanoparticles were well dispersed.

After the successful production of catalysts, to examine the catalytic systems for synthesis of organic compounds, we used the wool-SO$_3$H and Fe$_3$O$_4$@wool catalysts in the reaction media for synthesis of *N*-cyclohexyl-3,3-dimethyl-3,4-dihydroquinoxalin-2-amine (**4a**). Acetone (0.06 g, 1.0 mmol) and catalyst were added to a flask containing 6.0 cm$^3$ of the solvent and stirred at room temperature for 2 h. Then, 0.11 g *o*-phenylenediamine (1.0 mmol) and 0.11 g cyclohexyl isocyanide (1.0 mmol) were added to the reaction media and stirring was continued for the indicated time in Table 1. The results of optimizing the reaction conditions are shown in Table 1. From the data presented in this table, it is clear that 0.15 g of wool-SO$_3$H and 0.11 g of Fe$_3$O$_4$@wool catalyst provide the best results (entries 2, 6–8). The comparison of the results related to the effect of various solvents on the synthesis of compound *N*-cyclohexyl-3,3-dimethyl-3,4-dihydroquinoxalin-2-amine (**4a**) revealed that commercially available 96 % ethanol is the preferred solvent.

The synthesis of *N*-cyclohexyl-3,3-dimethyl-3,4-dihydroquinoxalin-2-amine (**4a**) was carried out successfully using the wool-SO$_3$H and Fe$_3$O$_4$@wool catalysts; therefore the usability of these catalytic systems were examined for the synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile, and (cyanophenylamino)acetamide derivatives. As indicated in Table 2, the results of the mentioned catalysts showed that the reactions were done under mild conditions at room temperature with good to high yields.

To extend the scope of the prepared catalysts, the syntheses of tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives were investigated. Optimization studies were performed with the synthesis of 2,3-dicyano-*N*-cyclohexyl-5,7,7-trimethyl-4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide (**8a**) as a model reaction. Using the stated catalysts, the reaction proceeded smoothly; this observation confirms the usability of the wool-SO$_3$H and Fe$_3$O$_4$@wool as acid catalyst. As shown in Table 3, the best result is obtained with 0.30 g of wool-SO$_3$H and 0.22 g of Fe$_3$O$_4$@wool catalyst (entry 1).

Finally, the synthesis of the various tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives using the synthesized catalysts (0.30 g wool-SO$_3$H or 0.22 g Fe$_3$O$_4$@wool) in methanol and H$_2$O as the preferred solvents at room temperature were studied, respectively (Table 4).

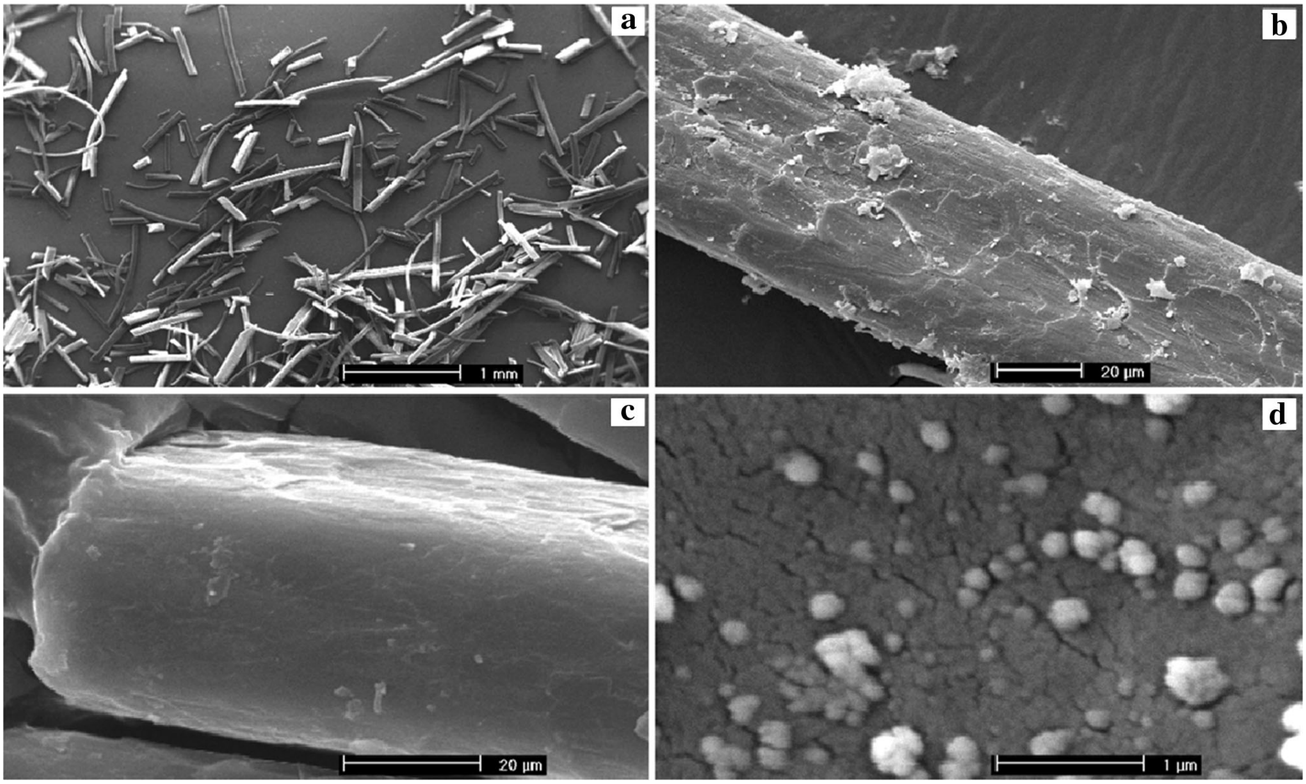


**Fig. 3** SEM images of wool (**a**, **b**), wool-$SO_3H$ (**c**), and $Fe_3O_4$@wool (**d**)

As illustrated in Table 5, using wool-$SO_3H$ and $Fe_3O_4$@wool catalysts, two different kinds of isocyanide were used to produce two new benzodiazepines and diazepines under mild reaction conditions in high yields.

The recyclability of the wool-$SO_3H$ and $Fe_3O_4$@wool were examined in the acid-catalyzed reactions. Catalysts were recovered from the reaction media used for the synthesis of *N*-cyclohexyl-3,3-dimethyl-3,4-dihydroquinoxalin-2-amine (**4a**) by filtration and an external magnet, respectively, and reused for four repetitive cycles. The results showed that the activity and performance of the wool-$SO_3H$ and $Fe_3O_4$@wool catalysts were saved during successive uses (Fig. 4).

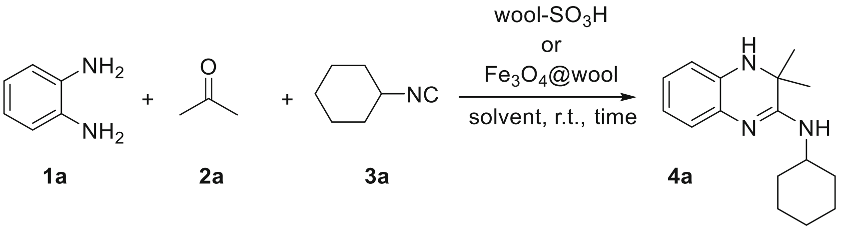
## Conclusion

Wool is an abundant, green, cheap, renewable, and biodegradable natural biopolymer and wool sulfonic acid (wool-$SO_3H$) as a solid acid catalyst was easily synthesized by oxidation of the –S–S– groups of wool. Nano magnetic iron oxides were supported on wool fibers and used in the synthesis of organic compounds. The distribution of $Fe_3O_4$ nanoparticles on the surface of wool fibers gave an active catalytic system and prevented aggregation and agglomeration of $Fe_3O_4$ nanoparticles. The synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile, (cyanophenylamino)acetamide, tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide, and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives could be catalyzed by wool-$SO_3H$ and $Fe_3O_4$@wool under mild reaction conditions. Both the synthetic catalysts have a high ability to be used in the synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile, (cyanophenylamino)acetamide, tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide, and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives, but $Fe_3O_4$@wool is the best one due to simple separation using an external magnet without the need for filtration and from the reaction time point of views. The recyclability of catalysts with no loss in activity, excellent yield, and easy workup are several advantages of wool-$SO_3H$ and $Fe_3O_4$@wool catalysts.

## Experimental

Natural white wool was washed with NaOH solution, distilled water, methanol, and acetone, and then cut into pieces. All reagents were obtained from Aldrich or Merck

**Table 1** Optimization of the reaction conditions for the synthesis of *N*-cyclohexyl-3,3-dimethyl-3,4-dihydroquinoxalin-2-amine (**4a**)



| Entry | Catalyst (g) | Time/h | Solvent | Yield[a]/% |
|---|---|---|---|---|
| 1 | Wool-$SO_3H$ (0.15) | 8 | MeOH | 68 |
| | $Fe_3O_4$@wool (0.11) | 4 | MeOH | 73 |
| 2 | Wool-$SO_3H$ (0.15) | 8 | EtOH | 92 |
| | $Fe_3O_4$@wool (0.11) | 4 | EtOH | 90 |
| 3 | Wool-$SO_3H$ (0.15) | 8 | $H_2O$ | Trace |
| | $Fe_3O_4$@wool (0.11) | 4 | $H_2O$ | Trace |
| 4 | Wool-$SO_3H$ (0.15) | 8 | THF | Trace |
| | $Fe_3O_4$@wool (0.11) | 4 | THF | Trace |
| 5 | Wool-$SO_3H$ (0.15) | 8 | $CH_3Cl$ | Trace |
| | $Fe_3O_4$@wool (0.11) | 4 | $CH_3Cl$ | Trace |
| 6 | Wool-$SO_3H$ (0.12) | 8 | EtOH | 65 |
| | $Fe_3O_4$@wool (0.09) | 4 | EtOH | 59 |
| 7 | Wool-$SO_3H$ (0.09) | 8 | EtOH | 47 |
| | $Fe_3O_4$@wool (0.07) | 4 | EtOH | 44 |
| 8 | Wool-$SO_3H$ (0.06) | 8 | EtOH | 15 |
| | $Fe_3O_4$@wool (0.05) | 4 | EtOH | 18 |

Reaction conditions: *o*-phenylenediamine (1.0 mmol), acetone (1.0 mmol), cyclohexyl isocyanide (1.0 mmol), and catalyst were stirred in 6.0 $cm^3$ solvent

[a] Isolated yield

and used without further purification. Fe determination was carried out on an FAAS (Shimadzu model AA-680 flame atomic absorption spectrometer) with Fe hollow cathode lamps at 248.33 nm, using an air–acetylene flame. Thermogravimetric analysis (TGA) was carried out using STA 1500 instrument at a heating rate of 10 °C $min^{-1}$ in air. The X-ray diffraction (XRD) pattern of catalysts was recorded on a STOE STADI P with a scintillation detector, secondary monochromator using Cu Kα radiation ($\lambda = 0.1540$ nm). Scanning electron microscopy (SEM) observations were carried out on an electron microscopy Philips XL-30 ESEM. All samples were sputtered with gold before observation. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1H$ NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 MHz; chemical shifts were reported in parts per million (ppm). The $^{13}C$ NMR spectra were recorded at 75.47 MHz; the chemical shifts were reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL.

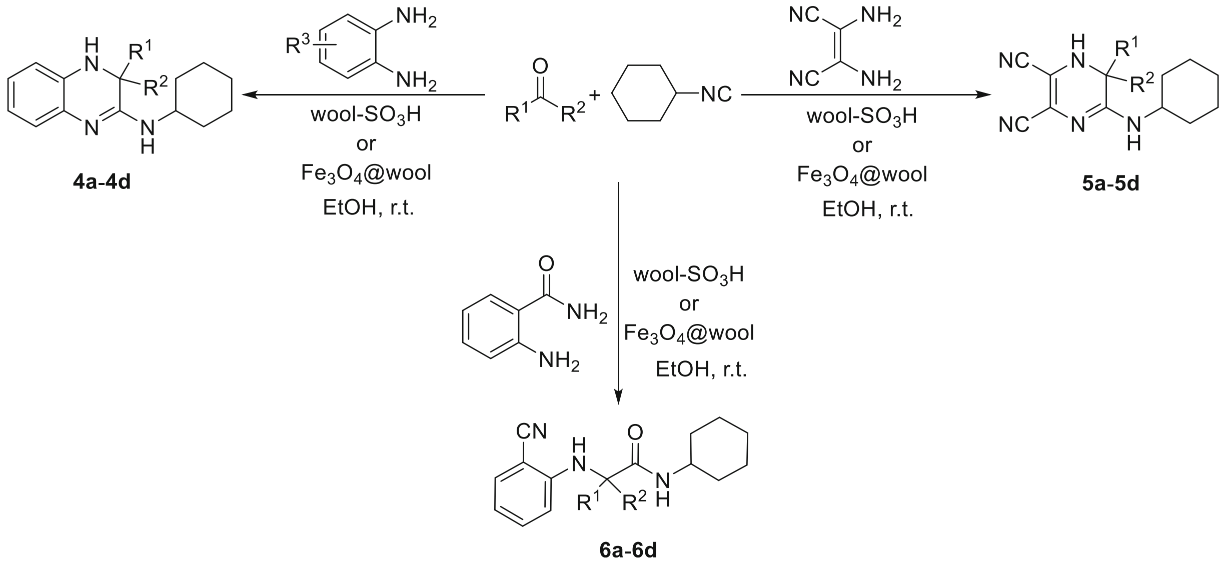
## Preparation of catalyst

Natural white wool (sheep of Kangavar/Iran) was washed with NaOH solution (0.01 M), distilled water, methanol, and acetone and cut with scissors to very short pieces (about 200 μm–2 mm, based on SEM images).

## Preparation of wool sulfonic acid catalyst (wool-$SO_3H$)

To a magnetically stirred suspension of 1.0 g wool pieces in 250 $cm^3$ of $H_2O$, a 0.10 M solution of $KMnO_4$

**Table 2** Synthesis of 3,4-dihydroquinoxalin-2-amine, 1,6-dihydropyrazine-2,3-dicarbonitrile, and (cyanophenylamino)acetamide derivatives

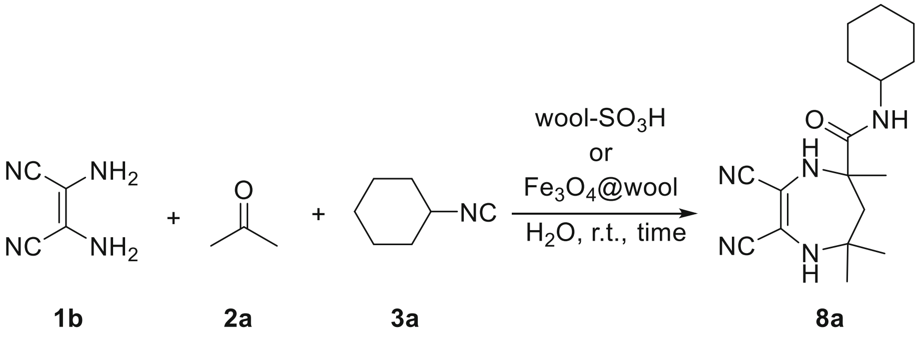


| Entry | Amine | Carbonyl compound | Product | Catalyst | Time/h | Yield[a]/% | M.p. (°C) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Found | Reported |
| 1 | *o*-Phenylenediamine | Acetone | **4a** | Wool-$SO_3H$ | 8 | 92 | 159–161 | 160–162 [32] |
| | | | | $Fe_3O_4$@wool | 4 | 90 | | |
| 2 | 4-Nitrobenzene-1,2-diamine | Benzaldehyde | **4b** | Wool-$SO_3H$ | 8 | 96 | 179–180 | 178–180 [32] |
| | | | | $Fe_3O_4$@wool | 4 | 93 | | |
| 3 | 4-Nitrobenzene-1,2-diamine | 4-Methoxybenzaldehyde | **4c** | Wool-$SO_3H$ | 8 | 90 | 174–176 | 175–176 [32] |
| | | | | $Fe_3O_4$@wool | 4 | 94 | | |
| 4 | 3,4-Diaminobenzophenone | 4-Nitrobenzaldehyde | **4d** | Wool-$SO_3H$ | 8 | 88 | >250 | >250 [32] |
| | | | | $Fe_3O_4$@wool | 4 | 82 | | |
| 5 | 2,3-Diaminomaleonitrile | Acetone | **5a** | Wool-$SO_3H$ | 8 | 93 | 256–258 | 255–258 [33] |
| | | | | $Fe_3O_4$@wool | 4 | 86 | | |
| 6 | 2,3-Diaminomaleonitrile | Cyclohexanone | **5b** | Wool-$SO_3H$ | 8 | 90 | 283–285 | 284–285 [33] |
| | | | | $Fe_3O_4$@wool | 4 | 89 | | |
| 7 | 2,3-Diaminomaleonitrile | Acetophenone | **5c** | Wool-$SO_3H$ | 8 | 88 | 230–231 | 230–233 [33] |
| | | | | $Fe_3O_4$@wool | 4 | 91 | | |
| 8 | 2,3-Diaminomaleonitrile | 4-Bromoacetophenone | **5d** | Wool-$SO_3H$ | 8 | 90 | 275–276 | 275–278 [33] |
| | | | | $Fe_3O_4$@wool | 4 | 93 | | |
| 9 | 2-Aminobenzamide | Benzaldehyde | **6a** | Wool-$SO_3H$ | 24 | 78 | 142–143 | 142–144 [34] |
| | | | | $Fe_3O_4$@wool | 20 | 86 | | |
| 10 | 2-Aminobenzamide | 3-Nitrobenzaldehyde | **6b** | Wool-$SO_3H$ | 24 | 84 | 165–166 | 164–166 [34] |
| | | | | $Fe_3O_4$@wool | 20 | 88 | | |
| 11 | 2-Aminobenzamide | 4-Methoxybenzaldehyde | **6c** | Wool-$SO_3H$ | 24 | 91 | 167–170 | 167–169 [34] |
| | | | | $Fe_3O_4$@wool | 20 | 87 | | |
| 12 | 2-Aminobenzamide | 4-Bromobenzaldehyde | **6d** | Wool-$SO_3H$ | 24 | 87 | 185–188 | 186 [34] |
| | | | | $Fe_3O_4$@wool | 20 | 85 | | |

Reaction conditions: amine (1.0 mmol), carbonyl compound (1.0 mmol), isocyanide (1.0 mmol), and 0.15 g wool-$SO_3H$ or 0.11 g $Fe_3O_4$@wool were stirred in 6.0 $cm^3$ ethanol 96 %

[a] Isolated yield

**Table 3** Optimization of the reaction conditions for the synthesis of 2,3-dicyano-*N*-cyclohexyl-5,7,7-trimethyl-4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide (**8a**)



| Entry | Catalyst (g) | Time/h | Yield[a]/% |
|---|---|---|---|
| 1 | Wool-$SO_3H$ (0.30) | 24 | 78 |
| | $Fe_3O_4$@wool (0.22) | 18 | 83 |
| 2 | Wool-$SO_3H$ (0.25) | 24 | 51 |
| | $Fe_3O_4$@wool (0.18) | 18 | 62 |
| 3 | Wool-$SO_3H$ (0.20) | 24 | 36 |
| | $Fe_3O_4$@wool (0.14) | 18 | 37 |
| 4 | Wool-$SO_3H$ (0.15) | 24 | 12 |
| | $Fe_3O_4$@wool (0.10) | 18 | 20 |

Reaction conditions: 2,3-diaminomaleonitrile (1.0 mmol), acetone (2.0 mmol), cyclohexyl isocyanide (1.0 mmol), and catalyst were stirred in 6 $cm^3$ $H_2O$

[a] Isolated yield

(100 $cm^3$) was added dropwise during 12 h at room temperature. The stirring was continued for 12 h; the mixture was filtered to give brown $MnO_2$@wool. Thereafter, the brown wool was dipped in a solution of $Na_2SO_3$ (50 g/$dm^3$) and acetic acid (25 mol/$dm^3$) and stirred at 50 °C for 10 min. After the wool turned white, it was washed with water several times and then dried at 80 °C. The number of $H^+$ sites of the wool-$SO_3H$ catalyst determined by acid–base titration was 0.70 meq/g.

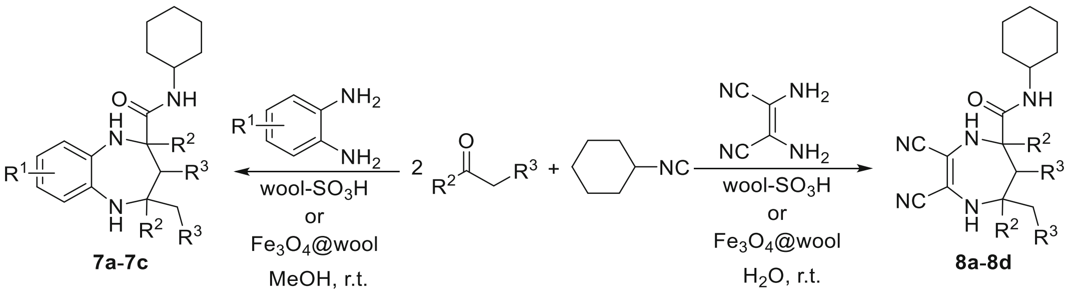
## Preparation of $Fe_3O_4$@wool catalyst

$Fe_3O_4$ nanoparticles, homogeneous in size and composition, were prepared from $FeCl_3$ and $FeCl_2$ solution according to the previous report by Kang and coworkers [38]. Wool-supported $Fe_3O_4$ nanoparticles were prepared in an aqueous solution with a molar ratio of Fe(III)/Fe(II) = 2 and pH 11–12. To a magnetically stirred suspension of 1.00 g wool pieces in 100 $cm^3$ of deionized water, 0.31 g of $FeCl_3$ and 0.12 g of $FeCl_2$ were successively dissolved in the solution with stirring. A solution of NaOH was added dropwise during 4 h into the resulting mixture under vigorous stirring at room temperature to give black $Fe_3O_4$@wool. The paramagnetism of the catalyst was checked in situ by placing a magnet near the $Fe_3O_4$@wool. The catalyst was isolated in the magnetic field and the supernatant was removed from the $Fe_3O_4$@wool by decantation and the residue washed with water several times. Then, the $Fe_3O_4$@wool catalyst was added to the HCl solution with stirring to neutralize the anionic charges on the nanoparticles. $Fe_3O_4$@wool was again separated and washed with water several times and dried at 80 °C.

## General procedure for the preparation of products 4a–4d, 5a–5d, 6a–6d, 7a–7d, and 8a–8e

In a general reaction for the synthesis of products **4a–4d**, **5a–5d**, and **6a–6d**, a carbonyl compound (1.0 mmol) was added to a flask containing catalyst (0.15 g wool-$SO_3H$ and 0.11 g $Fe_3O_4$@wool) and 6.0 $cm^3$ of 96 % ethanol. Amine (1.0 mmol) and then isocyanide (1.0 mmol) were

**Table 4** Synthesis of tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide and 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives



| Entry | Diamine | Carbonyl compound | Product | Catalyst | Time/h | Yield[a]/% | M.p. (°C) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Found | Reported |
| 1 | 4-Nitrobenzene-1,2-diamine | Acetone | **7a** | Wool-$SO_3H$ | 24 | 86 | 184–187 | 185–187 [35] |
| | | | | $Fe_3O_4$@wool | 18 | 91 | | |
| 2 | 3,4-Diaminobenzoic acid | Cyclohexanone | **7b** | Wool-$SO_3H$ | 24 | 90 | 212–213 | 213–214 [35] |
| | | | | $Fe_3O_4$@wool | 18 | 94 | | |
| 3 | 4,5-Dichlorobenzene-1,2-diamine | Acetone | **7c** | Wool-$SO_3H$ | 24 | 87 | 169–171 | 169–172 [35] |
| | | | | $Fe_3O_4$@wool | 18 | 89 | | |
| 4 | 2,3-Diaminomaleonitrile | Acetone | **8a** | Wool-$SO_3H$ | 24 | 78 | 169–170 | 169–172 [36] |
| | | | | $Fe_3O_4$@wool | 18 | 83 | | |
| 5 | 2,3-Diaminomaleonitrile | Acetophenone | **8b** | Wool-$SO_3H$ | 24 | 84 | 221–224 | 221–222 [36] |
| | | | | $Fe_3O_4$@wool | 18 | 90 | | |
| 6 | 2,3-Diaminomaleonitrile | 4-Bromo-acetophenone | **8c** | Wool-$SO_3H$ | 24 | 89 | 202–204 | 202–205 [36] |
| | | | | $Fe_3O_4$@wool | 18 | 87 | | |
| 7 | 2,3-Diaminomaleonitrile | 4-Methyl-acetophenone | **8d** | Wool-$SO_3H$ | 24 | 78 | 210–212 | 210–212 [36] |
| | | | | $Fe_3O_4$@wool | 18 | 85 | | |

Reaction conditions: amine (1.0 mmol), carbonyl compound (2.0 mmol), isocyanide (1.0 mmol), and 0.30 g wool-$SO_3H$ or 0.22 g $Fe_3O_4$@wool were stirred in 6.0 $cm^3$ solvent

[a] Isolated yield

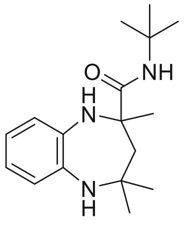
added to the reaction media and stirred at room temperature for the indicated time as in Table 2. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered off and washed with acetone and then precipitated and crystallized to give the products.

To synthesize products **7a**–**7d** and **8a**–**8e**, 2.0 mmol of carbonyl compound and 0.30 g of wool-$SO_3H$ or 0.22 g of $Fe_3O_4$@wool catalyst were utilized and methanol and $H_2O$ were used as solvent, respectively.

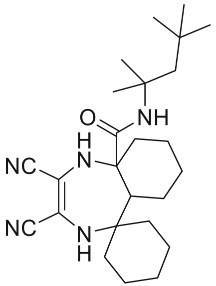
*N-(tert-Butyl)-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine-2-carboxamide* (**7d**, $C_{17}H_{27}N_3O$) M.p.: 197–200 °C; IR (KBr): $\bar{\nu} = 3422, 3332, 2970, 2925, 2859, 1653, 1594, 1524, 1487\ cm^{-1}$; $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta = 1.27$ (3H, s, $CH_3$), 1.30 (9H, s, 3 $CH_3$), 1.37 (3H, s, $CH_3$), 1.43 (3H, s, $CH_3$), 1.70 (1H, d, $J = 14.4$ Hz, 1H of $CH_2$), 2.53 (1H, d, $J = 14.4$ Hz, 1H of $CH_2$), 3.80 (1H, br s, NH), 6.59 (2H, br s, 2NH), 7.61–7.71 (4H, m, H–Ar) ppm; $^{13}C$ NMR (75.47 MHz, $CDCl_3$): $\delta = 29.2$, 29.7, 30.0, 30.1, 30.5, 33.2, 46.4, 51.0, 54.4, 61.1, 118.2, 118.5, 118.7, 119.2, 134.4, 144.1, 174.2 ppm.

*2,3-Dicyano-N-(2,4,4-trimethylpentan-2-yl)-1,4,6,7,8,9-hexahydrospiro[benzo[e][1,4]diazepine-5,1′-cyclohexane]-9a(5aH)-carboxamide* (**8e**, $C_{25}H_{39}N_5O$) M.p.: 182–185 °C; IR (KBr): $\bar{\nu} = 3434, 3359, 2944, 2866, 2213, 1550, 1479, 1452\ cm^{-1}$; $^1H$ NMR (300.13 MHz, DMSO-$d_6$): $\delta = 0.93$ (9H, s, 3 $CH_3$), 1.19–1.84 (27H, m, 2 $CH_3$, 10 $CH_2$, CH), 3.40 (1H, br s, NH), 6.07 (1H, br s,

**Table 5** Synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamide and tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide



**7d**



**8e**

| Entry | Diamine | Carbonyl compound | Product | Yield[a]/% |
|---|---|---|---|---|
| **1** | *o*-Phenylenediamine | Acetone | **7d** | 79 |
| **2** | 2,3-Diaminomaleonitrile | Cyclohexanone | **8e** | 87 |

Reaction conditions: amine (1.0 mmol), carbonyl compound (2.0 mmol), isocyanide (1.0 mmol), and 0.30 g wool-$SO_3H$ or 0.22 g $Fe_3O_4$@wool were stirred in 6.0 $cm^3$ solvent

[b] Isolated yield

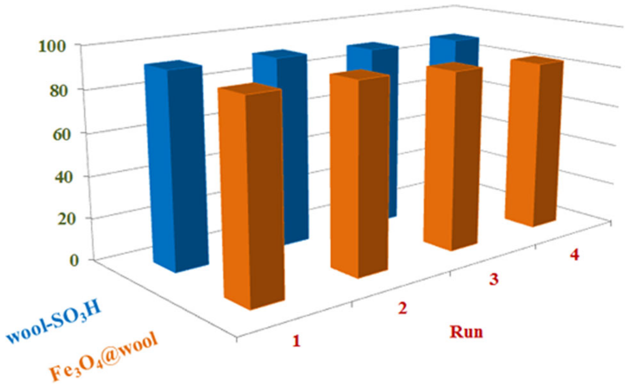


**Fig. 4** Successive use of the prepared catalysts for the synthesis of **4a**

NH), 6.85 (1H, br s, NH) ppm; $^{13}C$ NMR (75.47 MHz, DMSO-$d_6$): $\delta = 20.4$, 25.0, 29.3, 29.6, 31.6, 31.7, 31.8, 49.6, 51.5, 51.6, 56.4, 56.5, 108.1, 111.4, 115.2, 118.3, 152.8 ppm.

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