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# $Fe_3O_4$@Silica Sulfuric Acid Nanoparticles as a Magnetically Recoverable Solid Acid Catalyst for the Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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A new efficient method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and spiroquinazolinones *via* a condensation reaction of aldehydes and ketones with anthranilamide in the presence of nano $Fe_3O_4$@$SiO_2$-$SO_3H$ as catalyst in ethanol has been described. The reactions are completed in short times, and the corresponding dihydroquinazolinones are produced with high yields. The present procedure has several advantages, including short reaction times, high yields of products, facile experiment, simple work-up, eco-friendly reaction conditions, and reusability of the catalyst. The catalyst could simply be separated and recovered by an external magnet and reused in subsequent reactions with no considerable loss in activity.

**Keywords:** $Fe_3O_4$@$SiO_2$-$SO_3H$, Nanomagnetic solid acid, 2,3-Dihydroquinazolin-4(1*H*)-ones, Anthranilamide, Cyclocondensation

## INTRODUCTION

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of nitrogen-containing heterocyclic compounds that have been reported a wide range of biological and pharmaceutical activities [1,2]. 2,3-Dihydroquinazolinone derivatives can be easily oxidized to quinazolin-4(3*H*)-ones [3-5], which also have biological activities and exist in a variety of natural products, pharmaceutical candidates and agrochemicals [6-8].

Several methods have been reported for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones such as three-component reaction of aldehydes with isatoic anhydride and amines or ammonium acetate [9-12], reduction of quinazolin-4(3*H*)-ones [13], reductive cyclization of *o*-nitrobenzamides with aryl aldehydes, ketones or ethyl orthoformate [14], and condensation of anthranilamide (2-aminobenzamide) with aldehydes or ketones [15-23]. The last method, is still the most common and simple method to the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones. In recent years, various catalysts have been used to catalyze this reaction such as $H_3PW_{12}O_{40}$ [15], $ZrCl_4$ [16], 2-(N-morpholino) ethanesulfonic acid [17], bis(glycerol)boric acid [18], *p*-TsOH [19,20], poly(VPyPS)-PW [21], metal-CNTs [22] and nanocrystalline sulfated zirconia [23]. These catalysts are useful to facilitate the synthesis of desired products, however, most of reported procedures suffer from one or more limitations such as low product yields, prolonged reaction time, difficulty in work-up, the use of hazardous solvents and lack of reusability of the catalyst. So, effective, simple and mild methods for the of 2,3-dihydroquinazolin-4(1*H*)-ones synthesis are yet in demand.

Magnetic nanoparticles (MNPs) have been widely used for the preparation of heterogeneous catalysts because their paramagnetic properties enable the simple separation of the catalyst from the reaction mixture using an external magnet [24]. In recent years, the sulfuric acid functionalized silica-coated magnetite nanoparticles ($Fe_3O_4$@$SiO_2$-$SO_3H$, $Fe_3O_4$@silica sulfuric acid, and $Fe_3O_4$@SSA) as a recyclable powerful solid acid opens up a new path to present an effective system for simple recovery of the catalyst in various organic transformations [25-28].

Because of the importance of 2,3-dihydroquinazolin-4(1*H*)-ones as above-mentioned and the catalytic strength of

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$Fe_3O_4$@$SiO_2$-$SO_3H$ in chemical transformations, we now wish describe a new procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the cyclocondesation of aldehydes and ketones with anthranilamide in the presence of catalytic amounts of $Fe_3O_4$@silica sulfuric acid in EtOH at room temperature and under reflux conditions.

## EXPERIMENTAL

### General

All of the commercially available chemicals were purchased from Merck, Fluka and Aldrich and used with no further purification. $Fe_3O_4$, $Fe_3O_4$@$SiO_2$ and $Fe_3O_4$@SSA were prepared pursuant to the reported procedure [26]. All of the products were characterized for their physical properties and by comparison with authentic samples. The reactions were monitored by TLC on silica gel polygram SILG/UV 254 plates. Melting points were obtained in open capillary tubes and were measured with an electrothermal 9200 apparatus. Infrared (IR) spectra were recorded on KBr Pellets on a Shimadzu IRPresting-21 spectrophotometer in the range of 4000-400 $cm^{-1}$. NMR spectra were recorded in DMSO-$d_6$ on a Bruker Advanced DPX 400 MHz spectrometer using TMS as an internal reference.

### Preparation of $Fe_3O_4$@SSA

The nano $Fe_3O_4$@$SiO_2$-$SO_3H$ was prepared according to the reported method [26].

### Sulfonic Acid Loading of $Fe_3O_4$@SSA

To determine the acidity of the catalyst, to a 25 ml aqueous solution of NaCl (1 M, pH = 6.24), $Fe_3O_4$@$SiO_2$-$SO_3H$ (100 mg) was added and the resulting mixture was stirred for 24 h. The pH of the solution was reduced to 2.11, indicating the presence of 1.94 mmol $g^{-1}$ of $H^+$.

### General Procedure for the Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones

To a solution of anthranilamide (1 mmol) and aldehydes or ketones (1 mmol) in EtOH (5 ml), $Fe_3O_4$@SSA (0.05 g) was added and the mixture was stirred at r.t. or under reflux conditions for the suitable times as shown in Table 2. Upon the complete reaction, as indicated by TLC (EtOAc:*n*-hexane 1:1), the nanocatalyst was removed in the presence of an external magnet. Then, the resulting mixture was filtered off and recrystallized from the ethanol to afford the corresponding products in high yields. All of the 2,3-dihydroquinazolin-4(1*H*)-ones are known and were identified by comparison of their physical and spectroscopic data (IR, NMR) with those of authentic samples [15-23].

### Spectral Data for Respective Compounds

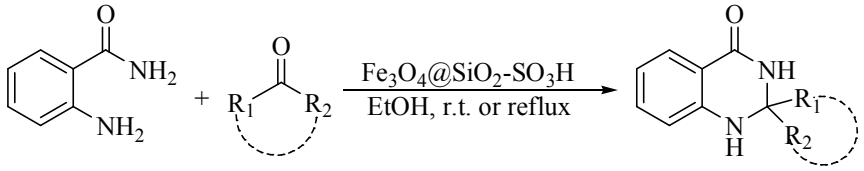
2,3-Dihydro-2-(4-methoxyphenyl)quinazolin-4(1*H*)-one (entry 3): IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3294, 3178, 3047, 2965, 1654, 1608, 1512, 1483; $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 3.42 (s, 1H, CH), 3.73 (s, 3H, $OCH_3$), 5.73 (br s, 1H, NH), 6.74-7.63 (8H, m, ArH), 8.23 (br s, 1H, NH-CO); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 55.1, 66.2, 113.5, 114.3, 114.9, 117.0, 127.3, 128.2, 133.2, 133.3, 148.0, 159.4, 163.7.

2,2'-Dispirocyclohexane-2,3-dihydroquinazolin-(1*H*)-4,4'-dione (entry 17): IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3433, 3259, 3174, 2987, 1631, 1585, 1512, 1481; $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 1.88 (s, 8H, $CH_2$), 6.55 (s, 2NH), 6.67 (m, 2H, ArH), 6.78 (m, 2H, ArH), 7.26 (m, 2H, ArH), 7.60 (m, 2H, ArH), 7.84 (m, 2H, 2NH-CO); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 32.0, 66.6, 114.7, 114.8, 116.9, 127.2, 133.3, 146.4, 163.2.

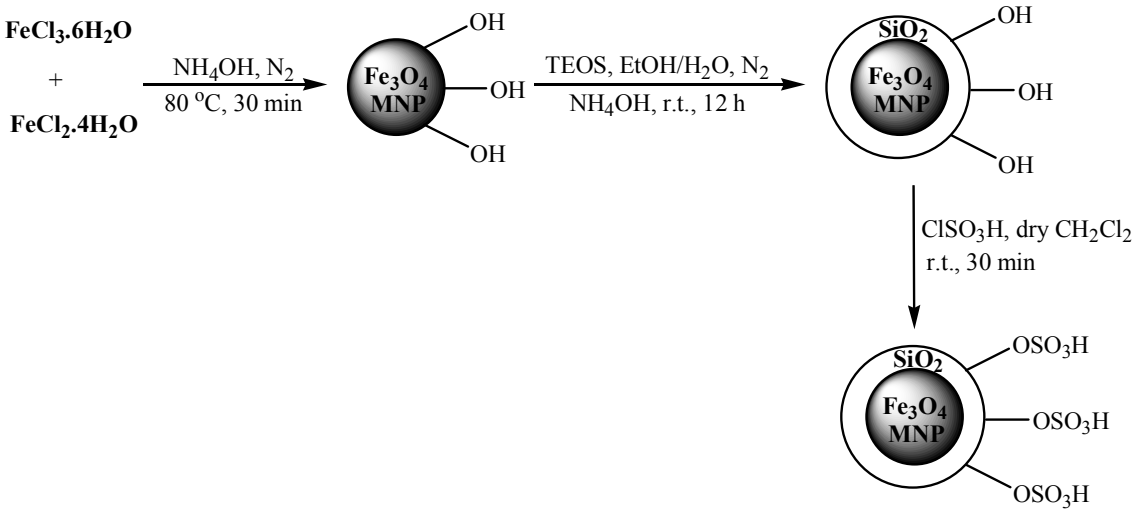
## RESULTS AND DISCUSSION

Nano $Fe_3O_4$ encapsulated silica sulfuric acid ($Fe_3O_4$@$SiO_2$-$SO_3H$) has received remarkable attention as a non-toxic, inexpensive, readily available and reusable catalyst for different organic reactions, to afford the desired products in high yields [25-28]. However, we did not find any report in literature on the synthesis of quinazolinones and their derivatives by use of this solid acid catalyst. We observed that $Fe_3O_4$@$SiO_2$-$SO_3H$ is an efficient catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the cyclocondesation of aldehydes and ketones with anthranilamide in EtOH at room temperature and under reflux conditions (Scheme 1).

The $Fe_3O_4$@$SiO_2$-$SO_3H$ catalyst was prepared following the reported procedure in three steps [26]. Magnetite nanoparticles were synthesized by the co-precipitation of $FeCl_2$ and $FeCl_3$ in ammonia solution. To improve the chemical stability of magnetite nanoparticles, their surface




*Scheme 1*. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by $Fe_3O_4$@$SiO_2$-$SO_3H$




*Scheme 2*. Preparation of $Fe_3O_4$@$SiO_2$-$SO_3H$

**Table 1.** Optimization of the Condensation Reaction between Anthranilamide and Benzaldehyde

| Entry | Catalyst (g) | Solvent | Temp. (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | No catalyst | EtOH | Reflux | 120 | trace |
| 2 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | EtOH | r.t. | 20 | 92 |
| 3 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | EtOH | Reflux | 10 | 90 |
| 4 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.025 g) | EtOH | r.t. | 60 | 89 |
| 5 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | $H_2O$ | r.t. | 90 | 87 |
| 6 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | MeCN | r.t. | 120 | Trace |
| 7 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | $CH_2Cl_2$ | r.t. | 120 | Trace |
| 8 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | PhMe | r.t. | 120 | Trace |
| 9 | $Fe_3O_4$@$SiO_2$-$SO_3H$ (0.05 g) | $Et_2O$ | r.t. | 120 | Trace |
| 10 | $Fe_3O_4$@$SO_3H$ (0.05 g) | EtOH | r.t. | 60 | 87 |

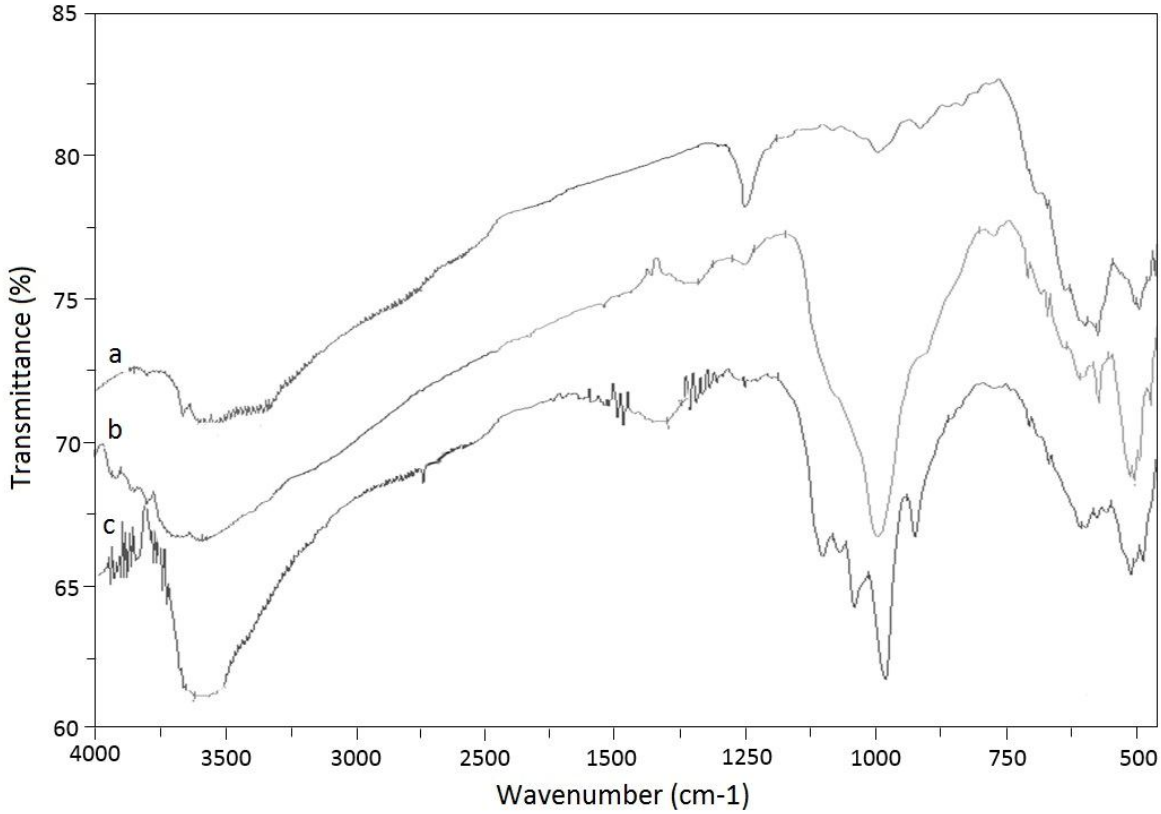



**Fig. 1.** FT-IR spectra of the bare $Fe_3O_4$ (a), $Fe_3O_4$@$SiO_2$ (b) and $Fe_3O_4$@$SiO_2$-$SO_3H$ nanoparticles.

**Fig. 2.** SEM image of $Fe_3O_4$@$SiO_2$-$SO_3H$ nanoparticles.

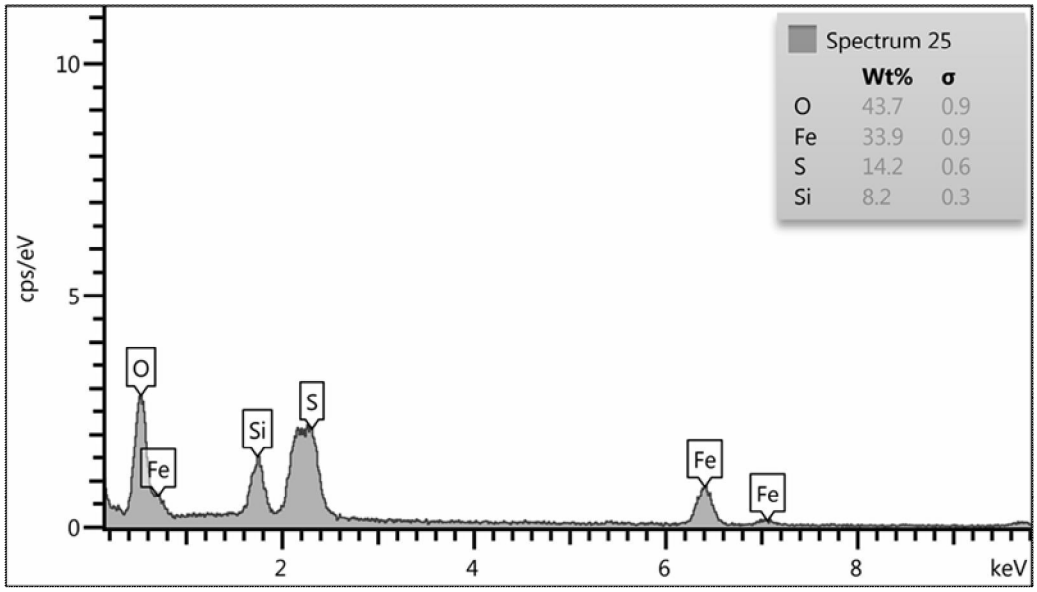



**Fig. 3.** EDS spectra of $Fe_3O_4$@$SiO_2$-$SO_3H$ nanoparticles.

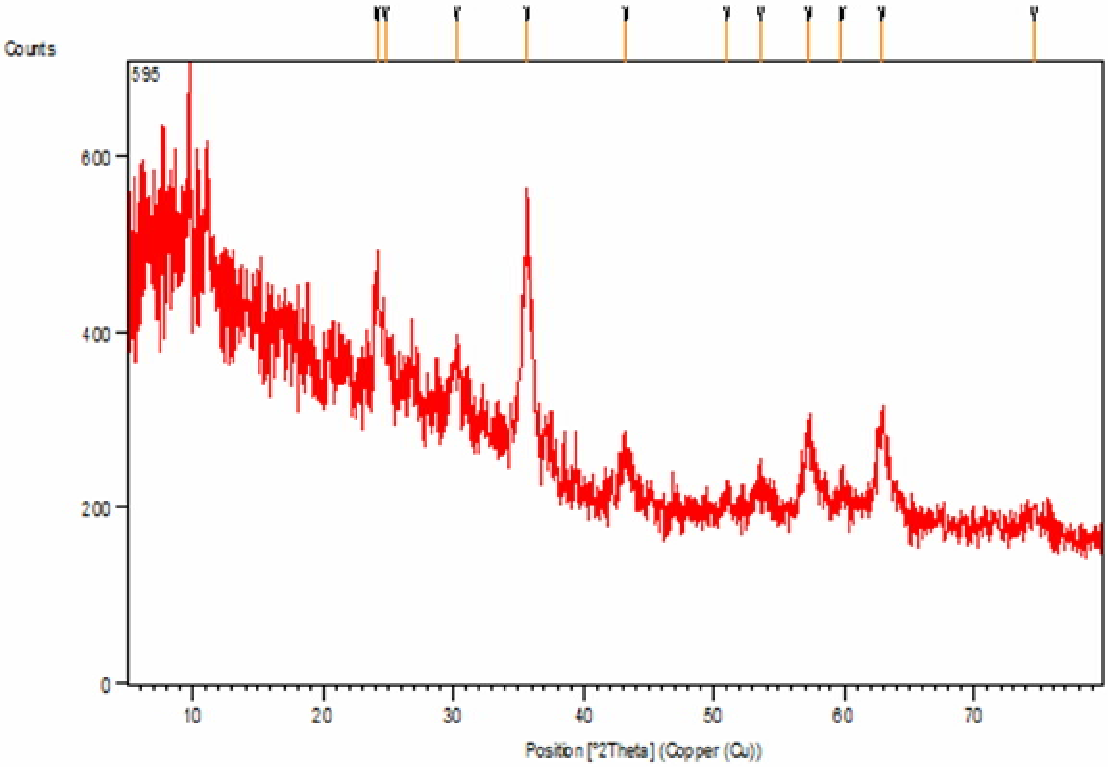



**Fig. 4.** XRD pattern of $Fe_3O_4$@$SiO_2$-$SO_3H$ nanoparticles.

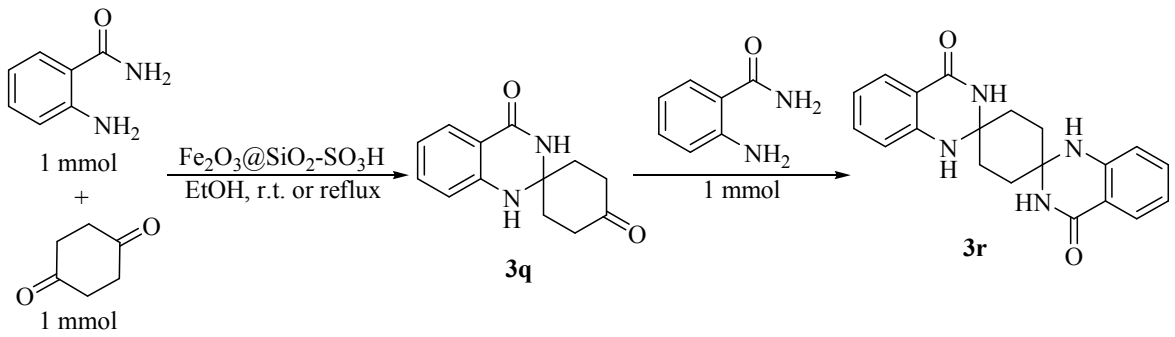
**Table 2.** Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones by Using $Fe_3O_4$@SSA in EtOH

| Entry | Aldehyde/ketone | Product[a] | Room temperature | | Reflux conditions | | m.p. (°C) | |
|---|---|---|---|---|---|---|---|---|
| | | | Time (min) | Yield (%)[b] | Time (min) | Yield (%)[b] | Found | Ref. |
| 1 | Benzaldehyde | 3a | 20 | 92 | 10 | 90 | 220-222 | [21] |
| 2 | 4-Methylbenzaldehyde | 3b | 30 | 89 | 20 | 91 | 231-233 | [21] |
| 3 | 4-Methoxybenzaldehyde | 3c | 30 | 92 | 20 | 89 | 187-189 | [21] |
| 4 | 2-Hydroxybenzaldehyde | 3d | 15 | 90 | 10 | 90 | 223-226 | [17] |
| 5 | 2-Chlorobenzaldehyde | 3e | 40 | 87 | 30 | 86 | 207-209 | [18] |
| 6 | 3-Chlorobenzaldehyde | 3f | 90 | 84 | 50 | 85 | 185-187 | [29] |
| 7 | 4-Chlorobenzaldehyde | 3g | 100 | 82 | 60 | 80 | 205-207 | [18] |
| 8 | 3-Nitrobenzaldehyde | 3h | 50 | 87 | 40 | 83 | 183-184 | [18] |
| 9 | 4-Dimethylaminobenzaldehyde | 3i | 100 | 85 | 60 | 86 | 209-210 | [17] |
| 10 | Cinnamaldehyde | 3j | 45 | 86 | 30 | 87 | 240-243 | [30] |
| 11 | 2-Furaldehyde | 3k | 90 | 93 | 40 | 91 | 166-168 | [21] |
| 12 | Cyclopentanone | 3m | 150 | 82 | 90 | 87 | 260-262 | [20] |
| 13 | Cyclohexanone | 3n | 20 | 93 | 10 | 91 | 217-219 | [20] |
| 14 | Cycloheptanone | 3o | 150 | 88 | 90 | 89 | 197-200 | [31] |
| 15 | Isatin | 3p | 140 | 85 | 90 | 80 | 215-217 | [32] |
| 16 | 1,4-Cyclohexanedione | 3q | 90 | 83 | 60 | 86 | >300 | [20] |
| 17[c] | 1,4-Cyclohexanedione | 3r | 35 | 82 | 20 | 83 | >300 | [20] |

[a]All products were characterized by IR, and $^1$H and $^{13}$C NMR, and their spectra were compared with those of the authentic samples. [b]Isolated yields. [c]Anthranilamide:ketone in a 2:1 ratio.

and electron-withdrawing groups were reacted with anthranilamide at the optimized reaction conditions and the corresponding products in excellent yields were obtained (Table 2, entries 2-10). Cinnamaldehyde and 2-furaldehyde as starting materials were also reacted under optimized reaction conditions and the desired products were obtained in excellent yields (Table 2, entries 11 and 12). Cyclic ketones and diketones were also reacted with anthranilamide successfully and the corresponding spiro-quinazolinones were obtained in high yields (Table 2, entries 12-16). When the reaction was performed between 1,4-cyclohexadione and anthranilamide in 1:2 ratio, the dispiro compound was formed (Scheme 3 and Table 2, entry 17).

The possibility of recycling the catalyst was tested in the cyclocondensation of benzaldehyde with anthranilamide by




*Scheme 3.* Condensation reaction between anthranilamide and 1,4-cyclohexadione

**Table 3.** Catalyst Reusability in the Condensation of Anthranilamide with Benzaldehyde in EtOH at r.t.

| Run | Time (min) | Yield (%) |
|---|---|---|
| 1 | 20 | 92 |
| 2 | 20 | 91 |
| 3 | 20 | 88 |
| 4 | 20 | 86 |

**Table 4.** Comparison of Various Catalysts for the Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-one from Benzaldehyde

| Entry | Catalyst | Conditions | Time (min) | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 | $Y(OTf)_3$ | EtOH, r.t. | 90 | 93 | [4] |
| 2 | $Ga(OTf)_3$ | EtOH, 70 °C | 55 | 83 | [14] |
| 3 | $ZrCl_4$ | EtOH, r.t. | 25 | 95 | [16] |
| 4 | MES | EtOH/$H_2O$, 60 °C | 150 | 93 | [17] |
| 5 | $H[Gly_2B]$ | 60 °C | 10 | 90 | [18] |
| 6 | Poly(VPyPS)-PW | EtOH, Ul. | 6 | 95 | [21] |
| 7 | $NH_4Cl$ | EtOH, r.t. | 15 | 92 | [32] |
| 8 | $Fe_3O_4$@$SiO_2$-$SO_3H$ | EtOH, reflux | 10 | 90 | This work |
| 9 | $Fe_3O_4$@$SiO_2$-$SO_3H$ | EtOH, r.t. | 20 | 92 | This work |

using $Fe_3O_4$@$SiO_2$-$SO_3H$ in ethanol at room temperature. Upon completion, the reaction mixture was filtered and the catalyst was separated by an external magnet and was washed with warm EtOH. The recovered catalyst could be reused at least 4 times without any considerable loss in its catalytic activity (Table 3).

By comparison, the obtained results for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one from benzaldehyde in the presence of various catalysts are given in Table 4. As shown in Table 4, $Fe_3O_4$@$SiO_2$-$SO_3H$ has greater efficiency and shorter reaction time than other catalysts.

## CONCLUSIONS

In conclusion, the present study described the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by using a new nanomagnetic catalyst, $Fe_3O_4$@$SiO_2$-$SO_3H$. This catalytic procedure offers several advantages, such as use of commercially available and inexpensive starting materials, simple work-up, gentle reaction conditions, recyclability and reusability of the catalyst, short time of reactions and high yield of products. So we think that this procedure could be considered a new and suitable addition to the existent methodologies in this area.

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