

Silica Sulfuric Acid-coated Fe_3O_4 Nanoparticles as a Highly Efficient and Reusable Solid Acid Catalyst for the Green Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones under Solvent-free Conditions



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DOI: 10.2174/1570178614666170711144740 Abstract: An efficient and eco-friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)ones and spiroquinazolinones in the presence of sulfuric acid functionalized silica-coated magnetite nanoparticles under solvent-free conditions has been described. The reactions are completed in short times, and the products are obtained in high isolated yields without any undesirable side reaction. This method has several advantages, including short reaction time, facile operation, easy work-up, ecofriendly reaction conditions, high isolated yields, and reusability of the catalyst. The catalyst could be easily separated and recovered from the reaction mixture by an external magnet and reused in subsequent reactions with no considerable loss in activity.

Keywords: 2,3-Dihydroquinazolin-4(1*H*)-ones, $Fe_3O_4@SiO_2-SO_3H$, nanomagnetic solid acid catalyst, cyclocondensation, solvent-free, green synthesis.

1. INTRODUCTION

Optimal use of material and energy, and an efficient waste management can be recognized as important factors for environmental protection. To realize this target, in recent decades, remarkable papers have appeared efficient solvent-free reactions [1-4]. This method has many advantages such as reduced pollution, eco-friendly reaction conditions, low cost, simplicity in operation, short reaction time, easier work-up, and green aspects by avoiding hazardous organic solvents. In addition, from the green and environmental acceptability, recently more attention has been paid to the application of nanomagnetic solid acid catalysts in organic transformations [5-7]. The main advantages of these catalysts are simple separation of the catalyst from the reaction mixture, and high efficiency, recyclability and reusability of the catalyst.

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of nitrogen-containing heterocyclic compounds have been reported a wide range of biological and pharmaceutical activities [8, 9]. 2,3-Dihydroquinazolinone derivatives can be easily oxidized to quinazolin-4(3*H*)-ones [10, 11], which also have biological activities and exist in a variety of natural products, pharmaceutical candidates and agrochemicals [12-14].

Several methods for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones have been reported [15-20]. The cyclocondensation of aldehydes and ketones with anthranilamide (2aminobenzamide), and three component reaction of isatoic anhydride and an aromatic aldehyde with ammonium acetate or primary amines are the general methods for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones. In the recent decade, various catalysts have been used to catalyze these reactions such as Sc(OTf)₃ [21], NH₄Cl [22], H₃PW₁₂O₄₀ [23], magnetic Fe₃O₄ nanoparticles [24], SrCl₂.6H₂O [25], ZrCl₄ [26], Amberlyst-15 [27, 28], 2-(N-morpholino) ethanesulfonic acid (MES) [29], bis(glycerol)boric acid (H[Gly₂B]) [30], p-TsOH [31, 32], Poly(VPyPS)-PW [33], metal-CNTs [34], nanocrystalline sulfated zirconia [35], Y(OTf)₃ [36], and titanium silicon oxide nanopowder [37]. These catalysts are useful to facilitate the synthesis of desired products, however, most of the reported procedures suffer from some limitations such as long reaction time, low product yields, the use of hazardous solvents, difficulty in work-up and lack of reusability of the catalyst. Therefore, mild, simple and effective processes for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones are still in demand.

In recent years, sulfuric acid functionalized silica-coated magnetite nanoparticles (Fe₃O₄@SiO₂-SO₃H) as recyclable strong solid acid catalyst opens up a new path to present an efficient system for facilitating catalyst recovery in different organic reactions [38-41]. Because of the importance of 2,3-dihydroquinazolin-4(1*H*)-ones and the catalytic strength of

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2. RESULTS AND DISCUSSION

Fe₃O₄@silica sulfuric acid core-shell nanocomposite (Fe₃O₄@SiO₂-SO₃H) has received remarkable attention as an inexpensive, readily available, non-toxic and reusable catalyst for various organic transformations, affording the corresponding products in high yields [38-41]. However, to the best of our knowledge there has been no report on the use of this solid acid catalyst for the synthesis of quinazolinones and their derivatives. We observed that Fe₃O₄@SiO₂-SO₃H is an efficient catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the cyclocondesation of aldehydes and ketones with anthranilamide under solvent-free conditions (Scheme 1).



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

The Fe₃O₄@SiO₂-SO₃H catalyst was prepared following the reported procedure [39]. Fe₃O₄ nanoparticles were synthesized by the co-precipitation of FeCl₂ and FeCl₃ in ammonia solution. To improve the chemical stability of magnetite nanoparticles, their surface engineering was successfully performed by the suitable deposition of silica onto nanoparticles surface by the ammonia-catalyzed hydrolysis of tetraethylorthosilicate (TEOS). Next, The SiO₂ spheres served as support for the immobilization of SO₃H groups by simple mixing of core-shell composite and chlorosulfonic acid in CH₂Cl₂ (Scheme **2**). The structure of the catalyst confirmed



Scheme (2). Schematic diagram for the synthesis of Fe₃O₄@SiO₂-SO₃H.



Fig. (1). FT-IR spectra of the bare Fe_3O_4 (**a**), Fe_3O_4 @SiO₂ (**b**) and Fe_3O_4 @SiO₂-SO₃H (**c**) nanoparticles.

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by FT-IR spectra (Fig. 1), SEM image (Fig. 2), EDS (Fig. 3) and XRD pattern (Fig. 4).



Fig. (2). SEM image of Fe₃O₄@SiO₂-SO₃H nanoparticles.

After preparation and characterization of the catalyst, initially, the reaction condition was optimized in the reaction of anthranilamide and benzaldehyde as model reaction. The results of optimization experiments were summarized in Table 1. The results clearly show that although this reaction proceeded in ethanol at room temperature and under reflux conditions, the best result was obtained under solvent-free conditions at room temperature. The reaction in the absence of catalyst did not complete after 2h in refluxing EtOH. The model reaction was performed in the presence of various amounts of Fe₃O₄@SO₃H and Fe₃O₄@SiO₂-SO₃H as catalyst. In the terms of reaction time and the yield of the product, 0.025 g Fe₃O₄@SiO₂-SO₃H was selected as the best amount of the catalyst.

Following the obtained results, the reaction of anthranilamide and benzaldehyde was carried out in the presence of 0.025 g Fe₃O₄@SiO₂-SO₃H under solvent-free conditions at room temperature and the corresponding 2,3dihydroquinazolin-4(1*H*)-one was obtained in 93% yield (Table **2**, entry 1).



Fig. (3). EDS spectra of Fe₃O₄@SiO₂-SO₃H nanoparticles.



Fig. (4). XRD pattern of Fe₃O₄@SiO₂-SO₃H nanoparticles.

Entry	Catalyst (g)	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	No catalyst	EtOH	reflux	120	trace
2	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	EtOH	r.t.	20	92
3	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	EtOH	reflux	10	90
4	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.025 g)	EtOH	r.t.	60	89
5	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	H ₂ O	r.t.	90	87
6	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	MeCN	r.t.	120	trace
7	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	CH ₂ Cl ₂	r.t.	120	trace
8	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	PhMe	r.t.	120	trace
9	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	Et ₂ O	r.t.	120	trace
10	Fe ₃ O ₄ @SO ₃ H (0.05 g)	EtOH	r.t.	60	87
11	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.05 g)	Neat	r.t.	1.5	90
12	Fe ₃ O ₄ @SiO ₂ -SO ₃ H (0.025 g)	Neat	r.t.	2	93

Table 1. The optimization of the cyclocondensation reaction of anthranilamide with benzaldehyde.

Table 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by Fe₃O₄@SiO₂-SO₃H under solvent-free conditions.

Entry	Aldehyde/Ketone	Product ^a	Time (min)	Yield (%) ^b	m.p. (°C)	
					Found	Reported
1	Benzaldehyde	3a	2	93	220-222	219-220 [33]
2	4-Methylbenzaldehyde	3b	3	90	231-233	230-232 [33]
3	4-Methoxybenzaldehyde	3c	2	94	187-189	185-187 [33]
4	2-Hydroxybenzaldehyde	3d	2	96	223-226	220-221 [29]
5	2-Chlorobenzaldehyde	3e	7	96	207-209	207-209 [30]
6	3-Chlorobenzaldehyde	3f	6	85	185-187	185-186 [42]
7	4-Chlorobenzaldehyde	3g	7	83	205-207	205-207 [30]
8°	3-Nitrobenzaldehyde	3h	5	92	183-184	182-184 [30]
9 ^d	2,5-Dimethoxybenzaldehyde	3i	8	88	167-169	164-165 [42]
10^{d}	3,4-Dihydroxybenzaldehyde	3ј	6	89	187-190	-
11 ^d	4-Dimethylaminobenzaldehyde	3k	7	84	209-210	208-210 [29]
12	Cinnamaldehyde	31	8	87	240-243	224-226 [43]
13	2-Furaldehyde	3m	6	95	166-168	165-167 [33]
14 ^c	Cyclopentanone	3n	9	90	260-262	264-266 [32]
15°	Cyclohexanone	30	2	93	217-219	220-222 [32]
16 ^c	Cycloheptanone	3p	15	95	197-200	-
17°	Isatin	3q	5	85	214-215	214-216 [22]
18 ^d	1,4-Cyclohexanedione	3r	4	82	>300	>300 [32]
19 ^{d,e}	1,4-Cyclohexanedione	3s	2	84	>300	>300 [32]

a) All of the products were characterized by IR, and ¹H and ¹³C NMR, and their spectra were compared with those of the authentic samples.

b) Isolated yields.

c) Reaction was carried out at 70°C in an oil bath.

d) Reaction was carried out at 90°C in an oil bath.

e) Anthranilamide: ketone in a 2:1 ratio.

The scope and generality of this procedure was investigated in the reaction of various types of aldehydes and ketones with anthranilamide (Table 2). Aldehydes with both electron-donating and electron-withdrawing substituents were reacted with anthranilamide at the same reaction conditions and the corresponding products were obtained in excellent yields (Table 2, entries 2-11). Cinnamaldehyde and 2furylaldehyde as starting materials were also reacted under optimized reaction conditions and the corresponding 2,3dihydroquinazolin-4(1*H*)-ones were produced in high yields (Table 2, entries 12 and 13). Cyclic ketones and diketones were also condensed with anthranilamide successfully and the corresponding spiroquinazolinones were obtained in good to excellent yields (Table 2, entries 14-18). When the reaction was carried out with anthranilamide: 1,4cyclohexanedione in 2:1 ratio, we found that the dispiro compound formed (Table 2, entry 19) was evidenced from the ¹H, ¹³C NMR spectra.

It is worthy to note that the catalyst can be reused several times with no appreciable loss in its activity. The catalyst was separated and recovered by an external magnet, and then it was reused at least four times for facile condensation of benzaldehyde and anthranilamide, and produced desired product in 93%, 91%, 88% and 85% yield, respectively (Table 3).

Table 3. Reusability of the catalyst in the reaction of anthranilamide with benzaldehyde.

Run	Time (min)	Yield (%)	
1	2	93	
2	2	91	
3	2	88	
4	2	85	

By comparison, the obtained results for the synthesis of 2,3-dihydroquinazolin-4(1H)-one from benzaldehyde in the presence of various catalysts are given in Table **4**. As shown in Table **4**, Fe₃O₄@SiO₂-SO₃H has greater efficiency and shorter reaction time than other catalysts.

3. EXPERIMENTAL

3.1. General Procedures

All of the commercially available chemicals were purchased from Fluka, Aldrich and Merck and used without further purification. Fe₃O₄, Fe₃O₄@SiO₂ and Fe₃O₄@SiO₂-SO₃H were prepared according to the reported method [39]. All of the products were characterized for their physical properties and by comparison with authentic samples. Products were characterized by comparison of their physical data, IR, ¹H-NMR and ¹³C-NMR spectra with known samples. NMR spectra were recorded in CDCl₃ on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. X-ray diffraction (XRD) patterns of samples were taken on a Philips X-ray diffractometer Model PW 1840. The particle morphology was examined by SEM (Philips XL30 scanning electron microscope).

3.2. Preparation of the Catalyst

The nano $Fe_3O_4@SiO_2-SO_3H$ was prepared according to the reported method [39].

3.3. General Procedure for the Synthesis of 2,3dihydroquinazolin-4(1*H*)-ones

 $Fe_3O_4@SiO_2-SO_3H$ (0.05 g) was added to the 1:1 mixture of anthranilamide (1 mmol) and aldehydes or ketones (1 mmol). The mixture was stirred at room temperature (or in an oil bath at 70-100°C) for the appropriate time as shown in Table 2. After completion of the reaction, as indicated by TLC (ethyl acetate:*n*-hexane 1:1), and cooling, hot ethanol (5 mL) was added to the mixture and stirred for 10 min. In the presence of an external magnet, the nanocatalyst was removed and then extracted solution was cooled to room temperature to recrystallize to afford the corresponding

 Table 4.
 Comparison of various catalysts for the synthesis of 2,3-dihydroquinazolin-4(1H)-one from benzaldehyde.

Entry	Catalyst	Conditions Time (min)		Yield (%)	Ref.
1	Ga(OTf) ₃	EtOH, 70°C	55	83	[19]
2	Sc(OTf) ₃	EtOH, 70°C	25	92	[21]
3	NH4Cl	EtOH, r.t.	15	92	[22]
4	$H_{3}PW_{12}O_{40}$	H ₂ O, r.t.	8	94	[23]
5	SrCl ₂ .6H ₂ O	EtOH/H ₂ O, reflux	42	93	[24]
6	ZrCl ₄	EtOH, r.t.	25	95	[25]
7	MES	EtOH/H ₂ O, 60°C	150	93	[26]
8	MES	EtOH/H ₂ O, MW	10	95	[26]
9	H[Gly ₂ B]	60°C	10	90	[27]
10	Poly(VPyPS)-PW	EtOH, Ul.	6	95	[30]
11	Y(OTf) ₃	EtOH, r.t.	90	93	[33]
12	Fe ₃ O ₄ @SiO ₂ -SO ₃ H	r.t.	2	93	This work

products in 82-96% yield. All of the 2,3-dihydroquinazolin-4(1H)-ones are known and were identified by comparison of their physical and spectroscopic data (IR, NMR) with those of authentic samples [21-37].

CONCLUSION

In conclusion, $Fe_3O_4@SiO_2-SO_3H$ nanoparticles has proved to be a highly efficient solid acid catalyst for the cyclocondensation reaction between aldehydes and ketones with anthranilamide under solvent-free conditions at room temperature. This procedure offers several advantages including mild reaction conditions, short reaction times, clean reaction profiles, ease of work-up, environmentally benign, recyclability and reusability of the catalyst, and high product yields, which makes it a useful, easy, mild, efficient and general method for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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