Sulfonated-Titanomagnetite Nanoparticles as Potential and Recyclable Catalyst for the Synthesis of Dihydroquinazoline and Hexahydroquinoline Derivatives under Solvent-Free Condition

Azarifar, Davood; Tavakoli, Elham; Asadpoor, Roshanak; Bazouleh, Mona
Department of Chemistry, Bu-Ali Sina University, Hamedan, I.R. IRAN

Jaymand, Mehdi **+*
Nano Drug Delivery Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, I.R. IRAN

ABSTRACT: *The performance of sulfonated-titanomagnetite nanoparticles ($Fe_{3-x}Ti_xO_4$-SO_3H NPs) as useful and recyclable nanocatalyst for the synthesis of dihydroquinazoline and hexahydroquinoline derivatives through multi-component reaction approach in solvent-free condition were investigated extensively. The successful synthesis of mentioned derivatives was confirmed using Fourier-Transform InfraRed (FT-IR) as well as $^1H/^{13}C$ nuclear magnetic resonance (NMR) spectroscopies. According to the results, the employed nanocatalyst has some advantages such as high catalytic activity in short reaction time, good-to-excellent isolated yields in most cases, easy workup process, smooth processing feature of the reactions, facile recovery using an external magnetic field, and re-usability for four times without significant loss in its activity.*

KEYWORDS: *Nanocatalyst; Magnetic nanoparticles; Multi-component reaction; Dihydroquinazolines; Hexahydroquinolines.*

INTRODUCTION

The continuous attempts for developing versatile and impressive strategies for the synthesis of heterocyclic compounds has always been a common subject in the synthetic community. The development of efficient catalysts for the facile synthesis of organic compounds under mild condition with high yield has a progressive research area in the field [1-10]. In this context, metal oxide NanoParticles (NPs) can be considered as potential candidates for developing efficient catalysts mainly due to inherent physicochemical properties, including high activity, recycling ability, long-term stability and high oxidation power [11-22]. Titanomagnetite ($Fe_{3-x}Ti_xO_4$) NPs include magnetic ferrites, titanium and oxygen elements with a spinel structure [23]. These NPs are more active and more efficient than those of the similar metal oxides due to the high oxidation number (IV) for titanium element,
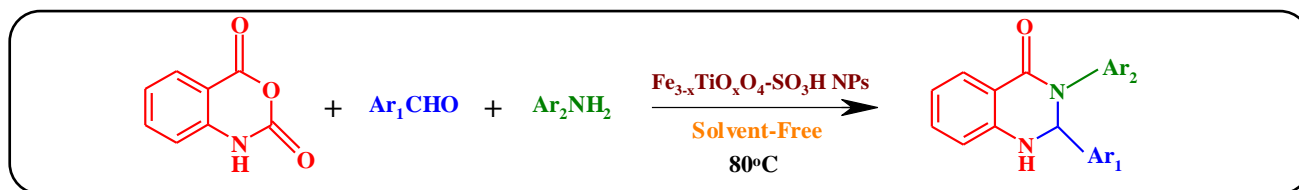
Scheme 1: Three-component synthesis of 2,3-dihydroquinazoline (1H)-4-ones catalyzed by $Fe_{3-x}Ti_xO_4$-SO_3H NPs.
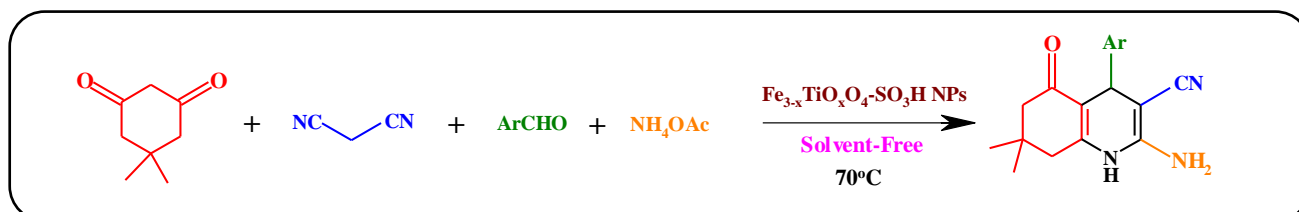
Scheme 2: Multi-component synthesis of 2-amino-3-cyano-hexahydroquinolines catalyzed by $Fe_{3-x}Ti_xO_4$-SO_3H NPs.

which lead to a large number of hydroxyl groups on the surface of $Fe_{3-x}Ti_xO_4$ NPs for further modification [1, 23].

Dihydroquinazolin-4(1H)-ones are an important class of heterocycle compounds with a wide range of pharmacological and biological activities. These organic compounds are known to be anti-tumor agents, diuretics, plant-growth regulators, herbicidal agents, anti-convulsants, and anti-fertility [24-31]. These compounds can be easily oxidized to their quinazolin-4(3H)-one analogues [32-34], which are important biologically active heterocyclic compounds and are found in some natural products [35-38]. According to importance of these compounds as biologically active reagents, there are several synthetic strategies, including cyclization of *O*-acylaminobenzamides [39], amidation of 2-aminobenzonitrile followed by oxidative ring closure [40], solid-phase synthesis of 2-arylamino-substituted quinazolinones [41], synthesis from isatoic anhydrides and "Schiff-Bases" [42], reduction of the azide functionality [43], and Pd-catalyzed heterocyclization of nitroenes [44] have been introduced for the synthesis of quinazolinone derivatives. On the other hand, hexahydroquinolines are biologically active heterocyclic compounds and exhibited anti-cancer, anti-inflammatory, anti-bacterial, anti-malarial, anti-asthmatic, anti-hypersensitive, and tyrosine kinase inhibitory features [1, 34, 45].

In this contribution, a facile strategy is reported for the synthesis of quinazolinone and quinolone derivatives through multi-component reactions under catalysis of sulfonated-titanomagnetite nanoparticles ($Fe_{3-x}Ti_xO_4$-SO_3H NPs; has been synthesized in our previous work [1]) under solvent-free conditions (Schemes 1 and 2). The reactions were optimized in terms of catalyst loading, time, temperature, and solvent.

EXPERIMENTAL SECTION
Materials

Chemical reagents as well as solvents in high purity were purchased from Merck (Darmstadt, Germany) and used without further purification. The nanocatalyst ($Fe_{3-x}Ti_xO_4$-SO_3H NPs) was synthesized in our laboratory [1].

Instrumentation

FT-IR spectra of the samples were provided using KBr pellets on a Shimadzu 435-U-04 FTIR (Kyoto, Japan) spectrometer. ^1H NMR spectra were performed on 90 and 250 MHz BRUKER AVANCE instruments using DSMO-d_6 as solvent at room temperature. Melting points were determined in open capillaries using a BUCHI 510 apparatus (Flawil, Switzerland).

Synthesis of $Fe_{3-x}Ti_xO_4$ MNPs

The $Fe_{3-x}Ti_xO_4$-SO_3H NPs were synthesized according to previously reported procedure [1]. In brief, $FeSO_4.7H_2O$ (3.806 g) was dissolved in distilled water (18.5 mL) and transferred into a round-bottomed reactor equipped with a condenser. The pH of the solution was then adjusted to < 1 through the addition of a HCl solution (1 mol/L). Afterward, $TiCl_4$ (1.6 mL) and hydrazine monohydrate (4 mL) were added, respectively. The resulted mixture was refluxed at 90 °C under an inert atmosphere (N_2 gass) for 30 min followed by consecutive drop-wise addition

Table 1: Optimization of catalyst amount.

Entry	Catalyst (g)	Temperature (°C)	Yield (%)
1	0.01	150	68
2	0.02	150	56
3	0.03	80	89
4	0.05	120	71

Table 2: Optimization of reaction condition for the synthesis of 2,3-dihydroquinazoline (1H)-4-ones.

Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	-	Solvent-free	80	120	18
2	0.03	Solvent-free	60	130	60
3	0.03	Solvent-free	80	90	89
4	0.03	Solvent-free	90	90	68
5	0.03	Solvent-free	100	90	74
6	0.03	Solvent-free	110	75	71
7	0.03	Water	Reflux	150	-
8	0.03	EtOH	Reflux	150	47
9	0.03	Water/EtOH (1:1)	Reflux	150	35
10	0.03	Water/EtOH (1:4)	r.t	150	43
11	0.03	EtOH	r.t	180	17
12	0.03	Water	r.t	180	-

ETOH: ethanol

of the solutions of NaOH (4.00 g) and NaNO$_3$ (2.00 g) in deionized water (18.5 mL) under vigorous stirring. At the end of this period, the resulted mixture was cooled to room temperature, the precipitated Fe$_{3-x}$Ti$_x$O$_4$-SO$_3$H NPs (2.8 g) were magnetically collected using a magnet bar, washed with deionized water several times, and dried in reduced pressure.

Synthesis of TMSPU-Fe$_{3-x}$Ti$_x$O$_4$ MNPs

In a typical experiment, the synthesized Fe$_{3-x}$Ti$_x$O$_4$ NPs (1.00 g) were suspended in dried xylene (30 mL) by sonication for 30 minutes. Afterward, 3-chloropropyltrimethoxysilyl urea silan coupling agent (TMSPU; 2 mL, 10 mmol) was added to the flask, and the reaction mixture was refluxed under N$_2$ atmosphere for 24 hours with vigorous stirring at 80 °C.

At the end of this time, the flask was cooled to room temperature in order to precipitate the TMSPU-modified MNPs, which were magnetically separated, washed several times with ethanol and dried in vacuum [1].
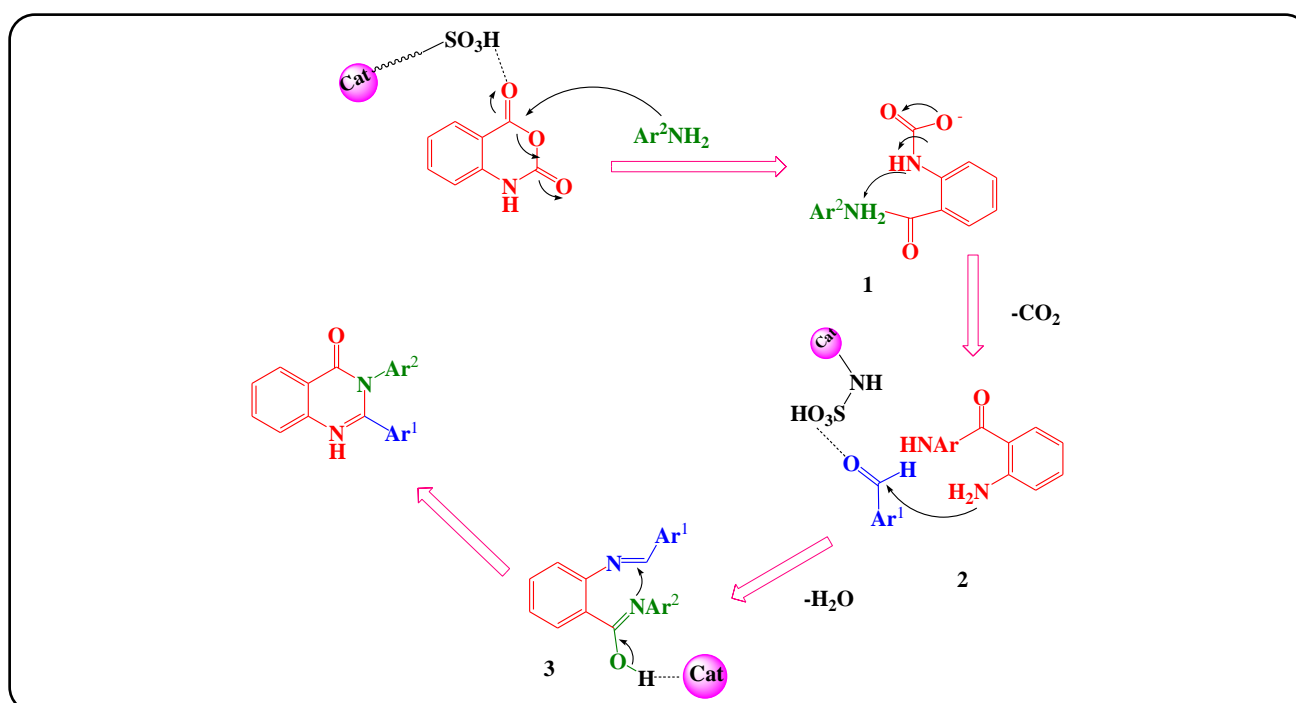
Synthesis of Fe$_{3-x}$Ti$_x$O$_4$-SO$_3$H

The synthesized TMSPU-Fe$_{3-x}$Ti$_x$O$_4$ NPs (0.80 g) in CH$_2$Cl$_2$ (20 mL) was sonicated for about 30 minutes. Then, chlorosulfonic acid (0.6 mL, 9 mmol) was added drop-wise during 1 hour at room temperature under vigorous stirring followed by shaking the resulted mixture for another 1 hour. The precipitated Fe$_{3-x}$Ti$_x$O$_4$-SO$_3$H MNPs were then magnetically separated from the reaction mixture, washed consecutively with CH$_2$Cl$_2$ and ethanol, and dried in reduced pressure at room temperature. The number of SO$_3$H groups per gram of the support NPs

Table 3: Three-component synthesis of 2,3-dihydroquinazoline (1H)-4-ones catalyzed by Fe₃₋ₓTiₓO₄-SO₃H NPs.

Entry	Product	Time (min)	Yield (%)	M.P. (°C)	
				Found	Reported
1		80	89	216-220	217-219[46]
2		75	91	243-247	248-250[47]
3		50	75	194-205	-
4		65	78	240-245	-
5		85	68	210-216	-
6		80	87	236-242	-
7		70	73	254-259	-
8		75	71	236-242	245-247[48]

Table 3: Three-component synthesis of 2,3-dihydroquinazoline (1H)-4-ones catalyzed by $Fe_{3-x}Ti_xO_4$-SO_3H NPs. (…)

9		60	94	173-178	197-198[46]
10		55	87	186-192	-
11		65	89	150-155	-
12		75	85	263-265	247-249[46]

Scheme 3: Proposed mechanism for the synthesis of 2,3-dihydroquinazoline (1H)-4-ones catalyzed by $Fe_{3-x}Ti_xO_4$-SO_3H NPs.

Table 4: Optimization of catalyst for the synthesis of 2-amino-3-cyano-hexahydroquinolines.

Entry	Catalyst (g)	Temperature (°C)	Yield (%)
1	-	80	21
2	0.01	60	71
3	0.02	70	83
4	0.03	70	90

Table 5: Optimization of reaction conditions for the synthesis of 2-amino-3-cyano-hexahydroquinolines.

Entry	Catalyst (g)	Solvent	Temperature (°C)	Time$_1$ (min)	Time$_2$ (min)	Yield (%)
1	-	Solvent-free	70	45	80	21
2	0.03	Solvent-free	60	35	45	78
3	0.03	Solvent-free	70	60	25	90
4	0.03	Solvent-free	80	30	20	65
5	0.03	Solvent-free	Reflux	45	20	63
6	0.03	H_2O	Reflux	40	60	18
7	0.03	EtOH	Reflux	25	60	65
8	0.03	EtOH/ H_2O (1:1)	Reflux	45	75	58
9	0.03	EtOH/ H_2O (1:1)	Reflux	60	60	61
10	0.03	EtOH	Reflux	55	120	43

was found to be 4.2 mmol through acid–base titration (Scheme 5) [1].

General procedure for the synthesis of 2,3-dihydroquinazoline (1H)-4-ones catalyzed by $Fe_{3-x}Ti_xO_4$-SO_3H NPs

The aldehyde (1 mmol), amine (1 mmol) and isatoic anhydride (1 mmol) were added to a reactor tube containing $Fe_{3-x}Ti_xO_4$-SO_3H NPs (0.03g) as the catalyst. The reaction mixture was warmed to 80 °C in the solvent-free condition and the progress of the reaction was monitored by thin layer chromatography (TLC) until total or steady conversion of the starting materials. After ensuring the completion of the reaction, hot ethanol (5 mL) was added to the resulting mixture and the catalyst was separated from the reaction mixture using an external magnet, followed by filtration through a filter paper and washing with additional ethanol (5 mL). The crude product obtained after evaporation of the solvent,

and was purified by re-crystallization in absolute ethanol.

### General procedure for the synthesis of 2-amino-3-cyano-hexahydroquinolines catalyzed by $Fe_{3-x}Ti_xO_4$-SO_3H NPs

A mixture of dimedone (1 mmol), ammonium acetate (1 mmol), malononitrile (1 mmol) and aldehyde (1 mmol) was added to a reactor tube containing $Fe_{3-x}Ti_xO_4$-SO_3H NPs (0.03 g) as the catalyst. The reaction mixture was stirred at 70°C and monitored by TLC until total or steady conversion of the starting materials. After completing the reaction, the appropriate amount of hot ethanol (8 mL) was added to the mixture and was stirred until complete dissolution of the formed precipitate. The catalyst was separated from the reaction mixture using an external magnet. The resulting mixture was cooled to room temperature, then distilled water (10 mL) was added to the flask and filtered through a filter paper. After drying the precipitate at room temperature, it was washed

Table 6: Multi-component synthesis of 2-amino-3-cyano-hexahydroquinolines catalyzed by Fe$_{3-x}$Ti$_x$O$_4$-SO$_3$H NPs.

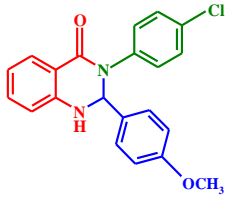| Entry	Product	Time (min)	Yield (%)	M.P. (°C)	
1		25	90	266-272	277-280[49]
2		20	72	278-284	285-287[50]
3		12	70	261-268	192-194[51]
4		15	81	287-290	288-290[50]
5		18	76	296-302	293-296[50]
6		10	97	281-289	298-299[50]
7		10	86	274-281	280-281[50]
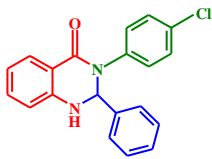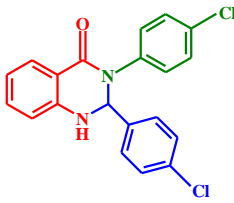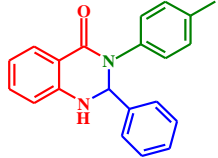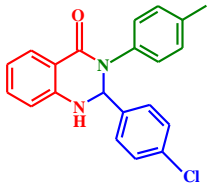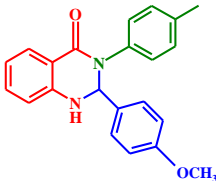
Table 6: Multi-component synthesis of 2-amino-3-cyano-hexahydroquinolines catalyzed by Fe₃₋ₓTiₓO₄-SO₃H NPs. (Continued)

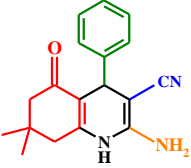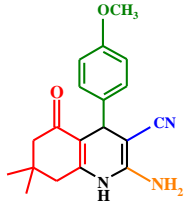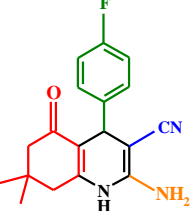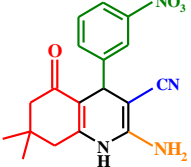|					
8		25	71	268-273	283-286[49]
9		25	68	256-264	261-265[49]
10		15	78	298-308	297-299[50]
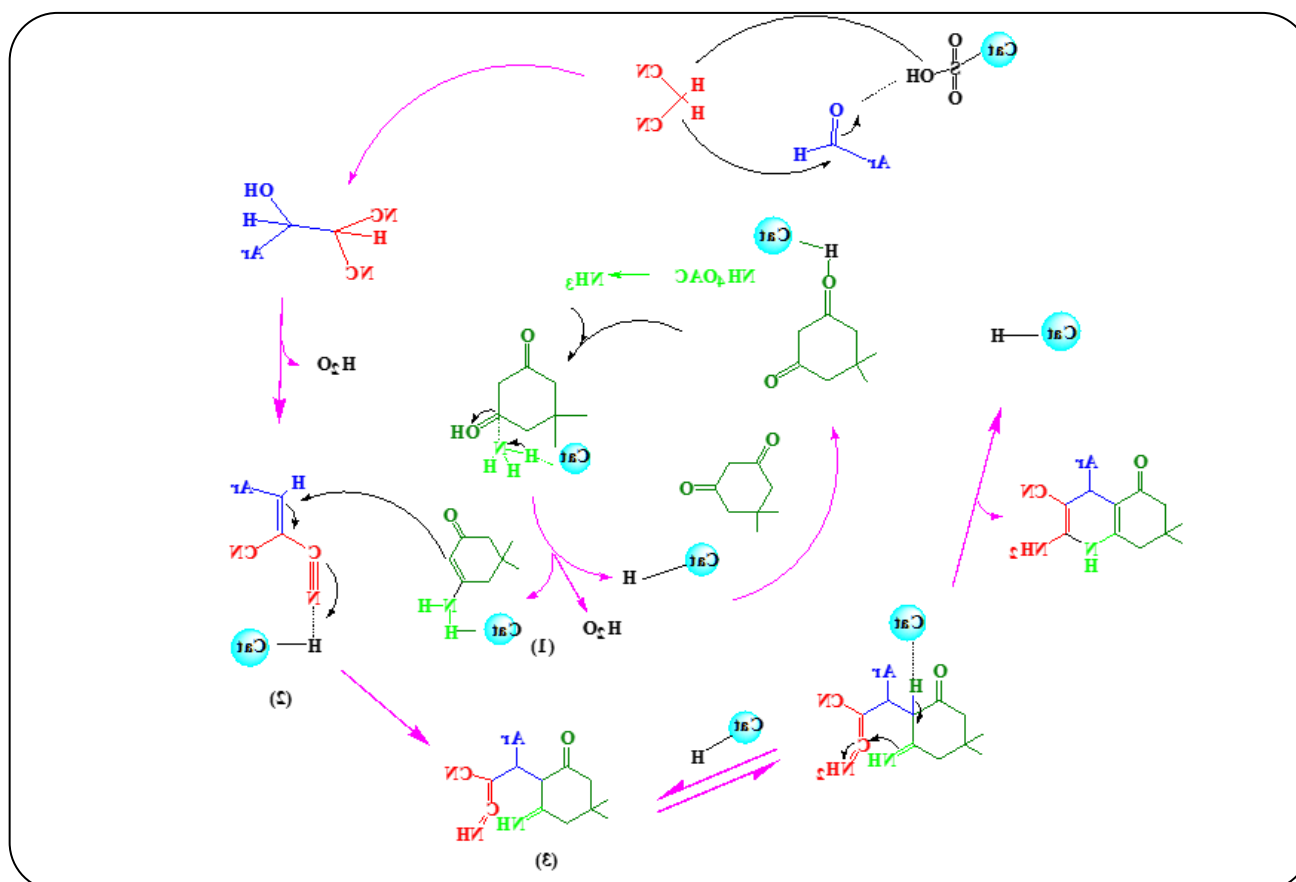
Scheme 4: Proposed mechanism for the synthesis of 2-amino-3-cyano-hexahydroquinolines catalyzed by Fe₃₋ₓTiₓO₄-SO₃H NPs.

Table 7: The efficiency of the $Fe_{3-x}Ti_xO_4$-SO_3H nanocatalyst in comparison with some other catalyst that employed for the synthesis of dihydroquinazoline.

Sample	Catalyst	Condition	T (°C)	Time (h)	Yield (%)	Ref
	$Fe_{3-x}Ti_xO_4$ .SO_3H	Solvent-free	80	1.20	89	Current
	Fe_3O_4 NPs	Reflux (H_2O)	100	5	85	46
	Starch(aq):ETOH	-	70	11	88	47
	[bmim]HSO_4	Water (reflux)	100	3	70	52
	$Fe_{3-x}Ti_xO_4$ -SO_3H	Solvent-free	80	1.15	91	Current
	Starch(aq):ETOH	-	50	4	92	47
	[bmim]HSO_4	Water (reflux)	100	4	72	52
	$Fe_{3-x}Ti_xO_4$ -SO_3H	Solvent-free	80	1.15	71	Current
	[bmim]HSO_4	Water (reflux)	100	3	78	52
	$Fe_{3-x}Ti_xO_4$ -SO_3H	Solvent-free	80	1	94	Current
	Fe_3O_4 NPs	Reflux	100	5	80	46
	$Fe_{3-x}Ti_xO_4$ -SO_3H	Solvent-free	88	1	87	Current
	Starch(aq):ETOH	-	70	9	79	47
	$Fe_{3-x}TixO_4$ .SO_3H	Solvent-free	80	1.20	71	Current
	Fe_3O_4 NPs	Reflux	100	5	73	46

Table 8: The efficiency of the Fe₃₋ₓTiₓO₄-SO₃H nanocatalyst in comparison with some other catalyst that employed for the synthesis of hexahydroquinoline.

Sample	Catalyst	Condition	T (°C)	Time (min)	Yield (%)	Ref
	$Fe_{3-x}Ti_xO_4.SO_3H$	Solvent-free	70	25	90	Current
	NH_4OAc	Reflux (water)	-	70	84	50
	NH_4OAc	Solvent-free	25	15	88	53
	NH_4OAc	Reflux	-	300	70	54
	$Fe_{3-x}Ti_xO_4 -SO_3H$	Solvent-free	70	20	72	Current
	$NH_4OAc/AcOH$	Reflux (water)	100	80	83	50
	$Fe_{3-x}Ti_xO_4 -SO_3H$	Solvent-free	70	10	97	Current
	NH_4OAc	Reflux (water)	100	57	90	50
	$Fe_{3-x}Ti_xO_4 @SPDETATSA\ MNPs$	Solvent-free	75	15	88	49
	Glycerol-promoted catalyst-free	Reflux	80	70	95	55
	$Fe_{3-x}TixO_4.SO_3H$	Solvent-free	70	10	86	Current
	NH_4OAc	Reflux	100	57	88	50
	NH_4OAc	Reflux	-	100	70	54

with ethyl acetate and the product was further purified through re-crystallized from absolute ethanol.

RESULTS AND DISCUSSION
Synthesis of 2,3-dihydroquinazoline (1H)-4-ones

Initially, in order to optimize the reaction condition the three-component reaction of isatoic anhydride, benzaldehyde, and aniline was selected as a simple model substrate through the catalysis by different amounts of the $Fe_{3-x}Ti_xO_4$-SO_3H NPs in different solvents such as water and ethanol at various temperatures (Tables 1 and 2).

As the results, it was found that solvent-free condition and employing 0.03 g of nanocatalyst at 80°C are the optimized conditions for the above mentioned reaction. So, a wide range of 2,3-dihydroquinazoline (1H)-4-ones were synthesized in modest-to-high isolated yields under optimized condition (Table 2).

As shown in Table 3, the direct three-component reactions worked well with a variety of arylaldehydes including both bearing electron-withdrawing and electron-donating groups and the desired compounds were obtained in good to excellent yields (Table 3, **entries 1–12**).
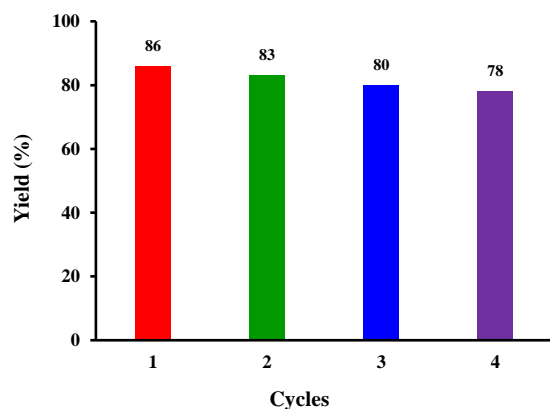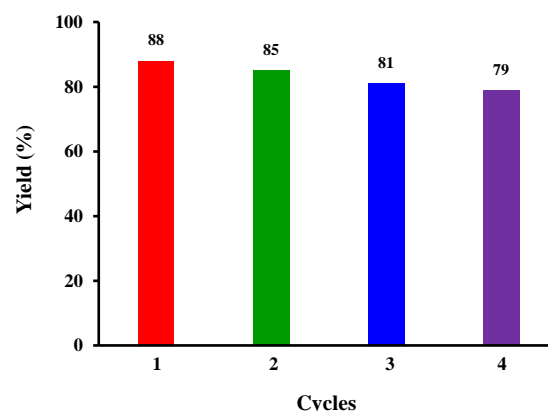
Fig. 1: Recyclability of the Fe₃₋ₓTiₓO₄-SO₃H nanocatalyst for the model reaction in the synthesis of dihydroquinazolines.

Fig. 2: Recyclability of the Fe₃₋ₓTiₓO₄-SO₃H nanocatalyst for the model reaction in the synthesis of hexahydroquinolines..

It is worth noting that under the mentioned optimized condition the reaction did not proceed by aliphatic aldehydes as the starting material.

According to our observation of evolvement in the reaction conditions and other reported mechanisms, we have suggested a mechanism for the $Fe_{3-x}Ti_xO_4$-SO_3H NPs-catalyzed synthesis of 2,3-dihydroquinazoline (1H)-4-ones as shown in Scheme 3. The $Fe_{3-x}Ti_xO_4$-SO_3H NPsplays pivotal role at all stages of the reaction. First, the sulfonic acid group interacted with steric group (position 4) of the anhydride molecule and facilitates the aniline nucleophilic attack to give the intermediate number (1), which in the next step with the loss of intermediate carbon dioxide amide (2) is formed. The activation of the carbonyl group of aromatic aldehyde facilitate the nucleophilic attack of the amine group in the intermediate (2) to aromatic aldehyde. In the following, with the removal of water an intermediate amine (3) is formed. Finally, by an intramolecular cyclization process the desired product is formed.

Synthesis of 2-amino-3-cyano-hexahydroquinolines

First, in order to optimize the reaction conditions a one-pot reaction between benzaldehyde, ammonium acetate, malononitrile and dimedone was tested as the model reaction under different conditions in terms of temperature and solvent. The results of this study are summarized in Tables 4 and 5. As seen in these tables, the best conditions are the application of 0.03 g of nanocatalyst in solvent-free condition at 70 °C. Then, the synthesis of various derivatives of 2-amino-3-cyano-hexahydroquinolines

were investigated under mentioned optimal condition. For this purpose, under the optimized condition a number of aromatic aldehydes were allowed to undergo multi-component reaction with dimedone, malononitrile, and ammonium acetate in the presence of $Fe_{3-x}Ti_xO_4$-SO_3H NPs (0.03 g) as the catalyst under solvent-free condition at 70 °C (Table 5). The results obtained are presented in Table 6. All the electron-rich and electron-deficient aldehydes worked well leading to excellent yields of the corresponding products.

In accordance with the possible mechanism as shown in Scheme 4, in the first step, ammonia produced from ammonium acetate under influence of the catalyst attacks the carbonyl dimedone group and forms the compound (1). In the next step, the activated malononitrile attacks to the carbonyl group of aldehyde and produces an arylidene malononitrile intermediate (2). The third stage is also affected by the acidic feature of the catalyst. At this stage, the compound (1) produced in the first stage attacks the intermediate (2) and creates an imine intermediate (3), which ultimately leads to the formation of the final product during an intramolecular cyclization process.

Catalyst and method efficiency

The efficiency of the $Fe_{3-x}Ti_xO_4$-SO_3H nanocatalyst as well as designed experimental method in comparison with some related studies for the synthesis of dihydroquinazoline and hexahydroquinoline derivatives are summarized in Tables 7 and 8, respectively. As seen, in the case of some products the developed $Fe_{3-x}Ti_xO_4$-SO_3H nanocatalyst and designed experimental process
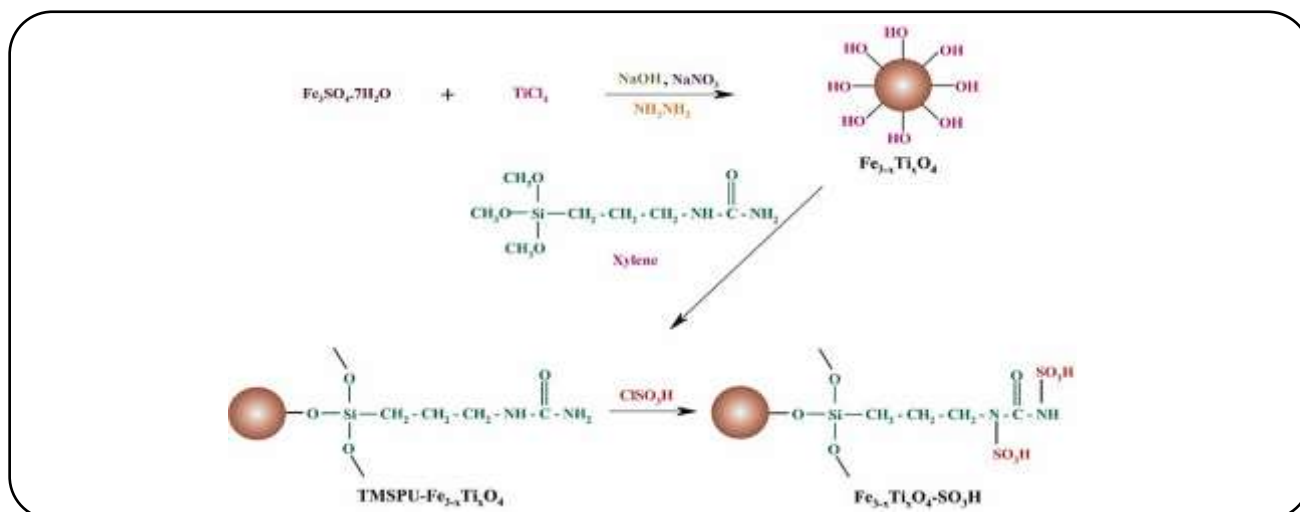
Scheme 5: The overall strategy for the synthesis of Fe3-xTixO4-SO3H NPs.

exhibited higher efficiency in comparison with some others that reported in the literatures.

Recyclability of the nanocatalyst

The synthesized $Fe_{3-x}Ti_xO_4$-SO_3H NPs were used for four times without significant loss in its activity. For this purpose, the potential recyclability and reusability of the nanocatalyst were investigated for the both model reaction in the synthesis of dihydroquinazoline and hexahydroquinoline derivatives. The nanocatalyst was recovered simply using an external magnet, washed with ethyl acetate (10 mL) and ethanol (10 mL), dried in vacuum oven at 50°C, and reused in the next four subsequent runs. The data summarized in Figs. 1 and 2, confirms the practical recyclability of the fabricated nanocatalyst without significant loss in its activity**.**

CONCLUSIONS

The multi-component synthesis of a variety of 2,3-dihydroquinazoline (1H)-4-ones has been effectively accomplished from isatoic anhydride, aldehyde and amine using $Fe_{3-x}Ti_xO_4$-SO_3H NPs as the catalyst. This catalyst has also been employed for the synthesis of 2-amino-3-cyano-hexahydroquinolines by reaction between dimedone, ammonium acetate, malononitrile and aromatic aldehydes. Both synthetic strategies are accomplished through one-pot reactions in solvent-free condition and the desired products were synthesized in good to excellentyields in most cases. These methods have some advantages in comparison with the reported approaches such as easy recoverability of the catalyst by external magnetic field, high catalytic activity, easy work up process, green reaction condition, wide substrate scope, short reaction time as well as cost benefit process.

Supporting Information

FT-IR, ^{1}H NMR and ^{13}CNMR spectra of synthesized samples are available as Supporting Information.

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