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$Fe(HSO_4)_3/SiO_2$: An efficient and heterogeneous catalyst for cyclization of 2-aminochalcones to 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

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ABSTRACT

Silica ferric hydrogensulfate is an efficient heterogeneous catalyst for the cyclization of 2- aminochalcones to the corresponding 2,3-dihydroquinolin- 4(1*H*)-ones. This intramolecular aza Michael reaction was carried out in high yields using chalcones bearing of electron donating and electron withdrawing groups. The catalyst is reusable without significant decreases in its activity after four times recycling.

***Keywords**: $Fe(HSO_4)_3$, Heterogeneous, Dihydroquinolone-4(1H)-ones, Chalcones, aza-Michael.*

1. Introduction

Substituted-2,3-dihydroquinolin-4(1H) ones are valuable precursors for the synthesis of medicinally important compunds [1]. 2-Aryl-2,3-dihydroquinolin-4(1H) ones are considered as a precious pharmacophore in drug discovery [2]. These compounds are eventually not readily accessible [3] and had been prepared from the corresponding 2-aminochalcones bearing substituents in the aromatic rings by an intramolecular aza- Michael reaction catalyzed by different catalysts such as, aluminium supported-$CeCl_3.7H_2O$-NaI [4], amberlyst-15 [5], silica gel supported $TaBr_5$ [6], ionic liquids [7], polyethylene glycol [8], PMA-SiO_2 [9], zinc triflate [10], chlorosulfonyl isocyanate [11], $InBr_3$ or $BiCl_3$ [12], antimony trichloride [13], and ytterbium (III) triflate [14].

Most of the existing procedures for the preparation of 2,3-dihydroquinolin-4(1*H*) one derivatives involve the use of corrosive reagents, limited synthetic scope, low yields, long reaction times, and need for large amount of catalyst, specialized solvents, or either microwave irradiation or high temperature. Therefore, the development of new methods that lead to a convenient procedure and better yield are still desirable.

Recently, ferric hydrogensulfate has emerged as a promising solid acid catalyst for acid catalyzed reactions [15-20]. The aim of this study is to investigate an efficient method for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*) ones through the cyclization of 2- aminochalcones using $Fe(HSO_4)_3$ in high yield under heterogeneous conditions.

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2. Experimental

2.1. General

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. The reactions were monitored by thin layer chromatography (TLC) carried out on silica plates. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. All yields refer to the isolated products. Melting points were recorded on an Electro thermal type 9100 melting point apparatus. IR spectra were recorded on a Thermo Nicolet AVATAR-370-FTIR spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker AC 100 spectrometer at 100 MHz. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. Elemental analyses were obtained on a Thermo Finnigan Flash EA micro- analyzer. Silica supported ferric hydrogensulfate prepared as we previously reported [15] and chalcones **1** with a reported procedure [21].

*2.2. General procedure for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones **2a-2k***

$Fe(HSO_4)_3/SiO_2$ (5 or 10 mol %) was added to a stirred solution of 2-aminochalcones (**1**) (1.0 mmol) in ethanol or acetonitrile (2.5 mL). The reaction mixture was heated with stirring at reflux conditions for the appropriate time (Table 2). After completion of the reaction as indicated by TLC, the mixture was cooled, filtered and diluted with CH_2Cl_2 (10 mL), washed with 5 % hydrochloric acid (10 mL), and water (10 mL) and dried before evaporation in vacuum. The insoluble catalyst was separated by filtration and rinsed with CH_2Cl_2 and absolute ethanol, dried and reused.

Spectral data

*2-Phenyl-2,3-dihydroquinolin-4(1H)-one (**2a**):*

m.p.= 148-150 °C, lit. [22] m.p.= 149-151 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.85 (dd, 1H, J_1=9.2, J_2=1.5), 7.10-7.50 (m, 2H), 7.50-7.70 (m, 4H), 6.50-6.90 (m, 2H), 4.70 (dd, 1H, J_1=11.4, J_2=6.2), 4.20 (d, 1H, J=5.2), 2.50-3.00 (m, 2H) ppm. IR (KBr): $\bar{\nu}$ = 3331(NH), 3031, 2924, 2851, 1658 (C=O), 1605, 1576 cm^{-1}. Yield 95 %.

*2-(4-Methylphenyl)-2,3-dihydroquinolin-4(1H)-one (**2b**):*

m.p.= 147-148 °C, lit. [22] m.p.= 147-149 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.95 (d, 1H, J_1=8.6), 7.10-7.50 (m, 5H), 6.60-6.90 (m, 2H), 4.75 (dd, 1H, J_1=11.7, J_2=6.2), 4.50 (bs, NH, 2H), 2.60-3.10 (m, 2H), 2.40 (s, 3H) ppm. IR (KBr): $\bar{\nu}$ = 3313(NH), 3064, 2920, 2851, 1652 (C=O), 1604, 1509 cm^{-1}. Yield 93 %.

*2-(4-Isopropylphenyl)-2,3-dihydroquinolin-4(1H)-one (**2c**):*

m.p.= 135-137 °C, lit. [23] m.p. not reported. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.90 (dd, 1H, J_1=7.7, J_2=1.5), 7.05-7.50 (m, 5H), 6.60-6.90 (m, 2H), 4.75 (dd, 1H, J_1=12.3, J_2=6.2), 4.20 (d, 1H, NH), 2.60-3.10 (m, 3H), 1.10-1.30 (m, 6H) ppm. IR (KBr): $\bar{\nu}$ = 3325 (NH), 3018, 2960, 2926, 1668 (C=O), 1609, 1482 cm^{-1}. Yield 96 %.

*2-(4-Methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (**2d**):*

m.p.= 148-150 °C, lit. [24] m.p.= 147-148 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.85 (d, 1H, J=7.7), 7.10-7.40 (m, 2H), 6.60-7.00 (m, 5H), 4.80 (br, 1H, NH), 4.60 (dd, 1H, J_1=12.3, J_2=5.5), 3.74 (s, 3H), 2.5-3.0 (m, 2H) ppm. IR (KBr) $\bar{\nu}$ = 3334 (NH), 3018, 2957, 2932, 2836, 1667 (C=O), 1608, 1511 cm^{-1}. Yield 93 %.

*2-(3-Methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (**2e**):*

m.p.= 127-129 °C, lit. [25] m.p.= 129-130 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.90 (dd, 1H, J_1=7.7, J_2=1.5), 7.20-7.40 (m, 2H), 6.60-7.10 (m, 5H), 4.70 (dd, 1H, J_1=12.3, J_2=6.45), 4.20 (d, 1H, J= 6.15, NH), 3.80 (s, 3H), 2.60-3.10 (m, 2H) ppm. IR (KBr): $\bar{\nu}$ = 3333 (NH), 3027, 2962, 2925, 2847, 1669 (C=O), 1611, 1483 cm^{-1}. Yield 93 %.

*2-(4-Chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (**2f**):*

m.p.= 170-171 °C, lit. [14] m.p.= 168-170 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.75-7.95 (m, 2H), 7.00-7.70 (m, 4H) 6.50-7.00 (m 2H), 5.60 (br, 1H, NH), 4.75 (dd, 1H, J_1= 11.7, J_2= 7.0), 2.60-3.15 (m, 2H) ppm. IR (KBr): $\bar{\nu}$ = 3329 (NH), 3015, 2925, 2851, 1644 (C=O), 1612, 1578 cm^{-1}. Yield 90 %.

*2-(2-Chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (**2g**):*

m.p.= 125-127 °C, lit. [22] m.p.= 126-128 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.10-8.20 (m, 6H), 6.50-6.90 (m, 2H), 4.70 (dd, 1H, J_1=11.4, J_2=6.2), 4.1(d, 1H, NH), 2.50-3.00 (m, 2H) ppm. IR (KBr): $\bar{\nu}$ = 3329 (NH), 3064, 3015, 2949, 1644 (C=O), 1610, 1579 cm^{-1}. Yield 88 %.

*2-(4-Nitrophenyl)-2,3-dihydroquinolin-4(1H)-one (**2h**):*

m.p.= 198-200 °C, lit. [14] m.p.= 199-200 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 8.30 (dd, 1H, J_1= 6.15, J_2= 3.0), 7.75-7.90 (m, 2H), 7.22-7.50 (m, 3H), 6.60-6.90 (m, 2H), 4.80 (dd, 1H, J_1=10.8, J_2=6.15), 4.30 (d, 1H, J_1= 4.6, NH), 2.50-3.05 (m, 2H) ppm. IR (KBr): $\bar{\nu}$ = 3343 (NH), 3076, 3020, 2924, 2850, 1705 (C=O), 1607, 1518 (NO_2), 1345 (NO_2) cm^{-1}. Yield 91 %.

*2-(4-Hydroxyphenyl)-2,3-dihydroquinolin-4(1H)-one (**2i**):*

m.p.= 180 °C, lit. [22] m.p. not reported. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 6.55-7.70 (m, 7H), 7.85 (d, J=7.7, 1H), 6.35 (br, 1H, OH), 4.60 (dd, 1H, J_1=10.0, J_2=6.15), 4.40 (br, 1H, NH), 2.50-3.00 (m, 2H, CH_2) ppm. IR (KBr): $\bar{\nu}$ = 3332 (OH), 2926, 1653 (C=O), 1604, 1513 cm^{-1}. Yield 94 %.

*2-(4-Diethylaminophenyl)-2,3-dihydroquinolin-4(1H)-one (**2j**):*

m.p.= 142-144 °C, lit. [22] m.p. not reported. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.90 (dd, , J_1=7.7, J_2=1.5, 1H), 7.70 (d, J_1=9.2, 1H), 7.11-7.42 (m, 4H), 6.50-6.90 (m, 2H) 4.62 (dd, 1H, J_1=12.3, J_2=4.6), 4.55 (d, 1H, NH), 3.00-3.65 (m, 4H), 2.50-3.05 (m, 2H), 1.21 (m, 6H) ppm. IR (KBr): $\bar{\nu}$ = 3446, 3334, 2971, 2933, 1650 (C=O), 1608, 1521 cm^{-1}. Yield 92 %.

*2-(3-Nitrophenyl)-2,3-dihydroquinolin-4(1H)-one (**2k**):*

m.p.= 158-160 °C, lit. [14] m.p.= 159-160 °C. ^{1}HNMR ($CDCl_3$, 100 MHz): δ= 7.25-8.50 (m, 6H), 6.58-6.90 (m, 2H), 4.95 (dd, 1H, J_1= 11.8, J_2= 6.15), 4.35 (br, 1H, NH), 2.85 (m, 2H, CH_2) ppm. IR (KBr): $\bar{\nu}$ = 3342 (NH), 3072, 3015, 2921, 2851, 1674 (C=O), 1611, 1526 (NO_2), 1351 (NO_2) cm^{-1}. Yield 93 %.

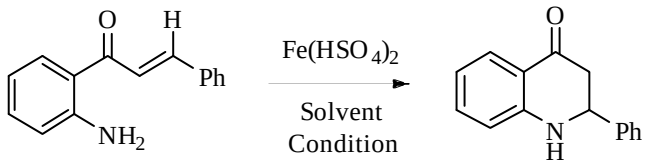
3. Results and Discussion

The first application of $Fe(HSO_4)_3/SiO_2$ in an aza-Michael reaction was demonstrated by intramolecular cyclization of 2- amino-chalcone (**1a**). (Scheme 1).

The effects of catalyst loading and solvent screening on the rate of cyclization reactions have been shown in Table 1 and 2. All reactions were carried out with 1 mmol of chalcone in 2.5 mL solvent at reflux conditions or in solvent-free condition at room temperature. When the reaction was performed without catalyst the conversion was failed. So, we selected the optimum conditions for conversion of 2-amino chalcones to the corresponding 2-aryl-2,3-dihydroxy quinolin-4(1*H*)ones as 10 mol % $Fe(HSO_4)_3/SiO_2$ in reflux condition of EtOH and CH_3CN.

Reusability of the catalyst in this reaction was investigated after the first use and simple filtration and rinse of the recovered catalyst with CH_2Cl_2 and absolute EtOH for further purification. After use of the catalyst in new runs (Table 2, entries 8-11) a significant decrease in its activity not observed after four times.

In order to show the generality of the intramolecolar aza- Michael reactions, various substituted chalcones were subjected to the cyclization using $Fe(HSO_4)_3/SiO_2$ as an efficient heterogeneous, recyclable catalyst (Scheme 2). Table 3 shows the results of these reactions.



1a **2a**

Scheme 1. Intramolecular cyclization of 2-aminochalcone (**1a**) in the presence of $Fe(HSO_4)_3/SiO_2$.

Table 1. Optimized conditions of the intramolecular cyclization of 2-aminochalcone (**1a**) in the presence of $Fe(HSO_4)_3/SiO_2$.

Entry	Catalyst (mol%)	Time (h)	Yield (%)
1[a]	No Catalyst	16	No Reaction
2	3	16	82
3	5	16	88
4	**10**	16	**95**
5	15	16	95
6	20	16	95

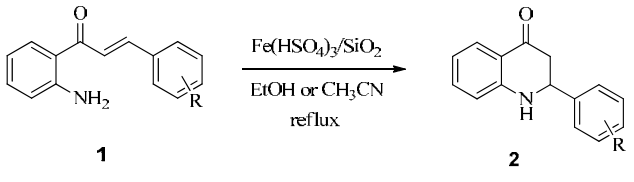
[a]2-Aminochalcone (**1a**) (1 mmol) and $Fe(HSO_4)_3/SiO_2$ (as catalyst) was refluxed in acetonitrile (2.5 mL).

Table 2. Optimized conditions of the intramolecular cyclization of 2-aminochalcone (**1a**) in the presence of $Fe(HSO_4)_3/SiO_2$.[a]

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	$Fe(HSO_4)_3/SiO_2$ (10)	CH_2Cl_2	39.8	16	34
2	$Fe(HSO_4)_3/SiO_2$ (10)	$CHCl_3$	61	16	27
3	$Fe(HSO_4)_3/SiO_2$ (10)	**CH_3CN**	**82**	16	95
4	$Fe(HSO_4)_3/SiO_2$ (10)	MeOH	65	16	73
5	$Fe(HSO_4)_3/SiO_2$ (10)	EtOH	25	16	35
6	$Fe(HSO_4)_3/SiO_2$ (5)	**EtOH**	**78.3**	**16**	**85**
7	$Fe(HSO_4)_3/SiO_2$ (10)	--------	25	2	No Reaction
8[b]	$Fe(HSO_4)_3/SiO_2$ (10)	CH_3CN	82	16	95
9[c]	$Fe(HSO_4)_3/SiO_2$ (10)	CH_3CN	82	16	93
10[d]	$Fe(HSO_4)_3/SiO_2$ (10)	CH_3CN	82	16	92
11[e]	$Fe(HSO_4)_3/SiO_2$ (10)	CH_3CN	82	16	90

[a]2-Aminochalcone (**1a**) (1 mmol) and $Fe(HSO_4)_3/SiO_2$ (10 mol%) was refluxed in solvent (2.5 mL).

[b-e]Reusability of the catalyst in the new runs.



R= H, OH, OMe, NEt_2, Cl, NO_2

Scheme 2. 2-Aryl-2,3-dihydroxyquinolin-4(1*H*)-ones synthesis.

However, oxa-Michael cyclization is faster than aza-Michael cyclization according to lower reaction times and catalyst loading [26]. Both electron donating and electron withdrawing substituted chalcones undergo the cyclization, the latter being more reaction. The results of Table 3 demonstrate the reaction is chemoselective and further oxidations to quinolone was not observed. Other functional group like hydroxyl group does not oxidize under these reaction conditions. Generally, ortho-substituted chalcones were cyclized in longer reaction times because of large steric hindrance effect. Therefore, the simplicity of the procedure, the mildness of the reaction conditions, high yields, the ease of catalyst separation and its reusability demonstrates the ability of this method. We suggested that the silica gel increased the stability, and facilitate the separation and reusability of the catalyst.

All the isolated products were well characterized by their IR, ^{1}H NMR spectral analysis. In the ^{1}H NMR (100 MHz, $CDCl_3$) spectra of compounds **2a-2k** show a doublets of doublet in 4.6-4.8 and a multiplet in 2.5-3.1 region as characteristic bands of 2,3-dihydroquinolones**.** NH group showed either a doublet or broad peak in 4.1-5.6 regions.

A plausible mechanism for this conversion is postulated in Scheme 3. The chalcones are activated by coordination with catalyst and amine groups attack to their nucleophilic carbon followed by the regeneration of catalyst. Over catalyst loading in the cases of 2-aminochalcones may be due to deactivation of the catalyst with amino-coordination which also result increase in the reaction time.

4. Conclusions

In conclusion, The present study represents the application of silica supported ferric hydrogensulfate as catalyst for the aza-Michael cyclization of 2-aminochalcones to the corresponding 2-aryl-2,3-dihydroquinolone derivatives, respectively. Therefore, the simplicity of the procedure, the mildness of the reaction conditions, high yields, the ease of catalyst separation and its reusability demonstrates the ability of this method.

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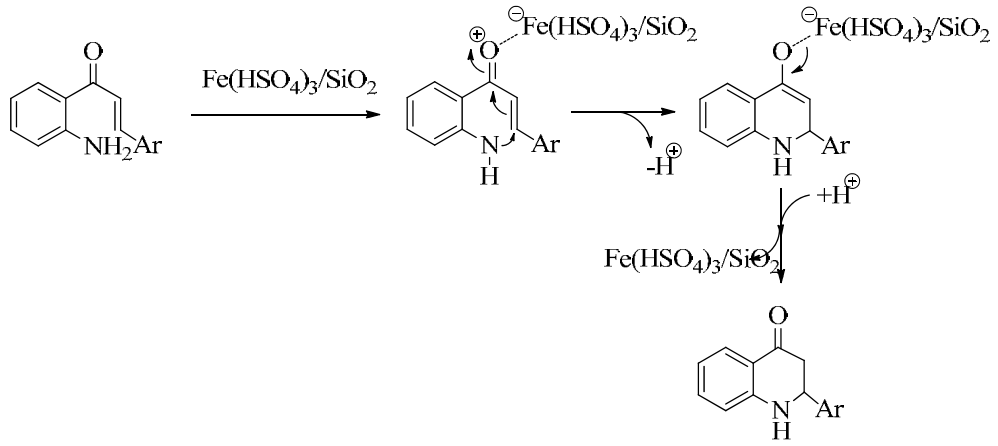
Table 3. 2-Aryl-2,3-dihydroxyquinolin-4(1H)-ones synthesis in the presence of $Fe(HSO_4)_3/SiO_2$.

Entry	R	Condition	Time (h)	Product	Yield %	m.p. (°C)		Ref.
						Found	Reported	
1	H	CH_3CN/reflux	16	**2a**	95	148-150	149-151	[22]
2	*p*-CH_3	CH_3CN/reflux	17	**2b**	93	147-148	147-149	[22]
3	*p*-*i*-Pr	CH_3CN/reflux	17	**2c**	96	135-137	Not reported	[23]
4	*p*-MeO	CH_3CN/reflux	21	**2d**	93	148-150	147-148	[24]
5	*m*-MeO	CH_3CN/reflux	15	**2e**	93	127-129	129-130	[25]
6	*p*-Cl	CH_3CN/reflux	15	**2f**	90	170-171	168-170	[14]
7	*o*-Cl	CH_3CN/reflux	20	**2g**	88	125-127	126-128	[22]
8	*p*-NO_2	CH_3CN/reflux	13	**2h**	91	198-200	199-200	[14]
9	*p*-OH	CH_3CN/reflux	19	**2i**	94	180	Not reported	[23]
10	*p*-NEt_2	CH_3CN/reflux	22	**2j**	92	142-144	Not reported	[22]
11	*m*-NO_2	CH_3CN/reflux	15	**2k**	93	158-160	159-160	[14]



Scheme 3. Suggested mechanism for the intramolecular aza-Michael reaction.

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