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An Efficient Synthesis of Substituted-2, 3-dihydroquinazolin-4(*1H*)-ones using $Fe_3O_4@SiO_2SO_3H$ Nano-catalyst

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ABSTRACT

An efficient and eco-friendly synthesis of substituted-2, 3-dihydroquinazolin-4(*1H*)-ones from direct cyclocondensation of anthranilamide with aromatic aldehydes using $Fe_3O_4@SiO_2SO_3H$ (MNPs) as a recoverable and recyclable nano-catalyst in good to excellent yields in ethanol at 80^0C. The catalyst was readily separated using an external magnet and reusable without significant loss of their catalytic efficiency.

Keywords: Substituted-2, 3-dihydroquinazolin-4(*1H*)-one, aromatic aldehydes, green chemistry, eco-friendly.

INTRODUCTION

Substituted-2, 3-dihydroquinazolin-4(*1H*)-one are an important class of heterocyclic compounds. This has made substituted-2, 3-dihydroquinazolin-4(*1H*)-one very useful moiety in pharmacologically active compounds [1, 2]. Among the various classes of nitrogen containing heterocyclic compounds, dihydroquinazolin-4(*1H*)-one are important components of several pharmacologically active compounds such as antitumor, analgesic, anti-fibrillatory, antibiotic, antipyretic, analgesic, anti-hypertonic, diuretic, antihistamine, antidepressant, and vasodilating behavior anti-spermatogenic and vasodilatory efficacy [3-8]. In addition, a variety of synthetic routes have been reported for the synthesis of 2, 3-dihydroquinazolin-4(*1H*)-ones derivatives [9-11]. Of these, the condensation of 2-anthranilamide with aldehydes or ketones is the most convenient methods for the synthesis of 2, 3-dihydro-

4(*1H*)-quinazolinones [12]. Various catalysts, such as $TiCl_4$–Zn [13], $Sc(OTf)_3$ [14], NH_4Cl [15], HCl [16], p-TSA [17], SmI_2 [18], DDQ [19], $CuCl_2$ [20], MnO_2 [21], I/KI [22], Yb(OTf) [23] and or solvent as oxidant [24], ionic liquid [25], ammonium chloride [26], tetrabutyl-ammonium bromide [27], trifluoroethanol [28], acetic acid [29] and sulfamic acid [30] have been used to promote this reaction. However, many of these methods involve extended reaction times, the use of costly reagents or toxic organic solvents and also require tedious work-up procedures. The development of green processes, such as employing safe catalysts, waste minimization, replacing toxic solvents with H_2O, and using O_2 as an environmentally benign oxidant, in the chemical industry has gained significant attention in recent years [31]. Some catalysts had to be prepared in advance and their preparation required special effort. Therefore, the development of simple and efficient methods for the synthesis of substituted-2, 3-dihydroquinazolin-4(*1H*)-one is of great importance.

RESULTS AND DISCUSSIONS

As part of our continuing research work in green chemistry [32], we were interested in developing an efficient synthetic route for the synthesis of 2, 3-di-hydroquinazolin-4(*1H*)-ones. Earlier, $Fe_3O_4@SiO_2SO_3H$ Nano catalyst was used for various organic transformations as a green catalyst. It was prepared according to the procedure reported in literature [33]. We performed the reaction between anthranilamide (1 mmol), 4-hydroxybenzaldehyde (1.2 mmol) and $Fe_3O_4@SiO_2SO_3H$ (50 mol%) in methanol under reflux condition to furnish 2-(4-hydroxyphenyl)-2, 3-dihydroquinazolinone-4(*1H*)-one with 79% yield. To optimize the better reaction conditions, the reaction was carried out in different solvents (Table 1). It was observed that in ethanol good yield was obtained. The effect of concentration (mol%) of $Fe_3O_4@SiO_2SO_3H$ nanoparticle was checked by performing reaction under different concentration (Table 2). It was observed that 20 mol% was sufficient nanocatalyst for better results.

Table 1: Effect of solvent on synthesis of substituted-2, 3-dihydroquinazolin-4(*1H*)-one

Entry	Solvent	Time (h)	Yield (%)
1	Chloroform	12	57
2	Acetone	12	52
3	Dichloromethane	12	49
4	**Ethanol**	**6**	**90**
5	Methanol	7	79
6	Toluene	10	57
7	Acetonitrile	11	53
8	DMF	7	75
9	DMSO	7	70

Reaction Conditions: Anthranilamide (1 mmol), 4-hydroxybenzaldehyde (1.2 mmol) and $Fe_3O_4@SiO_2SO_3H$ (50 mol%).

Table 2: Effect of concentration of $Fe_3O_4@SiO_2SO_3H$ nanoparticles

Entry	Catalyst mol%	Time (h)	Yields (%)
1	10	4	73
2	15	4	78
3	20	4	84
4	25	4	84

Reaction Conditions: Anthranilamide (1 mmol), 4-hydroxybenzaldehyde (1.2 mmol) and $Fe_3O_4@SiO_2SO_3H$ nanoparticles

To show the generality of the present method, the optimized system was utilized for the synthesis of other derivatives. Various examples illustrating this novel and general method for the synthesis of 2, 3-dihydro-4(*1H*)-quinazolinones are summarized in table 3. A verity of aryl aldehydes having different functionalities, such as halogen, methoxy, hydroxyl, and nitro groups furnished the corresponding substituted 2, 3-dihydro-4(*1H*)-quinazolinones with 65-90% yields (Scheme 1). It is important to note that the synthesis of 2, 3-dihydro-4(*1H*)-quinazolinones could not be achieved in the absence of the $Fe_3O_4@SiO_2SO_3H$ nano-catalyst. All products are known compounds and structures of them were verified by comparison with their known physical and spectral (^{1H} NMR and IR) data reported in literature [34].

Scheme 1

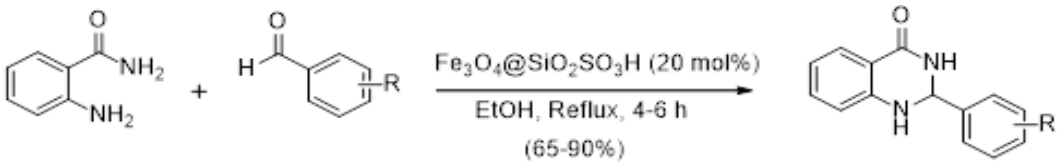
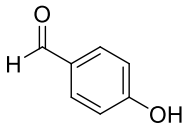
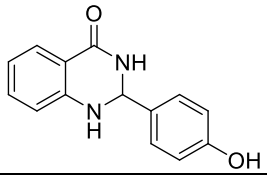
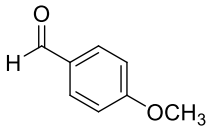
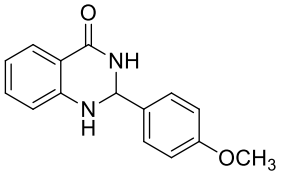
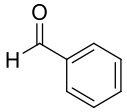
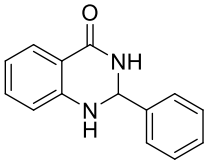
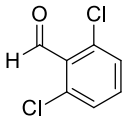
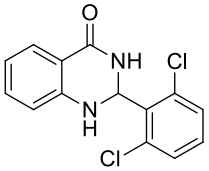
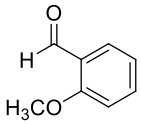
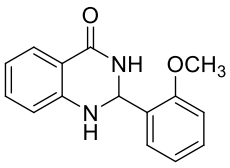
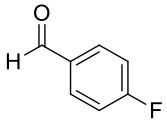
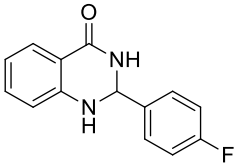
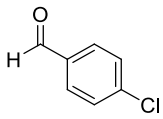
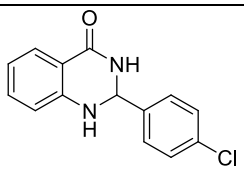
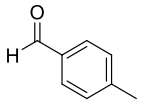
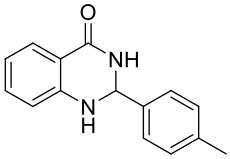
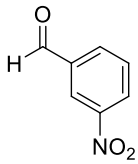
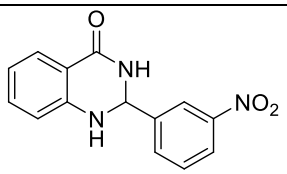
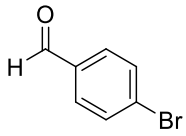
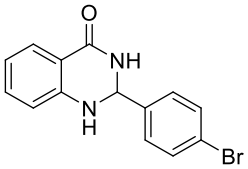
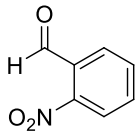
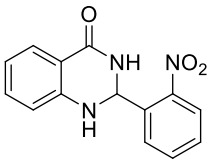
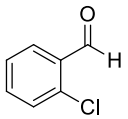
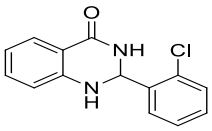
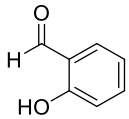
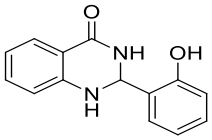
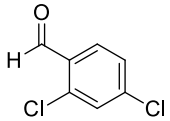
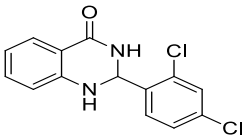
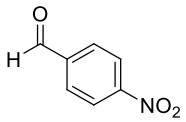
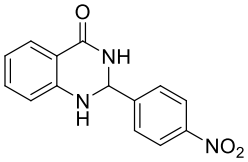


Table 3: Synthesis of substituted-2, 3-dihydroquinazolin-4(*1H*)-one

Entry	Aryl aldehydes	2, 3-Dihydroquinazolin-4(*1H*)ones	Time(h)	M.P.(°C)	Yield (%)
1			6	296	90
2			4	180	80
3			5.5	225	65
4			4	170	82
5			5	109	75
6			4.5	203	86

7			4	200	67
8			4.5	234	71
9			5	210	68
10			5.5	198	70
11			5	192	83
12			4.5	212	77
13			5	223	78
14			5.5	166	75
15			6	199	80

EXPERIMENTAL

General procedure for synthesis of substituted-2, 3-dihydroquinazolin-4(*1H*)-ones:

A mixture of anthranilamide (1 mmol), aldehyde (1.2 mmol) and Fe_3O_4@SiO_2SO_3H nano-catalyst (20 mol%) was reflux at 80 °C for the appropriate time indicated in Table 3. The progress of reactions was monitored by TLC. After completion of the reaction, the catalyst was removed easily by adsorbing onto the magnetic stirring bar. The reaction mixture was filtered. The solvent was removed under reduced pressure. The crude product was extracted from ethyl acetate, washed with water and brine solution. The organic layer was dried over anhydrous sodium sulphate. Then, the solvent ethyl acetate was evaporated under reduced pressure. The crude product was recrystallized in ethanol to obtain corresponding substituted-2, 3-dihydroquinazolin-4(*1H*)-ones with 65-90 % yields.

2-(4-hydroxyphenyl)-2, 3-dihydroquinazolin-4(*1H*)-one (Entry 1): ^{1H} **NMR** ($CDCl_3$, 400 MHz): δ 5.00 (s, *1H*), 6.80 (d, 2H), 7.28 (s, *1H*), 7.37 (t, *1H*), 7.4 (d, 2H), 7.5 (d, *1H*), 7.6 (d, *1H*), 7.7 (t, *1H*), 8.48 (s, *1H*), 16.20 (s, *1H*); **^{13}C NMR (**$CDCl_3$, 100 MHz**)**: δ 63.04, 113.45, 120.75, 124.52, 130.83, 131.86, 134.05, 142.59, 149.98, 156.21, 163.04, 167.32.

2-(4-methoxyphenyl)-2, 3-dihydroquinazolin-4(*1H*)-one (Entry 2): IR (KBr) νmax: 1463, 1514, 1572, 1609, 1670, 2932, 3053, 3181, 3297 cm^{-1}; ^{1H} **NMR** (DMSO-d_6, 300 MHz): δ 3.72 (s, 3H), 5.68 (s, *1H*), 6.62-6.73 (m, 2H), 6.90-6.98 (m, 3H), 7.18-7.25 (m, *1H*), 7.39 (d, 2H), 7.59 (d, *1H*), 8.15 (s, *1H*); **^{13}C NMR** (DMSO-d_6, 75 MHz): δ 55.99, 67.21, 114.50, 115.33, 115.80, 118.06, 128.27, 129.08, 134.22, 134.25, 148.88, 160.70, 164.75.

2-phenyl-2, 3-dihydroquinazolin-4(*1H*)-one (Entry 3): IR (KBr) νmax: 1439, 1511, 1611, 1656, 2933, 3059, 3184, 3303; ^{1H} **NMR** (DMSO-d_6, 300 MHz): δ 5.73 (s, *1H*), 6.74 (m, 2H), 7.12 (s, *1H*), 7.23 (t, *1H*), 7.35 (d, 3H), 7.47 (d, 2H), 7.59 (d, *1H*), 8.31 (s, *1H*); **^{13}C NMR** (DMSO-d_6, 75 MHz): δ 67.40, 115.30, 115.75, 118.05, 127.68, 128.25, 129.21 129.34, 134.2, 142.45, 148.70, 164.59.

2-(2, 6-Dichlorophenyl)-2, 3-dihydro-quinazolin-4(*1H*)-one (entry 4): IR (KBr): 1485, 1613, 1685, 3274 cm^{-1}; ^{1H} **NMR** ($CDCl_3$, 300 MHz): δ 6.57–6.65 (m, 2H), 6.74 (s, *1H*), 6.98 (s, *1H*), 7.17–7.23 (m, *1H*), 7.37–7.60 (m, 4H), 8.10 (s, *1H*).

CONCLUSION

An efficient and environmentally benign method has been developed for the synthesis of substituted-2, 3-dihydroquinazolin-4(*1H*)-ones. We believe the present protocol is convenient, inexpensive and environmentally-friendly process for the synthesis of 2, 3-dihydro-4(*1H*)-quinazolinones with potential biological application.

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