Eco-friendly and Efficient Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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A simple and facile method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the direct cyclocondensation of one-pot three-component cyclocondensation of isatoic anhydride, ammonium acetate (or primary amines) and aldehydes; and anthranilamide and aldehydes using silica supported ferric chloride (SiO_2-$FeCl_3$) as catalyst under solvent-free conditions is described.

Keywords solvent-free, synthetic methods, aldehydes, 2,3-dihydroquinazolin-4(1*H*)-one, anthranilamide, isatoic anhydride

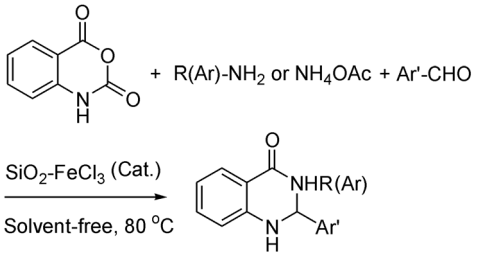
Introduction

Dihydroquinazolin-4(1*H*)-one skeletons constitute a governing class of synthetic compounds that have been long and widely employed for pharmacological properties and clinical applications.[1] In particular dihydroquinazolin-4(1*H*)-one scaffolds were found as a core unit in a number of biologically active compounds that include anticancer, antidituric, and anticonvulsant activities.[1]

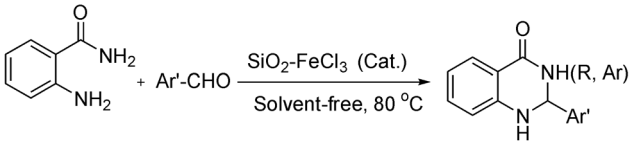
Literature survey showed that several methods in synthesis of quinazolinone derivatives were reported such as cyclization of *o*-acylaminobenzamides,[2] amidation of 2-aminobenzonitrile followed by oxidative ring closure,[3] solid-phase synthesis of 2-arylaminosubstituted quinazolinones,[4] reduction of the azide functionality,[5] reaction of isatoic anhydrides and Schiff bases,[6] conversion of 2-nitro-*N*-arylbenzamides to 2,3-dihydroquinazo-lin-4(1*H*)-ones using $SnCl_2$, and Pd-catalyzed heterocyclization of nitroenes.[7] Also, quinazolinones were prepared from a) three-component reactions of isatoic anhydride, primary amine or ammonium acetate and aldehydes in the presence of *p*-toluenesulfonic acids,[8] silica sulfuric acid,[9] $KAl(SO_4)_2$•$12H_2O$ (alum),[10] montmorillonite K-10,[11] zinc(II) perfluorooctanoate,[12] gallium(III) triflate,[13] Amberlyst-15,[14] and 1-butyl-3-methyl-imidazolium bromide[bmim]Br or [bmim]PF_6 as ionic liquids,[15] Fe_3O_4 nanoparticles,[16] copolymer-*p*-TSA,[17] $[Al(H_2PO_4)_3]$;[18] and b) the condensation of anthranilamide and aldehydes by using *p*-TSA/$NaHSO_3$,[19] $TiCl_4$/Zn,[20] $CuCl_2$,[21] and ionic liquid-water,[22] TFA,[23] ammonium chloride,[24] and chiral phosphoric acids[25] as catalysts. However, some of these procedures have certain limitations such as tedious process, long reaction times, high temperatures, harsh reaction conditions, expensive reagents, and low yields. Thus, the development of novel methods for the synthesis of dihydroquinazolin-4(1*H*)-ones is of great importance because of their potential biological and pharmaceutical activities.

As part of our ongoing research in the development of novel synthetic routes to the synthesis of biologically active heterocyclic compounds using heterogeneous and recyclable catalysts,[26] herein we report a simple and convenient method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives via a) one-pot three-component cyclocondensation of isatoic anhydride, ammonium acetate or primary amines, and aldehydes (Scheme 1); and b) two-component reaction of anthranilamide and aldehydes by using silica supported ferric chloride (SiO_2-$FeCl_3$)[27] as catalyst under thermal solvent-free conditions (Scheme 2).

Scheme 1



Scheme 2



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Experimental

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. SiO_2-$FeCl_3$ was prepared according to the reported procedure.[27] All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 500 MHz instrument. IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Mass spectra were recorded on an Agilent technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on Silica-gel polygram SILG/UV 254 plates.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in three-component reaction of isatoic anhydride, primary amine or ammonium acetate, and aldehydes using SiO_2-$FeCl_3$ as catalyst (Method a)

A stirred mixture of isatoic anhydride (1 mmol), primary amine (1.1 mmol) or ammonium acetate (1.2 mmol), aldehydes (1 mmol) and SiO_2-$FeCl_3$ (0.005 g) was reacted in an oil bath at 80 ℃ for the appropriated times. Completion of the reaction was indicated by TLC (eluent: *n*-hexane/ethyl acetate＝4/1). After completion of the reaction, it was cooled to room temperature and the crude solid product was dissolved in hot ethanol, and filtered for separation of the catalyst. The filtrate ethanol solution was concentrated. The solid product was purified by recrystallization procedure in aqueous EtOH (70%). All the products were characterized by comparison of their spectroscopic and physical data with the authentic samples. The spectral data for one selected product are given below:

2-(2,4-cyanophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, Entry 10) ^{1}H NMR (DMSO-d_6, 500 Hz) δ: 5.85 (s, 1H, CH), 6.67 (t, J＝7.45, 1H, Ar), 6.76 (d, J＝8.05, 1H, Ar), 7.23—7.27 (m, 2H, Ar & NH), 7.60 (d, J＝7.20, 1H, Ar), 7.66 (d, J＝8.25, 2H, Ar), 7.86 (d, J = 8.30, 2H, Ar), 8.46 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 500 Hz) δ: 65.50, 111, 114.5, 114.9, 117.4, 118.6, 127.4, 127.6, 132.3, 133.5, 147.27, 147.29, 163.3; IR (KBr) v: 3336 & 3353 (2NH), 2227 (CN), 1666 (C＝O), 1611, 1508, 1485 cm^{-1}; MS (EI, 70 eV) m/z: 249 (M^+, 26), 248 (26), 247 (36), 147 (100), 120 (48), 119 (53), 92 (34), 65 (15).

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in direct reaction of anthranilamide and aldehydes using SiO_2-$FeCl_3$ as catalyst (Method b)

A mixture of aromatic aldehydes (1 mmol), anthranilamide (1 mmol), and SiO_2-$FeCl_3$ (0.005 g) under solvent-free conditions was stirred at 80 ℃ for a specified time (Table 3). Completion of the reaction was indicated by TLC (eluent: *n*-hexane ∶ ethyl acetate＝4 ∶ 1, *V* ∶ *V*). After completion of the reaction, it was cooled to room temperature and the crude solid product was dissolved in hot ethanol, and filtered for separation of the catalyst. The filtrate ethanol solution was concentrated. The solid product was purified by recrystallization procedure in aqueous EtOH (70%). All the products were characterized by comparison of their spectroscopic and physical data with the authentic samples.

Results and discussion

Firstly, when a mixture of isatoic anhydride (1 mmol), ammonium acetate (1.2 mmol) and benzaldehyde (1 mmol) was stirred under thermal solvent-free conditions in the absence of SiO_2-$FeCl_3$ as catalyst, the reaction was not progressed within 24 h. Thus, the reaction requires catalyst for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones. At the second stage, to optimize the reaction conditions, we carried out the reaction of isatoic anhydride (1 mmol), ammonium acetate (1.2 mmol), and benzaldehyde (1 mmol) in the presence of different amounts of the catalyst at different temperature under solvent-free conditions (Table 1). As it was shown from Table 1, the best results were obtained using 0.005 g of SiO_2-$FeCl_3$ as catalyst at 80 ℃.

Table 1 Optimization amount of SiO_2-$FeCl_3$ as catalyst and reaction temperature in the reaction of isatoic anhydride (1 mmol), ammonium acetate (1.2 mmol), and benzaldehyde (1 mmol) for preparation of 2,3-dihydroquinazolin-4(1*H*)-ones

Entry	Catalyst/g	T/℃	Time/min	Yield[a]/%
1	0.1	125	9	60
2	0.05	125	8	66
3	0.025	125	7	67
4	0.01	125	6	68
5	0.005	125	6	75
6	0.005	100	8	85
7	0.005	80	18	89
8	0.005	50	75	55
9	0.005	25 (r.t.)	120	—

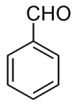
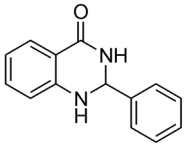
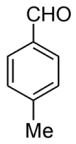
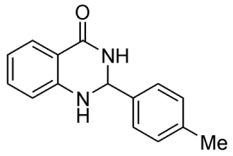
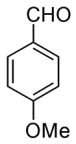
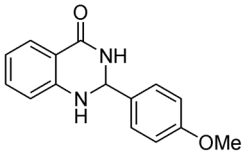
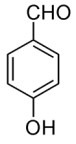
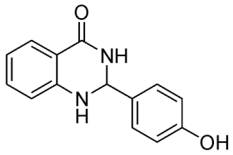
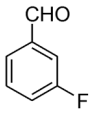
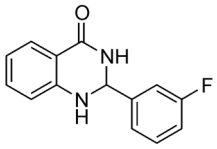
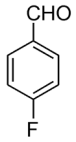
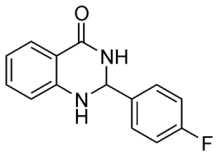
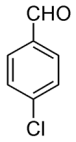
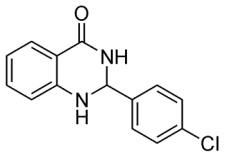
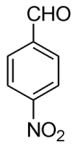
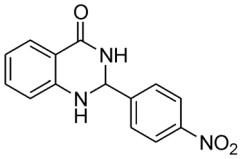
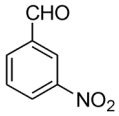
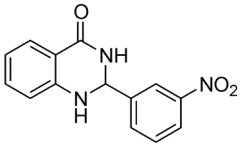
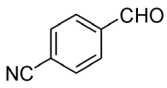
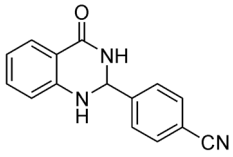
[a] Isolated yield.

Using these optimized reaction conditions, the cyclocondensation reaction between isatoic anhydride, aryl aldehydes and ammonium acetate as source of ammonia or primary amines proceeded well and afforded the desired products (Table 2) in good to excellent yields.

As shown in Table 2, aryl aldehydes bearing either electron-donating or electron-withdrawing groups on the aromatic ring were investigated. The substitution group on the phenyl ring did not make any difference in this reaction.

In continuation of our work, using these optimized

Table 2 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives using isatoic anhydride (1 mmol), primary amine (1.1 mmol) or ammonium acetate (1.2 mmol), aldehydes (1 mmol) and SiO_2-$FeCl_3$ (0.005 g) under solvent-free conditions (Method a)

Entry	Aldehyde	Amine	Product	Time/min	Yield[a]/%
1		NH_4OAc		18	89
2		NH_4OAc		10	87
3		NH_4OAc		17	71
4		NH_4OAc		80	45
5		NH_4OAc		60	88
6		NH_4OAc		22	87
7		NH_4OAc		27	90
8		NH_4OAc		11	91
9		NH_4OAc		9	89
10		NH_4OAc		15	87

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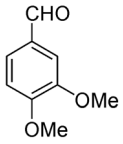
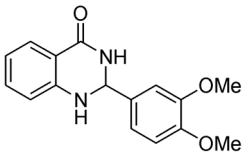
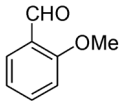
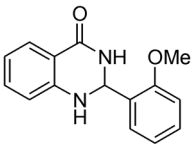
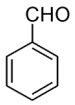
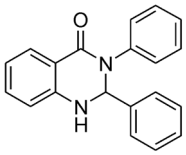
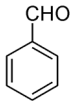
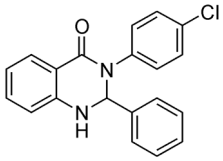
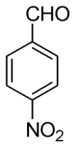
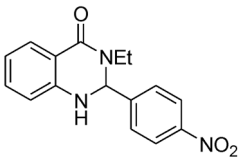
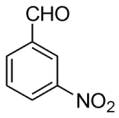
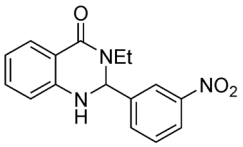
11		NH_4OAc		20	80
12		NH_4OAc		50	75
13		Aniline		27	89
14		4-Chloroaniline		60	75
15		Ethylamine		6	88
16		Ethylamine		120	89

[a] Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[2-18]

reaction conditions, the scope and efficiency of the reaction were explored for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives through direct condensation of aromatic aldehydes (1 mmol), anthranilamide (1 mmol) and SiO_2-$FeCl_3$ (0.005 g) as catalyst under solvent-free conditions (Table 3).

We can compare results of preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives through the direct cyclocondensation of a) one-pot three-component cyclocondensation of isatoic anhydride, ammonium acetate (or primary amines) and aldehydes (Table 2); and b) anthranilamide and aldehydes (Table 3) using silica supported ferric chloride (SiO_2-$FeCl_3$) as catalyst under solvent-free conditions. Method a produces 2,3-dihydroquinazolin-4(1*H*)-ones in shorter reaction times and higher yields than method b, because isatoic anhydride is more reactive than anthranilamide. Loss of CO_2 from isatoic anhydride is an excellent driving force for the reaction and preparation of a more reactive intermediate for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in shorter reaction times and higher yields.

The suggested mechanism of the SiO_2-$FeCl_3$ catalyzed preparation of quinazolinone is shown in Scheme 3. According to observation of evolution in the reaction conditions and also other reported mechanism in the literature,[18] interaction of SiO_2-$FeCl_3$ as catalyst and isatoic anhydride to produce a reactive intermediate (**I**). The *N*-nucleophilic primary amine attacks on the carbonyl unit of **I** to produce a reactive intermediate **II**, which in turn affords **III** through decarboxylation reaction. The proton transfer of **III** affords 2-amino-*N*-substituted-amide **IV**. Subsequently, the reaction of activated aldehyde with **IV** proceeds to produce the imine intermediate **V**. The part of amide functional group in intermediate **IV** could be formed using tautomerism phenomenon in the presence of the catalyst. Thus, intermediate **VI** could be prepared by intermolecular nucleophilic attack of the amide nitrogen on activated imine carbon, followed by a 1,5-proton transfer to yield the final 2,3-dihydroquin-azoline-4-(1*H*)-ones as

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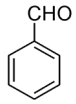
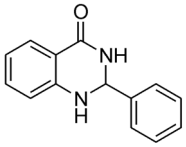
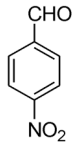
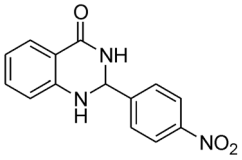
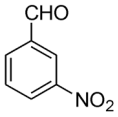
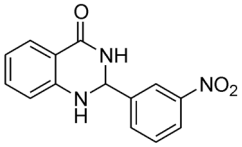
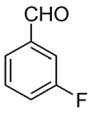
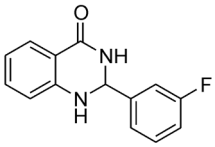
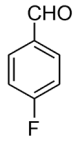
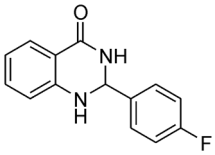
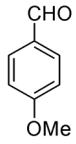
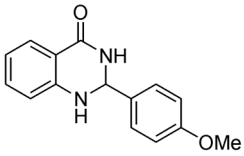
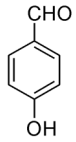
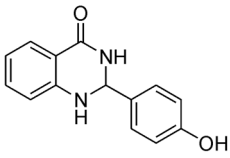
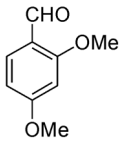
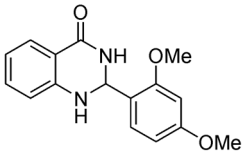
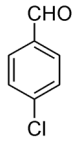
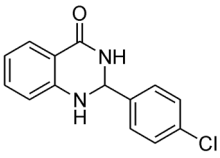
Table 3 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives using aldehydes (1 mmol), anthranilamide (1 mmol) and SiO_2-$FeCl_3$ (0.005 g) under solvent-free conditions (Method b)

Entry	Aldehyde	Product	Time/h	Yield[a]/%
1			6	87
2			4	93
3			16	91
4			72	96
5			11	81
6			3	77
7			17	84
8			42	90
9			7	87

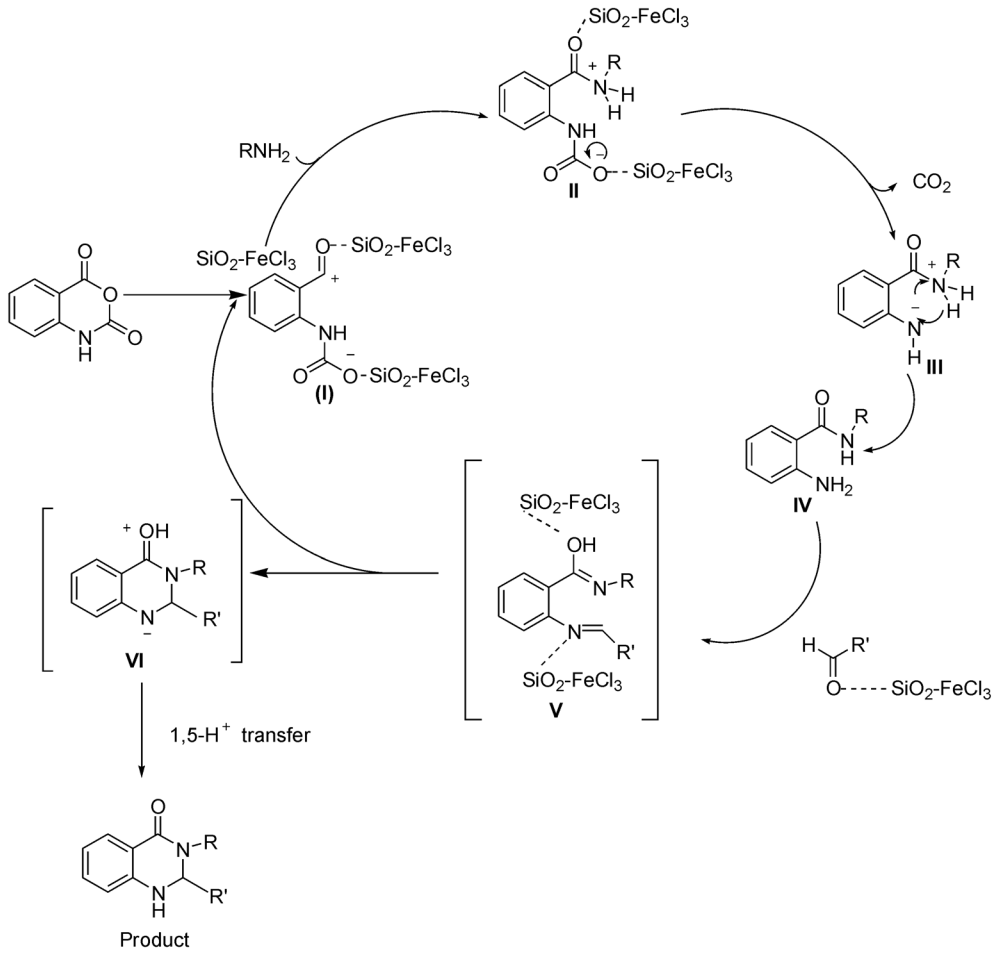
[a] Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[19-25]

products.

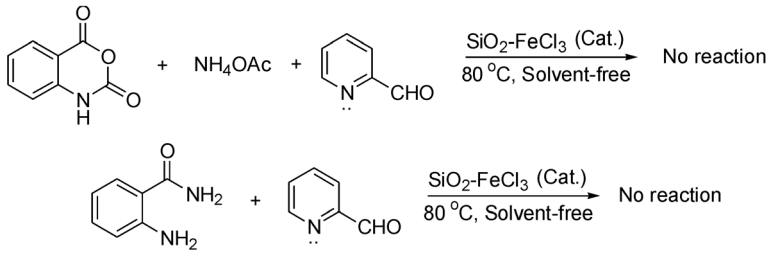
It is noteworthy, the reaction of 2-pyridine carbaldehyde in method a and b in the presence of the catalyst did not react and failed to give any desired product because pyridine ring with its lone pair of electrons acts as base and inactive catalyst for activation of substrates and intermediates in the path of the reaction (Scheme 4).

In addition, the reaction of anthranilic acid instead of isatoic anhydride did not afford any product after 24 h in 100 ℃ (Scheme 5).

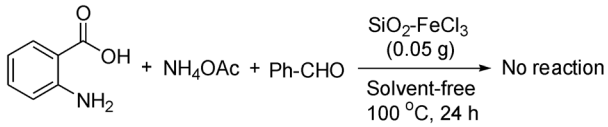
Scheme 3



Scheme 4



Scheme 5



Conclusion

An efficient procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the direct cyclocondensation of a) one-pot three-component cyclocondensation of isatoic anhydride, ammonium acetate (or primary amines) and aldehydes; and b) anthranilamide and aldehydes using silica supported ferric chloride (SiO_2-$FeCl_3$) as catalyst under solvent-free conditions is described. Simple reaction and work-up procedure, solvent-free conditions using heterogeneous silica supported ferric chloride as catalyst are advantages of the present work.

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