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$FeCl_3$/Egg Shell: An Effective Catalytic System for the Synthesis of 2,3-Dihydroquinazolin-4-ones at Room Temperature

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Abstract: The $FeCl_3$/egg shell has been a new and efficient catalyst for the rapid and simple synthesis of 2,3-dihydroquinazolin-4-ones in ethanol at room temperature. The present method has advantages of low cost, mild reaction conditions, simple workup process, better recovery and reusability of catalyst, excellent yields and environmentally friendly procedure.

Keywords: $FeCl_3$/egg shell, 2,3-dihydroquinazolin-4-ones, heterogeneous catalysis.

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INTRODUCTION

Quinazolin-4-ones are a significant class of heterocyclic compounds because of their biological and pharmacological properties as antagonist (1), anti-tumor (2), anti-inflammatory (3), insecticidal and antimicrobial activities (4), anticancer (5), antiviral (6), anti-tubercular agents (7), anticonvulsant (8), antifungal (9), antimalarial (10) and antidituric (11) activities. In recent years, a number of synthetic strategies have been developed for the preparation of quinazolin-4-ones by the reaction of substituted aldehydes and ketones with 2-aminobenzamide using differents catalysts, such as 2-morpholinoethane sulfonic acid (12), p-TSA/$NaHSO_3$ (13), $TiCl_4$/Zn (14), $CuCl_2$ (15), ionic liquid-water (16), TFA (17), metal-CNTs (18), PEG-400 (19), nanocrystalline sulfated zirconia (20) , SmI_2 (21), TBAB/$CuCl_2$ (22), I_2/KI (23) , $Y(OTf)_3$ (24) and $Yb(OTf)_3$ (25). Herein, we report an efficient process for synthesis of 2,3-dihydroquinazolin-4-ones **3a-l** derivatives in the presence of $FeCl_3$/egg shell as a heterogeneous catalyst at room temperature by reacting the 2-aminobenzamide with different aldehydes.

MATERIALS AND METHODS

All products were purchased from Merck Chemical Company. TLC using silica gel monitored the progress of the reactions. Melting points were taken on a KOFLER hot stage apparatus and are uncorrected. The ^1H NMR spectra were measured in dimethyl sulfoxide-d_6 (DMSO-d_6) solutions on a Brucker 300 MHz spectrometer.

Typical Procedure for the Preparation of $FeCl_3$/egg shell catalyst

The waste of egg shells were collected, cleaned, and dried in an oven at 100 °C during 24 h. The shells obtained, without calcinations, are transformed by crushing into white soft powder. A mixture of 10 mmol of $FeCl_3 \cdot 6H_2O$ and 10 g of egg shell powder were mixed in 80 ml of water and then evaporated to dryness and dried for 2 h at 150 °C before use.

General procedure of the synthetic of 2,3-dihydroquinazolin-4-ones **3a-l**

To a solution of 2-aminobenzamide **1** (1 mmol) and aldehyde or ketone **2** (1 mmol) in ethanol (1 mL), was added the catalyst $FeCl_3$/egg shell (1 mg) was added to of 1 mmol of a different aldehyde. The mixture was then stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude reaction mixture was dissolved in EtOH, and the catalyst was separated out by filtration. The filtered was recrystallized from EtOH to give compounds **3a-l** in high yields (Table 3).

The all products prepared **3a-l** are known compounds and characterized by comparing their ^{1}H NMR data with authentic samples reported in the literature (26-30).

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4-one **3a**: mp 203-205 °C (Lit.(26) 201-203°C). ^{1}H NMR (*δ* ppm): 8.20 (s, 1H, NHCO), 7.60 (d, *J* = 7.7 Hz, 1H, ArH), 7.40-7.44 (m, 1H, ArH), 7.34-7.38 (m, 2H, ArH), 7.25 (t, *J* = 6.7 Hz, 1H, ArH), 7.00 (s, 1H, NH), 6.76 (d, *J* = 7.7 Hz, 1H, ArH), 6.74 (dd, *J* = 6.7, 7.8 Hz, 1H, ArH), 6.16 (s, 1H, CH). Anal. Calcd for $C_{14}H_{11}N_2OCl$: C, 64.75; H, 4.28; N, 10.82; Cl, 13.65%. Found: C, 64.88; H, 4.30; N, 10.84; Cl, 13.62%.

2-Phenyl-2,3-dihydroquinazolin-4-one **3b**: mp 224-226°C (Lit.(26) 225-227°C).^{1}H NMR (*δ* ppm): 8.21 (s, 1H, NHCO), 7.00-7.63 (m, 9H, ArH), 6.93 (s, 1H, NH), 6.75 (s, 1H, CH). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.65; H, 8.82; N, 12.44%. Found: C, 74.67; H, 5.86; N, 12.47%.

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4-one **3c**: mp 210-212°C (Lit.(26) 208-210°C).^{1}H NMR (*δ* ppm): 8.21 (s, 1H, NHCO), 7.68 (d, *J* = 7.8 Hz, 2H, ArH), 7.48-7.50 (m, 2H, ArH), 7.38-7.40 (m, 2H, ArH), 7.27 (t, *J* = 6.8 Hz, 1H, ArH), 7.01 (s, 1H, NH), 6.78 (d, *J* = 7.8 Hz, 1H, ArH), 6.73 (dd, *J* = 6.8, 7.9 Hz, 1H, ArH), 6.15 (s, 1H, CH). Anal. Calcd for $C_{14}H_{11}N_2OCl$: C, 64.75; H, 4.28; N, 10.82; Cl, 13.65%. Found: C, 64.88; H, 4.30; N, 10.84; Cl, 13.62%.

2-p-Tolyl-2,3-dihydroquinazolin-4-one **3d**: mp 230-232°C (Lit.(26) 229-230°C). ^{1}H NMR (*δ* ppm): 8.18 (s, 1H, NHCO), 8.00 (d, *J* = 7.6 Hz, 2H, ArH), 7.80 (t, *J* = 7.6 Hz, 2H, ArH), 7.60 (dt, *J* = 6.0, 7.5 Hz, 2H, ArH), 7.37 (t, *J* = 6.2 Hz, 1H, ArH), 7.19 (t, *J* = 7.5 Hz, 1H, ArH), 7.00 (s, 1H, NH), 6.16 (s, 1H, CH), 2.23 (s, 3H, CH_3). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.93; H, 5.52; N, 11.81%. Found: C, 75.90; H, 5.50; N, 11.83%.

2-(4-Nitrophenyl)-2.3-dihydroquinazolin-4-one **3e**: mp 201-203 °C (Lit.(28) 198-200 °C). ^{1}H NMR (*δ* ppm): 8.23 (s, 1H, NHCO), 8.17 (d, *J* = 7.8 Hz, 2H, ArH), 7.76 (d, *J* = 7.8 Hz, 2H, ArH), 7.64 (d, *J* = 7.6 Hz, 1H, ArH), 7.31 (s, 1H, NH), 7.29 (t, *J* = 7.4 Hz, 1H, ArH), 6.79 (d, *J* = 7.6 Hz, 1H, ArH), 6.70 (t, *J* = 7.4 Hz, 1H, ArH), 6.08 (s, 1H, CH). Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.44; H, 4.11; N, 15.60%. Found: C, 62.46; H, 4.12; N, 15.50%.

2-(2-Hydroxyphenyl)-2.3-dihydroquinazolin-4-one **3f**: mp 221-223°C (Lit.(27) 223-225°C). ^{1}H NMR (*δ* ppm): 8.25 (s, 1H, NHCO), 7.64 (d, *J* = 7.5 Hz, 1H, ArH), 7.36 (d, *J* = 7.5 Hz, 1H, ArH), 7.24 (t, *J* = 7.1 Hz, 1H, ArH), 7.16 (t, *J* = 7.1 Hz, 1H, ArH), 7.00 (s,

1H, NH), 6.88 (s, 1H, OH), 6.74-6.81 (m, 3H, ArH), 6.68 (t, *J* = 7.5 Hz, 1H, ArH), 6.07 (s, 1H, CH). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.10; N, 11.66%. Found: C, 70.12; H, 5.11; N, 11.57%.

2-(4-Dimethylaminophenyl)-2,3-dihydroquinazolin-4-one **3g**: mp 208-210°C (Lit. (28) 206-208 °C). ^{1}H NMR (*δ* ppm): 8.17 (s, 1H, NHCO), 7.62 (d, *J* = 7.5 Hz, 1H, ArH), 7.31 (d, *J* = 7.6 Hz, 2H, ArH), 7.24 (dd, *J* = 7.2, 7.6 Hz, 1H, ArH), 6.90 (s, 1H, NH), 6.64-6.74 (m 4H, ArH), 6.00 (s, 1H, CH), 2.85 (s, 6H, $(CH_3)_2$). Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72%. Found: C, 72.01; H, 6.47; N, 15.65%.

1'H-spiro[cyclohexane-1,2'-quinazolin]-4'-one **3h**: mp 224-226°C (Lit.(29) 223-225°C). ^{1}H NMR (*δ* ppm): 7.91 (s, 1H, NHCO), 6.62-7.56 (m, 4H, ArH), 6.57 (s, 1H, NH), 1.22-2.04 (m, 10H, CH_2). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96%. Found: C, 72.22; H, 7.49; N, 13.03%.

2-(4-Hydroxyphenyl)-2,3-dihydroquinazolin-4-one **3i**: mp 208-210°C (Lit.(30) 210-212°C). ^{1}H NMR (*δ* ppm): 8.22 (s, 1H, NHCO), 7.63 (d, *J* = 7.5 Hz, 1H, ArH), 7.32 (d, *J* = 7.5 Hz, 2H, ArH), 7.26 (t, *J* = 7.1 Hz, 1H, ArH), 7.08 (s, 1H, NH), 6.94 (s, 1H, OH), 6.66-6.78 (m, 4H, ArH), 6.12 (s, 1H, CH). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.10; N, 11.66%. Found: C, 70.12; H, 5.11; N, 11.57%.

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4-one **3j**: mp 201-203°C (Lit.(30) 200-202°C). ^{1}H NMR (*δ* ppm): 8.26 (s, 1H, NHCO), 8.16 (d, *J* = 7.4 Hz, 2H, ArH), 8.02 (7, *J* = 7.5 Hz, 2H, ArH), 7.67 (dt, *J* = 6.2, 7.5 Hz, 2H, ArH), 7.14 (s, 1H, NH), 6.96 (t, *J* = 6.2 Hz, 1H, ArH), 6.85 (t, *J* = 7.5 Hz, 1H, ArH), 6.75 (s, 1H, CH). Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.44; H, 4.11; N, 15.60%. Found: C, 62.46; H, 4.12; N, 15.50%

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4-one **3k**: mp 181-183°C (Lit.(30) 182-184°C). ^{1}H NMR (*δ* ppm): 8.20 (s, 1H, NH-CO), 8.26 (d, *J* = 7.6 Hz, 2H, ArH), 8.00 (t, *J* = 7.6 Hz, 2H, ArH), 7.8 (dt, *J* = 6, 7.5 Hz, 2H, ArH), 7.62 (s, 1H, NH), 7.57 (t, *J* = 6.2 Hz, 1H, ArH), 7.39 (t, *J* = 7.5 Hz, 1H, ArH), 6.00 (s, 1H, CH), 3.43 (s, 3H, OCH_3). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.83; H, 5.54; N, 11.01%. Found: C, 70.85; H, 5.56; N, 11.05%

2-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydroquinazolin-4-one **3l**: mp 218-219°C (Lit. (30) 219-221°C). ^{1}H NMR (*δ* ppm): 8.25 (s, 1H, NHCO), 7.60 (d, *J* = 7.5 Hz, 1H, ArH), 7.23 (dd, *J* = 7.1, 7.7 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 7.00 (s, 1H, NH), 6.92 (s, 1H, OH), 6.87 (d, *J* = 7.4 Hz, 1H, ArH), 6.75 (t, *J* = 7.6 Hz, 2H, ArH), 6.67 (t, *J* = 7.4 Hz,

1H, ArH), 6.10 (s, 1H, CH), 3.74 (s, 3H, CH_3). Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.64; H, 5.21; N, 10.35%. Found: C, 66.63; H, 5.19; N, 10.38%.

RESULTS AND DISCUSSION

General information for the catalyst

The analysis by the X-ray powder diffraction (XRD) of the egg shell (Figure 1) showed a well-crystallized phase. The presence of calcite was confirmed by the characteristic peaks 012, 104, 006, 110, 113, 202, 024, 018, 116, 211, 122, 214 and 300 reflections at 23.17°, 29.52°, 31.58°, 36.19°, 39.52°, 43.33°, 47.30°, 47.78°, 48.73°, 56.99°, 57.62°, 60.96°, 63.34° and 64.92° (2θ) (reported on the JCPDS: 47-1743).

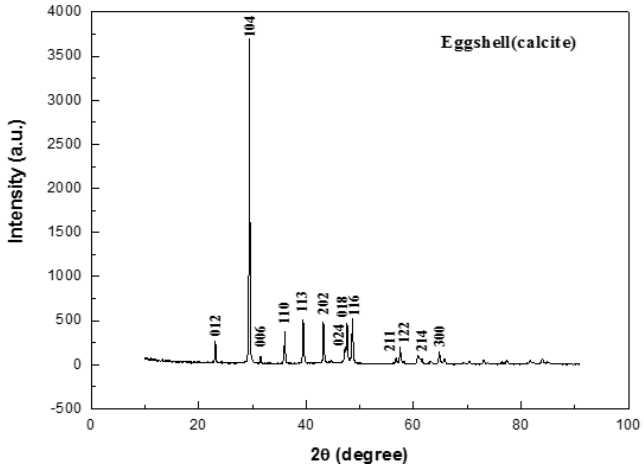


Figure 1: XRD analysis for egg shell (calcite).

The scanning electron microscopy of egg shell (Figure 2) shows it can be observed that the egg shell does not have irregular shape, resulting of the comminution process used and shows the high porosity of the egg shell powder particles. The egg shell (calcite) powder has an average specific surface of 1.02 m^2/g by the measurements which were carried out by the BET (Brunauer, Emmett, and Teller).

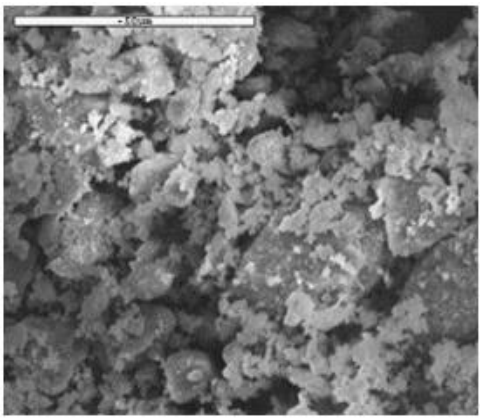


Figure 2: SEM photographs of egg shell (calcite).

The FT-IR spectra of egg shell (Figure 3) shows that the spectrum can be divided into five parts with peaks around 3455, 3515, 2360, 1799, 1417, 1385, 875 and 713 cm^{-1}, which can be associated to CO_3^{2-} ions in $CaCO_3$**.** By observing the spectra, it appears that a prominent absorption peak of carbonate was observed at 1417 cm^{-1}, respectively, attributed to alkyl group. Besides, the FT-IR result also showed the absorption peak of calcite at 875 cm^{-1} of CO_3^{2-}. This agrees well with the result reported by Islam *et al.* (31) in which they observed the absorption peak of calcite at 875 cm^{-1} of CO_3^{2-} .

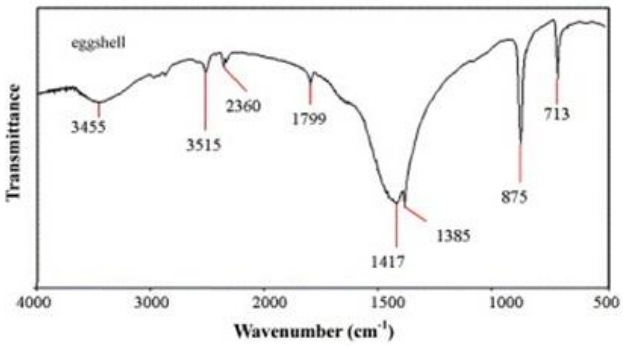
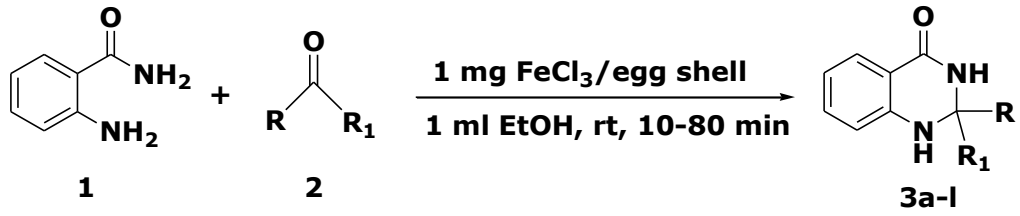


Figure 3: FT-IR spectra of egg shell (calcite).

Catalytic testing for the synthesis of 2,3-dihydroquinazolin-4-ones

Initially, to optimize the reaction conditions, we carried out the reaction of 2-amino benzamide **1**, with 4-chloro benzaldehyde **2a** in ethanol as a model reaction (Scheme 1). Different heterogeneous catalysts were tested such as egg shell, $SnCl_2$/egg shell, $ZnCl_2$/egg shell, $NiCl_2$/egg shell, $BaCl_2$/egg shell, $CoCl_2$/egg shell, $CaCl_2$/egg shell, $FeCl_3$/egg shell, and $FeCl_3$. The results listed in Table 1 show that $FeCl_3$/egg shell (entries 18-22, Table 1) is the most effective catalyst for this synthesis of 2-(4-chlorophenyl) quinazolin-4-one **3a**. Moreover, we found that the yields were affected by the amount of

$FeCl_3$/egg shell loaded. Therefore, 1 mg of $FeCl_3$/egg shell was sufficient and optimal amount of catalyst for the completion of the condensation at room temperature (entry 21, Table 1).



Scheme 1: Synthesis of 2,3-dihydroquinazolin-4-ones using $FeCl_3$/egg shell.

Similarly, as shown in Table 2, among the solvent effect, such as ethanol, methanol, toluene, dioxane and DMF, it was found that the reaction proceeded efficiently in EtOH and resulted in high yields of desired product (Entry 2, Table 2).

The generality of the reaction was confirmed by using substituted aldehydes having both electron-withdrawing and donating substituent's (Table 3). In almost all the cases, the reaction was completed with desired products in efficient yields.

Table 1. Comparison of catalytic activities for the synthesis of **3a**[a]

Entry	Catalyst	Amount (mg)	Condition	Yield (%)[b]
1	Egg Shell	4	Reflux	94
2	Egg Shell	4	r.t	95
3	Egg Shell	1	Reflux	96
4	$SnCl_2$/egg shell	4	Reflux	54
5	$SnCl_2$/egg shell	4	r.t	55
6	$SnCl_2$/egg shell	1	Reflux	54
7	$ZnCl_2$/egg shell	4	Reflux	66
8	$ZnCl_2$/egg shell	4	r.t	67
9	$ZnCl_2$/egg shell	1	Reflux	66
10	$NiCl_2$/egg shell	4	Reflux	10
11	$NiCl_2$/egg shell	4	r.t	10
12	$NiCl_2$/egg shell	1	Reflux	11
13	$BaCl_2$/egg shell	1	Reflux	96
14	$BaCl_2$/egg shell	1	r.t	95
15	$CoCl_2$/egg shell	1	Reflux	56
16	$CoCl_2$/egg shell	1	r.t	54
17	$CaCl_2$/egg shell	1	Reflux	80
18	$FeCl_3$/egg shell	4	Reflux	96
19	$FeCl_3$/egg shell	3	Reflux	96
20	$FeCl_3$/egg shell	3	r.t	96
21	$FeCl_3$/egg shell	1	r.t	98
22	$FeCl_3$/egg shell	2	r.t	97
23	$BaCl_2$	1	Reflux	70
24	$FeCl_3$	1	Reflux	72

[a] 2-aminobenzamide **1** (1 mmol) and 4-chlorobenzaldehyde **2a** (1 mmol), 1 mL EtOH, 30 min.
[b] Isolated yield.

Table 2: Optimization of solvent in the synthesis of **3a**[a].

Entry	Solvent	Time (min)	Yield (%)[b]
1	Solvent-free	30	25
2	EtOH	30	98
3	EtOH	20	94
4	EtOH	10	93
5	MeOH	30	93
6	MeOH	60	93
7	Toluene	30	69
8	Dioxane	10	70
9	Dioxane	30	72
10	DMF	30	--
11	DMF	90	--

[a]2-aminobenzamide **1** (1 mmol) and 4-chlorobenzaldehyde **2a** (1 mmol), 1 mL solvent, r.t, 1mg of catalyst.

[b] Isolated yield.

As shown in Table 4, the recoverability of the catalyst was investigated in the pilot experiment for the synthesis of **3a**. The recycled catalyst was reused in the subsequent fresh reactions without any treatment and no considerable loss of its catalytic activity was observed. As a result, it can be classified as an excellent catalyst in industry for large-scale synthesis.

Table 3. Synthesis of 2,3-dihydroquinazolin-4-ones **3a-l**

Product	R	R_1	Time (min)	Yield (%)[a]
3a	4-ClC_6H_4	H	30	99
3b	C_6H_5	H	18	95
3c	2-ClC_6H_4	H	30	93
3d	4-MeC_6H_4	H	15	91
3e	4-$NO_2C_6H_4$	H	70	89
3f	2-OHC_6H_4	H	10	94
3g	4-$N(Me)_2C_6H_4$	H	40	97
3h	$(CH_2)_5$		80	75
3i	4-OHC_6H_4	H	60	79
3j	3-$NO_2C_6H_4$	H	55	88
3k	4-$CH_3OC_6H_4$	H	25	90
3l	4-HO-3-$CH_3OC_6H_3$	H	30	85

[a] Isolated yield.

Table 4: Recovery results of the catalyst in the model reaction.

Run	Time (min)	Yield (%)[a]
1	30	98
2	30	97
3	30	96
4	30	95
5	30	94
6	30	93
7	30	90

[a] Isolated yields.

To show the merit of our work, the reaction of 2-aminobenzamide and 4-chloro benzaldehyde was compared with literature data. As shown in Table 5, the reported methods suffer from more disadvantages such as elevated reaction temperatures and longer reaction times. Therefore, we believe the present work is an improvement with respect to other procedures.

Table 5. Comparison of the efficiency of catalyst and the reaction conditions with some other reports on the model reaction.

Catalyst	Solvent	Time (min)	Temp. (°C)	Yield (%)	Lit.
$NaHSO_4$	H_2O	10	60	94	(30)
L-Proline nitrate	MeCN	20	r.t.	75	(32)
CAN	MeCN	120	60	92	(33)
Fe_3O_4/chitosan	EtOH	32	r.t	97	(34)
Amberlyst-15	H_2O	30	r.t	98	(35)
$[Bmim]PF_6$	-	35	75	89	(16)
NH_4Cl	EtOH	15	r.t.	92	(36)
Sulfamic acid	MeOH	20	r.t.	89	(37)
Boric acid	Free	13	120	81	(38)
$FeCl_3$/egg shell	EtOH	30	r.t	98	This work

CONCLUSIONS

In summary, a highly efficient and simple procedure was developed for the synthesis of quinazolin-4-one derivatives by using 2-aminobenzamide and various aldehydes in the presence of $FeCl_3$/egg shell as an efficient and reusable catalyst. The present work include several advantages such as avoiding the use of non toxic solvent or expensive catalyst, high yields, short reaction times, ease of product isolation, recyclability of the catalyst and good agreement with the green chemistry protocols. It can be classified as a useful, practical and attractive protocol for the synthesis of heterocyclic compounds.

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