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COMMUNICATION

Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of Fe_3O_4@nano-cellulose–OPO_3H as a bio-based magnetic nanocatalyst

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Abstract

In this research, we have used Fe_3O_4@nano-cellulose–OPO_3H as magnetic bio-based nanocatalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via condensation of 2-aminobenzamide and different aldehydes. The major advantages of the present methodology are good yields, ecofriendly catalyst, and easy workup.

KEYWORDS

2,3-Dihydroquinazolin-4(1*H*)-ones, 2-Aminobenzamide, bio-based catalyst, Fe_3O_4@nano-cellulose–OPO_3H, heterogeneous catalyst, magnetic nanocatalyst

1 | INTRODUCTION

Quinazolinones and their derivatives are used to synthesize similar drugs such as hypnotic/sedatives[1] and antimalarial,[2] antibacterial and antioxidant,[3] antitumor,[4] antifungal and cytotoxic,[5] antiproliferative,[6] and inhibitory activities on α-glucosidase.[7] In Figure 1, the structure of metolazon (hypertensive),[8] febrifugine (antimalaria), and methaqualone (sedative) were shown. Quinazolinones are synthesized via condensation of 2-aminobenzamide with aldehydes in the presence of an acidic catalyst. Previously, this reaction has been catalyzed by I_2,[9] $ZnFe_2O_4$,[10] silver triflate,[11] $Sc(OTf)_3$,[12] lactic acid,[13] $CeCl_3$,[14] $FeCl_3$/egg shell,[15] bismuth (III) bromide,[16] Zn-2-amino-3-hydroxy-pyridine-MCM-41,[17] silica sulfuric acid,[18] succinimide-*N*-sulfonic acid,[19] ammonium chloride,[20] and nano-Fe_3O_4/$TiCl_2$/cellulose.[21] Fe_3O_4@nano-cellulose–OPO_3H (Fe_3O_4@NCs-PA) was previously synthesized in our laboratory for the first time and used for the synthesis of dihydro-2-oxopyrroles.[22] In this work, we decided to investigate the efficiency of Fe_3O_4@NCs-PA for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

2 | RESULTS AND DISCUSSION

The catalytic activity of Fe_3O_4@NCs-PA was investigated for the synthesis of quinazolinone via a reaction of 2-aminobenzamide and aldehydes. For optimization of the reaction conditions, the reaction of 2-aminobenzamide and 4-chlorobenzaldehyde was investigated as a model reaction under various conditions (Table 1). As shown in Table 1, entry 10, it was found that using Fe_3O_4@NCs-PA on 1 mmol of any substance under reflux condition in water and ethanol (1:1) is the best reaction condition. The reusability of the Fe_3O_4@NCs-PA was investigated using the model reaction (Table 1, entries 12–15). After the completion of the reaction, the Fe_3O_4@NCs-PA was washed with ethanol, dried, and reused for another run. No any significant reduction in yield was observed.

Finally, the above optimized reaction conditions were applied for the synthesis of quinazolinone derivatives (Scheme 1, Table 2). The aromatic aldehydes containing electron-withdrawing groups were reacted in this protocol with high yields.

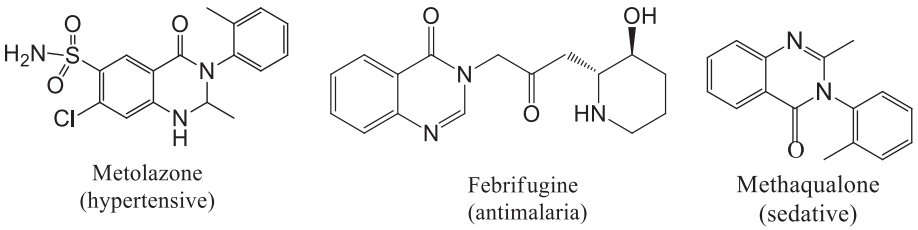
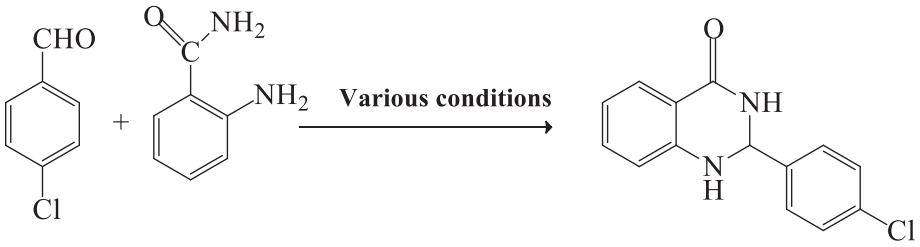


FIGURE 1 Some quinazolinones with pharmaceutical activity

TABLE 1 Synthesis of 2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*) one under various conditions[a]



Entry	Solvent	Catalyst (g)	Condition	Time (hr)	Yield[b]	Ref.
1	—	Catalyst[c] (0.04)	Grinding	0.25	—	
2	—	Catalyst[c] (0.04)	100°C	1.5	71	
3	—	Catalyst[c] (0.04)	R.T.	2	—	
4	*n*-hexane	Catalyst[c] (0.04)	Reflux	3.5	43	
5	H_2O	Catalyst[c] (0.04)	Reflux	3	—	
6	EtOH	Catalyst[c] (0.04)	Reflux	1	74	
7	MeOH	Catalyst[c] (0.04)	Reflux	1	82	
8	H_2O, EtOH	Nano-Fe_3O_4 (0.04)	Reflux	4	60	
9	H_2O, EtOH	Catalyst[c] (0.05)	Reflux	1.25	95	
10	H_2O, EtOH	Catalyst[c] (0.04)	Reflux	1.25	95	
11	H_2O, EtOH	Catalyst[c] (0.03)	Reflux	1.75	81	
12	H_2O, EtOH	Catalyst[c] (0.04) ^{second}	Reflux	1.25	87	
13	H_2O, EtOH	Catalyst[c] (0.04)^{third}	Reflux	2.30	85	
14	H_2O, EtOH	Catalyst[c] (0.04)^{fourth}	Reflux	4	82	
15	H_2O, EtOH	Catalyst[c] (0.04)^{fifth}	Reflux	5	75	
16	EtOAc	I_2 (0.05 equiv)	O_2/hv	15	88	[9]
17	H_2O	Lactic acid (20 mol%)	60°C	0.33	88	[13]
18	Ethanol	Sc $(OTf)_3$(5 mol%)	70°C	0.41	91	[12]
19	H_2O	$ZnFe_2O_4$ (30 mol%)	M.W	0.17	92	[10]
20	Dimethylcarbonate	$CeCl_3$(5 mol%)	100°C	8	90	[14]
21	Ethanol	$FeCl_3$/egg shell	r.t	0.17	99	[15]
22	H_2O	Zn-2-amino-3-hydroxy-pyridine-MCM-41	90°C	2	98	[17]

[a]4-Chlorobenzaldehyde (1 mmol), 2-aminobenzamide (1 mmol).
[b]Isolated yield.
[c]Fe_3O_4@NCs-PA.

In addition to aldehydes, we also applied ketones for the production of 2, 3-dihydroquinazolin-4(1*H*)-ones. If we had applied cyclic ketones such as cyclohexanone or cyclopentanone, the product 2, 3-dihydroquinazolin-4 (1*H*)-ones with spiro skeleton might have been formed (Scheme 2).

2.1 | Spectroscopic data for selected compounds

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 1): White solid, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.45 (brs, 1 H), 8.16 (m, 1 H), 8.02 (m, 2 H), 7.83 (m, 3 H), 7.69 (brs, 1 H), 7.37 (brs, 1 H), 7.26 (m, 1 H), 7.15 (brs, 1 H), 6.27 (*s*, 1 H). Fourier Transform Infrared (FT-IR) (cm^{-1}): 3301, 3176, 3062, 1653, 1610, 1509, 1482.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 2): yellow solid, ^{1}H NMR (acetone-d_6, 400 MHz): δ 8.26 (d, J = 8 Hz, 2 H), 7.87 (d, J = 8 Hz, 2 H), 7.78 (m, 1 H), 7.52 (brs, 1 H), 7.30 (m, 1 H), 6.84–6.79 (m, 2 H), 6.51 (brs, 1 H), 6.11 (s, 1 H). FT-IR (cm^{-1}): 3352, 3291, 1658, 1609, 1513, 1484, 1346.

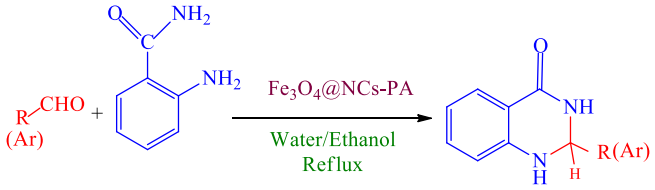
2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 3): Light yellow solid, ^{1}H NMR (acetone-d_6, 400 MHz): δ 8.46 (brs, 1 H), 8.24 (brs, 1 H), 8.06 (brs, 1 H), 7.77 (brs, 1 H), 7.72 (brs, 1 H), 7.60 (brs, 1 H), 7.31 (brs, 1 H), 6.86 (brs, 1 H), 6.79 (brs, 1 H), 6.53 (brs, 1 H), 6.14 (s, 1 H). FT-IR (cm^{-1}): 3281, 3186, 3074, 1649, 1605, 1520, 1483, 1349, 862, 747, 680.

2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 4): Yellow solid. ^{1}H NMR (acetone-d_6, 400 MHz): δ 8.06 (d, J = 7.6 Hz, 1 H), 7.99 (d, J = 7.2 Hz, 1 H), 7.78–7.80 (m, 2 H), 7.62–7.66 (m, 1 H), 7.27–7.32 (m, 2 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.76–6.80 (m, 1 H), 6.50 (s, 1 H), 6.32 (brs, 1 H) FT-IR (cm^{-1}): 3419, 3182, 3005, 1661, 1608, 1531, 1463, 1349, 738.

2-(4-Isopropylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 6) Pale yellow solid, ^{1}H NMR (Acetone-d_6, 400 MHz): δ 7.78 (brs, 1 H), 7.49 (brs, 2 H), 7.29 (brs, 3H), 7.11 (brs, 1H), 6.84 (m, 1H), 6.77 (m, 1H), 6.16 (brs, 1H), 5.86 (s, 1H), 2.50 (m, 1 H), 1.23 (d, J = 6.4 Hz, 6 H). FT-IR (Cm^{-1}): 3291, 2952, 1653, 1608, 1433, 751.

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*) one (Table 2, entry 7): White solid, ^{1}H NMR (Acetone-d_6, 400 MHz): δ 7.78 (m, 2 H), 7.39–7.45 (m, 3 H), 7.25–7.29 (m, 2 H), 6.86 (brs, 1 H), 6.79 (brs, 1 H), 6.33 (brs, 1 H), 6.24 (brs, 1 H). FT-IR (cm^{-1}): 3358, 3183, 3065, 1643, 1608, 1500, 1431, 1122, 1032, 742.

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*) one (Table 2, entry 8). White solid, ^{1}H NMR (Acetone-d_6,

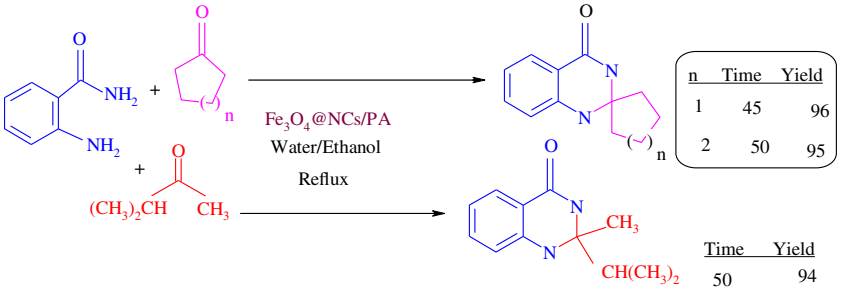


SCHEME 1 Synthesis of quinazolinones in the presence of Fe_3O_4@NCs-PA

TABLE 2 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of Fe_3O_4@NCs-PA[a]

Entry	R (Ar)	Time (h)	Yield (%)[b]	M.P.[c] observed	M.P.[c] Reported[Ref]
1	Ph-H	1.5	83	208–210	221–222[12]
2	4-$NO_{2\text{-Ph}}$	1	92	307–309	>300[14]
3	3-$NO_{2\text{-Ph}}$	0.5	89	190–193	194–196[14]
4	2-$NO_{2\text{-Ph}}$	1.75	73	191–192	191–193[17]
5	4-OH-Ph	1.5	75	199–200	209–211[16]
6	4-$(CH_3)_2$CH-Ph	2	78	157–161	158–161[11]
7	2-Cl-Ph	1	79	206–208	210–212 [15]
8	4-Cl-Ph	1	95	193–194	203–205[15]
9	2,4-$(Cl)_{2\text{-Ph}}$	0.85	82	165–169	166–169[21]
10	2,4-$(OMe)_{2\text{-Ph}}$	1.17	71	184–186	185–189[21]
11	4-$(Me)_2$N-Ph	075	70	190–195	206–208[15]
12	4-OH, 3-OMe-Ph	075	88	213–216	218–219[15]
13	Ph-CH_2CH_2-	1.15	85	200–202	204[23]
13	Ph-CH=CH-	1.50	89	160–162	155–157[24]
14	Cyclohexyl	3	90	175–176	174–175[23]
16	*n*-Pentyl	1.20	80	147–149	154[23]
17	H	1.50	82	>160[c]	—[25]
18	4-HCO-Ph	3	80	243–245	245–246[26]

[a]Aldehyde (1 mmol), 2-aminobenzamide (1 mmol), and Fe_3O_4@NCs-PA (0.04 g) were used.
[b]Isolated yield.
[c]Decomposed.



SCHEME 2 Synthesis of quinazolinones via condensation of 2-aminobenzamide and ketones

400 MHz): δ7.78 (brs, 1 H), 7.62 (brs, 2 H), 7.44 (brs, 2 H), 7.29 (brs, 2 H), 6.82 (m, 2 H), 6.28 (brs, 1 H), 5.94 (s, 1 H). FT-IR (cm^{-1}): 3305, 3180, 3059, 1652, 1604, 1507, 1433, 1089, 749.

2-(2,4-Dichlorophenyl)-2,3-dihydroquinazolin-4 (1*H*) one (Table 2, entry 9): White solid, ^{1}H NMR (Acetone-d_6, 400 MHz): δ 7.79 (brs, 2 H), 7.53 (brs, 1 H), 7.46 (brs, 1 H), 7.33 (m, 2 H), 6.80–6.85 (m, 2 H), 6.29–6.32 (m, 2 H). FT-IR (cm^{-1}): 3431, 3182, 1646, 1610, 1513, 1435, 1150, 1127, 795, 741.

2-(2,4-Dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 10): off white solid, ^{1}H NMR (Acetone-d_6, 400 MHz): δ 11.10 (brs, 1 H), 8.36 (brs, 1 H), 8.17 (brs, 1 H), 7.78 (brs, 1 H), 7.70 (brs, 1 H), 7.46 (brs, 1 H), 6.77 (brs, 3H), 6.50 (m, 1 H), 3.91 (s, 3 H), 3.85 (s, 3 H). FT-IR (cm^{-1}): 3316, 1676, 1589, 1481, 1264, 1017, 822, 752.

2-(4-Dimethylaminophenyl)-2,3-dihydroquinazolin-4 (1*H*) one (Table 2, entry 11). White solid, ^{1}H NMR ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (m, 1 H), 7.29–7.15 (m, 3 H), 6.68–6.59 (m, 4 H), 6.00 (s, 1 H), 5.64 (s, 1 H), 5.09 (s, 1 H), 2.14(s, 3H). FT-IR (cm^{-1}): 3283, 1650, 1610, 1508, 1163, 815, 750.

2-(3-Methoxy,4-hydroxy-phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 12) off white solid, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (s, 1 H, OH), 7.17 (d, J = 7.8 Hz, 1 H), 6.90 (s, 1 H), 6.67 (t, J = 7.8 Hz, 1 H), 6.57 (s, 1 H), 6.30 (d, J = 7.7 Hz, 1H), 6.26 (d, J = 7.8 Hz, 1 H), 6.19 (d, J = 7.9 Hz, 1 H), 6.13 (t, J = 7.8 Hz, 1 H), 5.87 (s, 1 H), 5.11 (s, 1 H), 3.35 (s, 3 H). FT-IR (cm^{-1}): 3385, 3343, 1641, 1607, 1158, 761.

3 | EXPERIMENTAL

3.1 | Materials and methods

The chemicals were purchased from Merck and Aldrich companies and were used without any additional purification. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus. Bruker (DRX-400 Avance) and Bruker (DRX-500 Avance) NMR were used to record the ^{1}H NMR spectra.

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

In a 25 ml round-bottom flask, a mixture of Fe_3O_4@NCs-PA(0.04 g), 2-aminobenzamide (1 mmol), aldehyde (1 mmol), and water: EtOH (1;1, 3 ml) were mixed under reflux condition. After completion of the reactions that were monitored by thin layer chromatography (TLC) (EtOAc: *n*-Hexane, 1:4).), the catalyst was removed from the hot reaction mixture using an external magnet. By adding water to the residue, solid products were obtained and were filtered, dried, and finally recrystallized from ethanol and water.

4 | CONCLUSIONS

In summary, we have applied Fe_3O_4@NCs-PA as a bio-based, ecofriendly, and efficient catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. Easy workup, excellent yields, and reusability of the catalyst are some of the advantages of this novel protocol.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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