An Efficient One-Pot Solvent-Free Synthesis of 2,3-Dihydroquinazoline-4(1H)-ones *via* Al/Al_2O_3 Nanoparticles

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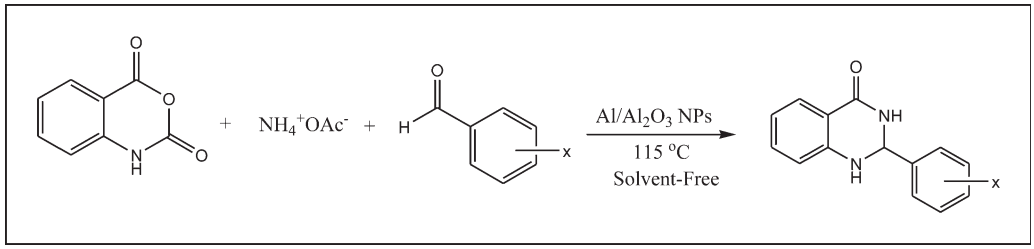

An efficient one-pot, solvent-free method is reported for the synthesis of 2-phenyl-2,3-dihydroquinazoline-4(1H)-one as well as its *o*-Cl, *o*-OMe, *m*-Br, *m*-NO_2, *p*-OH, *p*-NO_2, *p*-CN, *p*-$PhCH_2O$, *p*-Cl, *p*-F, *p*-Br, *p*-Me, and *o,m*-dichloro derivatives, using our ''as-prepared'' arc discharge fabricated Al/Al_2O_3 nanoparticles. Compared with our previous report and other known methods, this route gives higher yields with shorter reaction times, whereas its green catalyst appears recyclable at least four times-with minor decrease in its catalytic activity, under mild conditions.

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INTRODUCTION

Dihydroquinazolinones and their derivatives are important heterocyclic compounds, which influence numerous cellular processes. They are analgesic, diuretic, and vasodilating agents, displaying a broad range of biological, medicinal, and pharmacological properties [1–10]. Also, they are constituents of antitumor, antibiotic, antidefibrillatory, antipyretic, antihypertonic, antihistamine, and antidepressant drugs. In addition, these compounds can easily be oxidized to their quinazolin-4(3H)-one analogues [11], which also include important pharmacologically active compounds [12]. Several routes, including our recent method, using iodine as the catalyst, have been reported for the synthesis of 2,3-dihydroquinazolinones [13–19]. Yet, development of a green, simple, efficient, and general method for the synthesis of these widely used organic compounds, from readily available reagents, remains one of the major challenges in organic synthesis. In this manuscript, we have made use of the novel, recently reported metal and metal oxide nanoparticles, which exhibit high-surface/volume ratio, quantum size, and quanta tunnel effects [20–23]. We think our new procedure is cleaner and more environment friendly than our previous one, where we used the relatively toxic iodine catalyst [19]. Specifically, we employ small amounts of novel, recyclable, nontoxic, and inexpensive Al/Al_2O_3 nanocatalyst with a high-surface/volume ratio in, a three-component one-step synthesis of 2,3-dihydroquinazolin-4(1H)-ones (Scheme 1).

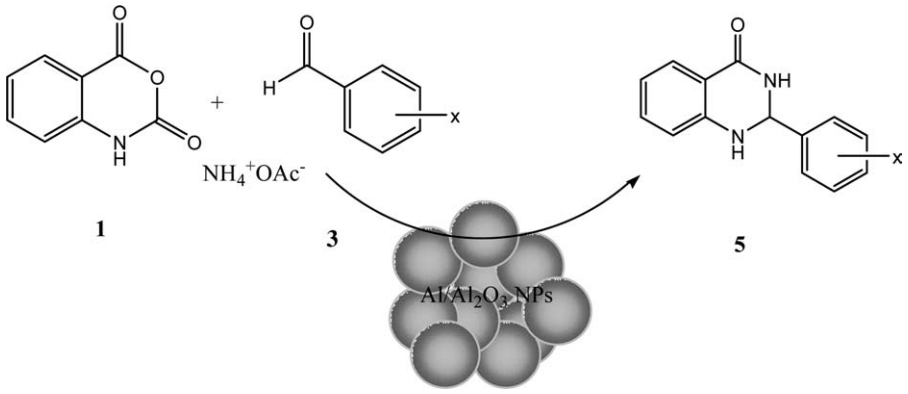
RESULTS AND DISCUSSION

After demonstrating the impact of media and current on the arc fabrication of Al nanoparticles [24], we wondered if we could substitute Al/Al_2O_3 nanoparticles for iodine in the preparation of 2,3-disubstituted quinazolin-4(3H)-ones through multicomponent reactions, which we had already reported [19]. The reason was our immense desire to adopt rather green and economical reaction conditions, since the vapor of iodine was toxic at high-temperatures, and to remove the excess iodine we had to use saturated $Na_2S_2O_3$. Also the previous catalyst was not reusable.

The scanning electron microscopy (SEM) images showed spherical arc fabricated Al/Al_2O_3 NPs with a size range of 30 – 40 nm (Fig. 1).

The X-ray diffraction (XRD) pattern confirmed the formation of Al/Al_2O_3 NPs with similar average grain size range estimated *via* Scherer's equation [25], using the maximum peak (111) was used (Fig. 2). At a scanning speed of 2°/min from 20° to 80° (2θ), the XRD pattern showed five peaks, which were characteristic of

Scheme 1. Three-component one-step synthesis of 2,3 dihydroquinazolin-4(1H)-ones.



aluminum (2θ = 38.56°; 44.84°; 65.25°; 78.33°, and 82.59°), corresponding to Miller indices (111), (200), (220), (311), and (111), revealing the formation of face-centered cubic (fcc) Al NPs. Besides, it illustrated the lines (110), (104), and (220) at 2θ = 45.93°; 66.98°; 85.09°, respectively, for γ-Al_2O_3.

Catalytic amounts of this as-prepared Al/Al_2O_3 NPs was added to a well-stirred mixture of isatoic anhydride (**1**), an aromatic aldehyde (**3**, either with electron-donating or electron-withdrawing groups), and ammonium acetate. It gave the corresponding 2,3-dihydroquinazolin-4(1H)-ones (**5a – o**) in 65 – 98% yields, at 115°C, under solvent-free conditions (Table 1).

Reactions were completed under smooth conditions within 8 – 30 min, and the products were isolated by a simple workup procedure. Thus an easy and rather green method for the synthesis of a novel class of the quinazolinone family was found. However, no simple relationship was observed between the electronic properties of the aryl groups and the corresponding quinazolinone products. Specifically, the amount of the catalyst (Al/Al_2O_3 NPs) for this condensation reaction was probed at 0.00, 0.06, 0.012, 0.036, and 0.048 g against isatoic anhydride (0.163 g, 1.0 mmol), ammonium acetate, and 4-chlorobenzaldehyde (0.14 g, 1.0 mmol), under solvent-free condition, at 115°C (Table 2).

The best results were obtained using 0.036 g of catalyst (yield = 94%). Increasing the amount of catalyst higher than 0.048 g did not affect the reaction time and yield. The absence of the catalyst required considerably higher reaction time giving the lowest yield (75%).

To check the reusability of our catalyst, the prepared Al/Al_2O_3 NPs (0.036 g) was stirred for 2 min with isatoic anhydride (0.163 g, 1 mmol), aromatic aldehyde (0.14 g, 1 mmol), and ammonium acetate, at room temperature. Then the mixture was heated in a paraffin bath at 115°C, for different periods of time (Table 1). After completion of the reaction excess ammonium acetate was washed away by water (5 mL). Subsequently, the hydroquinazolinone products were extracted by ethanol (50 mL). The solid residue was our catalyst, which was dried and reused for at least four cycles (Fig. 3).

The question is how this catalyst works? Evidently, the Al/Al_2O_3 NPs function as a good Lewis acid, which attracts and activates the carbonyl and imine groups involved and provides a surface on which the reactions

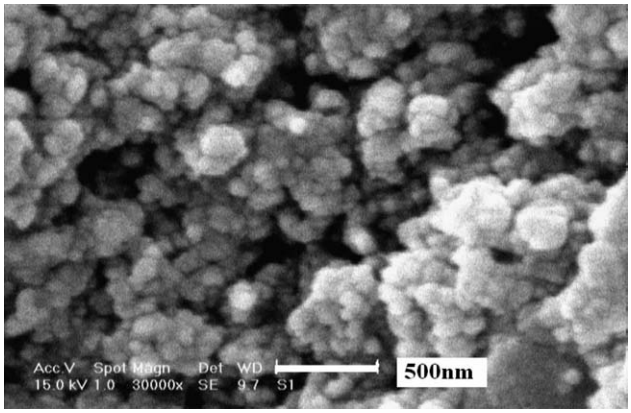


Figure 1. The SEM image of the as-prepared Al/Al_2O_3 nanoparticles.

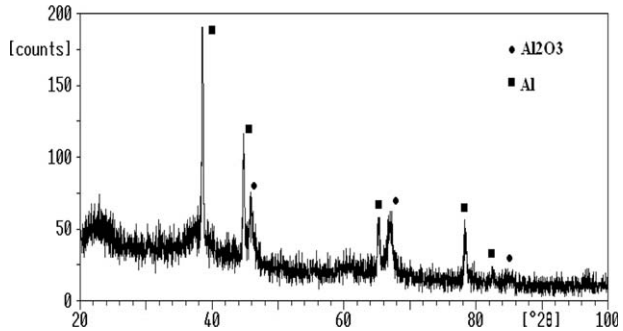


Figure 2. The XRD pattern of the as-prepared Al/Al_2O_3 nanoparticles.

Table 1

The reaction time and the % yield of hydroquinazolin product.

Product	Ar	Time (min)	Yield (%)[a]	M.P (°C) Found	M.P (°C) Reported
5a	4-OHC_6H_4	8	91	285 – 287	278 – 280 [19]
5b	4-$NO_2C_6H_4$	8	78	300 – 302	310 – 312 [19]
5c	4-CNC_6H_4	15	75	350 – 351	350 – 351 [19]
5d	4-$PhCH_2$–O–C_6H_4	15	98	238 – 240	238 – 240 [19]
5e	4-ClC_6H_4	15	94	207 – 208	207 – 208 [19]
5f	4-FC_6H_4	30	89	279 – 280	279 – 280 [19]
5g	4-BrC_6H_4	10	80	195 – 197	195 – 197 [19]
5h	2-ClC_6H_4	12	79	230 – 231	230 – 231 [19]
5i	2-$OMeC_6H_4$	10	82	173 – 175	173 – 175 [19]
5j	3-BrC_6H_4	15	95	229 – 230	229 – 230 [19]
5k	2,3-$Cl_2C_6H_3$	5	90	232 – 233	232 – 233 [19]
5l	4-$MeOC_6H_4$	8	80	183 – 184	183 – 184 [19]
5m	C_6H_5	15	88	225 – 226	225 – 226 [19]
5n	4-MeC_6H_4	15	92	228 – 230	229 – 231 [19]
5o	3-$NO_2C_6H_4$	30	65	180 – 182	180 – 182 [19]

[a] Isolated yield.

occur sequentially leading to the desired products (Scheme 2).

Specifically, decarboxylation of **1** occurs through its condensation with ammonium acetate in the presence of Al/Al_2O_3 NPs, affording antranylamide intermediate **2**, which reacts with the aromatic aldehyde **3** and gives the imine intermediate **4** that cyclizes to yield the corresponding hydroquinazolinone **5**.

CONCLUSION

We have employed Al/Al_2O_3 NPs as an effective catalyst in the one-pot multicomponent synthesis of 2,3-dihydroquinazolin-4(1H)-ones. This catalyst is highly efficient, easily available, economical, operationally simple, and requires mild reaction conditions. Also the products were formed in excellent yields with short reaction times. This method offers several advantages, such as omitting toxic solvents or catalyst, very simple workups, and needs no chromatographic method for purification of the products. The starting materials are also inexpensive and commercially available.

Table 2

The reaction time and the yield of hydroquinazolin product as a function of the amount of the employed catalyst (Al/Al_2O_3 NPs).

Entry	Amount of Catalyst (g)	Temperature (°C)	Reaction Time (min)	Yield (%)[a]
1	0.000	115	55	75
2	0.006	115	30	81
3	0.012	115	25	82
4	0.024	115	20	84
5	0.036	115	15	94
6	0.048	115	15	95

[a] Isolated yield

EXPERIMENTAL

General remarks. Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H and ^{13}C NMR spectra were measured on a Bruker DRX-300 spectrometer, at 300 and 75 MHz, using TMS as an internal standard. Chemical shifts (δ) were reported relative to TMS, and coupling constants (*J*) were reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70-eV ionization potential. Elemental analyses of new compounds were performed using a Vario EL III 0 Serial No.11024054 instrument. The particle shape and morphology were characterized by SEM of a Holland Philips XL30 microscope with an accelerating voltage of 20 kV. A Holland

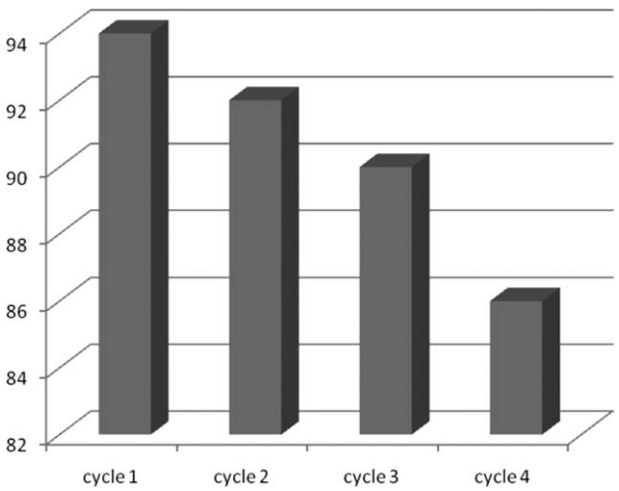
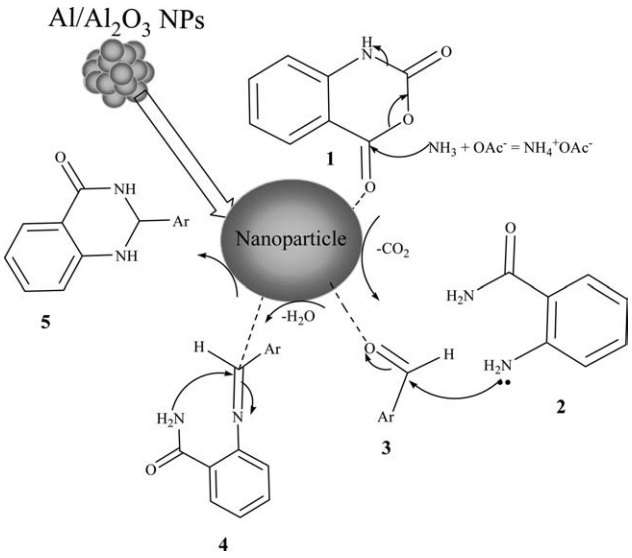


Figure 3. Catalytic recyclability of Al/Al_2O_3 NPs.

Scheme 2. A provisional mechanism for the synthesis of dihydroquinazoline in the presence of Al/Al_2O_3 NPs.



Philips X-pert X-ray powder diffraction (XRD) diffractometer was employed for characterization of nanoparticles.

Fabrication of Al/Al_2O_3 NPs. Nanoparticles used in this work were fabricated through arc discharge. The electrodes were customized by cutting commercial 2 mm diameter rather pure aluminum rods (95.50%) into 40 mm length segments. A current of 100 A was passed through the electrodes in ethylene glycol, until visible explosions occurred (0.01 – 1s). To maintain a stable current discharge, with an average voltage of 25 V, the cathode-anode gap was set at $\sim$ 1 mm with an angle of 85°.

General procedure for the synthesis of hydroquinazolinone. Prepared Al/Al_2O_3 NPs (0.036 g) was stirred for 2 min with isatoic anhydride (0.163 g, 1 mmol), aromatic aldehyde (1 mmol), and ammonium acetate at room temperature. Then the mixture was heated in a paraffin bath at 115°C for different periods of time (Table 1). After completion of the reaction (monitored by thin-layer chromatography, TLC; *n*-hexane and EtOAc, 2:1), excess ammonium acetate was washed away by water (5 mL). Subsequently the hydroquinazolinone products were crystallized from ethanol.

Spectral data for some compounds. ***4-(1,2,3,4-tetrahydro-4-oxoquinazolin-2-yl)benzonitrile (5c).*** This compound was obtained as a white crystalline solid, mp 350 – 351°C (Lit. mp 350 – 351 [19]), IR: 1602, 1677, 2225, 3027, 3124, 3169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.84 (s, 1H, CH), 7.55 (t, J = 6.0 Hz, CH), 7.76 (d, J = 6.0 Hz, 1H, CH), 7.87 (m, 1H, CH), 8.02 (d, J = 6.0 Hz, 2H, CH), 8.16 (d, J = 6.0 Hz, 1H, CH), 8.32 (d, J = 6.0 Hz, 2H, CH), 12.7 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-*d6*): δ = 65.5, 113.6, 118.3, 121.2, 125.9, 127.2, 127.7, 128.6, 132.5, 134.7, 136.9, 150.9, 162.1; MS (EI): m/e = 249 (M^+), 247, 119, 92, 50.

2,3-dihydro-2-(3-nitrophenyl)quinazolin-4(1H)-one (5o). This compound was obtained as an yellow crystalline solid, mp 180–182°C (Lit. mp 180 – 182 [19]), IR: 1608, 2910, 3050, 3245, 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.66 (t, 1H, J = 6.0 Hz, CH), 6.77 (d, 1H, J = 6.0 Hz, CH), 7.26 (d, t, J_1 = 1.2 *Hz*, J_2 = 9.0 Hz, 1H, CH), 7.33 (s, 1H, NH), 7.59 (d, 1H, J = 9.0 Hz, CH), 7.69 (t, J = 6.0 Hz, 1H, CH), 7.83 (m, 1H, CH), 7.92 (d, 1H, J = 9.0 Hz, CH), 8.19 (d, 1H, J = 6.0 Hz, 8.34 (s, 1H, CH), 8.54 (s, 1H, NH); ^{13}C NMR (75MHz, DMSO-*d6*): δ = 65.1, 114.6, 114.9, 117.5, 121.6, 122.7, 123.3, 125.9, 127.4, 131.3, 133.4, 133.6, 134.7, 144.3, 144.3, 147.3, 147.7, 163.3; MS (EI): m/e = 269 (M^+), 221, 147, 120, 92, 65, 39.

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