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CATION-EXCHANGE RESIN AS AN EFFICIENT HETEROGENEOUS CATALYST FOR ONE-POT THREE-COMPONENT SYNTHESIS OF 2,3-DIHYDRO-4(1*H*)-QUINAZOLINONES

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Various mono- and disubstituted 2,3-dihydro-4(1H)-quinazolinones were synthesized efficiently by a one-pot three-component condensation of isatoic anhydride, aromatic aldehydes, and ammonium salts or primary amines using a strong acidic cation-exchange resin as the catalyst in EtOH–H_2O solution. The catalyst is cheap, efficient, stable, and reusable under the reaction conditions. The novel method offers several advantages, such as excellent yields, environmentally friendly reaction media, and simple procedure.

Keywords: 2,3-dihydro-4(1*H*)-quinazolinones, isatoic anhydride, cation-exchange resin, multicomponent reactions.

2,3-Dihydroquinazolinones are an important class of heterocycles that exhibit biological activities, such as anti-inflammatory and analgesic [1], antitumor [2], anticancer [3], antibacterial [4], and diuretic activities [5]. In addition, these compounds can easily be oxidized to their corresponding quinazolin-4(3*H*)-ones [6], which are important biologically active heterocyclic compounds too [7, 8].

Different strategies for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones have been described in the literature: a) condensation of anthranilamide with an aldehyde or ketone using *p*-toluenesulfonic acid as a catalyst [3]; b) desulfurization of 2-thioxo-4(3*H*)-quinazolinones [9]; c) reaction of isatoic anhydride with Schiff bases [10]; d) one-step conversion of 2-nitrobenzamides to 2,3-dihydro-4(1*H*)-quinazolinones [11]; e) condensation of anthranilamide with benzil [12]; f) two-step synthesis starting from isatoic anhydride and amines, then annelated with ketones [13].

Multicomponent reactions (MCR) are highly flexible, chemoselective, convergent, and atom efficient processes. In 2005, Salehi and Dabiri first reported MCR preparation methods for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones from isatoic anhydride, aldehydes, and amines [14, 15]. Later some acid catalysts like *p*-toluenesulfonic acid [16], $Zn(PFO)_2$ [17], $Ga(OTf)_3$ [18], ionic liquid [19, 20], $Al(H_2PO_4)_3$ [21], and I_2 [22] were also reported for this conversion. Recently solid acid catalysts, such as Al/Al_2O_3 nanoparticles [23], copolymer-PTSA [24], MCM-41-SO_3H [25], silica sulfuric acid [26], silica-bonded *N*-propylsulfamic acid [27], montmorillonite K-10 [28], and Amberlyst-15 microwave-assisted [29] have also been reported. However, the majority of them suffers from one or more disadvantages: low conversion rate, high cost and toxicity of the

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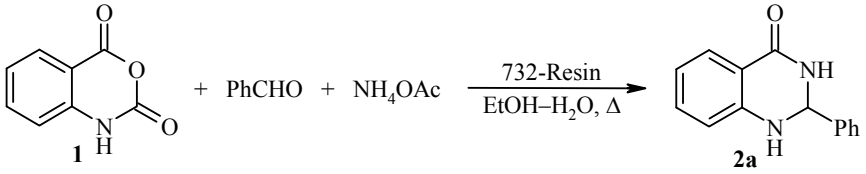
solvent, and the need to use additional microwave irradiation. As a part of our study towards the synthesis of highly substituted heterocycles and the application of solid acid catalysts, we wish to report an efficient procedure for the synthesis of mono- and disubstituted 2,3-dihydro-4(1*H*)-quinazolinones *via* a one-pot condensation of isatoic anhydride, aldehydes, and ammonium salts or primary amines in the presence of a strong acid cation-exchange resin (732-resin) under classical heating conditions.

At the outset, to optimize the reaction conditions, we carried out the reaction of isatoic anhydride (**1**) (5.5 mmol) with benzaldehyde (5.0 mmol) and ammonium acetate (5.5 mmol) as a model reaction in the presence of different amounts of solvent and catalyst under reflux (Table 1). The reactions were carried out in pure water, EtOH, or EtOH–H_2O. After several runs, the results showed that the EtOH–H_2O, 1:3, system was the best choice.



The recyclability of the catalyst was investigated also by using the above model reaction. After completion of the reaction, the resin catalyst was filtered, washed and dried. Then, the recycled catalyst was used for further runs and its catalytic activity did not show any decrease even after four runs (entries 9–12).

Next, we applied the optimal reaction conditions to synthesize monosubstituted 2,3-dihydro-4(1*H*)-quinazolinones **2a–i**. In order to compare the efficiency of ammonium salts, the reactions were carried out using ammonium acetate, carbonate, and chloride under the same conditions (Table 2). In all cases, ammonium acetate and ammonium carbonate afforded the products in good yields. However, the reaction did not proceed with

TABLE 1. Optimization of the Solvent and the Catalyst for the Synthesis of 2-Phenyl-2,3-dihydro-4(1*H*)-quinazolinone **2a**

Entry	Solvent (ml)	Mass of 732-resin, g	Time, h	Yield, %
1	EtOH (5)	0.00	2.0	39
2	EtOH (5)	0.03	2.0	62
3	EtOH (5)	0.06	2.0	70
4	EtOH (5)	0.12	2.0	64
5	H_2O (5)	0.06	2.0	52
6	EtOH–H_2O = 1:1 (5)	0.06	1.0	68
7	EtOH–H_2O = 3:1 (5)	0.06	2.0	65
8	EtOH–H_2O = 1:3 (5)	0.06	1.0	84
9	EtOH–H_2O = 1:3 (3)	0.06	1.0	87
10	EtOH–H_2O = 1:3 (3)	0.06	1.0	85*
11	EtOH–H_2O = 1:3 (3)	0.06	1.0	87*[2]
12	EtOH–H_2O = 1:3 (3)	0.06	1.0	86*[3]
13	—	0.06	1.0	76*[4]

* Catalyst of entry 9 was reused for the first time.
*[2] Catalyst of entry 9 was reused for the second time.
*[3] Catalyst of entry 9 was reused for the third time.
*[4] Reaction temperature was kept at 90°C.

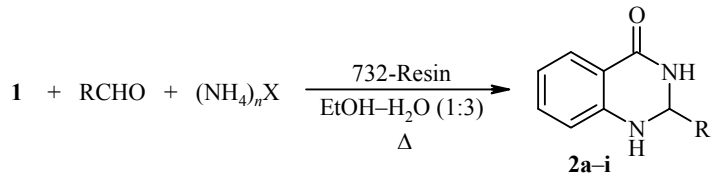


TABLE 2. Cation-exchange Resin-catalyzed Synthesis of 2-Substituted 2,3-Dihydro-4(1*H*)-quinazolinones **2a–i**

Com-pound	R	$(NH_4)_nX$	Time, h	Yield, %	Mp, °C
2a	Ph	NH_4OAc	1.0	87	218-220 (218-220 [28])
		$(NH_4)_2CO_3$	0.7	95	—
		NH_4Cl	8.0	0	—
2b	$2\text{-}O_2NC_6H_4$	NH_4OAc	4.0	93	192-194 (190-192 [30])
		$(NH_4)_2CO_3$	2.5	92	
2c	$3\text{-}O_2NC_6H_4$	NH_4OAc	2.0	94	197-199 (190-192 [30])
		$(NH_4)_2CO_3$	5.0	92	
2d	$4\text{-}O_2NC_6H_4$	NH_4OAc	3.0	93	198-200 (198-200 [30])
		$(NH_4)_2CO_3$	2.0	95	
2e	$2\text{-}ClC_6H_4$	NH_4OAc	2.0	80	202-204 (203-205 [30])
		$(NH_4)_2CO_3$	2.0	86	
2f	$4\text{-}ClC_6H_4$	NH_4OAc	1.0	92	204-206 (205-206 [18])
		$(NH_4)_2CO_3$	0.7	89	
2g	$4\text{-}MeC_6H_4$	NH_4OAc	0.5	90	222-224 (225-227 [31])
		$(NH_4)_2CO_3$	0.7	87	
2h	$4\text{-}MeOC_6H_4$	NH_4OAc	1.0	94	177-179 (178-180 [28])
		$(NH_4)_2CO_3$	3.0	85	
2i	$4\text{-}Me_2NC_6H_4$	NH_4OAc	0.5	86	207-209 (206-208 [30])
		$(NH_4)_2CO_3$	1.0	85	

ammonium chloride. Aromatic aldehydes were found to be effective substrates. All the products **2a**–**i** were known compounds and were identified by comparing their physical and spectral data with those of authentic samples [18, 28, 30, 31].

Disubstituted 2,3-dihydro-4(1*H*)-quinazolinones **3a**–**m** were also synthesized by treatment of isatoic anhydride with aromatic aldehydes and primary amines in the presence of 732-resin in refluxing EtOH–H_2O under optimal conditions (Table 3). In general, aromatic aldehydes bearing either electron-donating or electron-withdrawing groups all afforded the corresponding disubstituted 2,3-dihydro-4(1*H*)-quinazolinones in good yields. Further, this three-component reaction also proceeded very smoothly when aliphatic amines were used.

According to the reported mechanism in the literature [18], we propose a plausible mechanism for the strong acidic cation-exchange resin-catalyzed preparation of quinazolinones. Taking the synthesis of 2,3-di-substituted 2,3-dihydro-4(1*H*)-quinazolinones **3** as an example, first, isatoic anhydride **1** is activated by H^+ followed by the *N*-nucleophilic attacks of amine on the carbonyl. After loss of carbon dioxide, *N*-substituted 2-aminobenzamide **4** is generated. Meanwhile, H^+ increases the electrophilic character of the aldehydes.

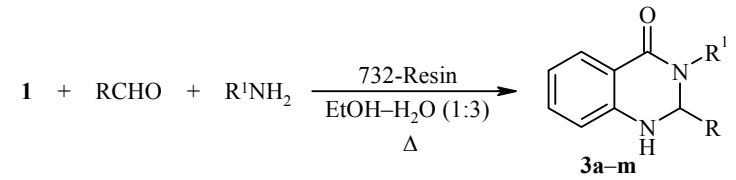
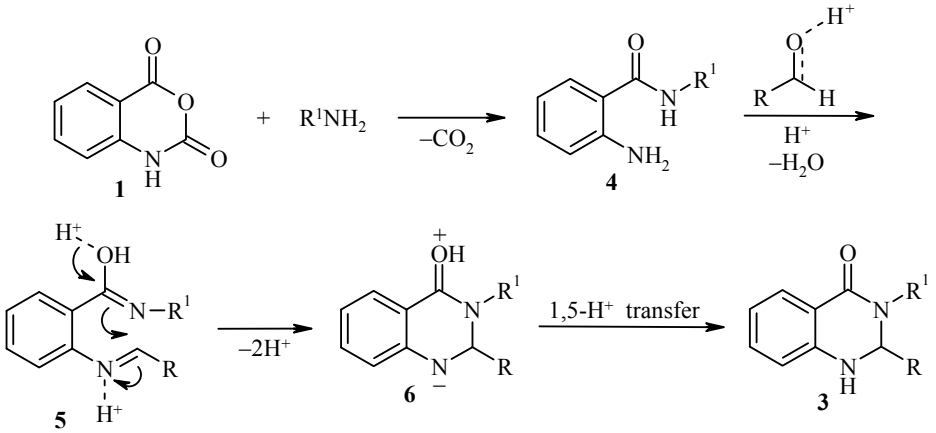


TABLE 3. Cation-exchange Resin-catalyzed Synthesis of 2,3-Disubstituted 2,3-Dihydro-4(1*H*)-quinazolinones **3a–m**

Compound	R	R^1	Time, h	Yield, %	Mp, °C
3a	Ph	Ph	1.5	91	210-212 (214-215 [18])
3b	4-ClC_6H_4	Ph	2.0	98	224-226 (219-220 [18])
3c	4-$MeOC_6H_4$	Ph	1.0	95	205-207 (204-205 [17])
3d	Ph	4-ClC_6H_4	2.0	93	206-208 (210-212 [17])
3e	Ph	4-MeC_6H_4	1.5	93	195-197 (196-199 [17])
3f	4-$O_2NC_6H_4$	4-MeC_6H_4	1.0	92	205-208
3g	4-$O_2NC_6H_4$	Me	0.2	80	207-209
3h	Ph	Et	6.0	82	133-136 (134-137 [28])
3i	3-$O_2NC_6H_4$	Et	3.0	88	178-180 (176-178 [28])
3j	4-ClC_6H_4	Et	6.0	78	132-134 (132-135 [28])
3k	Ph	*n*-Pr	6.0	94	128-130
3l	Ph	*n*-Bu	6.0	74	120-122 (120-122 [17])
3m	Ph	$PhCH_2$	6.0	90	157-159

Subsequently, the activated aldehyde reacts with compound **4** to afford intermediate **5**. The imine fragment in intermediate **5** is activated by H^+. Thus, intermediate **5** could convert to intermediate **6** by an intramolecular cyclization. Finally, disubstituted 2,3-dihydro-4(1*H*)-quinazolinones **3** could be formed by a 1,5-proton transfer of compound **6**.



Thus, we have developed an efficient one-pot procedure for the synthesis of structurally diverse mono- and disubstituted 2,3-dihydro-4(1*H*)-quinazolinones by a three-component condensation of isatoic anhydride, aromatic aldehydes, and ammonium salts or primary amines in the presence of cation-exchange 732-resin in EtOH–H_2O. The catalyst could be easily recovered and reused for at least four cycles without any loss of activity. We believe that the present methodology could be an important addition to the existing methodologies.

EXPERIMENTAL

IR spectra were recorded on a Varian Scimitar 2000 series Fourier Transform instrument using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-500 spectrometer in DMSO-d_6 using TMS as internal standard. Mass spectra were obtained with an Agilent 1100 series LC/MSD VL ESI instrument, electrospray ionization (ESI). Elemental analyses were carried out on an EA 2400II elemental analyzer (PerkinElmer). Melting points were determined using an RD-II micromelting point apparatus (Tianjin Tianguang Optical Instrument Limited Company). The progress of the reactions was monitored by TLC using silica gel polygram SIL G/UV 254 plates and *n*-hexane–EtOAc, 2:1, as eluent.

The catalyst used in this study was a commercial strong acid cation-exchange 732-resin and was obtained from Tianjin Guangfu Fine Chemical Research Institute (China). It is based on a styrene–divinylbenzene copolymer and contains sulfonic acid groups. It had the following properties: exchange capacity (mmol/g [H^+])≥4.2, bead size 0.3–1.2 mm (≥95%), moisture content 46–52%, true density 1.24–1.28 g/ml, apparent density 0.77–0.87 g/ml.

One-pot Synthesis of 2,3-Dihydro-4(1*H*)-quinazolinones 2a–i and 3a–m (General Method). A stirred mixture of isatoic anhydride (**1**) (0.90 g, 5.5 mmol), aldehyde (5.0 mmol), ammonium salt or primary amine (5.5 mmol) and 732-resin (0.06 g) in EtOH–H_2O (1:3 (v/v), 3 ml) was refluxed for an appropriate time as indicated in Tables 2 and 3. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled to room temperature, and hot EtOH (25 ml) was added. The catalyst was filtered, washed with hot EtOH, and dried. The pure product was recrystallized from EtOH.

3-(4-Methylphenyl)-2-(4-nitrophenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3f). Pale-blue crystals. IR spectrum, ν, cm^{-1}: 3650, 3030, 2361, 1660, 1594, 1515, 1457, 762. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.41 (1H, s, NH); 8.82 (1H, s, H-2); 8.37 (2H, d, *J* = 8.7, H Ar); 8.20 (2H, d, *J* = 8.7, H Ar); 7.84 (1H, dd, *J* = 1.0, *J* = 6.5, H Ar); 7.62-7.56 (3H, m, H Ar); 7.45 (1H, t, *J* = 7.4, H Ar); 7.36 (1H, d, *J* = 7.8, H Ar); 7.12 (2H, d, *J* = 8.3, H Ar); 2.25 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 160.5; 149.1; 148.2; 141.0; 136.3; 132.5; 131.6; 130.2; 129.8; 129.2; 129.1; 126.7; 124.0; 119.5; 119.0; 70.2; 20.3. Mass spectrum, *m/z* (I_{rel}, %): 360 $[M+H]^+$ (100), 361 (25), 358 (7), 227 (8). Found, %: C 70.30; H 4.89; N 11.53. $C_{21}H_{17}N_3O_3$. Calculated, %: C 70.18; H 4.77; N 11.69.

3-Methyl-2-(4-nitrophenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3g). Yellow crystals. IR spectrum, ν, cm^{-1}: 3309, 2360, 1644, 1599, 1521, 1457, 1407, 763. 1H NMR spectrum, δ, ppm (*J*, Hz): 8.74 (1H, s, NH); 8.37 (3H, d, *J* = 8.5, H-2, H Ar); 8.20 (2H, d, *J* = 8.6, H Ar); 7.76 (1H, d, *J* = 6.9, H Ar); 7.53 (1H, t, *J* = 6.9, H Ar); 7.35 (1H, t, *J* = 7.4, H Ar); 7.27 (1H, d, *J* = 7.8, H Ar); 2.80 (3H, d, *J* = 4.6, CH_3). ^{13}C NMR spectrum, δ, ppm: 160.2; 149.0; 148.2; 141.1; 131.2; 129.9; 129.7; 129.2; 126.5; 124.0; 119.0; 70.1; 26.1. Mass spectrum, *m/z* (I_{rel}, %): 284 $[M+H]^+$ (100), 282 (22). Found, %: C 63.44; H 4.55; N 14.97. $C_{15}H_{13}N_3O_3$. Calculated, %: C 63.60; H 4.63; N 14.83.

2-Phenyl-3-(*n*-propyl)-2,3-dihydro-4(1*H*)-quinazolinone (3k). White crystals. IR spectrum, ν, cm^{-1}: 3303, 3065, 2361, 1630, 1588, 1507, 1458, 748. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.65 (1H, dd, *J* = 1.2, *J* = 6.5, NH); 7.34-7.27 (6H, m, H Ar); 7.18 (1H, dt, *J* = 1.5, *J* = 6.8, H Ar); 6.66-6.62 (2H, m, H Ar); 5.83 (1H, d, *J* = 2.5, H-2); 3.86-3.81 (1H, m) and 2.75-2.69 (1H, m, C$\underline{H}_2$CH_2CH_3); 1.63-1.41 (2H, m, C$\underline{H}_2$CH_3); 0.82 (3H, t, *J* = 7.4, CH_3). ^{13}C NMR spectrum, δ, ppm: 162.1; 146.2; 141.2; 133.0; 128.4; 128.2; 127.3; 126.0; 117.0; 115.0; 114.2; 70.1; 46.0; 20.6; 11.1. Mass spectrum, *m/z* (I_{rel}, %): 267 $[M+H]^+$ (100), 268 (19). Found, %: C 76.81; H 6.73; N 10.39. $C_{17}H_{18}N_2O$. Calculated, %: C 76.66; H 6.81; N 10.52.

3-Benzyl-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (3m). White crystals. IR spectrum, ν, cm^{-1}: 3401, 3023, 2361, 1633, 1580, 1502, 1447, 749. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.70 (1H, dd, *J* = 1.4, *J* = 6.4, NH); 7.36-7.20 (12H, m, H Ar); 6.69-6.63 (2H, m, H Ar); 5.74 (1H, d, *J* = 2.6, H-2); 5.34 (1H, d, *J* = 15.4) and 3.83 (1H, d, *J* = 15.4, C$\underline{H}_2$Ph). ^{13}C NMR spectrum, δ, ppm: 162.3; 146.2; 140.5; 137.4; 133.3; 128.5; 128.4; 127.6; 127.4; 127.1; 126.1; 117.2; 114.6; 114.3; 69.8; 47.1. Mass spectrum, *m/z* (I_{rel}, %): 315 $[M+H]^+$ (100), 316 (24). Found, %: C 80.34; H 5.86; N 8.77. $C_{21}H_{18}N_2O$. Calculated, %: C 80.23; H 5.77; N 8.91.

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