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ORIGINAL PAPER

Efficient synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using copper benzenesulfonate as a reusable catalyst in aqueous solution

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Abstract Copper benzenesulfonate was found to be an effective catalyst for one-pot three-component cyclocondensation of isatoic anhydride, aromatic aldehydes, and ammonium salts or primary amines in aqueous solution to afford the corresponding mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in good yields. The catalyst is reusable and could be recycled for several times without distinct decrease in its efficiency.

Keywords 2,3-Dihydroquinazolin-4(1*H*)-ones · Metal benzenesulfonate · Multicomponent reaction · Isatoic anhydride · Heterocycle

Introduction

2,3-Dihydroquinazolinones are a class of heterocycles that have attracted much attention because they are reported to possess a wide range of pharmacological properties such as anti-inflammatory and analgesic [1], antitumor [2], anticancer [3], antibacterial [4], and diuretic activities [5]. In addition, these compounds can be easily oxidized to the corresponding quinazolin-4(3*H*)-ones [6], which are important biologically active heterocyclic compounds, too [7, 8]. Therefore, various procedures have been developed for preparing this important class of compounds. The usual procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones involves condensation of anthranilamide with an aldehyde or ketone using *p*-toluenesulfonic acid as a catalyst [3]. Other methods including desulfurization of 2-thioxo-4(3*H*)-quinazolinones [9], one-step conversion of 2-nitrobenzamides to 2,3-dihydroquinazolin-4(1*H*)-ones [10], reaction of isatoic anhydride with Schiff bases [11], condensation of anthranilamide with benzyl [12], and a two-step synthesis starting from isatoic anhydride and amines, followed by annulation with ketones [13] were also reported.

In 2005, Salehi and Dabiri [14, 15] reported a more attractive and atom-efficient strategy for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones, which involves a one-pot three-component reaction of isatoic anhydride, aldehydes, and amines. Multicomponent reactions (MCRs) are especially attractive synthesis strategies because the products are formed in a single step and diversity could be achieved simply by varying the reacting components. Therefore, MCRs have provided a very efficient way to access heterocycles in the past decade. So far only a few acid catalysts, e.g., *p*-toluenesulfonic acid [16], silica sulfuric acid [17], zinc(II) perfluorooctanoate [18], gallium(III) triflate [19], ionic liquid [20, 21], $Al(H_2PO_4)_3$ [22], I_2 [23], montmorillonite K-10 [24], Amberlyst-15 [25], Al/Al_2O_3 and Fe_3O_4 nanoparticles [26, 27], *p*-toluenesulfonic acid–paraformaldehyde copolymer [28], MCM-41-SO_3H [29], and silica-bonded *N*-propylsulfamic acid [30], have been reported to accomplish this three-component reaction. However, some of these methods have certain drawbacks such as long reaction times, low yields, use of expensive and large amounts of catalyst, and high reaction temperatures. Therefore, it is desirable to develop a green and efficient protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

In recent years, metal sulfonates have received considerable attention as inexpensive and recyclable catalysts [31–34]. Low toxicity, easy preparation, moisture resistance, and air tolerance are their common features.

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Continuing our work on the application of metal sulfonates in organic reactions, we now report a copper benzenesulfonate ($Cu[C_6H_5SO_3]_2{\cdot}6H_2O$)-catalyzed one-pot MCR of isatoic anhydride, aromatic aldehydes, and ammonium salts or primary amines for the synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in aqueous solution (Scheme 1).

Results and discussion

The three-component reaction of isatoic anhydride (5.5 mmol), benzaldehyde (5 mmol), and ammonium acetate (5.5 mmol) was selected as a model reaction to optimize the reaction conditions (Table 1). The catalytic activity of 11 metal benzenesulfonates in the model reaction was examined (entries 2–12). The reactions catalyzed by all metal benzenesulfonates gave moderate to high yields. $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$ was relatively cheaper and gave the best result so it was chosen as the most suitable catalyst. In contrast, the reaction was slower and afforded a lower yield in the absence of catalyst (entry 1).

Next, we examined the effect of different solvents on this conversion (entries 13–18). Considering water and ethanol are green solvents, we tried to carry out the reaction in pure H_2O, ethanol, and in a mixed solvent system ($EtOH/H_2O$). The $EtOH/H_2O$ (1:3, v/v) system was found to be the best for the catalytic reactions in terms of yield, and the optimal volume is 3 cm^3 (entry 17).

Scheme 1

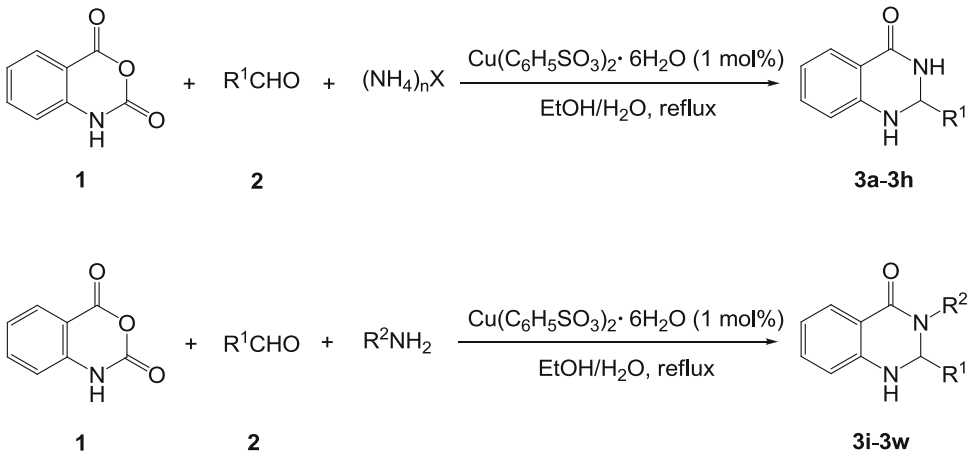


Table 1 Reaction of isatoic anhydride, benzaldehyde, and ammonium acetate under various conditions

Entry	Catalyst	Solvent	Solvent/cm^3	Time/h	Yield/%
1	–	EtOH	5	3	43
2	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	EtOH	5	3	79
3	$Ce(C_6H_5SO_3)_3{\cdot}4H_2O$	EtOH	5	3	79
4	$Er(C_6H_5SO_3)_3{\cdot}4H_2O$	EtOH	5	3	79
5	$La(C_6H_5SO_3)_3{\cdot}2H_2O$	EtOH	5	3	78
6	$Pr(C_6H_5SO_3)_3{\cdot}2H_2O$	EtOH	5	3	77
7	$Sm(C_6H_5SO_3)_3{\cdot}4H_2O$	EtOH	5	3	76
8	$Ca(C_6H_5SO_3)_2{\cdot}4H_2O$	EtOH	5	3	73
9	$Al(C_6H_5SO_3)_3{\cdot}7H_2O$	EtOH	5	3	72
10	$Co(C_6H_5SO_3)_2{\cdot}6H_2O$	EtOH	5	3	72
11	$Fe(C_6H_5SO_3)_2{\cdot}6H_2O$	EtOH	5	3	72
12	$Zn(C_6H_5SO_3)_2{\cdot}6H_2O$	EtOH	5	3	68
13	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	H_2O	5	2	65
14	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	$EtOH/H_2O = 3:1$[a]	5	2	70
15	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	$EtOH/H_2O = 1:1$	5	1	80
16	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	$EtOH/H_2O = 1:3$	5	1	94
17	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	$EtOH/H_2O = 1:3$	3	0.5	93, 92, 90, 88[b]
18	$Cu(C_6H_5SO_3)_2{\cdot}6H_2O$	–	–	0.5	81[c]

All reactions were carried out under reflux, the amount of metal benzenesulfonate is 1 mol%

[a] Volume ratio (v/v)

[b] The catalyst was reused for four runs

[c] Reaction temperature was kept at 90 °C

The reusability is one of the important properties of $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$. After the reaction, the product precipitated from the reaction mixture and was separated by simple filtration. The catalyst remaining in the aqueous phase could be recovered by evaporating the filtrate and then reused directly with fresh substrates under identical conditions without further purification. The results showed that $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$ could be used for four runs without a noticeable drop in its catalytic activity (entry 17).

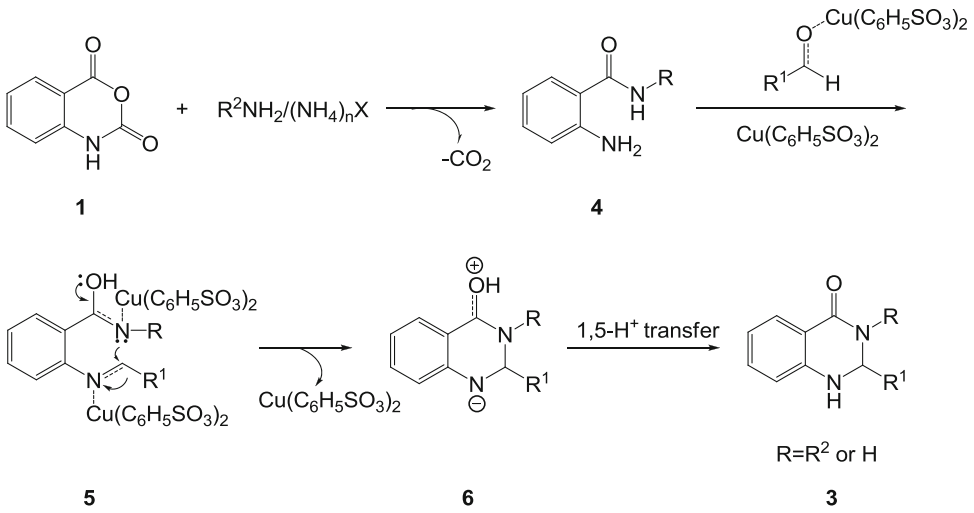
To explore the scope and limitation of this method, the $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$-catalyzed reaction was extended to isatoic anhydride, various aromatic aldehydes, and ammonium salts or primary amines (Table 2). As expected, this reaction proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aromatic aldehydes with either electron-withdrawing or electron-donating groups were investigated. The property and position of substitutents on the aromatic ring had no obvious effect on the yield. Aromatic and aliphatic primary amines worked well under the reaction conditions.

We also examined reactions of aromatic heterocyclic aldehydes, unsaturated aldehydes, and aliphatic aldehydes with isatoic anhydride and ammonium salts or primary amines, but no desired product was obtained after 6 h. Subsequently, ammonium chloride was also employed as the source of ammonia for synthesizing 2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone under the optimized reaction conditions. However, only a trace of the corresponding product was produced after 6 h.

Table 2 One-pot three-component reaction of isatoic anhydride, aromatic aldehydes, and ammonium salts or primary amines catalyzed by $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$

Entry	R^1	X/R^2	Product	Time/h	Yield/%	M.p./°C	
						Found	Reported
1	C_6H_5	CO_3	**3a**	0.7	92	217–219	218–220 [24]
		OAc		0.5	93		
2	3-$NO_2C_6H_4$	CO_3	**3b**	0.7	87	195–196	190–192 [35]
		OAc		1.2	91		
3	4-$NO_2C_6H_4$	CO_3	**3c**	0.8	93	199–201	198–200 [35]
		OAc		1.5	87		
4	2-ClC_6H_4	CO_3	**3d**	0.8	90	208–210	203–205 [35]
		OAc		1.0	88		
5	4-ClC_6H_4	CO_3	**3e**	0.7	86	206–207	205–206 [19]
		OAc		0.5	93		
6	4-MeC_6H_4	CO_3	**3f**	0.3	89	224–226	225–227 [36]
		OAc		0.5	89		
7	4-$MeOC_6H_4$	CO_3	**3g**	0.5	93	184–186	178–180 [24]
		OAc		1.0	91		
8	4-$(CH_3)_2NC_6H_4$	CO_3	**3h**	0.6	82	210–212	206–208 [35]
		OAc		0.5	77		
9	C_6H_5	C_6H_5	**3i**	1.5	91	217–218	214–215 [19]
10	2-ClC_6H_4	C_6H_5	**3j**	2.0	93	217–218	214–217 [14]
11	4-ClC_6H_4	C_6H_5	**3k**	2.0	90	222–224	219–220 [19]
12	4-$CH_3OC_6H_4$	C_6H_5	**3l**	1.2	95	203–205	204–205 [18]
13	C_6H_5	4-ClC_6H_4	**3m**	1.5	84	215–217	210–212 [18]
14	C_6H_5	4-$CH_3C_6H_4$	**3n**	1.0	82	200–202	196–199 [18]
15	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	**3o**	0.7	93	210–212	–
16	4-$NO_2C_6H_4$	Me	**3p**	0.5	84	196–198	–
17	4-ClC_6H_4	Me	**3q**	5.0	71	194–196	190 [24]
18	C_6H_5	Et	**3r**	6.0	69	136–138	134–137 [24]
19	3-$NO_2C_6H_4$	Et	**3s**	5.0	95	181–183	176–178 [24]
20	4-ClC_6H_4	Et	**3t**	6.0	62	132–134	132–135 [24]
21	C_6H_5	*n*-Pr	**3u**	6.0	94	126–127	–
22	C_6H_5	*n*-Bu	**3v**	6.0	72	125–127	120–122 [18]
23	C_6H_5	$C_6H_5CH_2$	**3w**	6.0	93	164–166	163–165 [37]

Scheme 2



We propose the following mechanism to account for the $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$-catalyzed reaction (Scheme 2) [19]. First, isatoic anhydride **1** is activated by $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$ followed by nucleophilic attack of the amine on the carbonyl to generate 2-amino-*N*-substituted benzamide **4** after loss of carbon dioxide. Meanwhile, $Cu(C_6H_5SO_3)_2$ acting as a Lewis acid increases the electrophilic character of the aldehydes. Subsequently, the activated aldehyde reacts with **4** to afford intermediate **5**. The imine moiety in intermediate **5** is also activated by $Cu(C_6H_5SO_3)_2$. Thus, intermediate **5** could convert to intermediate **6** by an intramolecular cyclization. Finally, mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones **3** could be formed by a 1,5-proton transfer of **6**.

In summary, $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$ has been demonstrated to be an efficient catalyst for the one-pot three-component reaction of isatoic anhydride, aromatic aldehydes, and ammonium salts or primary amines in aqueous solution. The catalyzed reaction produced mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in high yields. Compared with *p*-toluenesulfonic acid [16], $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$ can be recycled several times and the amount of catalyst required can be decreased to only 1 mol%. The method offers several advantages including a nontoxic and recyclable catalyst, clean and mild reaction conditions, a wide range of substrates, and simple workup procedure.

Experimental

Melting points were determined using an RD-II micro-melting point apparatus. Infrared spectra were recorded on a Varian Scimitar 2000 series Fourier transform instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on an EA 2400II elemental analyzer (Perkin Elmer).

General procedure for the synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones ***3***

A stirred mixture of isatoic anhydride (5.5 mmol), aromatic aldehyde (5 mmol), ammonium salt or primary amine (5.5 mmol), and $Cu(C_6H_5SO_3)_2{\cdot}6H_2O$ (0.05 mmol) in 3 cm^3 EtOH/H_2O (1:3, v/v) was refluxed for the time indicated in Table 2. When the reaction was complete (monitored by TLC), the mixture was cooled to room temperature. The corresponding pure product was obtained by simple filtering, washed with 3 × 10 cm^3 50% aqueous ethanol, and recrystallized from EtOH. The filtrate containing the catalyst was evaporated under reduced pressure to give the recovered catalyst, which could be reused without further treatment. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR, LC/MS, and elemental analysis.

2,3-Dihydro-3-(4-methylphenyl)-2-(4-nitrophenyl)-quinazolin-4(1H)-one (**3o**, $C_{21}H_{17}N_3O_3$)
Pale blue crystals; m.p.: 210–212 °C; IR (KBr): $\bar{\nu}$ = 3,650, 3,030, 2,361, 1,660, 1,594, 1,515, 1,457, 762 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.41 (s, 1H), 8.82 (s, 1H), 8.37 (d, J = 8.7 Hz, 2H), 8.20 (d, J = 8.7 Hz, 2H), 7.84 (dd, J = 1.0, 6.5 Hz, 1H), 7.62–7.56 (m, 3H), 7.45 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 2.25 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 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, 20.4 ppm; LC/MS: *m/z* (%) = 360 ([M + H]$^+$, 100), 361 (25), 358 (7), 227 (8).

2,3-Dihydro-3-methyl-2-(4-nitrophenyl)quinazolin-4(1H)-one (**3p**, $C_{15}H_{13}N_3O_3$)
Yellow crystals; m.p.: 196–198 °C; IR (KBr): $\bar{\nu}$ = 3,309, 2,361, 1,645, 1,600, 1,521, 1,457, 1,407, 763 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.74 (s, 1H), 8.37 (d, J = 8.5 Hz, 3H), 8.20 (d, J = 8.6 Hz, 2H), 7.76 (d, J =

6.9 Hz, 1H), 7.53 (t, $J = 6.9$ Hz, 1H), 7.35 (t, $J = 7.4$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 2.80 (d, $J = 4.6$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 160.2$, 149.0, 148.3, 141.1, 131.2, 129.9, 129.7, 129.2, 126.5, 124.0, 119.0, 70.1, 26.1 ppm; LC/MS: *m/z* (%) = 284 ($[M + H]^+$, 100), 282 (22).

2,3-Dihydro-2-phenyl-3-propylquinazolin-4(1H)-one (**3u**, $C_{17}H_{18}N_2O$)

White crystals; m.p.: 126–127 °C; IR (KBr): $\bar{\nu} = 3{,}303$, 3,065, 2,360, 1,630, 1,588, 1,507, 1,458, 748 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.65$ (dd, $J = 1.2$, 6.5 Hz, 1H), 7.34-7.27 (m, 6H), 7.18 (dt, $J = 1.5$, 6.8 Hz, 1H), 6.66–6.62 (m, 2H), 5.83 (d, $J = 2.5$ Hz, 1H), 3.86–3.81 (m, 1H), 2.75–2.69 (m, 1H), 1.63–1.41 (m, 2H), 0.82 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 162.2$, 146.2, 141.2, 133.0, 128.4, 128.2, 127.3, 126.0, 117.0, 115.0, 114.2, 70.1, 46.0, 20.7, 11.1 ppm; LC/MS: *m/z* (%) = 267 ($[M + H]^+$, 100), 268 (19).

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