Cerous Methanesulfonate Catalyzed Facile Synthesis of 2-Substituted-2,3-dihydro-4(1*h*)-quinazolinones by Grinding Technique

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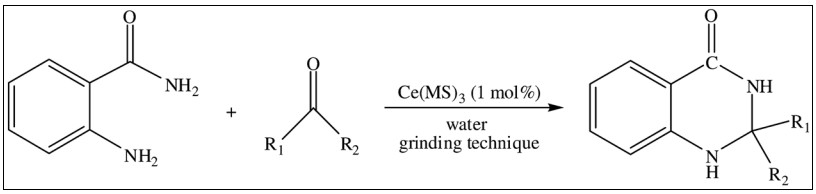

2-Substituted-2,3-dihydro-4(1*H*)-quinazolinones were synthesized in high to excellent yields through direct cyclocondensation of 2-anthranilamide with aldehydes or ketones in the presence of a recyclable cerous methanesulfonate by grinding technique under aqueous conditions.

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INTRODUCTION

2,3-Dihydro-4(1*H*)-quinazolinones are a class of fused heterocycles that have drawn much attention due to their potential biological and pharmaceutical activities such as antibacterial [1], diuretic [2], and anticancer [3]. Some 2,3-dihydro-4(1*H*)-quinazolinones are herbicides and plant-growth regulators [4, 5]. Furthermore, they could be easily oxidized to 2-substituted-4(3*H*)-quinazolinones [6], which are useful as growth inhibitor against leukemia cells [7] and potent poly(ADP-ribose)polymerase-1 inhibitors [8]. Because of the importance of 2,3-dihydro-4(1*H*)-quinazolinones derivatives, the development of environmentally benign, high-yielding, and clean synthesis of them is in demand.

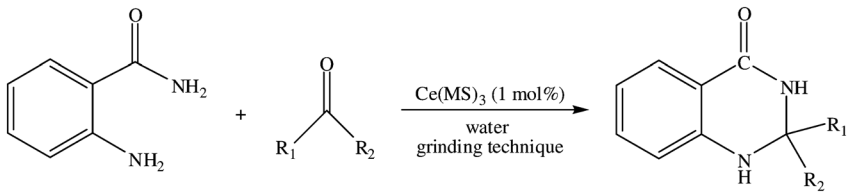
In recent years, a number of methods for preparing 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones have been reported in the literature [9, 10]. The most common approach involves condensation of 2-anthranilamide with structurally diverse aldehydes or ketones in the presence of various catalysts such as *p*-TSA [3], HCl [11], SmI_2 [12], $TiCl_4$-Zn [13], $Sc(OTf)_3$ [14], and NH_4Cl [15]. In addition, some modified procedures were also described. For example, 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones could be synthesized in ionic liquid without additional catalyst [16]. Xu *et al*. carried out these reactions in refluxing 2,2,2-trifluoroethanol [17]. Wang *et al*. also reported that 2,3-dihydro-4(1*H*)-quinazolinones could be obtained with satisfied yields using heteropoly acid as a catalyst at room temperature [18]. Though all of these reactions can obtain the object, some of them associated with certain drawbacks such as costly reagent, harmful solvent, large excess of raw material and catalyst, and low yields. Moreover, all the reported reactions were proceeded under uniform stirring conditions.

Today much emphasis is laid on the development of clean synthetic procedures which avoids toxic and hazardous chemicals and solvents. In our continuous work to explore simple and eco-friendly procedures for the synthesis of organic compounds, grinding technique has drawn our attention because it provides simple manipulation, greater selectivity, shorter reaction periods, and higher product yields. Here, we report first a simple and efficient method for the synthesis of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones via direct cyclocondensation of 2-anthranilamide with aromatic aldehydes or ketones in the presence of 1 mol % (based on 2-anthranilamide) cerous methanesulfonate ($Ce(MS)_3$) by grinding technique under aqueous conditions. (Scheme 1).

RESULTS AND DISCUSSION

At the onset of our research, we investigated the model reaction between 2-anthranilamide and benzaldehyde at room temperature under different reaction conditions (Table 1). After screening four metal methanesulfonates, $Ce(MS)_3$ was determined to be the most effective catalyst, because it provided the highest yield of the desired product (entries 1–4). Compared with the reactions carried out without solvent, the condensation in 1 mL of water provided a higher yield (entry 5). In addition, the amount of catalyst affected the reaction significantly. We observed that 1 mol % $Ce(MS)_3$ could catalyze the reaction efficiently and diminishing the amount of catalyst decreased the yields (entries 5 and 7). Further, the reusability of $Ce(MS)_3$ was investigated. When the reaction was completed, the reaction mixture was washed with water. The catalyst remaining in

Scheme 1



1 **2** **3a~3p**

aqueous phase could be recovered by evaporating the filtrate. Then $Ce(MS)_3$ was recovered and reused for four consecutive reactions (entry 5). It demonstrated that $Ce(MS)_3$ was water-tolerant and recyclable for this condensation.

In order to examine the scope and limitation of this approach, we applied these optimal reaction conditions to a variety of aldehydes and ketones. The results were illustrated in Table 2. Generally, the cyclocondensation reaction proceeded well and afforded the desired products **3a**–**3n** in good to excellent yields. The reaction was compatible with a variety of electron-donating and electron-withdrawing substituents in the aromatic aldehydes. Steric hindrance seems to have no effects on the efficiency of this transformation. Besides aromatic aldehydes, cyclohexanone (**3n**) also yielded the desired product. However, heteroaryl aldehyde (**3o**) and aliphatic aldehyde (**3p**) could not afford the corresponding products even if prolonged the reaction time or elevated the reaction temperature.

In order to investigate the effect of grinding step on the yield, we also carried out a reaction of 2-anthranilamide with 2-nitrobenzaldehyde without grinding, that is to say we heated the ungrounded reaction mixture at 60°C in the presence of catalyst and water directly after weighting. After 0.5 h, only 23% yield was produced. The result demonstrated that the grinding technique is very efficient for synthesizing the title compounds.

A possible mechanism for this transformation is proposed in Scheme 2 [21]. The first step may be involves the condensation of 2-anthranilamide **1** with aldehyde/ketone **2** promoted by $Ce(MS)_3$ to produce intermediate **4**. The parts of carbonyl and imine in intermediate **4** could be activated by Ce^{3+}. Thus, intermediate **4** could be converted to intermediate **5** by intramolecular nucleophile attack of the nitrogen on imine carbon. Subsequently, 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones **3** could formed by a 1,5-proton transfer of **5**.

Table 1

Screening of different reaction conditions for the condensation of 2-anthranilamide with benzaldehyde.[a]

Entries	Catalyst (mol %)	Solvent (mL)	Yield (%)
1	$Cu(MS)_2{\cdot}4H_2O$ (1)	None	52
2	$Al(MS)_3{\cdot}4H_2O$ (1)	None	70
3	$La(MS)_3{\cdot}2H_2O$ (1)	None	78
4	$Ce(MS)_3{\cdot}2H_2O$ (1)	None	87
5	$Ce(MS)_3{\cdot}2H_2O$ (1)	H_2O (1)	91, 89, 88, 85
6	$Ce(MS)_3{\cdot}2H_2O$ (1)	H_2O (2)	86
7	$Ce(MS)_3{\cdot}2H_2O$ (0.5)	H_2O (1)	46
8	None	H_2O (1)	11

[a]Grinding for 0.3 h at room temperature.

CONCLUSIONS

In conclusion, a novel and environmentally benign method for synthesizing 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones was achieved by using aqueous grinding technique in the presence of $Ce(MS)_3$. It features simple operation, short reaction time, stoichiometric raw materials, easy recyclable catalyst, mild reaction conditions, and good yields. It makes a valuable contribution to the synthesis of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones.

EXPERIMENTAL

Melting points were determined using RY-1 micromelting point apparatus. Infrared spectra were recorded on Scimitar 2000 series Fourier Transform instrument of VARIAN. ^{1}H NMR spectra were recorded on Bruker AV-500 spectrometer in DMSO-d_6 using TMS as an internal standard. Mass spectra were obtained with an Agilent 1100 series LC/MSD VL ESI instrument. Elemental analyses were carried out on EA 2400II elemental analyzer (PerkinElmer) and agreed favorably with the calculated values. Methanesulfonates were synthesized according to ref. 22.

General procedure for the synthesis of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones (3). To a equivalent mixture of a 2-anthranilamide **1** (5 mmol) and an aldehyde or ketone **2** (5 mmol) was added $Ce(MS)_3$ (0.05 mmol) and H_2O (1 mL) in a mortar and ground well with a pestle at room temperature. Then the mixture (except **3a**) was heated at 60°C for appropriate time under atmosphere. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1/1), the reaction mixture was cooled to room temperature. Water (15 mL) was added to the reaction mixture, and the crystalline products were collected by filtration to give the crude product. The crude products thus obtained were crystallized from EtOH to give pure products. The catalyst remaining in the aqueous phase could be recovered by evaporating the filtrate. The pure products were identified by mp, IR, ^{1}H NMR,

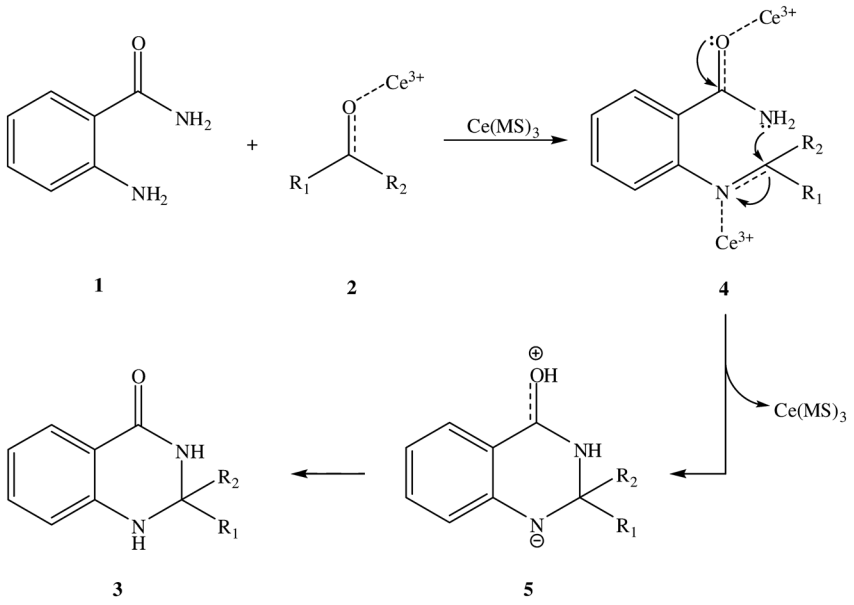
Table 2

Reactions of 2-anthranilamide with diverse aldehydes or ketones in the presence of $Ce(MS)_3$.

Entries	R_1	R_2	Time (h)[a+b]	Yield (%)	Mp (°C) Found	Mp (°C) Reported
3a	C_6H_5-	H	0.3 + 0	91	225–227	224–226 19]
3b	2-NO_2-C_6H_4-	H	0.2 + 0.5	93	190–192	191–194 [19]
3c	3-NO_2-C_6H_4-	H	0.2 + 1.5	85	200–202	-
3d	4-NO_2-C_6H_4-	H	0.2 + 0.5	92	197–200	-
3e	2-Cl-C_6H_4-	H	0.2 + 0.5	94	203–205	-
3f	4-Cl-C_6H_4-	H	0.2 + 0.5	93	206–207	205–206 [17]
3g	2,4-Cl_2-C_6H_3-	H	0.2 + 0.5	90	174–176	181–185 [20]
3h	4-CH_3-C_6H_4-	H	0.2 + 0.5	85	223–225	225–227 [12]
3i	4-OCH_3-C_6H_4-	H	0.2 + 0.5	92	183–185	180–182 [12]
3j	2-OH-C_6H_4-	H	0.2 + 0.5	91	221–223	–
3k	4-OH-C_6H_4-	H	0.2 + 1.0	84	217–219	–
3l	4-OH-3-OCH_3-C_6H_3-	H	0.2 + 0.5	93	226–227	–
3m[c]	4-$(CH_3)_2N$-C_6H_4-	H	0.2 + 4.0	93	206–208	–
3n[c]	-$(CH_2)_5$-(spirocyclohexanyl)	–	0.2 + 3.0	86	221–223	225–226 [17]
3o	2-Furyl-	H	0.2 + 20	0	–	–
3p	CH_3CH_2-	H	0.2 + 20	0	–	–

[a]Grinding time at room temperature.
[b]Time for reaction mixture kept at 60°C.
[c]The molar ratio of 2-anthranilamide to aldehyde/ketone is 1:1.3.

Scheme 2



MS, and elemental analysis. The characteristic data of some new 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones are given below:

2-(3-Nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone (3c). Yellow solid. IR (KBr): 3337, 3147, 1673, 1635, 1589, 1526, 1447, 1386, 1187, 971, 772 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.76 (d, 2H, *J* = 7.4 Hz, ArH), 8.42 (t, 2H, *J* = 7.5 Hz, ArH), 7.97 (brs, 1H, NH—CO), 7.87 (dt, 2H, *J* = 6, 7.5 Hz, ArH), 7.62 (brs, 1H, NH), 7.57 (t, 1H, *J* = 6.2 Hz, ArH), 7.38 (t, 1H, *J* = 7.5 Hz, ArH), 7.26 (s, 1H, CH). MS (ESI): *m/z* (%) 270 (M^++H, 100). Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.31; H, 4.09; N, 15.68.

2-(4-Nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone (3d). Yellow solid. IR (KBr): 3363, 3291, 1661, 1613, 1520, 1485, 1348, 1162, 1012, 859, 753 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.53 (s,

1H, NH—CO), 8.27 (d, 2H, *J* = 8.6 Hz, ArH), 7.76 (d, 2H, *J* = 8.6 Hz, ArH), 7.64 (d, 1H, *J* = 7.6 Hz, ArH), 7.33 (s, 1H, NH), 7.29 (t, 1H, *J* = 7.4 Hz, ArH), 6.79 (d, 1H, *J* = 8.1 Hz, ArH), 6.71 (t, 1H, *J* = 7.4 Hz, ArH), 5.93 (s, 1H, CH). MS (ESI): *m/z* (%) 270 (M^++H, 100). Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.63; H, 4.15; N, 15.52.

2-(2-Chlorophenyl)-2,3-dihydro-4(1H)-quinazolinone (3e). White solid. IR (KBr): 3362, 3196, 1647, 1614, 1503, 1330, 1188, 1054, 853, 745 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.21 (s, 1H, NH—CO), 7.67 (d, 2H, *J* = 7.8 Hz, ArH), 7.50−7.47 (m, 1H, ArH), 7.41−7.38 (m, 2H, ArH), 7.27 (t, 1H, *J* = 6.8 Hz, ArH), 7.01 (s, 1H, NH), 6.77 (d, 1H, *J* = 7.8 Hz, ArH), 6.73 (dd, 1H, *J* = 6.8, 7.9 Hz, ArH), 6.14 (s, 1H, CH). MS (ESI): *m/z* (%) 259 (M^++H, 100). Anal. Calcd. for $C_{14}H_{11}N_2OCl$: C, 65.00; H, 4.29; N, 10.83. Found: C, 65.17; H, 4.24; N, 10.78.

2-(2-Hydroxylphenyl)-2,3-dihydro-4(1H)-quinazolinone (3j). White solid. IR (KBr): 3410, 3157, 1647, 1616, 1507, 1464, 1332, 1161, 843, 744 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.85 (s, 1H, NH—CO), 7.93 (s, 1H, NH), 7.64 (d, 1H, *J* = 7.0 Hz, ArH), 7.36 (d, 1H, *J* = 7.5 Hz, ArH), 7.24 (t, 1H, *J* = 7.1 Hz, ArH), 7.16 (t, 1H, *J* = 7.5 Hz, ArH), 6.88 (d, 1H, *J* = 8.0 Hz, OH), 6.81−6.74 (m, 3H, ArH), 6.68 (t, 1H, *J* = 7.5 Hz, ArH), 6.02 (s, 1H, CH). MS (ESI): *m/z* (%) 241 (M^++H, 100). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.04; N, 11.66. Found: C, 70.14; H, 5.01; N, 11.72.

2-(4-Hydroxylphenyl)-2,3-dihydro-4(1H)-quinazolinone (3k). White solid. IR (KBr): 3338, 3184, 1670, 1605, 1523, 1490, 1288, 1237, 1185, 848, 766 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.52 (s, 1H, NH—CO), 8.14 (s, 1H, NH), 7.64 (d, 1H, *J* = 7.5 Hz, ArH), 7.33 (d, 2H, *J* = 8.5 Hz, ArH), 7.26 (t, 1H, *J* = 7.5 Hz, ArH), 6.94 (t, 1H, *J* = 8.5 Hz, OH), 6.79−6.67 (m, 4H, ArH), 5.67 (s, 1H, CH). MS (ESI): *m/z* (%) 241 (M^++H, 100). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.04; N, 11.66. Found: C, 69.83; H, 5.09; N, 11.73.

2-(4-Hydroxyl-3-methoxylphenyl)-2,3-dihydro-4(1H)-quinazolinone (3l). White solid. IR (KBr): 3389, 3354, 1650, 1610, 1499, 1428, 1157, 1021, 860, 766 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.06 (s, 1H, NH—CO), 8.09 (s, 1H, NH), 7.62 (d, 1H, *J* = 6.5 Hz, ArH), 7.25 (dd, 1H, *J* = 7.2, 8.0 Hz, ArH), 7.09 (s, 1H, ArH), 6.94 (s, 1H, OH), 6.89 (d, 1H, *J* = 6.5 Hz, ArH), 6.77 (t, 2H, *J* = 8.1 Hz, ArH), 6.69 (t, 1H, *J* = 7.4 Hz, ArH), 5.65 (s, 1H, CH), 3.76 (s, 3H, OCH_3). MS (ESI): *m/z* (%) 271 (M^++H, 100). Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.48; H, 5.25; N, 10.43.

2-(4-Dimethylaminophenyl)-2,3-dihydro-4(1H)-quinazolinone (3m). Pale yellow solid. IR (KBr): 3295, 3192, 1655, 1615, 1509, 1487, 1355, 1189, 1065, 819, 754 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.07 (s, 1H, NH—CO), 7.63 (d, 1H, *J* = 7.5 Hz, ArH), 7.31 (d, 2H, *J* = 8.6 Hz, ArH), 7.24 (dd, 1H, *J* = 7.2, 8.0 Hz, ArH), 6.92 (s, 1H, NH), 6.75−6.65 (m, 4H, ArH), 5.64 (s, 1H, CH), 2.87 (s, 6H, $N(CH_3)_2$). MS (ESI): *m/z* (%) 268 (M^++H, 100). Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 72.07; H, 6.34; N, 15.80.

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