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CERIUM(IV) AMMONIUM NITRATE CATALYZED GREEN SYNTHESIS OF 2-SUBSTITUTED 2,3-DIHYDRO-QUINAZOLIN-4(1*H*)-ONES USING A GRINDING TECHNIQUE

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An efficient and facile method for the synthesis of 2-substituted 2,3-dihydro-quinazolin-4(1H)-ones from anthranilamide with aldehydes or ketones in the presence of cerium(IV) ammonium nitrate in water by a grinding technique has been developed. The structures of the new products were proved by IR, ^{1}H NMR, MS, and elemental analysis. A plausible mechanism for the formation of these products is proposed.

Keywords: anthranilamide, cerium(IV) ammonium nitrate, 2,3-dihydroquinazolin-4(1*H*)-one, grinding technique.

2,3-Dihydroquinazolin-4(1*H*)-ones are a class of heterocycles that has attracted much attention because they possess potential pharmaceutical activities [1–3]. They can be easily oxidized, using $KMnO_4$, to quinazolin-4(3*H*)-ones that are useful as growth inhibitor against leukemia cells [4] and potent poly(ADP-ribose)polymerase-1 inhibitors [5].

A number of classical methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported in literature [3, 6–11]. For example, they were obtained by reductive cyclization of *o*-nitrobenzamide or *o*-anthranilamide with aldehydes and ketones using *p*-TSA [3], HCl [6], SmI_2 [7], $TiCl_4$–Zn [8], $Sc(OTf)_3$ [9], NH_4Cl [10], and $H_3PW_{12}O_{40}$ [11] as catalysts. There were also reports carrying out these reactions in ionic liquids or 2,2,2-trifluoroethanol without catalyst [12, 13]. Despite the diverse routes developed so far, some of them had to be performed in harmful organic solvent. All of the reported reactions were carried out under uniform stirring conditions. Therefore, the development of an environmentally benign, high yielding, and novel protocol for synthesizing 2,3-dihydroquinazolin-4(1*H*)-ones is significant.

Cerium(IV) ammonium nitrate (CAN), a versatile single-electron oxidant, has been widely used in organic transformations due to its many advantages such as high reactivity, commercial availability, ease of

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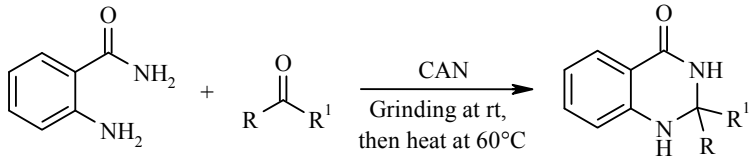
handling, and stability in different solvents. The use of this reagent for numerous transformations involving C–C, C–O, C–N, and C–S bond formation has been described [14–20]. However, application of CAN is limited due to its poor solubility in common organic solvents. Therefore, adopting water as the solvent is a good alternative. Organic reactions in water have attracted much attention because water is cheap, abundant, and environmentally benign. During the course of our studies on green chemistry, we discovered a new technique for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones, which involved the grinding of anthranilamide **1** with aldehydes or ketones **2a**–**n** in a mortar at room temperature in the presence of CAN and water (Scheme 1). Then, the reaction mixture was kept at 60°C until completion of the reaction.

Scheme 1



1 **2a–n** **3a–n**

2, 3 a–l,n R = H; **m** R + R^1 = $(CH_2)_5$; **a** R^1 = Ph, **b** R^1 = 2-$NO_2C_6H_4$, **c** R^1 = 3-$NO_2C_6H_4$, **d** R^1 = 4-$NO_2C_6H_4$, **e** R^1 = 2-ClC_6H_4, **f** R^1 = 4-ClC_6H_4, **g** R^1 = 2,4-$Cl_2C_6H_3$, **h** R^1 = 4-MeC_6H_4, **i** R^1 = 4-$MeOC_6H_4$, **j** R^1 = 2-HOC_6H_4, **k** R^1 = 4-HO-3-$MeOC_6H_3$, **l** R^1 = 4-$Me_2NC_6H_4$, **n** R^1 = Et

In our study, we first carried out a model reaction between anthranilamide **1** (5 mmol) and 4-nitrobenzaldehyde **2d** (5 mmol) in the presence of CAN to investigate the optimal reaction conditions. Initially, the reaction mixture was ground well with a pestle at room temperature for 0.2 h. The grinding step is crucial for this conversion because the likely formation of the melt phase on the solid particles facilitates chemical reactions [21]. A much lower yield (27%) would be produced without the grinding step. After several trials, we determined that the appropriate time for grinding is 0.2 h.

Different reaction temperatures, catalyst amounts, and water amounts were tried; the results are shown in Table 1. It can be seen that the reaction temperature had obvious effect on the yields. The rate of substrate conversion could be improved by increasing the reaction temperature (entries 1–4). However, when the reaction temperature reached 80°C the reaction mixture solidified too fast to complete the reaction (entry 4). Therefore, the suitable reaction temperature is 60°C. In addition, almost no product was produced in the absence of catalyst (entry 7). After these trials, the best result was obtained when the reaction was carried out at 60°C in the presence of 0.5 mol% CAN and 2 ml water (entry 3).

TABLE 1. Condensation of Anthranilamide (**1**) and 4-Nitrobenzaldehyde (**2d**) under Various Conditions

Entry	*T*, °C	Cat., mol%	Water, ml	Heating time, h*	Yield, %
1	20	0.5	2	1.5	13
2	40	0.5	2	1.5	67
3	60	0.5	2	1.5	94
4	80	0.5	2	1.0	88
5	60	1.0	2	1.5	96
6	60	0.2	2	1.5	62
7	60	0	2	1.5	Trace
8	60	0.5	0	1.5	75
9	60	0.5	1	1.5	87
10	60	0.5	3	1.5	83

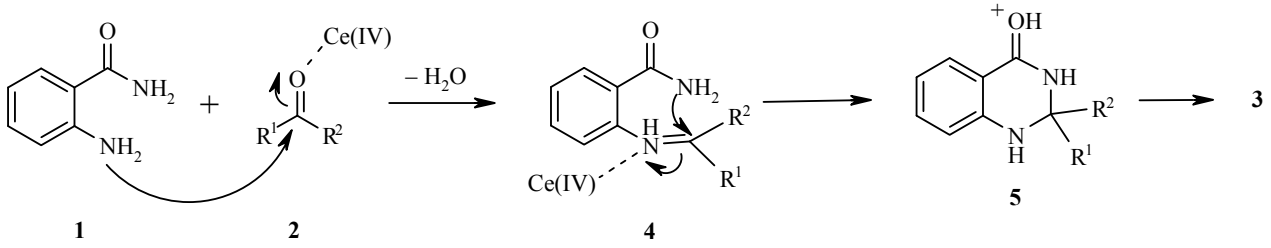
* The reaction mixtures were ground at room temperature for 0.2 h first.

TABLE 2. Reactions of Anthranilamide **1** with Aldehydes or Ketones **2a-n** in the Presence of CAN

Compound	Grinding time, h	Heating time, h	Yield, %	mp, °C	
				Found	Reported
3a	0.3	–	93	225–227	224–226 [22]
3b	0.2	1.5	90	190–192	191–194 [22]
3c	0.2	1.0	97	200–202	—
3d	0.2	1.5	94	198–200	—
3e	0.2	1.0	93	202–204	—
3f	0.2	1.0	92	204–206	205–206 [13]
3g	0.2	1.0	93	174–176	181–185 [23]
3h	0.2	2.0	92	224–225	225–227 [7]
3i	0.2	1.5	94	183–185	180–182 [7]
3j	0.2	2.0	90	222–224	—
3k	0.2	1.0	95	219–221	—
3l	0.2	2.0	81	203–205	—
3m	0.2	2.5	62	225–226	225–226 [13]
3n	0.2	8.0	—	—	—

To explore the scope and limitations of this reaction, we extended the cyclocondensation of anthranilamide **1** with various aromatic aldehydes, aliphatic aldehydes, and ketones. The results are summarized in Table 2. Aromatic aldehydes carrying both electron-donating groups and electron-withdrawing groups were all suitable for use, and steric effects did not influence the yield of products **3a**–**l**. The condensation yield with ketone **2m** was lower than that with aromatic aldehydes (compound **3m**). Furthermore, aliphatic aldehyde **2n** failed to give the desired product **3n**.

Scheme 2



The postulated mechanism for this reaction is shown in Scheme 2 [24]. The first step involves the condensation of anthranilamide **1** with aldehyde/ketone **2** promoted by catalyst to produce intermediate **4**. The amide part of the intermediate **4** could be activated by Ce^{4+}. Thus, intermediate **4** could be converted to intermediate **5** by intramolecular nucleophilic attack of the nitrogen on the imine carbon. Subsequently, quinazolinones **3** could be formed by a 1,5-proton transfer of intermediate **5**.

In conclusion, we have demonstrated that 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones can be synthesized efficiently from 2-anthranilamide with aromatic aldehydes or ketones in the presence of CAN and water by the grinding technique. The method is simple, novel, and environmentally benign. It may be an alternative to the known literature methods.

EXPERIMENTAL

The IR spectra were recorded on a Varian Scimitar 2000 series Fourier Transform instrument in KBr. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6 using TMS as an internal standard. ESI mass spectra were obtained with an Agilent 1100 series LC/MSD VL ESI instrument. Elemental analyses were carried out on a Perkin-Elmer EA 2400II elemental analyzer. Melting points were determined using an RY-1 micromelting point apparatus (Tianjin Tianguang Optical Instrument Limited Company, China).

Synthesis of 2-Substituted 2,3-Dihydroquinazolin-4(1*H*)-ones 3a–n (General method). To a mixture of anthranilamide **1** (5 mmol) and the corresponding aldehyde or ketone **2a–n** (5 mmol) in a mortar, CAN (0.025 mmol, 0.5 mol%) and water (2 ml) were added. The mixture was ground well with a pestle at room temperature for an indicated time and then kept at 60°C in an oven under atmosphere for the appropriate time (Table 2) until the completion of reaction, as indicated by TLC (ethyl acetate–*n*-hexane, 1:1). The reaction mixture was cooled to room temperature and was washed thoroughly with water during vacuum filtration. The products were purified further by crystallization from ethanol.

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3c). Yellow solid. IR spectrum, ν, cm^{-1}: 3337, 3147, 1674, 1636, 1589, 1526, 1447, 1386, 1187, 971, 772. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.76 (2H, d, *J* = 7.4, H Ar); 8.42 (2H, t, *J* = 7.5, H Ar); 7.97 (1H, br. s, CONH); 7.87 (2H, dt, *J* = 6.0, *J* = 1.5, H Ar); 7.62 (1H, br. s, NH); 7.57 (1H, dt, *J* = 6.2, *J* = 1.4, H Ar); 7.38 (1H, t, *J* = 7.5, H Ar); 7.26 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 163.3; 147.7; 147.2; 144.2; 133.5; 133.3; 129.9; 127.4; 123.2; 121.5; 117.5; 114.9; 114.5; 65.2. Mass spectrum, *m/z* (I_{rel}, %): 270 $[M+H]^+$ (100). Found, %: C 62.56; H 4.17; N 15.49. $C_{14}H_{11}N_3O_3$. Calculated, %: C 62.45; H 4.12; N 15.61.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3d). Yellow solid. IR spectrum, ν, cm^{-1}: 3363, 3291, 1661, 1613, 1521, 1486, 1348, 1162, 1012, 859, 753. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.53 (1H, s, CONH); 8.27 (2H, d, *J* = 8.6, H Ar); 7.76 (2H, d, *J* = 8.6, H Ar); 7.64 (1H, d, *J* = 7.6, H Ar); 7.33 (1H, s, NH); 7.29 (1H, t, *J* = 7.4, H Ar); 6.79 (1H, d, *J* = 8.1, H Ar); 6.71 (1H, t, *J* = 7.4, H Ar); 5.93 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 163.2; 149.2; 147.4; 147.2; 133.4; 127.9; 127.3; 123.5; 117.4; 114.8; 114.5; 65.2. Mass spectrum, *m/z* (I_{rel}, %): 270 $[M+H]^+$ (100). Found, %: C 62.57; H 4.05; N 15.53. $C_{14}H_{11}N_3O_3$. Calculated, %: C 62.45; H 4.12; N 15.61.

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e). White solid. IR spectrum, ν, cm^{-1}: 3362, 3197, 1647, 1614, 1504, 1330, 1188, 1054, 853, 745. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.21 (1H, s, CONH); 7.67 (2H, d, *J* = 7.8, H Ar); 7.50−7.47 (1H, m, H Ar); 7.41−7.38 (2H, m, H Ar); 7.27 (1H, t, *J* = 6.8, H Ar); 7.01 (1H, s, NH); 6.78 (1H, d, *J* = 7.8, H Ar); 6.73–6.99 (1H, m, H Ar); 6.14 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 163.5; 147.6; 137.8; 133.3; 131.8; 130.2; 129.5; 128.6; 127.4; 127.3; 117.4; 114.6; 114.5; 63.6. Mass spectrum, *m/z* (I_{rel}, %): 259 $[M+H]^+$ (100). Found, %: C 65.12; H 4.34; N 10.74. $C_{14}H_{11}ClN_2O$. Calculated, %: C 65.00; H 4.29; N 10.83.

2-(2-Hydroxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3j). White solid. IR spectrum, ν, cm^{-1}: 3410, 3157, 1648, 1616, 1508, 1464, 1332, 1161, 843, 744. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.85 (1H, s, CONH); 7.93 (1H, s, NH); 7.64 (1H, d, *J* = 7.0, H Ar); 7.36 (1H, d, *J* = 7.5, H Ar); 7.24 (1H, t, *J* = 7.1, H Ar); 7.16 (1H, t, *J* = 7.5, H Ar); 6.88–6.86 (1H, m, OH); 6.81−6.74 (3H, m, H Ar); 6.68 (1H, t, *J* = 7.5, H Ar); 6.01 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 163.9; 148.0; 135.0; 133.1; 129.2; 127.2; 127.1; 127.0; 118.7; 116.9; 115.3; 114.7; 114.5; 61.2. Mass spectrum, *m/z* (I_{rel}, %): 241 $[M+H]^+$ (100). Found, %: C 69.83; H 5.09; N 11.74. $C_{14}H_{12}N_2O_2$. Calculated, %: C 69.99; H 5.04; N 11.66.

2-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3k). White solid. IR spectrum, ν, cm^{-1}: 3389, 3354, 1650, 1610, 1500, 1428, 1157, 1021, 860, 766. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.06 (1H, s, CONH); 8.09 (1H, s, NH); 7.62 (1H, dd, *J* = 6.5, *J* = 1.2, H Ar); 7.25 (1H, m, H Ar); 7.09 (1H, d, *J* = 1.2, H Ar); 6.94 (1H, s, OH); 6.89 (1H, dd, *J* = 6.5, *J* = 1.5, H Ar); 6.77 (2H, t, *J* = 8.1, H Ar); 6.69 (1H, t, *J* = 7.4, H Ar); 5.65 (1H, s, CH); 3.76 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm: 167.2; 149.3; 147.8; 133.2; 132.1;

131.9; 129.8; 128.9; 127.9; 127.3; 117.0; 114.9; 114.3; 66.5; 56.0. Mass spectrum, *m/z* (I_{rel}, %): 271 $[M+H]^+$ (100). Found, %: C 66.75; H 5.14; N 10.27. $C_{15}H_{14}N_2O_3$. Calculated, %: C 66.66; H 5.22; N 10.36.

2-(4-Dimethylaminophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3l). Pale-yellow solid. IR spectrum, ν, cm^{-1}: 3295, 3192, 1655, 1615, 1509, 1487, 1356, 1189, 1066, 819, 754. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.07 (1H, s, CONH); 7.63 (1H, d, *J* = 7.5, H Ar); 7.31 (2H, d, *J* = 8.6, H Ar); 7.24–7.21 (1H, m, H Ar); 6.91 (1H, s, NH); 6.75−6.65 (4H, m, H Ar); 5.64 (1H, s, CH); 2.86 (6H, s, $N(CH_3)_2$). ^{13}C NMR spectrum, δ, ppm: 163.7; 150.6; 148.1; 133.0; 128.6; 127.6; 127.2; 116.8; 115.0; 114.3; 111.8; 66.6; 40.1. Mass spectrum, *m/z* (I_{rel}, %): 268 $[M+H]^+$ (100). Found, %: C 72.01; H 6.35; N 15.80. $C_{16}H_{17}N_3O$. Calculated, %: C 71.89; H 6.41; N 15.72.

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