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SYNTHESIS OF 3-SUBSTITUTED 4(3H)-QUINAZOLINONES CATALYZED BY CERIC AMMONIUM NITRATE

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The synthesis of 3-substituted 4(3H)-quinazolinones from anthranilic acid, orthoesters, and amines in the presence of ceric ammonium nitrate has been studied. The reaction occurred in a few minutes at room temperature under solvent-free conditions and in excellent yields. The probable conversion mechanism has been discussed.

Keywords: ceric ammonium nitrate, 4(3H)-quinazolinones, catalysis, cyclization, solvent-free condition.

One of the most frequently encountered heterocyclic compounds in medicinal chemistry is 4(3H)-quinazolinone, which exhibits interesting pharmacological activities. A series of methods has been developed previously for the synthesis of 3-substituted 4(3H)-quinazolinones from anthranilic acid, orthoesters, and amines in the presence of various catalysts [1-8]. The drawbacks of these methods are expensive catalyst, high temperature (60-80^{o}C), long reaction time (20 h), etc. In addition, anilines having strong electron-withdrawing substituents, e.g., Cl and NO_2, gave generally no products at room temperature in previous reports. Hence, it was of interest to develop a more universal method for the synthesis of these products.

During the course of our studies towards the development of green catalytic processes, we found that ceric ammonium nitrate (CAN) as an inexpensive and commercially available catalyst can efficiently catalyze one-pot synthesis of 3-substituted 4(3H)-quinazolinones **4** *via* triple-component condensation of anthranilic acid **1**, orthoesters **2**, and amines **3** (Scheme 1). The reaction was carried out under solvent-free conditions at room temperature. The triple-component interaction has been studied in the present work with the aim of extending the scope of reactants and of clarifying the mechanism.

First, a blank experiment with anthranilic acid, triethyl orthoformate, and aniline in the absence of a catalyst was investigated. The result showed that only 5% product was obtained after 1 h. Then the scope and limitations of the condensation of anthranilic acid **1**, triethyl or trimethyl orthoformate **2**, and different substituted arylamines or alkylamine **3** catalyzed by CAN were studied; the results are shown in Table 1. All the reactions proceeded smoothly at room temperature. Both triethyl orthoformate and trimethyl orthoformate

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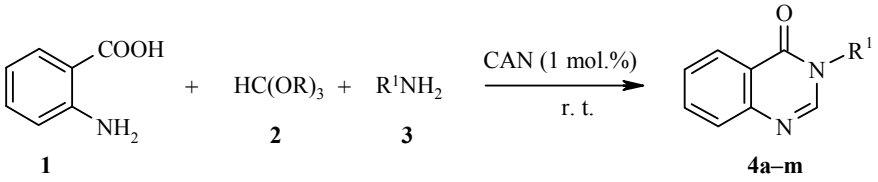
were equally utilized for the preparation of 3-substituted 4(3H)-quinazolinones. The reaction time of trimethyl orthoformate was longer than that of triethyl orthoformate. Therefore, trimethyl orthoformate proved to be less active than triethyl orthoformate.

Scheme 1



1 **2** **3** **4a–m**

R = Me or Et

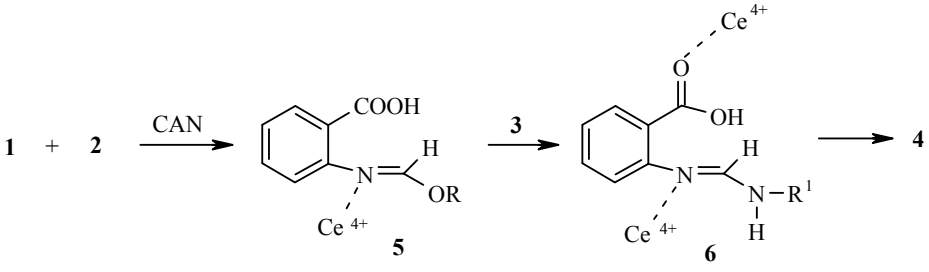
TABLE 1. Preparation of 3-Substituted 4(3H)-Quinazolinones **4a-m** Catalyzed by CAN

Com-pound	R^1	Time, h	Yield, %	Time, h	Yield, %	Mp, °C
		$HC(OEt)_3$		$HC(OMe)_3$		
4a	Ph	0.6	94	3.0	74	138-140
4b	2-MeC_6H_4	0.7	96	2.0	97	155-157
4c	4-MeC_6H_4	0.2	85	0.6	87	148-150
4d	2-$MeOC_6H_4$	0.5	92	2.3	90	150-152
4e	4-$MeOC_6H_4$	0.1	89	0.8	86	133-135
4f	2-ClC_6H_4	0.1	88	0.2	96	117-119
4g	4-ClC_6H_4	0.1	61	0.2	68	124-125
4h	4-BrC_6H_4	0.1	86	0.2	92	145-147
4i	2-$O_2NC_6H_4$	3.5	40	0.8	36	157-158
4j	3-$O_2NC_6H_4$	0.2	89	0.1	90	154-156
4k	4-$O_2NC_6H_4$	0.2	86	0.1	87	163-165
4l	4-$HOOCC_6H_4$	0.1	64	0.1	50	240-242
4m	$PhCH_2$	0.1	21	0.5	15	153-155

Arylamines carrying either electron-donating or electron-withdrawing groups all afforded high yields at room temperature. The position of the substituents on the aromatic amines shows no effects on this conversion. The products derived from 2-NO_2-substituted aniline are formed in lower yields than the others, which may be attributed to the double effects of steric hindrance and the strong electron-withdrawing substituent (product **4i**). Aliphatic aldehyde also gave low yields of product **4m**.

A mechanism for this reaction has been also postulated, as shown in Scheme 2. The first step in this reaction involves the CAN-catalyzed formation of imidic ester **5**, which was stabilized by Ce^{4+}. Imidic ester **5** may be very prone to react with arylamine **3**, thus leading to amidine intermediate **6**. Then amidine intermediate **6** activated by Ce^{4+} was cyclized to form quinazolinone **4**.

Scheme 2



EXPERIMENTAL

Melting points were determined using an RY-1 micromelting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Scimitar 2000 series Fourier Transform instrument (Varian). ^{1}H NMR spectra were recorded on a Bruker ARX-500 spectrometer (500 MHz) in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on an EA 2400II elemental analyzer (Perkin–Elmer).

Synthesis of Compounds 4a-m (General Method). A mixture of anthranilic acid (10 mmol), orthoester (12 mmol), amine (12 mmol), and CAN (0.1 mmol) was stirred at room temperature for an appropriate time (Table 1). The reaction was monitored by TLC. After completion, all products were washed thoroughly with EtOH during gravity filtration and dried. All crude products obtained were pure enough without further purification. The products were identified by IR, ^{1}H NMR spectra, and elemental analysis. Spectral data for compounds **4a-m** are as follows:

3-Phenylquinazolin-4(3H)-one (4a). Pale-yellow solid. IR spectrum, ν, cm^{-1}: 1689, 1598, 1463. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.32 (1H, s, CH); 8.19 (1H, d, *J* = 7.6, H Ar); 7.78-7.72 (2H, m, H Ar); 7.49 (1H, t, *J* = 7.5, H Ar); 7.35–7.27 (5H, m, H Ar). Found, %: C 75.54; H 4.57; O 7.24. $C_{14}H_{10}N_2O$. Calculated, %: C 75.66; H 4.54; O 7.20.

3-(2-Methylphenyl)quinazolin-4(3H)-one (4b). White solid. IR spectrum, ν, cm^{-1}: 1687, 1595, 1489. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.56 (1H, s, CH); 8.31 (1H, d, *J* = 7.2, H Ar); 7.75-7.52 (2H, m, H Ar); 7.24-7.07 (5H, m, H Ar); 2.31 (3H, s, CH_3). Found, %: C 76.39; H 5.09; O 6.74. $C_{15}H_{12}N_2O$. Calculated, %: C 76.26; H 5.12; O 6.77.

3-(4-Methylphenyl)quinazolin-4(3H)-one (4c). White solid. IR spectrum, ν, cm^{-1}: 1682, 1595, 1456. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.49 (1H, s, CH); 8.07 (1H, d, *J* = 7.6, H Ar); 7.71-7.69 (2H, m, H Ar); 7.42 (1H, t, *J* = 7.5, H Ar); 7.31 (2H, d, *J* = 7.2, H Ar); 7.15 (2H, d, *J* = 7.3, H Ar); 3.16 (3H, s, CH_3). Found, %: C 76.18; H 5.13; O 6.80. $C_{15}H_{12}N_2O$. Calculated, %: C 76.26; H 5.12; O 6.77.

3-(2-Methoxyphenyl)quinazolin-4(3H)-one (4d). White solid. IR spectrum, ν, cm^{-1}: 1681, 1595, 1457. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.36 (1H, s, CH); 8.21 (1H, d, *J* = 7.7, H Ar); 7.45 (1H, d, *J* = 6.8, H Ar); 7.25 (1H, t, *J* = 7.0, H Ar); 7.08–7.03 (2H, m, H Ar); 6.94 (1H, t, *J* = 7.1, H Ar); 6.78 (1H, d, *J* = 8.2, H Ar); 6.54 (1H, t, *J* = 7.3, H Ar); 3.85 (3H, s, OCH_3). Found, %: C 71.53; H 4.74; O 12.62. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.80; O 12.68.

3-(4-Methoxyphenyl)quinazolin-4(3H)-one (4e). White solid. IR spectrum, ν, cm^{-1}: 1716, 1591, 1453. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.54 (1H, s, CH); 8.05 (1H, d, *J* = 7.5, H Ar); 7.54-7.51 (2H, m, H Ar); 7.16 (1H, t, *J* = 7.5, H Ar); 6.97 (4H, dd, *J* = 8.5, *J* = 9.5, H Ar); 3.76 (3H, s, OCH_3). Found, %: C 71.30; H 4.85; O 12.73. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.80; O 12.68.

3-(2-Chlorophenyl)quinazolin-4(3H)-one (4f). Yellow solid. IR spectrum, ν, cm^{-1}: 1667, 1600, 1414. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.57 (1H, s, CH); 8.02 (1H, d, *J* = 7.7, H Ar); 7.73-7.71 (2H, m, H Ar); 7.61 (1H, t, *J* = 7.6, H Ar); 7.25–7.16 (2H, m, H Ar); 6.76 (1H, d, *J* = 8.1, H Ar); 6.53 (1H, t, *J* = 7.2, H Ar). Found, %: C 65.64; H 3.54; N 10.87; O 6.18. $C_{14}H_9ClN_2O$. Calculated, %: C 65.51; H 3.53; N 10.91; O 6.23.

3-(4-Chlorophenyl)quinazolin-4(3H)-one (4g). Pale-yellow solid. IR spectrum, ν, cm^{-1}: 1672, 1616, 1485. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.52 (1H, s, CH); 7.71-7.69 (2H, m, H Ar); 7.24-7.20 (2H, m, H Ar); 6.75 (2H, d, *J* = 7.5, H Ar); 6.52 (2H, d, *J* = 7.2, H Ar). Found, %: C 65.38; H 3.55; N 10.99; O 6.27. $C_{14}H_9ClN_2O$. Calculated, %: C 65.51; H 3.53; N 10.91; O 6.23.

3-(4-Bromophenyl)quinazolin-4(3H)-one (4h). White solid. IR spectrum, ν, cm^{-1}: 1713, 1587, 1443. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.55 (1H, s, CH); 8.01 (1H, d, *J* = 7.7, H Ar); 7.60 (1H, t, *J* = 7.5, H Ar); 7.46-7.44 (4H, m, H Ar); 7.19 (2H, d, *J* = 7.5, H Ar). Found, %: C 55.72; H 3.03; N 9.33; O 5.35. $C_{14}H_9BrN_2O$. Calculated, %: C 55.84; H 3.01; N 9.30; O 5.31.

3-(2-Nitrophenyl)quinazolin-4(3H)-one (4i). Yellow solid. IR spectrum, ν, cm^{-1}: 1697, 1602, 1476. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.52 (1H, s, CH); 8.19 (1H, d, *J* = 7.7, H Ar); 7.71-7.66 (2H, m, H Ar); 7.53 (1H, t, *J* = 7.6, H Ar); 7.25-7.19 (4H, m, H Ar). Found, %: C 63.03; H 3.37; O 17.91. $C_{14}H_9N_3O_3$. Calculated, %: C 62.92; H 3.39; O 17.96.

3-(3-Nitrophenyl)quinazolin-4(3H)-one (4j). Yellow solid. IR spectrum, ν, cm^{-1}: 1711, 1596, 1471. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.51 (1H, s, CH); 8.10 (1H, d, *J* = 7.6, H Ar); 7.67–7.62 (2H, m, H Ar); 7.45 (1H, t, *J* = 7.4, H Ar); 7.24–7.13 (4H, m, H Ar). Found, %: C 62.81; H 3.43; O 18.01. $C_{14}H_9N_3O_3$. Calculated, %: C 62.92; H 3.39; O 17.96.

3-(4-Nitrophenyl)quinazolin-4(3H)-one (4k). Yellow solid. IR spectrum, ν, cm^{-1}: 1701, 1624, 1477. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.51 (1H, s, CH); 8.12 (1H, d, *J* = 7.6, H Ar); 7.82 (2H, m, H Ar); 7.53 (1H, t, *J* = 7.4, H Ar); 6.98 (2H, d, *J* = 8.5, H Ar); 6.73 (2H, d, *J* = 8.6, H Ar). Found, %: C 63.05; H 3.36; O 17.89. $C_{14}H_9N_3O_3$. Calculated, %: C 62.92; H 3.39; O 17.96.

3-(4-Carboxylphenyl)quinazolin-4(3H)-one (4l). White solid. IR spectrum, ν, cm^{-1}: 1700, 1593, 1483. ^1H NMR spectrum, δ, ppm (*J*, Hz): 10.49 (1H, s, COOH); 8.35 (1H, s, CH); 7.92–7.88 (3H, m, H Ar); 7.71 (2H, t, *J* = 8.5, H Ar); 7.63 (1H, d, *J* = 5.5, H Ar); 7.31 (1H, d, *J* = 8.5, H Ar); 6.56 (1H, d, *J* = 5.5, H Ar). Found, %: C 67.79; H 3.74; O 18.08. $C_{15}H_{10}N_2O_3$. Calculated, %: C 67.67; H 3.79; O 18.03.

3-Benzylquinazolin-4(3H)-one (4m). White solid. IR spectrum, ν, cm^{-1}: 1677, 1620, 1459. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.52 (1H, s, CH); 8.00 (1H, d, *J* = 7.5, H Ar); 7.54–7.47 (2H, m, H Ar); 7.41-7.37 (4H, m, H Ar); 7.32 (1H, t, *J* = 6.8, H Ar); 7.14 (1H, t, *J* = 7.0, H Ar); 4.61 (2H, s, CH_2). Found, %: C 76.13; H 5.16; O 6.81. $C_{15}H_{12}N_2O$. Calculated, %: C 76.26; H 5.12; O 6.77.

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