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ONE-POT SYNTHESIS OF 2-SUBSTITUTED QUINAZOLINONES BY COUPLING OF 2-BROMO BENZAMIDE, BENZALDEHYDE AND AMMONIA CATALYSED BY $Cr(NO_3)_3.9H_2O$

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ABSTRACT
A series of 2-substituted quinazolinone derivatives have been synthesized in excellent yields by one-pot reaction using 2-bromobenzamide, benzaldehyde, ammonia. The desired products were isolated in moderate to excellent yields in the presence of $Cr(NO_3)_3.9H_2O$. All the products were identified by spectral (^{1}H NMR, ^{13}C NMR and mass) and analytical data.

KEYWORDS: 2-Substituted Quinazolinone, One-pot reaction, ammonia, synthesis, Heterocyclic compound.

INTRODUCTION
Among all the known heterocycles, quinazolinone core and its derivatives consist an important class of compounds, as they are existing in a large family of products with extensive biological activities.[I] They generally display useful therapeutic and pharmacological properties such as anticonvulsant, antihypertensive and antimalarial activities.[II] Furthermore, the heterocyclic core constitutes more than 40 alkaloids isolated from natural products.[III] 4(3H)-Quinazolinones are present in a large family of products with pharmacological properties including antitumor, fungicidal, antimicrobial, and anti-inflammatory.[IV] A small number of quinazolinones have been reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example, 3-arylquinazoline-2,4(1H,3H)-diones as antimycobacterial agents[V] and quinazolinone derivatives as antitubercular agents.[VI] Recently, these moieties have been evaluated as antagonists of various biological receptors, such as 5-HT5A related diseases,[VII] Due to the wide range and applicability of quinazolinones and its related derivatives, their synthesis has drawn interests from organic chemists.[VIII]
In view of their importance, a number of methods for 4(3H)-quinazolinone preparation have been developed. Recently, Willis and co-workers reported a straight forward procedure for the

synthesis of quinazolinones.[IX] They used N-(o-halophenyl)- imidates as their substrates, and the desired products were produced in good yields.

A convenient and transition-metal free protocol for quinazolinones synthesis with *o*-aminobenzamides and benzyl amines as substrates has been developed by using H_2O_2 as the oxidant by Xiao Feng Wu *et al*. (2016).[X] Very recently, several methods have been reported. Quinazolin-4-(*3H*)-one derivatives have been prepared from isatoic anhydride, ammonium acetate/amines, and aldehydes in one-pot reaction catalyzed by $Ga(OTf)_3$ by Weike Su *et al*.[XI] An efficient synthesis of quinazolinone derivatives has been performed from by the condensation of halide benzamide with amino acid using magnetically recyclable GO/Fe_3O_4–CuI as catalyst by Li-Yan Fan *et al.* (2016).[XII] An efficient and simple $VO(acac)_2$ catalyzed approach to the synthesis of quinazolinones has been developed by Shuang Gao *et al*. (2016).[XIII] Jin Zhang *et al*. (2016) studied an environmentally benign nano CuO catalyzed strategy for one-pot synthesis of quinazolinone Schiff base derivatives and bis-2,3-dihydroquinazolin-4(1*H*)-ones by use of hydrazine hydrate.[XIV] A series of quinazolinone derived Schiff base derivatives were synthesized by manu kumar *et al*. (2016).[XV] An efficient one-pot, three-component synthesis of quinazolinone derivatives containing 3-acrylamino motif was carried out using CeO_2 nanoparticles as catalyst has been developed by Yuan Yao *et al*. (2016).[XVI] A concise approach for the synthesis of 2-Amino-substituted-4(3*H*)-quinazolinones via an efficient metal-free reaction between 2-aminobenzamide derivatives and carbonimidic dibromides has been developed by Behrooz Mirza *et al*. (2016).[XVII] Osamu Kitagawa *et al*. (2016) has been performed an efficient synthesis of optically active N–C axially chiral quinazolinone (mebroqualone) derivatives by using (R)-DTBM-SEGPHOS-$Pd(OAc)_2$ as efficient catalyst.[XVIII] A series of novel quinazolinone derivatives were synthesized by Karl Hemming *et al*. (2017).[XIX] Tandem cyclization of 2-halobenzoic acids with amidines provides a new facile quinazolinones using Cerium(III) chloride reported by Lalitha kumari *et al*. (2017).[XX] A concise approach for the synthesis of a series of tricyclic quinazolinones have been accomplished starting from anthranilamide and 1,3-cyclicdione promoted by $TsOH{\cdot}H_2O$ based on retro-Dieckmann type reaction has been developed by Krishnaiah *et al*. (2017).[XXI] An efficient protocol for the synthesis of Quinozolinones derivatives is achieved using BBr_3 as effective catalyst by Hari Krishna, *et al.*[XXII] Thriveni *et al*. (2017) studied the synthesis of new series of Quinazolinone derivatives by one-pot reaction using a three-component condensation of anthranilic acid, amines, and ortho esters at room temperature under solvent-free conditions.[XXIII] A congeneric series of novel imidazolone fused quinazolinone derivatives were synthesized by Deepak Kumar *et al*. (2017).[XXIV] Therefore new methodologies for quinazolinones synthesis are still under request.

During the course of our studies on the development of quinazolinones synthesis, we found that $Cr(NO_3)_3.\ 9H_2O$ an inexpensive and commercially available catalyst, can efficiently catalyze a one-pot synthesis of 2-substituted-4(3H)-quinazolinones via a three-component condensation of 2-bromobenzamide, benzaldehyde and aqueous ammonia (Scheme 1). The products were formed with excellent yields. In our present work, we unzip our results for preparation of Quinazolinone derivatives with high yields which is superior to other methods.

Experimental Section

NMR spectra were recorded on Bruker Avance 300 and Bruker ARX 400 spectrometers. Chemical shifts (ppm) are given relative to solvent: references for $CDCl_3$ were 7.26 ppm (1H NMR) and 77.00 ppm (13C NMR). Multiplets were assigned as s (singlet), d (doublet), t (triplet),

dd (doublet of doublet), m (multiplet) and br. s (broad singlet). All measurements were carried out at room temperature unless otherwise stated. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV). High resolution mass spectra (HRMS) were recorded on Agilent 6210. The data are given as mass units per charge (m/z).

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^1H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^1H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm.

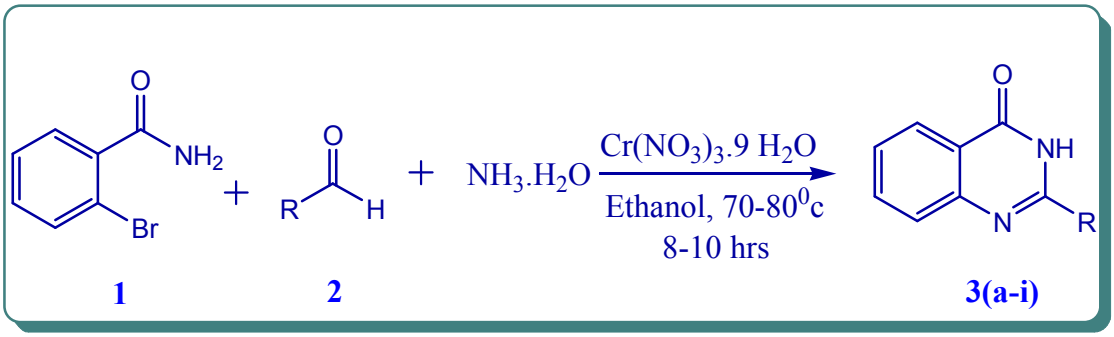
Typical Procedure for the synthesis of 2-substituted Quinazolinone derivatives 3(a-i):

To a mixture of 2-bromobenzamide compound (80 mg, 0.4 mmol), benzaldehyde (82 mL, 0.8 mmol), $Cr(NO_3)_3$. $9H_2O$ (10 mmol) in Ethanol (6 mL) was added 26% aqueous ammonia (0.5 mL) in a round bottom flask. The mixture was stirred at 70-80^{0}C for 6-8 hrs. After being cooled to room temperature, the resulting mixture was poured into crushed ice, stirred for 10-15 min and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford quinazolinone in 76% yield. The structure were established by spectral (IR, ^1H NMR, ^{13}C NMR and mass) and analytical data.

Scheme I:

The synthetic route was depicted in scheme I. The title compounds 3(a-i) were synthesised in one pot reaction. The 3(a-i) were obtained in moderate yields. The structure were established by spectral (^1H NMR, ^{13}C NMR and mass) and analytical data.

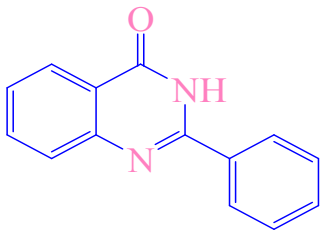
Scheme 1



Synthesis of 2-substituted Quinazolinone derivatives

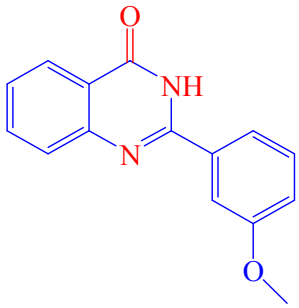
Spectral data for selected compounds:

2-Phenylquinazolin-4(3*H*)-one (3a):



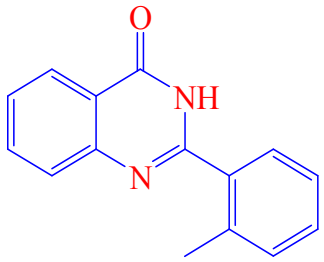
yellow solid
^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.94 (1H, s), 8.05 (1H, d, *J* = 7.2 Hz), 7.99- 7.98 (2H, m), 7.57-7.55 (2H, m), 7.33- 7.29 (3H, m), 7.27- 7.21 (1H, m);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 152.3, 149.2, 134.3, 132.9, 131.2, 129.5, 128.6, 128.1, 127.6, 126.3, 126.0, 121.1;
HRMS (ESI-MS): m/z=223 (M+H), positive mode; Anal. Calcd for C14H10N2O: C, 75.66; H, 4.54; N, 12.60%. Found: C, 75.81; H, 4.51; N, 12.53%.

2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (3b):



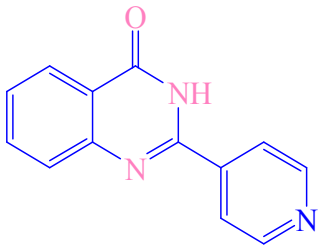
white solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.39 (1H, s, br), 8.18 (2H, d, *J* = 8.5 Hz), 8.13 (1H, d, *J* = 7.0 Hz), 7.81 (1H, t, *J* = 6.5 Hz), 7.70 (1H, d, *J* = 8.0 Hz), 7.48 (1H, t, *J* = 7.0 Hz), 7.09 (2H, d, *J* = 9.0 Hz), 3.86 (3H, s);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.7, 162.4, 152.2, 149.4, 134.9, 129.9, 127.7, 126.5, 126.3, 125.3, 121.2, 114.5, 55.9;
HRMS (ESI-MS): m/z=253 (M+H), positive mode; Anal. Calcd for C15H12N2O2: C, 71.42; H, 4.79; N, 11.10%. Found: C, 71.57; H, 4.71; N, 11.26%.

2-(o-Tolyl)quinazolin-4(3*H*)-one (3c):



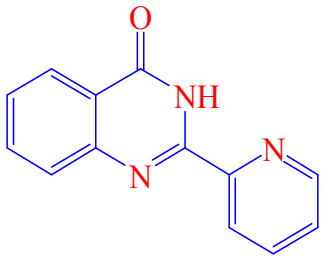
white solid
^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.49 (1H, s, br), 8.34 (1H, d, *J* = 7.6 Hz), 8.16 (2H, d, *J* = 8.0 Hz), 7.82 (2H, t, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 8.0 Hz), 7.38 (2H, d, *J* = 2.0 Hz), 2.47 (3H, s);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 151.8, 149.6, 142.1, 134.8, 130.0, 129.7, 127.9, 127.4, 127.3, 126.5, 126.3, 120.8, 21.5;
HRMS (ESI-MS): m/z=237 (M+H), positive mode; Anal. Calcd for C15H12N2O: C, 76.25; H, 5.12; N, 11.86%. Found: C, 76.12; H, 5.18; N, 11.96%.

2-(Pyridin-4-yl)quinazolin-4(3*H*)-one (3d):



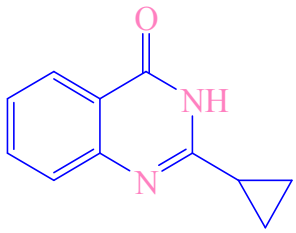
White solid.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.77 (1H, s), 8.78 (2H, d, *J* =4.0 Hz), 8.18 (1H, d, *J* = 7.6 Hz), 8.12 (2H, d, *J* = 4.5 Hz), 7.89(1H, t, *J* = 7.5 Hz), 7.79 (1H, d, *J* = 7.9 Hz), 7.58 (1H, t, *J* = 7.2Hz).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 151.0, 150.7, 140.4, 135.3, 128.2, 127.9, 126.4, 122.0, 121.9.
HRMS (ESI-MS): m/z cald. for C13H9N3O (M+H) 224.0824, found 224.0820.

2-(Pyridin-2-yl)quinazolin-4(3*H*)-one (3e):



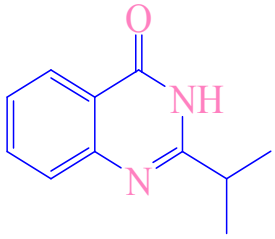
white crystalline solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.82 (1H, s, br), 8.74 (1H, d, *J* = 4.4 Hz), 8.43 (1H, d, *J* = 8.0 Hz), 8.17 (1H, d, *J* = 8.0 Hz), 8.06 (1H, t, *J* = 8.0 Hz), 7.86 (1H, t, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.65-7.62 (1H, m), 7.56 (1H, t, *J* = 7.6 Hz);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.3, 150.3, 149.5, 149.0, 148.8, 138.5, 135.2, 128.1, 127.8, 127.0, 126.5, 122.6, 122.4;
HRMS (ESI-MS): m/z=224 (M+H), positive mode; Anal. Calcd for C13H9N3O: C, 69.95; H, 4.06; N, 18.82%. Found: C, 69.86; H, 4.15; N, 18.75%.

2-Cyclopropylquinazolin-4(3*H*)-one (3f):



White solid.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.59 (s, br, 1H), 8.24 (d, 1H, *J* = 8.0 Hz), 7.71-7.68 (m, 1H), 7.58 (d, *J* = 8, 1H), 7.41-7.37 (m, 1H), 1.99-1.93 (m, 1H), 1.33-1.29 (m, 2H), 1.14 - 1.10 (m, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz,): δ 163.9, 157.9, 149.7, 134.8, 126.9, 126.2, 125.6, 120.4, 14.7, 9.7.
GCMS (EI, 70 eV): m/z (%): 186 (63, M+), 185 (100), 119 (26), 92 (15).

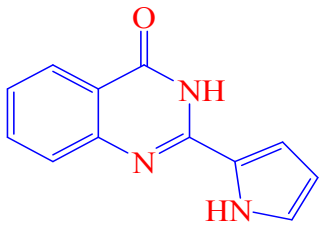
2-isopropylquinazolin-4(*3H*)-one (3g):



White solid
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (d, *J* = 6.8 Hz, 6H), 2.97-3.08 (m, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.70-7.79 (m, 2H), 8.29 (d, *J* = 7.6Hz, 1H), 10.95 (s, 1H);

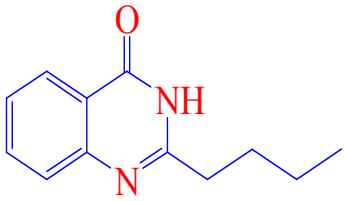
^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 35.0, 120.8, 126.2, 126.4, 127.4, 134.7, 149.4, 160.5, 163.7;
HRMS (ESI): m/z [M+H]+ calcd. for C11H12N2O 189.1022; found 189.1027.

2-(1*H*-Pyrrol-2-yl)quinazolin-4(3*H*)-one (3h):



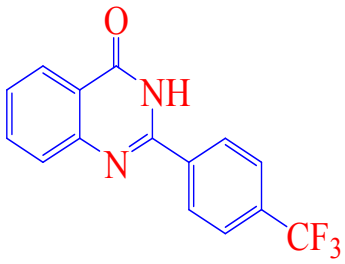
Brown powder
^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.18 (1H, s), 11.70 (1H, s), 8.08 (1H, d, *J* = 7.6 Hz), 7.77 (1H, t, *J* = 7.6 Hz), 7.62 (1H, d, *J* = 8.0 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 7.29 (1H, s), 7.05 (1H, s), 6.21 (1H, s);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.4, 149.7, 146.8, 135.0, 126.9, 126.4, 125.7, 124.7, 124.3, 120.9, 112.9, 110.2;
HRMS (ESI-MS): m/z=212 (M+H), positive mode; Anal. Calcd for C12H9N3O: C, 68.24; H, 4.29; N, 19.89%. Found: C, 68.15; H, 4.36; N, 19.78%.

2-Butylquinazolin-4(3*H*)-one (3i):



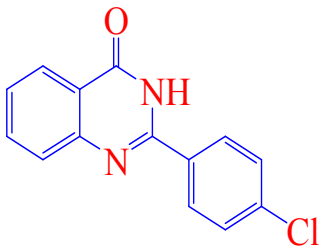
White solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.02 (1H, s), 8.29 (1H, d, *J* = 8.0 Hz), 7.77 (1H, t, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.47 (1H, t, *J* = 8.0 Hz), 2.81 (2H, t, *J* = 8.0 Hz), 1.92- 1.82 (2H, m), 1.51 (2H, q, *J* = 7.4 Hz), 1.00 (3H, t, *J* = 8.0 Hz);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.4, 157.0, 149.5, 134.8, 127.2, 126.3, 126.2, 120.5, 35.7, 29.7, 22.4, 13.8;
HRMS (ESI-MS) cald. for C12H14N2O (M+H) 203.1184, found 203.1187.

2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3H)-one (3j):



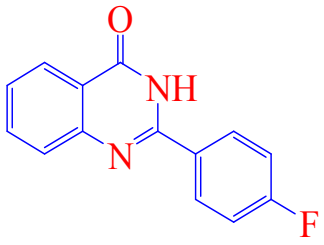
White solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.54 (t, J= 7.2 Hz, 1H), 7.76 (d, J= 7.6 Hz, 1H), 7.83– 7.86 (m, 1H), 7.90 (d, J ¼ 7.6 Hz, 2H), 8.15 (d, J= 7.2 Hz, 1H), 8.36 (d, J= 8.0 Hz, 2H), 12.76 (s, 1H);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 121.7, 124.4, 125.9, 126.4, 127.5, 128.1, 129.2, 131.6, 135.2, 137.1, 148.9, 151.7, 162.7.
HRMS (ESI) calcd for C15H10F3N2O $[M + H]^+$ 291.0740, found 291.0737.

2-(4-Chlorophenyl)quinazolin-4(3H)-one (3k):



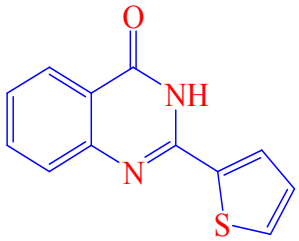
Light yellow solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.52 (t, J= 7.2 Hz, 1H), 7.61 (d, J= 8.4 Hz, 2H), 7.73 (d, J= 7.6 Hz, 1H), 7.83 (t, J= 8.0 Hz, 1H), 8.14 (d, J= 8.0 Hz, 1H), 8.19 (d, J= 8.4 Hz, 2H), 12.58 (br s, 1H);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 121.5, 126.4, 127.3, 128.0, 129.2, 130.1, 132.0, 135.2, 136.8, 149.0, 151.9, 162.6.
MS (ESI) m/z 257.8 $[M + H]^+$

2-(4-Fluorophenyl)quinazolin-4(3H)-one (3i):



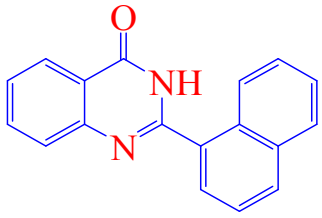
Yellow solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.36– 7.40 (m, 2H), 7.49–7.53 (m, 1H), 7.72 (d, J ¼ 7.2 Hz, 1H), 7.80– 7.84 (m, 1H), 8.12–8.15 (m, 1H), 8.23–8.25 (m, 2H), 12.55 (s, 1H);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 116.1, 121.3, 126.3, 127.1, 127.9, 129.7, 130.8, 135.1, 149.1, 151.8, 162.7, 164.5.
MS (ESI) m/z 241.1 $[M + H]^+$

2-(Thiophen-2-yl)quinazolin-4(3H)-one (3m):



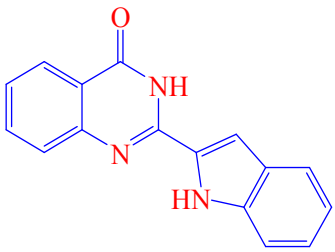
Light yellow solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.20–7.22 (m, 1H), 7.44–7.48 (m, 1H), 7.63 (d, J ¼ 8.0 Hz, 1H), 7.75–7.78 (m, 1H), 7.82–7.85 (m, 1H), 8.10 (d, J ¼ 8.0 Hz, 1H), 8.21–8.22 (m, 1H), 12.63 (s, 1H);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 121.3, 126.5, 126.8, 127.4, 129.0, 129.9, 132.6, 135.2, 137.8, 148.3, 149.1, 162.3.
MS (ESI) m/z 229.3 $[M + H]^+$

2-(Naphthalen-1-yl)quinazolin-4(3H)-one (3n):



Light yellow solid
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.55–7.66 (m, 4H), 7.72 (d, J=7.6 Hz, 1H), 7.78 (d, J= 6.8 Hz, 1H), 7.85 (t, J= 6.8 Hz, 1H), 8.02–8.05 (m, 1H), 8.11 (d, J =8.4 Hz, 1H), 8.15–8.17 (m, 1H), 8.21 (d, J ¼ 7.6 Hz, 1H), 12.66 (s, 1H);
^{13}C NMR (DMSO-d_6, 100 MHz): δ 121.7, 125.6, 125.6, 126.3, 126.8, 127.3, 127.6, 128.0, 128.2, 128.8, 130.7, 130.9, 132.2, 133.6, 135.0, 149.2, 154.2, 162.4.
MS (ESI) m/z 273.5 $[M + H]^+$

2-(1*H*-Indol-2-yl)quinazolin-4(3*H*)-one (3o):



Yellow solid.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.62 (1H, s), 11.82 (1H, s), 8.17 (1H, d, *J* = 8.0 Hz), 7.88- 7.85 (1H, m), 7.75 (1H, d, *J* = 8.0 Hz), 7.68 (1H,s), 7.66 (1H, d, *J* = 8.0 Hz), 7.54 (2H, t, *J* = 7.2 Hz), 7.24 (1H, t, *J*= 8.4 Hz), 7.07 (1H, t, *J* = 7.2 Hz).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 149.2, 147.0, 138.1, 135.2, 130.5, 127.9, 127.4, 126.8, 126.4, 124.5, 122.1, 121.6, 120.4, 112.9, 105.5.
HRMS (ESI-MS): m/z cald. for $C_{16}H_{11}N_3O$ (M+H) 262.0980, found 262.0980.

RESULTS AND DISCUSSION

In our preliminarily investigation on the model reaction, it was found that the reaction could be finished under very simple reaction conditions in the presence of $Cr(NO_3)_3.9H_2O$ which gives the desired 2-substituted Quinazolinone derivatives in good yield. $Cr(NO_3)_3.9H_2O$ can efficiently catalyze a one-pot synthesis of 2-substituted quinazolinones from 2-bromobenzamide with benzaldehyde and aqueous ammonia under air (**Scheme 1**). Electron-donating or electron withdrawing groups attaching to aromatic ring were investigated. The substitution groups on the aromatic ring of aldehyde had no obvious effect on the yield. The reaction was carried out under very simple reaction conditions which gives the desired 2-substituted Quinazolinone derivatives in good yield.

CONCLUSION

The present work concludes that, $Cr(NO_3)_3.9H_2O$ has been employed as a novel and efficient catalyst for the synthesis of 2-substituted quinazolinones. The present methodology is very simple, cheap and shows some specific advantages such as mildness, short reaction times. Thus, the developed methodology could be an alternative for the academic as well as industrial applications.

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