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An efficient and convenient synthesis of quinazoline derivatives catalyzed by cyanuric chloride in water

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ABSTRACT

In this work, an eco-friendly procedure for the preparation of 2,3-dihydroquinazoline-4(1*H*)-ones was developed by condensation reaction of benzylic and heterocyclic aldehydes with 2-aminobenzamide in the presence of catalytic amounts of cyanuric chloride (2,4,6-trichloro-1,3,5-triazin) as an available and inexpensive organo-catalyst under aqueous media as a green conditions. The new compounds characterized by IR, ^{1}HNMR, ^{13}CNMR, Mass spectrometry, and CHN elemental analysis. Excellent yield, clean reaction media, simple workup and easy purification are advantages of this methodology.

***Keywords**: Cyanuric chloride, Organo-catalyst, Quinazoline, Green chemistry, Aldehyde, Water.*

1. Introduction

Modern organic synthesis is faced with the challenge of developing new, efficient, economical, and eco-friendly processes that enable the preparation of various products in a rapid and cost-effective manner. According to the green chemistry principles, using recyclable and safe solvents, or solvent-free systems in organic chemistry reactions is recommended. In this regard, water can be best replacement for organic solvents for biochemical reactions. It is a nonvolatile, nonflammable, nontoxic, and inexpensive solvent [1-2].

The heterocyclic nitrogen compounds like quinazolinone derivatives are one of the most important products in modern chemistry. 2,3-Dihydroquinazoline-4(1H)-one derivatives have been reported to possess a wide range of pharmacological and biological activities (Figure 1) such as antimalarial [3], anticancer [4], antibacterial [5], antifungal [6], anticonvulsant [7], and herbicidal [8] activities. Several methods and catalysts have been proposed for the preparation of quinazoline derivatives, for example, *p*-sulfonic acid calix arene [9], Starch solution [10] Heteropoly acids (HPAS) [11], ammonium bromide [12], TiO_2 NPs [13], Gallium(III) triflate [14], *β*-cyclodextrin-SO_3H [15], $ZrCl_4$ [16], Agar [17].

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But most of them are associated with several drawbacks including, long reaction time, harsh conditions, poor selectivity and high cost.

Inexpensive, available and nontoxic catalysts are very important for chemist and specially pharmacists. Cyanuric chloride (2,4,6-Trichloro-1,3,5-triazine) is low-cost, non-volatile, available reagent which has been used as a catalyst for the preparation of different types of compounds. Mahadevan's group reported the synthesis of indoles and spiro-oxindoles [18], Li et al. described one-step method for the preparation of Benzo [1,3] dioxoles [19], Shariat et al. prepared benzoxazin-4-one derivatives in the presence of cyanuric chloride as a cyclizing agent [20], and Bigdeli used this catalyst for the synthesis of benzoxazin [21]. Here we wish to report a facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives using catalytic amounts of cyanuric chloride as inexpensive, available catalyst, via the cyclocondensation of 2-aminobenzamide with aldehydes in water.

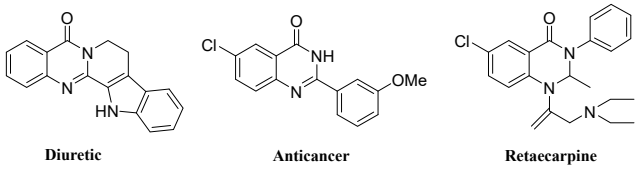


Fig. 1. Biologically active quinazolinone based natural product [22].

2. Experimental

2.1. Materials and Solvents

The reagents and solvents were purchased from Merck and Aldrich Chemical companies and were used as received. The samples were analyzed by FT-IR spectroscopy (JASCO FT/IR-460 plus spectrometer) and melting points were measured by Electrothermal 9100 apparatus. ^{1}HNMR and ^{13}CNMR spectra of compounds were recorded on a Bruker DRX-400 Avance instrument in DMSO-d_6. The mass spectra for the new compounds were recorded on an Agilent Technology HP 5973 MSD mass spectrometer operating at an ionization potential of 70 eV and Elemental analyses were performed using a Heraeus CHN- Rapid analyzer.

2.2. General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives:

A mixture of an aldehyde (1.0 mmol), 2-aminobenzamide (1.0 mmol, 0.136 g) and cyanuric chloride (20 mol%) in water (2 mL) was stirred at 80°C. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was filtered. The residue was washed with water and recrystallized from ethanol. Products were identified by FTIR, ^{1}HNMR, ^{13}CNMR, mass spectroscopy and CHN elemental analysis.

Selected spectral data

*2,3-Dihydro-2-phenylquinazolin-4(1H)-one (**Table 3, entry 1**):*

White crystal. m.p.= 221-222°C. IR (KBr): $\bar{\nu}$ = 3291, 3035, 1651, 1610, 1488 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 8.29 (s, 1H), 7.60 (d, 1H), 7.48 (d, 2H, J = 7.4 Hz), 7.33-7.40 (m, 3H), 7.23 (t, 1H), 7.08 (s, 1H), 6.75 (d, 1H), 6.69 (t, 1H, J = 7.4 Hz), 5.75 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 164.4, 149, 143.5, 134.2, 129.5, 129, 128.3, 127.7, 118.1, 115.8, 114.9, 67.6 ppm.

*2-p-Tolyl-2,3-dihydroquinazolin-4(1H)-one (**Table 3, entry 4**):*

White solid. m.p.= 225-226°C. IR (KBr): $\bar{\nu}$ = 3312, 3065, 1656, 1611, 1542, 1487 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 8.19 (s, 1H), 7.63 (d, 1H, J = 7.5 Hz), 7.40 (d, 2H, J = 7.9 Hz), 7.26−7.17 (m, 3H), 7.02 (s, 1H), 6.75 (d, 1H, J = 8.0 Hz), 6.71 (t, 1H, J = 7.4 Hz), 5.70 (s, 1H), 2.31 (s, 3H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 162.4, 149, 148, 146, 133.5, 127.5, 126, 123.6, 121.3, 116.6, 115.5, 65.3 ppm.

*2-(4-hydroxy-3-methoxy-5-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**Table 3, entry 10**):*

Yellow solid. m.p= 192-193°C, IR (KBr): $\bar{\nu}$ = 3360, 3206, 1681, 1612, 1544, 1514, 1489, 1346 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 3.90 (s, 3H), 5.80 (s, 1H), 6.72 (t, 1H), 6.80 (d, 2H), 7.29 (t, 1H), 7.48 (d, 1H, J = 2.0), 7.57 (d, 1H, J= 2.0), 7.63 (dd, 1H), 8.35 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ = 164, 150, 148, 143, 136.8, 133.5, 132, 128, 118, 115.5, 65, 58 ppm. MS (EI, 70 eV): m/z (%)= 315 (M^+), 314 (M-1). Anal. Calcd. for $C_{15}H_{13}N_3O_5$: C, 53.08, H, 3.86, N, 12.37; Found: 53.16, H, 3.97, N, 12, 39.

*2-(2,6-dichlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (**Table 3, entry 11**):*

White solid. m.p.= 210-211°C, IR (KBr): $\bar{\nu}$ = 3433, 3190, 1650, 1615, 1575, 1518, 1489 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ = 8.16 (s, 1H), 7.64 (dd, 1H), 7.54 (d, 2H), 7.45 (d, 1H), 7.25 (m, 1H), 7.25 (s, 1H), 6.78 (d, 1H), 6.65 (dd, 2H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 163.30, 148.28, 136.5, 134, 133.80, 131.50, 130.30, 127.70, 117, 114.10, 113.80, 65 ppm. MS (EI, 70 eV): m/z (%)= 293 (M^+), 292 (M-1), 294 (M+1). Anal. Calcd. for $C_{14}H_{10}ClN_2O$: C, 56.69, H, 3.39, N, 9.43; Found: C, 56.95, H, 3.43, N, 9.51.

3. Results and Discussion

Following our recent studies directed towards the development of practical, facile, inexpensive and eco-friendly procedures for synthesis of compounds. Most of the synthetic protocols for quinazolinone reported so far suffer from harsh reaction conditions such as pyridine/DMF [23], long reaction time [10], poor selectivity [24,25] and expensive methods [26]. In addition, the transition metal-containing compounds often used for synthesis of this compounds [16,27,28] (Table 1). We used cyanuric chloride as a source of HCl as a suitable catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives.

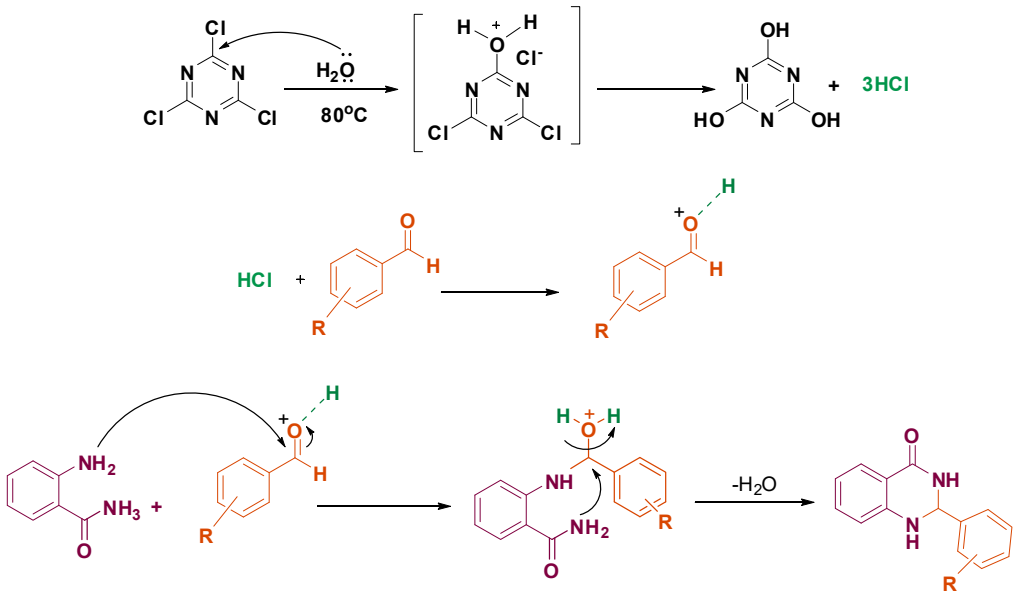
Cyanuric chloride is an organo-catalyst and the advantages of this catalyst are available and inexpensive also the procedures of reaction is simple, efficient and environmentally friendly. An acceptable mechanism is shown in Scheme 1. Cyanuric chloride reacts with water and releases 3 moles of HCl and cyanuric acid (removable by washing with water) as by-product. The *in situ* generated HCl acts as a protic acid and activates the carbonyl oxygen to promote the condensation reaction [21]. Subsequently, the activated aldehyde reacted with 2-aminobenzamide to give the products.

To achieve suitable conditions for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives, the reaction between 4-chlorobenzaldehyde and 2-aminobenzamide as a simple model system was carried out under aqueous conditions using various amounts of catalyst and different temperatures (Table 2). As could be seen in Table 2, the best result was obtained with 20 mol% cyanuric chloride as a catalyst at 80ºC. Using less catalyst resulted in lower yields, whereas higher amounts of catalyst did not affect reaction times and yields.

Table 1. The catalysts used for the preparation of quinazolinones.

Entry	Catalysts	Time (h)	Temp. (°C)	Yield (%)[a]	Ref.
1	$ZrCl_2$	0.25	r.t	95	[16]
2	Starch solution	4	r.t	90	[10]
3	Tetra-n-butyl ammonium bromide	0.5	105	90	[12]
4	$SrCl_2$ $6H_2O$	0.7	85	93	[27]
5	$CuCl_2/Fe_3O_4$-TEDETA	0.5	80	96	[28]
5	Cyanuric chloride	0.5	80	93	This work

[a]For benzaldehyde.



Scheme 1.

Table 2. Synthesis of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-ones under various conditions[a].

Entry	Catalyst amount (mol%)	Time (min)	Temp. (°C)	Yield (%)
1	0	90	80	No reaction
2	10	45	80	83
3	20	90	25	50
4	20	90	50	67
5	20	35	80	98
6	30	30	80	98

[a]Reaction conditions: 4- chlorobenzaldehyde (1.0 mmol), 2-aminobenzamide (1.0 mmol).

Encouraged by this success, variety of aldehydes were used for preparation of quinazoline under similar conditions. The results were summarized in Table 3. Benzaldehyde derivatives with both electron-donating and electron-withdrawing substituents were reacted with 2-aminobenzamide at the same reaction conditions and the corresponding 2-aryl-2,3-dihydroquinazolin-4(1H)-ones were obtained in the 82–97% yields (Table 3, entry 1-11). 2-Thiophen-2,3-dihydroquinazolin-4(1H)-one and 2-furyl-2,3-dihydroquinazolin-4(1H)-one were also obtained using thiophene-2-carbaldehyde and 2-furancarbaldehyde as heterocyclic starting material in good yield at short reaction time (Table 3, entry 12,13).

Table 3. Synthesis of various 2,3-dihydro-2-phenylquinazolin-4(1*H*)-ones in the presence of cyanuric chloride.[a]

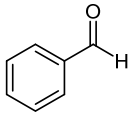
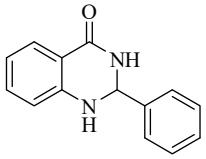
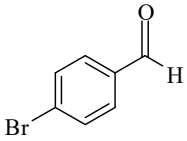
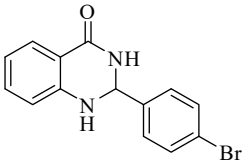
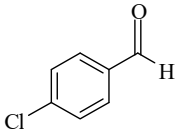
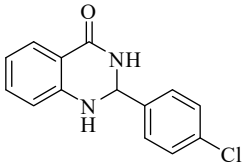
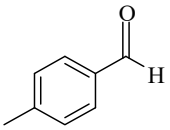
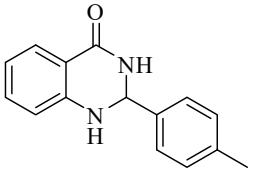
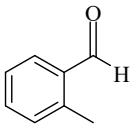
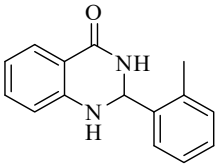
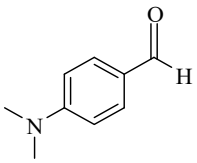
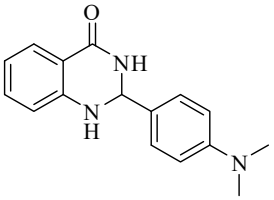
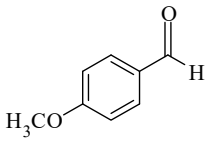
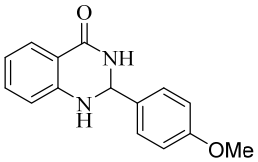
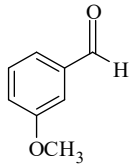
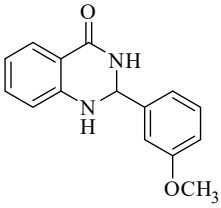
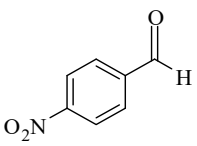
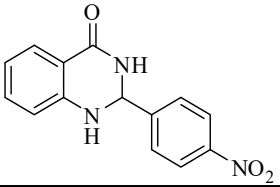
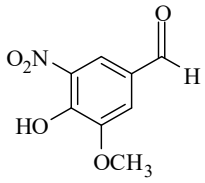
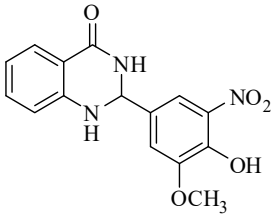
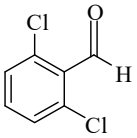
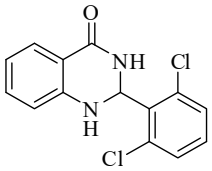
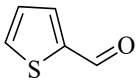
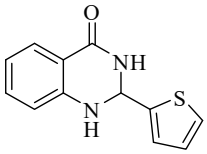
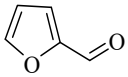
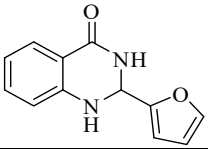
Entry	Aldehyde	Product	Time (min)	Yield (%)[b]	m.p. (°C)		Ref.
					Found	Reported	
1			30	93	221-222	218–220	[16]
2			20	98	197-198	197-198	[29]
3			35	98	203-205	206–208	[12]
4			15	98	225-226	227–229	[29]
5			55	83	188-189	188–189	[30]
6			20	98	220-222	227–229	[12]
7			20	94	181-182	181-182	[29]
8			25	91	147–149	147–149	[15]
9			30	74	214-215	214–216	[12]

Table 3. (*Continued*).

10			35	95	192-193	-	-
11			50	89	210-211	-	-
12			30	93	192-193	191–193	[30]
13			40	91	166-167	166–168	[14]

[a]Reaction conditions: aldehyde (1.0 mmol), 2-Aminobenzamide (1.0 mmol)**,** Cyanuric chloride (20 mol%) in water at 80°C.
[b]Isolated yields.

4. Conclusions

In summary, a simple and highly efficient methodology for the generation of bioactive quinazolinone derivatives in water is reported. This compounds were synthesized by condensation reaction of benzylic and heterocyclic aldehydes with 2-aminobenzamide in the presence of catalytic amounts of cyanuric chloride as available catalyst. In addition, the media for this procedure is water and "fast", "green" and "low cost" method for the synthesis of these products are the advantages for this protocol. Cyanuric acid as by-product is removable by washing with water. This easy elimination of the catalyst makes this method a better choice for chemical industries.

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