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A Choline hydroxide catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones in an aqueous medium

Pravin N. Borase<sup>‡</sup>, Pranila B. Thale<sup>‡</sup> and G. S. Shankarling<sup>\*</sup>

A simple, metal and ligand-free protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones derivatives using choline hydroxide (ChOH) as an effective catalyst in an aqueous medium has been developed. The good to high yield of the desired product is obtained, with low environmental factor and high atom economy. The ChOH was found to be recyclable up to six consecutive runs without significant loss in its activity. The use of water as an environmentally benign solvent, ease of work up and efficient recyclability of the catalyst makes this process more advantageous and greener.

#### 1. Introduction

2,3-dihydraquinazolinones, a nitrogen containing heterocyclic compounds are found as the core structural skeleton in a of drug molecules<sup>1–4</sup> varietv (Scheme 1). 2.3dihydraguinazolinones derivatives have drawn much attention due to their potential in biological and pharmaceutical activities such as antidepressant, analgesic, diuretic, sedative, antihistamine and antihy-pertensive agent<sup>5,6</sup>. It is also useful in various anticancer activities like inhibition of tubulin formation, inhibition against VEGFR2 tyrosine kinase and cell proliferation<sup>7</sup>. Generally, ortho-amino or ortho-nitro benzoic acid derivatives are used for 2,3-dihydroquinazolin-4(1H)-ones synthesis. Grieß et al, has reported the first synthesis of quinazolinone scaffold from anthranilic acid and cyanogen<sup>8</sup>. Later, Von Niementowski optimized the reaction involving the fusion of anthranilic acid analogues with amides<sup>9</sup>. In recent years, synthesis of 2,3-dihydroquinazolin-4(1H)-ones has been reported in the presence of various acid and metal catalyst<sup>10-</sup> More recently, synthesis of 2-substituted dihydroquinazolinones was published by Jian Wu and coworker using anthranilamide and carbonyl compounds in the presence of  $\beta$ -cyclodextrin as a catalyst<sup>14</sup>. Other homogeneous catalysts such as  $K_3PO_4^{15}$  and  $ZnCl_2^{16}$  have also been reported for effective cyclization of the dihydroquinazolinones. However, their major shortcomings are need of higher temperature, longer reaction time and difficulty in the recycling of the catalyst. To overcome the issue of separation, recently Tamaddon et al<sup>17</sup> have reported Amberlyst A26-OH as heterogeneous catalyst for the synthesis of 2,3а

dihydroquinazolin-4(1H)-ones. But, this method also suffers few drawbacks like the use of binary solvent mixture and comparatively longer reaction time is needed. Owing to the above limitations, the development of an inexpensive and environmentally benign catalyst for 2,3-dihydroquinazolin-4(1H)-ones synthesis has been a major area of the research.



Scheme 1: Selected examples of pharmaceutically active quinazolinone derivative

In the current era, aqueous media for organic synthesis has a great importance in the context of greener solvent media<sup>18–20</sup>. Water is a readily available, non-toxic, environmentally friendly and has a strong hydrogen bonding ability, which can lead to unusual reactivity which is not seen in traditional organic solvents. Water is potentially safer than other organic solvents and considered as an environmentally benign and non-hazardous solvent<sup>21–25</sup>.

Choline chloride is cheaply available and choline based ionic liquids plays a crucial role in a variety of organic

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#### ARTICLE

transformations<sup>26–29</sup>. It also offers attractive industrial forecasts in terms of sustainable and viable chemistry<sup>30</sup>. It has several advantages in terms of availability, low price, biodegradability and environmentally benign features<sup>31–33</sup>. Choline hydroxide possesses a strong basic characteristic. Therefore, the developed protocol offers a use of the environmentally benign solvent and the recyclable catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Herein, we report an efficient, metal and ligand free, economically inexpensive catalytic strategy for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones derivatives in an aqueous medium (Scheme 2). The recyclable and inexpensive catalyst in an aqueous medium stand out, to be a valuable alternative for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones derivatives.



Scheme 2: General reaction scheme

#### 2. Result and Discussion:

In the current protocol, we have used 2-aminobenzonitrile and benzaldehyde as a model substrates for the optimisation of the reaction condition (Scheme 2). We have thoroughly investigated the effect of base by conducting series of reaction with different inorganic bases, such as KOH, NaOH, Na<sub>2</sub>CO<sub>3</sub>,  $K_2CO_3$ , and  $Cs_2CO_3$  which gave the desired product in the range 60% to 40% yields (Table 1). Whereas, in the presence of ChOH as a catalyst in an aqueous medium we obtained the desired product in good yield 96% (Table 1, Entry 5). The higher yield of the product was obtained with ChOH because it acts as a homogeneous catalyst in an aqueous medium which helps to improve the solubility of the reactants through hydrogen bonding and hence increases the rate of the reaction. Next, we have screened various solvents among which water was the most effective solvent for cyclization of the Schiff base intermediate. (Table 1, Entry 21). The poor yield of the target product was obtained in toluene and dioxane solvents. However, other solvents such as methanol, ethanol and dimethylformamide (DMF) gave low yield in comparison to that of water. To determine the catalyst loading, a model reaction of 2-aminobenzonitrile and benzaldehyde with the different percentage of ChOH in water was carried out. The reaction occurred smoothly in the presence of 30% ChOH as a catalyst and water as a solvent, affording a single product in 96% yield. Increasing the amount of catalyst, more than 30% showed no substantial improvement in the yield (Table 1, Entry 6). The suitable temperature for the reaction was found to be 80°C. (Table 1, Entry 14). Therefore, optimised reaction parameter includes 1.0 mmol of 2-aminobenzonitrile, 1.2 mmol of aldehyde, 30% of ChOH as a catalyst and water as a

solvent at 80°C. Similarly, we have studied the role of various bases over the different substrates of aldehyde (benzaldehyde, p-chloro benzaldehyde and p-tolualdehyde). For this, we have conducted a series of reaction with different inorganic bases and ChOH. From the table 2, it can be seen that the yield of the desired product is maximum when choline hydroxide is used as a catalyst. Increasing the amount of inorganic bases will not improve the yield of the product<sup>15</sup>. With the optimised parameters in hand we have also performed wide substrate study with different aliphatic, aromatic and heteroaromatic aldehydes for the synthesis of 2,3-dihydroquinazolin-4(1H)ones derivatives (Table 3). Good to excellent yields of the desired product were obtained with heterocyclic, aliphatic and electron withdrawing aromatic aldehydes. However, electron donating aromatic substituents provided moderate yield of the desired product.

Tabla	1.	Ontimization	of	reaction	condition
rable	Τ:	Optimization	01	reaction	condition

Entry	Catalyst	V/V %	Temp	Time	Solvent	Yield (%)	
Effect of Catalyst							
1	Neat		80°C	24h	Water	NR	
2	ChCl	30%	80°C	24h	Water	NR	
3	ChOH	10%	80°C	6h	Water	86%	
4	ChOH	20%	80°C	2h	Water	89%	
5	ChOH	30%	80°C	30min	Water	96%	
6	ChOH	40%	80°C	30min	Water	96%	
		Effect of o	other bas	ic catalyst			
7	K <sub>2</sub> CO <sub>3</sub>	2.5°	80°C	8h	Water	40%	
8	Cs <sub>2</sub> CO <sub>3</sub>	2.5 <sup>ª</sup>	80°C	8h	Water	35%	
9	$Na_2CO_3$	2.5°	80°C	8h	Water	30%	
10	NaOH	2.5°	80°C	8h	Water	50%	
11	КОН	2.5 <sup>°</sup>	80°C	8h	Water	60%	
		Effect	of Tempe	erature			
12	ChOH	30%	40°C	30min	Water	45%	
13	ChOH	30%	60°C	30min	Water	70%	
14	ChOH	30%	80°C	30min	Water	96%	
15	ChOH	30%	100°C	30min	Water	96%	
		Effe	ect of Solv	/ent			
16	ChOH	30%	80°C	4h	MeOH	80%	
17	ChOH	30%	80°C	4h	EtOH	85%	
18	ChOH	30%	80°C	6h	DMF	60%	
19	ChOH	30%	80°C	8h	Toluene	45%	
20	ChOH	30%	80°C	8h	Dioxane	50%	
21	ChOH	30%	80°C	30min	Water	96%	

Conditions: 2-aminobenzonitrile (1mmol), Benzaldehyde (1.2mmol), 30% V/V of ChOH in water 3.5mL,  $^{a}$ Base used (2.5 equiv.)

Scheme 3: Substrate study with base catalyst



$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Entry	Catalyst	Catalyst	Yield (%) <sup>c</sup> , Time			
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Entry	Catalyst	loading	R <sub>2</sub> = -H	$R_2 = -CH_3$	$R_2 = -CI$	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1	ChOH	30%ª	96 (30min)	89 (110min)	90 (50min)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2	K <sub>2</sub> CO <sub>3</sub>	2.5 <sup>b</sup>	40 (8h)	Traces (8h)	Traces (8h)	
$\begin{array}{cccc} 4 & Na_2CO_3 & 2.5^{b} & 30  (8h) & Traces & Traces \\ (8h) & (8h) & \\ 5 & NaOH & 2.5^{b} & 50  (8h) & 20  (8h) & 25  (8h) \\ \hline 6 & KOH & 2.5^{b} & 60  (8h) & 45  (8h) & 50  (8h) \end{array}$	3	Cs <sub>2</sub> CO <sub>3</sub>	2.5 <sup>b</sup>	35 (8h)	Traces (8h)	Traces (8h)	
5 NaOH 2.5 <sup>b</sup> 50 (8h) 20 (8h) 25 (8h)   6 KOH 2.5 <sup>b</sup> 60 (8h) 45 (8h) 50 (8h)	4	$Na_2CO_3$	2.5 <sup>b</sup>	30 (8h)	Traces (8h)	Traces (8h)	
6 KOH 2.5 <sup>b</sup> 60 (8h) 45 (8h) 50 (8h)	5	NaOH	2.5 <sup>b</sup>	50 (8h)	20 (8h)	25 (8h)	
	6	6 KOH 2.5 <sup>b</sup>		60 (8h)	45 (8h)	50 (8h)	

Conditions: 2-Aminobenzonitrile (1mmol), aldehyde (1.2mmol), 330% V/V of ChOH in water 3.5mL, <sup>b</sup>Base used (2.5 equiv.) and Temp: 80°C; <sup>c</sup>Isolated yield

Based on the present experimental observations and literature reports<sup>34–38</sup>, the proposed reaction mechanism is depicted in scheme 4. The reaction was initiated with the formation of Schiff base intermediate between aldehyde and 2-aminobenzonitrile in the presence of ChOH catalyst. Then simultaneously, nucleophilic attack of counter hydroxide ion of ChOH on the electrophilic carbon of nitrile was favoured because of which intramolecular cyclization was initiated. The nucleophilic attack of nitrile nitrogen on the electron-deficient carbon of Schiff base resulted in the formation of cyclized product through 1,5 proton shift to give 2,3-dihydroquinazolin-4(1H)-ones derivative. To confirm the above proposed reaction mechanism, we have isolated the Schiff base intermediate (Schiff base INT\_1) and characterised it by using <sup>1</sup>H-NMR (Figure S2) and ESI-MS mass analysis technique.



The intrinsic atom economy was found to be 100%, which markedly influence the greenness of the current protocol. The environmental factor (E-factor) was calculated to understand the amount of waste generated and effectiveness of the protocol. The E-factor was calculated form the ratio of total

amount of waste generated with respect to the total amount of product formed and it was found in the range of 14 to 30% (Table 3). This is in a good accordance with the principle of green chemistry. Thus, ChOH based catalytic protocol provides an astonishing reactivity in presence of water for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Table	3:	ChOH	catalyzed	synthesis	of	2,3-
dihydro	oquina	zolinone-4	l(1H)-ones			
		<	Insert Table 3	>		

Conditions: 2-Aminobenzonitrile (1mmol), aldehyde (1.2mmol), 30% V/V of ChOH in water 3.5mL, Temp: 80°C; <sup>a</sup>Isolated yield; <sup>b</sup>E-factor = environmental factor

#### 3. Experimental section:

#### 3.1 Materials and Methods:

IR spectra of the compounds were recorded on Jasco FT-IR ATR-PRO/4100 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on Agilent 500 MHz spectrometer in DMSO solvent. Mass spectral data were obtained with a Finnigan LCQ Advantage max spectrometer. Choline chloride, Pottasium hydroxide, Methanol, Benzaldyhde and its derivatives were purchased from S.D. Fine Chemical Ltd., India. and 2-aminibenzonitrile was purchased from Sigma Aldrich Chemicals.

# 3.2 General procedure for the synthesis of choline hydroxide (ChOH):

To a solution of choline chloride (1 mol) in methanol, one mole equivalent of potassium hydroxide was added slowly at room temperature. Later, it was heated at  $60^{\circ}$ C for 12 h with constant stirring. After cooling to room temperature, the reaction mixture was filtered to remove solid KCl salt. The obtained solution was concentrated to remove excess of methanol and was used without further purification.

#### 3.3 Determination of Basicity of ChOH:

The basicity of the ChOH hydroxide was determined by the conventional acid-base titration method. 1.5 ml of ChOH was taken in 50 ml of water and titrated against the standardized 0.1M HCl solution using phenolphthalein as an indicator. The concentration of  $OH^{-}$  ions was found to be 0.0052 meg/mL.

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

In a general procedure, a mixture of 2-aminobenzonitrile (1.0 mmol), benzaldehyde (1.2 mmol), ChOH 30% volume by volume in water (3.5 ml) was stirred at 80°C and the progress of the reaction was monitored on the TLC. After completion of the reaction the reaction mass was cooled, the solid product was filtered and washed with water. The crude product was purified by column chromatography on silica gel using hexane: ethyl acetate (6:4) as an eluent to obtain the desired product. Yield 96%, 0.67 g, m.p. 208°C. All compounds were analysed by melting point, mass, IR and <sup>1</sup>H-NMR techniques.

#### 3.5 Recyclability studies:

To understand the process viability and feasibility, the reaction of 2-aminobenzonitrile and benzaldehyde was scaled-up to 1 g.

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#### ARTICLE

The ChOH was recovered and used for recyclability study (Figure 1). After filtration of the crude product from reaction mass, the filtrate was used for the next recycle study. The ChOH was recycled up to six consecutive runs without any significant loss in its activity. The Fresh and reused ChOH have been characterized by ATR-FTIR spectroscopy. The comparative study of the fresh and reused catalyst illustrate that, there is no change in the functional group values in the FT-IR spectrum (Figure S1). The broad absorption peak at 3352 cm<sup>-1</sup> is characteristics of O-H stretching vibration. The band at 1293 and 1078 cm<sup>-1</sup> corresponds to stretching vibration of C-N and C-O bond respectively. The C-H bending vibrations was observed at 862 cm<sup>-1</sup>.





#### 4. Conclusion:

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In summary, we have demonstrated a simple, metal and ligand free strategy for the synthesis of 2,3-dihydroquinazolin-4(1H)ones derivatives in an aqueous medium. The catalyst was efficient and recyclable up to six consecutive runs. The low range of E-factor, high atom economy, use of greener aqueous media and recyclable catalyst satisfies the principles of green chemistry.

#### 5. Acknowledgements

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#### Notes

‡ These others contributes equally

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### **Figures and Table captions**

- 1) Scheme 1: Selected examples of pharmaceutically active quinazolinone derivative
- 2) Scheme 2: General reaction scheme
- 3) Scheme 3: Substrate study with base catalyst
- 4) Scheme 4: Plausible reaction mechanism
- 5) Table1: Optimization of reaction conditions
- 6) Table 2: Effect of base catalyst over aldehyde substrate.
- 7) Table 3: ChOH catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones
- 8) Figure 1: Recyclability study of ChOH catalyst

Scheme 1: Selected examples of pharmaceutically active quinazolinone derivative.



Scheme 2: General reaction scheme.



Scheme 3: Substrate study with base catalyst







Entry.	Catalyst	V/V %	Temp	Time	Solvent	Yield (%)		
Effect of Catalyst								
1	Neat		80°C	24h	Water	NR		
2	ChCl	30%	80°C	24h	Water	NR		
3	ChOH	10%	80°C	6h	Water	86%		
4	ChOH	20%	80°C	2h	Water	89%		
5	ChOH	30%	80°C	30min	Water	96%		
6	ChOH	40%	80°C	30min	Water	96%		
		Effect o	f other ba	sic catalyst				
6	$K_2CO_3$	2.5 <sup>a</sup>	80°C	8h	Water	40%		
7	$Cs_2CO_3$	<b>2</b> .5 <sup>a</sup>	80°C	8h	Water	35%		
8	$Na_2CO_3$	2.5 <sup>a</sup>	80°C	8h	Water	30%		
9	NaOH	<b>2</b> .5 <sup>a</sup>	80°C	8h	Water	50%		
10	КОН	2.5 <sup>a</sup>	80°C	8h	Water	60%		
Effect of Temperature								
11	ChOH	30%	40°C	30min	Water	45%		
12	ChOH	30%	60°C	30min	Water	70%		
13	ChOH	30%	80°C	30min	Water	96%		
14	ChOH	30%	100°C	30min	Water	96%		
		E	ffect of So	lvent				
15	ChOH	30%	80°C	4h	MeOH	80%		
16	ChOH	30%	80°C	4h	EtOH	85%		
17	ChOH	30%	80°C	6h	DMF	60%		
18	ChOH	30%	80°C	8h	Toluene	45%		
19	ChOH	30%	80°C	8h	Dioxane	50%		
20	ChOH	30%	80°C	30min	Water	96%		

Conditions: 2-aminobenzonitrile (1mmol), Benzaldehyde (1.2mmol), 30% V/V of ChOH in water 3.5mL, <sup>a</sup>Base used (2.5 equiv.)

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Entry	Catabust	Catalyst	Yield (%) <sup>c</sup> , Time		
Entry	Catalyst	loading	R <sub>2</sub> = -H	$R_2 = -CH_3$	$R_2 = -CI$
1	ChOH	30% <sup>a</sup>	96 (30min)	89 (110min)	90 (50min)
2	K <sub>2</sub> CO <sub>3</sub>	2.5 <sup>b</sup>	40 (8h)	Traces (8h)	Traces (8h)
3	Cs <sub>2</sub> CO <sub>3</sub>	2.5 <sup>b</sup>	35 (8h)	Traces (8h)	Traces (8h)
4	$Na_2CO_3$	2.5 <sup>b</sup>	30 (8h)	Traces (8h)	Traces (8h)
5	NaOH	2.5 <sup>b</sup>	50 (8h)	20 (8h)	25 (8h)
6	КОН	2.5 <sup>b</sup>	60 (8h)	45 (8h)	50 (8h)

Table 2: Effect of base catalyst over aldehyde substrate.

Conditions: 2-Aminobenzonitrile (1mmol), aldehyde (1.2mmol), <sup>a</sup>30% V/V of ChOH in water 3.5mL, <sup>b</sup>Base used (2.5 equiv.) and Temp: 80°C; <sup>C</sup>Isolated yield

Table 3: ChOH catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones

Entry	Starting material	Product	Time (min)	Yield (%) <sup>a</sup>	E- factor <sup>b</sup>
1	٥	NH NH NH	30	96%	0.09
2	0 <sup>°</sup> CI	NH H C	50	90%	0.17
3	OCOH	NH NH NH CH	80	86%	0.22
4	0 NO2	NH NH NO <sub>2</sub>	90	85%	0.24
5	0~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NH NH NH CCH <sub>3</sub>	100	92%	0.15
6	0		110	89%	0.18
7	o N	NH NH NH	120	85%	0.24

#### **RSC** Advances



Conditions: 2-Aminobenzonitrile (1mmol), aldehyde (1.2mmol), 30% V/V of ChOH in water 3.5mL, Temp: 80°C; <sup>a</sup>Isolated yield; <sup>b</sup>E-factor = environmental factor



Figure 1: Recyclability study of ChOH catalyst

# A Choline hydroxide catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones in an aqueous medium



Graphical abstract