Original Article: $ZnCl_2$-SiO_2 Supported Synthesis and Characterization of Novel 2-Phenylquinazolin-4(3*H*)-One Derivatives

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ABSTRACT

The present report describes a convenient novel synthetic method to synthesize quinazolin-4(3*H*)-ones from simple and readily available 2-aminobenzamide and benzaldehyde in the presence of catalyst $ZnCl_2$-SiO_2 giving corresponding 2-phenylquinazolin-4(3*H*)-one derivatives **3A-3F**. These newly synthesized products have been characterized by FT-IR, ^{1}H-NMR, and mass spectroscopic techniques.

Introduction

The finding of the novel catalyst for the preparation of medicinally potent compounds is an essential need to reflect the advantages of green chemistry [1-2]. Before the invention of the greener reagent, the aqueous inorganic acids had been used for the organic transformation including H_3PO_4, H_2SO_4, HNO_3, HF and HCl [3-4]. However, the use of high Brønsted acids was not good for the separation and environmental problems [5-6].

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In recent years, the development of the greener solvent-free methods development has superior advantages to solve the basic problems including environmental toxicity, eco-friendly synthetic methodologies by the use of water as a greener solvent [7-10]. In recent years, research has associated solving the problem related to the environmental toxicity with the development of the novel, eco-friendly synthetic methodologies, which conform to the green chemistry protocol. The utilization of water as a green reaction medium has gained momentum and has a greater advantage over the use of toxic solvent [11-14]. In the literature, there are various solvent-free methods and reactions in the numerous solvent have been reported in the last two decades [15-17]. Recently the phenylquinazolin-4(3*H*)-one derivative has been synthesized with heterogeneous solid supported catalyst catalysed by $SbCl_3$[18]; the major benefit of the solid-supported catalyst is the reaction undergoes minimum degradation that is useful for the extension of catalyst lifetime and simplified product isolation [19]. Nature has shown more tendency towards the quinazoline derivatives and their biological activity [20] (Figure 1).

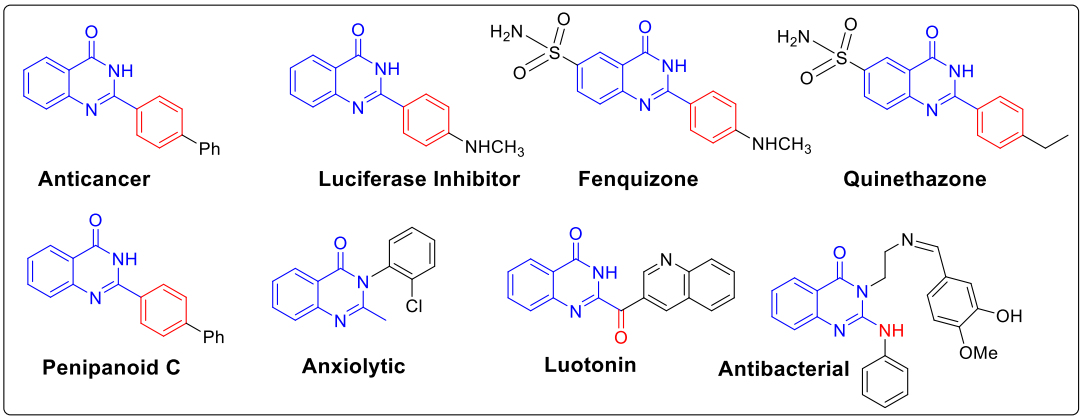


Figure 1. Bioactive phenylquinazolin-4(3*H*)-one derivatives

The quinazolin4(3H)-ones have been found to display antimalarial [21], anti-inflammatory [22], antibacterial [23], as well as other biological activities. Some of the most important bioactive phenylquinazolin-4(3*H*)-one derivatives are shown in Figure 1. Traditionally, phenylquinazolin-4(3*H*)-one derivative has been prepared from the anthranilic acids [24], anthranilamides [25], 2-halobenzamides [26], isotonic anhydrides [27], and 2-azidobenzamides [28]. However, most methods are disadvantageous with high catalyst loading, poor yields, prolonged reaction times, and the use of toxic organic reagents or solvents. We are always interested in the synthesis of nitrogen-containing heterocyclic compounds [29-33]. Here, we have developed a novel methodology for the synthesis of 2-phenylquinazolin-4(3*H*)-one derivative via the reaction of 2-aminobenzamide with benzaldehyde.

Experimental

The chemical and required apparatus was as per international standard rules. The M.P. of the newly synthesized compound was recorded over the thermal IA9100 (Bibby Scientific Limited, Staffordshire, UK). The spectra data were reported over the 1HNMR, 13 CNMR Bruker-300MHz, and Bruker-400

MHz instruments. The Bruker FTIR instruments were used for the meaning FT-IR.

Preparation of catalyst ($SiO_2/ZnCl_2$)

The SiO_2-supported $ZnCl_2$ catalyst was prepared from the literature reported method. 2.7 g of solid $ZnCl_2$ (12 mmol) was poured into the 9.1 gram of white SiO_2 (60, 230-400 Mesh) in the 60 Ml of ethanol solvent. The reaction mixture was refluxed with stirring for 1h under dark conditions, filtered and washed with dry CCl_4, and dried under vacuum at 160 °C for 10 h.

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

White solid. Mp 237–238 °C[33], FT-IR cm^{-1}: 3318, 1665 ^1H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.52–7.66 (4H, m, H Ar); 7.74 (1H, d, J = 8.6, H Ar); 7.88 (1H, t, J = 8.4, H Ar); 8.18 (1H, d, J = 8.2, H Ar); 8.18 (2H, d, J = 7.4, H Ar); 12.45 (1H, s, NH). (^{13}C 100MHz)δ, ppm: 162.4, 153.1; 149.2; 134.4; 132.5; 130.3; 128.9; 127.9; 127.8; 126.7; 126.2; 120.8.

2-(4-chlorophenyl)quinazolin-4(3H)-one (3B)

White solid: Mp 299–302 °C. ^1H NMR (400 MHz, DMSO-d6); δ 12.46 (bs, 1H), 8.23–8.18 (m, 2H), 8.17–8.13 (dd, J = 0.8, 7.6 Hz, 1H), 7.87–7.83 (m, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.65–7.60 (m, 2H), 7.54 (m, 1H); 13C NMR (100 MHz, DMSO-d6) δ 169.2, 166.9, 139.4, 136.1, 133.1, 132.7, 130.6, 129.4, 128.6, 128.3, 127.5, 118.7.

2-(4-fluorophenyl)quinazolin-4(3H)-one (3G)

White solid:Mp 296–297 °C[33]; ^1H NMR (500 MHz,$CDCl_3$) δ 12.57 (bs, 1H), 8.32–8.21 (m, 2H), 8.16 (dd, J = 8.0, 1.7 Hz, 1H), 7.84 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.52 (m, 1H), 7.43–7.35 (m, 2H).; 13C NMR (100 MHz, DMSO-d6) δ 163.9(d, 1JC–F = 248.0 Hz), 162.2, 151.3, 148.5, 134.5, 130.2(d, 3JC–F = 9.0 Hz), 129.2, 127.3, 126.5, 125.7, 120.7, 115.5(d, 2JC–F = 22 Hz).

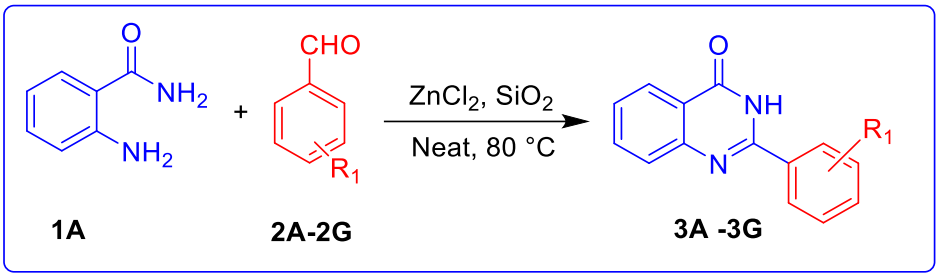
2-(o-tolyl)quinazolin-4(3H)-one (3H)

2-(*o-Toly*l)quinazolin-4(3*H*)-one (3d). White solid (0.072 g, 61% yield). M.P. 220–222 °C ^1H NMR (400 MHz, $CDCl_3$) δ 10.56 (*bs*, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 3.6 Hz, 2H), 7.58 (m, 1H), 7.53–7.48 (m, 1H), 7.46–7.40 (m, 1H), 7.35 (m, 2H), 2.53 (s, 3H); ^{13}CNMR(100 MHz, DMSO-d_6) δ 161.7, 154.3, 148.7, 136.1, 134.4, 134.2, 130.5, 129.8, 129.1, 127.3, 126.6, 125.7, 125.6, 120.9, 19.5.

Results and Discussion

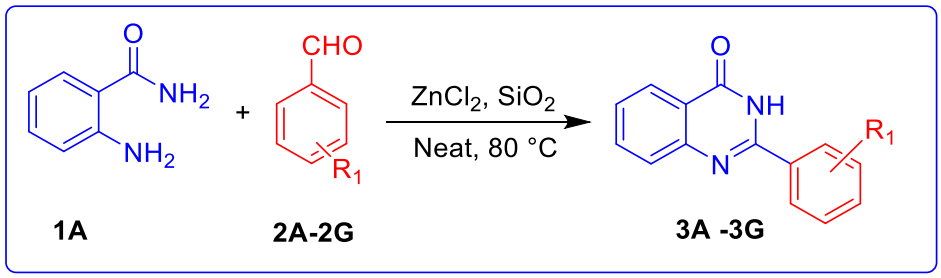
Initially, the reaction was performed with the substrate 2-aminobenzamide with benzaldehyde as a model reaction. When the first experimental reaction was performed without the use of a reagent, there is no conversion of product. As the reaction was performed in the presence of $ZnCl_2$ (0.5 Mol%) reagent and in a DCM solvent, the formation of **2-phenylquinazolin-4(3*H*)-one derivatives was observed with** 35% yield. As we increased the mole % of $ZnCl_2$ (0.5 to 1.0 mol%) and temperature, from the 50 °C to 75 °C, the formation of **3A** with **40% to 50%** (**Table 1, Entry 2,4**) yield was observed. Further, no change in the yield was observed. Then, we moved towards the $ZnCl_2/SiO_2$Catalyst (0.5 Mol%). At the beginning the reaction was performed at 0 °C to 60 °C. The formation of desire product was observed with a 65% (**Table 1, Entry 8**). Then, we increased the temperature as well as mole % of silica supported $ZnCl_2$; the formation of **3A** with increase in yield was observed (**up to 89%)** (**Table 1, Entry 10**).

Table 1. Optimization of the reaction conditions using $ZnCl_2/SiO_2$Catalyst



Sr/No	Reagent	Solvent	Temp	Time	Yields
1	NO	DCM	R.T	12	00
2	$ZnCl_2$	DCM	60	12	35
3	$ZnCl_2$	DCM	65	12	40
4	$ZnCl_2$	DCM	75	12	50
5	$ZnCl_2/SiO_2$Catalyst	NO	RT	12	20
6	$ZnCl_2/SiO_2$Catalyst	NO	RT	12	30
7	$ZnCl_2/SiO_2$Catalyst	NO	50 °C	8	55
8	$ZnCl_2/SiO_2$Catalyst	NO	60°C	6	65
9	$ZnCl_2/SiO_2$Catalyst	NO	70°C	6	80
10	$ZnCl_2/SiO_2$Catalyst	NO	80 °C	6	86

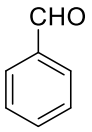
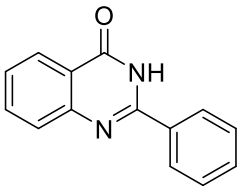
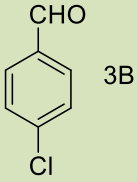
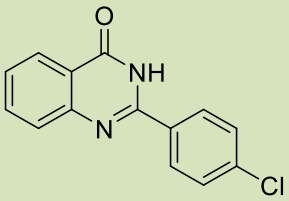
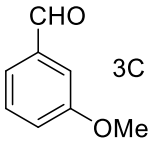
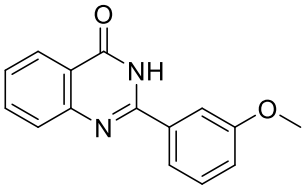
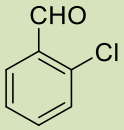
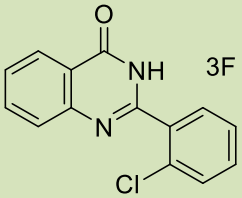
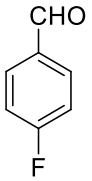
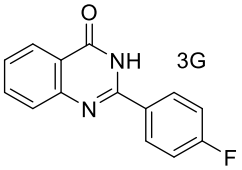
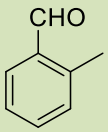
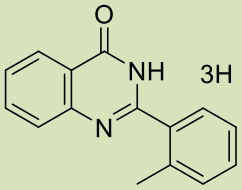
From the results, it was concluded that the best was observed with the $ZnCl_2/SiO_2$Catalyst with 80 °C temperature after 6 h; therefore, this condition was selected as the optimized condition to study the generality of developed methodology.



Scheme 1. Synthesis of 2-phenylquinazolin-4(3*H*)-one derivatives

Further, we examined the reaction between a series of numerous aldehydes with 2-amino benzamide under optimal conditions to produce the corresponding novel 2-phenyl quinazolin-4(3*H*)-one derivatives 3A-3G (**Scheme 1**). In the experiment, we found that the substrate with electron-withdrawing groups as well as electron-donating groups present in the nucleus proceeded with a very good yield. All the newly prepared compounds were characterized with the ^{1}HNMR, ^{13}NMR, FT-IR, and mass spectroscopy techniques, confirmed by comparing with the literature melting point.

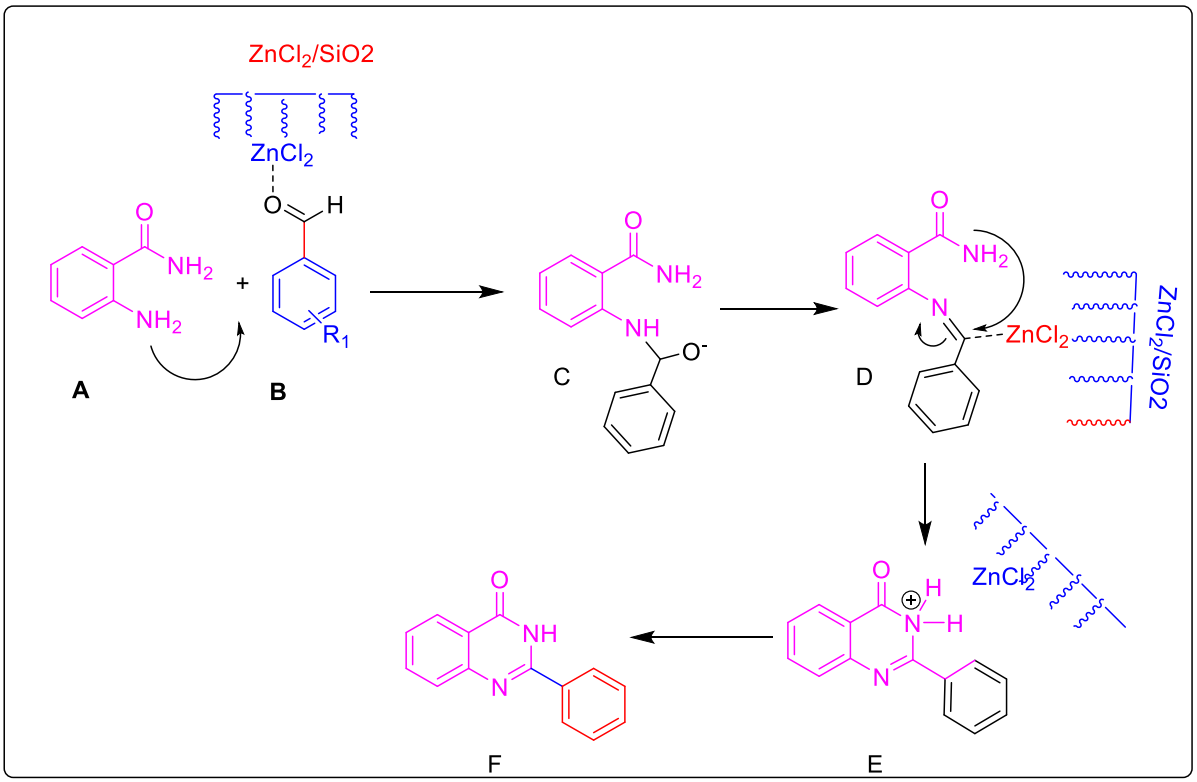
Table 2. Synthesis of 2-phenylquinazolin-4(3*H*)-one derivative using in the presence of $ZnCl_2/SiO_2$ Catalyst

Sr/No	Aldehyde	Product	Yield	M.P.
1			86%	236–237°C[33]
2			85%	295–298 °C[33]
3			80%	205–207°C[34]
4			78%	198–199°C[34]
5			77%	294-296 °C[33]
6			69%	223-225 °C

Mechanism

We have proposed the mechanism for the preparation of desired product novel 2-phenylquinazolin-4(3*H*)-one derivative. The compound 2-aminobenzamide A with benzaldehyde **B** reacts with react other in the presence of acidic $ZnCl_2/SiO_2$ Catalyst. The $ZnCl_2/SiO_2$ Catalyst activated the electrophilic center of aldehyde and NH2 from the 2-aminobenzamide attack on the carbonyl carbon from the intermediates of imines **D**. The Imine **D** further reacted with the NH_2 of benzamide followed by removal of hydrogen in

an acidic condition produce desire novel 2-phenylquinazolin-4(3*H*)-one (**F**) derivatives



Conclusion

A novel method from the simple and readily available starting chemical material has been developed to prepare the novel series of 2-phenylquinazolin-4(3*H*)-one derivative. The use of SiO2-supported $ZnCl_2$ proceeds the reaction smoothly in the solvent-free condition to produce 2-phenylquinazolin-4(3*H*)-one derivative with very good to excellent yield. The preparation of reagent and availability of starting material and very simple procedure make this the present methodology useful in the organic preparation.

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Conflict of Interest

We have no conflicts of interest to disclose.

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