An Efficient and Simple Method for Synthesis of 2-Phenyl-2,3-Dihydroquinazolin-4(1H)-Ones Catalyzed by ImidazoliumIonic Liquids

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Abstract:3-carboxymethyl-1-methyl imidazolium trifluoroacetate ([Cmim] CF_3COO) ionic liquid catalyzed, an efficient method for the preparation of 2-phenyl- 2,3-dihydroquinazolin-4(1H)-ones by the one pot three component cyclocondensation of isatoic anhydride, ammonium acetate and aromatic aldehydes in ethanol : water solvent system. This procedure have several advantageous such as short reaction time, easy work up, excellent yields and reuse of ionic liquid.

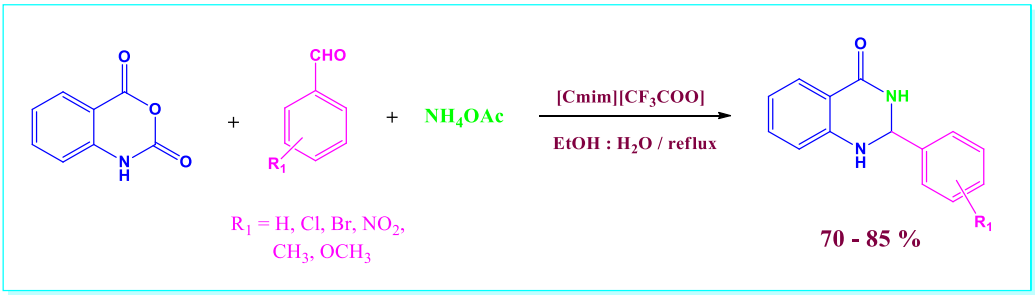
***Index Terms*:** Isatoic anhydride, ionic liquid, ammonium acetate, 2,3-dihydroquinazolin-4(1H)-one

I. INTRODUCTION

Heterocycles formed by far the prevalent of the classical division of organic chemistry. Furthermore, they are of huge significance, not only both biologically and industrially but to the execution of any developed human society as well. Their contribution in a wide range of areas cannot be undervalued. The majority of the pharmaceutically products that mimic natural products with biological activity are heterocycles. Quinazoline is a heterocyclic compound made up of two fused six- membered simple aromatic rings, a benzene ring and a pyrimidine ring.

Medicinally quinazoline derivative has been used in various areas especially as an antimalerial agent and in cancer treatment. The various route for the synthesis of quinazolin derivatives includes the heating 2-acylanilides in the presence of ammonia or amines. [1] The attempt was made to prepare the synthesis of quinazoline derivatives by Niementowski in 1895. This involves reaction of anthranilic acids with amides to form 4-oxo-3,4-dihydroquinazolines or also known as quinazolinone derivative . [2] The condensation reaction of anthranilamide with aldehydes or ketone using p-toluenesulfonic acids as catalyst [3], The reductive cyclization of o-nitrobenzamide or o-azidobenzamide with aldehydes or ketones [4] desulfurization of 2-thioxo-4(3H)-quinazolinones [5], a two-step synthesis starting from isatoic anhydride and amines, followed by annulation with ketones [6], (e) reaction of isatoic anhydride with Schiff-bases [7], f) Condensation of anthranilamide with benzyl [8] and the condensation of isatoic anhydride, aldehydes and ammonium acetate or primary amine [9-10].

More attractive and convenient method for synthesis of such significant heterocycles is three-component condensation of isatoic anhydride, aldehydes, and ammonium acetate. The literature survey for this reaction covers the use of catalysts such as Al/Al_2O_3,[11]Cation exchange resin [12], MCM-41-SO_3H [13], CAN [14], Zn $(PFO)_2$[15], Solid phase synthesis [16], $Sc(OTf)_3$[17], Amberlyst-15 [18]& silica –$HClO_4$[19], [Bmim]BF_4[20], $Ga(OTF_3)$[21], K-10[22], Bronsted acid catalyst [23], Heteropoly acid [24], Catalyst free and solvent free [25], $B(HSO_4)_3$[26], SiO_2-$ZnCl_2$[27], Cerous methanesulfonate [28], Thiamine hydrochloride (VB_1)[29], Clay supported heteropoly acid [30], TCT, PEG-400 [31], SPINOL phosphoric acid [32], Sc (III) inda-pybox [33], Cu-CNTs [34], Co-CNTs [35], Ag-CNTs [36], K_3PO_4 [37], $SnCl_2$ [38] However, many of these methods have its own advantages and disadvantages taking into consideration of disadvantages; such as long reaction time, low yields and use of large amount of catalyst therefore there is need to develop a method for one-pot synthesis of 2-phenyl- 2,3-dihydroquinazolin-4(1H)-ones.



Scheme: Reaction of isatoic anhydride, ammonium acetate and aldehyde for the synthesis of 2-phenyl-2,3-dihydroquinazolin-4(1H)-ones.

II. RESULTS AND DISCUSSION

Initially, to evaluate the efficiency and applicability of catalyst to synthesis of 2-phenyl- 2,3-dihydroquinazolin-4(1H)-ones, we choose isatoic anhydride (2mmol), benzaldehyde (2 mmol), ammonium acetate (3 mmol) as a substrates and 20 mol% of ionic liquid as catalyst proportion for model reaction. Successively, we focused our initial investigation on the effect of various solvents and their mixtures on model reaction at different temperatures **(Table 1)**. It was observed that, the reaction doesn't marches successfully in sole solvents like water, EtOH, acetonitrile and MeOH even after prolonged stirring at room temperature

(Table 1, entries 1-4). Next, we examined the above reaction in different solvent under reflux condition for 4-5 h. Only water and ethanol, were investigated to standardize the reaction condition. It seems that EtOH / H_2O (1/1 (v/v)) system is the best for catalytic reactions in terms of yield, which afforded 87% yield of targeted molecules within 2.5 hours **(Table 1, entry 8).**

Next, the same model reaction was carried out at 80ºC in excess of ionic liquid, only trace amount of product was formed, furthermore at solvent free condition the reaction didn't progressed even after prolonged stirring **(Table 1, entries 15,16).** The results revealed that the reaction temperatures and choice of solvents significantly influence on the product yield and time of reaction completion.

Table 1: Optimization of reaction solvent and reaction conditions for the synthesis of 2-phenyl- 2,3-dihydroquinazolin-4(1H)-ones

Entry	Solvent	Temperature	Time (h)	Yield (%) [a]
1	Water	RT	7	-- [b]
2	Ethanol	RT	7	-- [b]
3	Acetonitrile	RT	7	--- [b]
4	Methanol	RT	7	-- [b]
5	Water	80	5	-- [b]
6	Ethanol	78	5	62
7	Methanol	64	5	58
8	Water + Ethanol (1:1)	80	2.30	85
9	Water + Ethanol (2:1)	80	2.30	70
10	Water + Ethanol (1:2)	80	2.30	77
11	Acetonitrile	80	3	42
12	Dichloromethane	40	3	20
13	Chloroform	61	3	33
14	DMF	80	3	56
15	[[Cmim]CF_3COO Ionic liquid	80	3	Trace
16	---	80	8	--- [b]

Reaction conditions: Isatoic anhydride (2 mmol), benzaldehyde (2 mmol), ammonium acetate (3 mmol), [Cmim]CF_3COO ionic liquid (20 mol%); [a] Isolated yield; [b] No reaction

Using these optimized conditions of 20 mol% of [Cmim]CF_3COO ionic liquid and aqueous ethanol (1:1) to check the generality and versatility of the protocol we reacted several substituted aryl aldehydes, isatoic anhydride and ammonium acetate which afforded good to excellent yields **(Table 2, entries 1–9).**In general, we found that the reactions of aromatic aldehydes containing electron withdrawing group at different positions (**Table 2, entries 2-5**) prove to be predominant attributed to high yield of products than the reactions of aldehydes containing electron donating group **(Table 4.2.4, entries 7, 8, 9).** All the products were crystalline and characterized on the basis of their melting points and spectral data (IR, ^1H NMR, ^{13}C NMR and LC–MS) with those of authentic sample.

III. EXPERIMENTALSECTION

All the chemicals were purchased from Aldrich, Spectro-chem, Merck chemicals and were used without further purification, unless otherwise stated. All melting points were measured on Veego digital melting point apparatus and are uncorrected. IR spectra were measured as KBr pellets on a Perkin Elmer Spectrum RX FTIR spectrophotometer. The NMR spectra were recorded on a Bruker Avance II 400 MHz instrument. The ionic liquid was prepared as per reported method elsewhere.

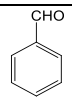
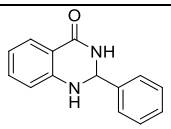
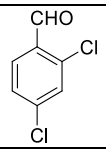
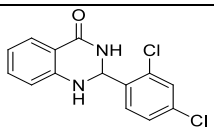
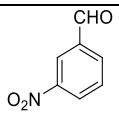
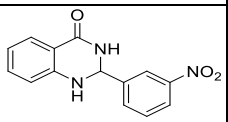
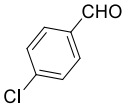
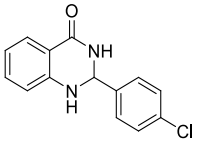
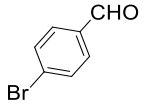
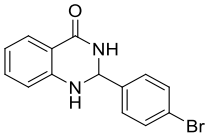
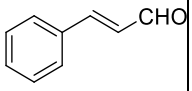
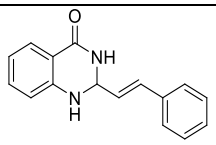
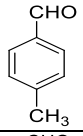
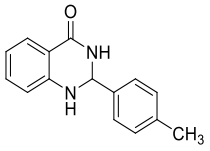
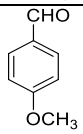
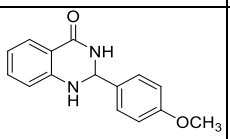
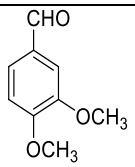
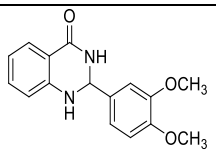
3.1 General Procedure

A mixture of isatoic anhydride (5 mmol), ammonium acetate (7.5 mmol), aromatic aldehydes (5 mmol) and 3-carboxymethyl-1-methyl imidazolium trifluoroacetate ([Cmim]CF_3COO) ionic liquid (20 mol%) in ethanol: water solvent system (1:1) was heated under reflux condition for appropriate time. The progress of the reaction was monitored by TLC after completion of the reaction the reaction mixture was cooled and solid formed was filter and recrystallized with ethanol to afford the desired compound in pure form. All the compounds are known compounds and were characterized by spectral data and comparison of their physical data with literature data.

IV. CONCLUSION

This procedure offers several advantages for the synthesis of 2-phenyl- 2,3-dihydroquinazolin-4(1H)-ones derivatives, such as water/ ethanol system as solvent, use of catalytic amount of ionic liquid, high to excellent yields and clean reactions. In addition, product isolation is easily accomplished by simple filtration, as the product is insoluble in the solvent. The ionic liquid is easily recovered by the distillation process and further reused three times without change in the yield of the product.

Table 2: Synthesis of 2-phenyl, 2,3-dihydroquinazolin-4(1H)-ones [a]

Sr. No.	Aldehyde	Product [b]	Time (h)	Yield [c] (%)	Mp. ° C	Lit. [ref.]
1			2.5	85	217-219	(218-220) [21]
2			3.0	78	160-162	(162-164) [32]
3			2.5	80	194 – 196	(197-199) [12]
4			2.0	85	201-203	(204-206) [12]
5			2.5	82	195-197	199-200 [32]
6			3.0	70	211-213	209-211 [31]
7			2.0	76	220-224	(222-224) [12]
8			3.0	80	178-180	(178-180) [21]
9			3.5	78	205 – 207	(210-213) [21]

[a] Reaction condition: isatoic anhydride (5mmol), ammonium acetate (7.5mmol), aromatic aldehydes (5 mmol) and ionic liquid (20mol%). [b] All the product were characterized by IR spectral data and comparison of their melting point with those of the authentic samples. Also the structures of the some products were confirmed by ^{1}H NMR spectral data. [c] Isolated yield.

V. SPECTRAL DATA

2-phenyl-2,3-dihydroquinazolin-4(1H)-one : IR (KBr, cm^{-1}): 3303(-NH), 3186(-NH), 3062(-CH),, 1652(-CO), 1613(-CO-NH),1511, 1391, 1300, 1148, 809, 748, 699; ^{1}H NMR (DMSO-d$_6$, 400MHz) □: 8.29 (s, 1H), 7.61 (d, 1H), 7.49 (d, 2H), 7.41–7.32 (m, 3H), 7.24 (t, 1H), 7.11 (s, 1H), 6.74 (d, 1H), 6.67 (t, 1H), 5.75 (s, 1H) ppm ; ^{13}C NMR (DMSO-d$_6$, 400MHz) □: 164.06 148.34, 142.10, 133.78, 128.92, 128.79, 127.82, 127.33, 117.58, 115.42, 114.87, 67.04Mass: 301 (M+1)

2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 4)
IR (KBr, cm^{-1}): 3308, 3186, 3066, 1654, 1609, 1509, 1485, 1426, 1296, 1092, 1015, 752, 666, 503; ^{1}H NMR (DMSO-d$_6$, 400MHz) □: 8.20 (s, 1H), 7.64 (d, 1H), 7.49 (d, 2H), 7.46 (d, 2H), 7.22 (t, 1H), 6.98 (s, 1H), 6.75 (d, 1H), 6.68 (t, 1H), 5.77 (s, 1H) ppm.^{13}C NMR (DMSO-d$_6$, 400MHz) □: 164.06, 148.34, 142.10, 133.78, 128.92, 128.79, 127.82, 127.33, 117.58, 115.42, 114.87, 67.04.Mass: 260 (M+2), 258 (M)

(E)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 6)

IR (KBr, cm^{-1}): 3289 (-NH), 3193(-NH), 3059 (-CH), 1648 (-CO), 1610 (-CO-NH), 1512, 1486, 1299, 965, 753, 692.^{1}H NMR (DMSO-d_6, 400MHz) □: 5.31 (d, 1H, -NH), 6.33- 6.38 (q, 1H, NH-CH-NH), 6.64 - 6.69 (m, 2H, CH=CH-Ph), 7.20-7.27 (m, 2H, Ar-H), 7.30-7.34 (m, 2H), 7.39 – 7.46 (m, 3H), 7.62 – 7.67 (m, 2H), 8.14 (s, 1H, -NH) ,Mass: 251 (M+1)

2-p-tolyl-2,3-dihydroquinazolin-4(1H)-one (Table 2, entry 7)

IR (KBr, cm^{-1}): 3309, 3190, 1654, 1611, 1512, 1488.^{1}H NMR (DMSO-d_6, 400MHz) □: 8.20 (s, 1H), 7.55 (d, 1H), 7.32 (d, 2H), 7.10-7.18 (m, 3H), 6.99 (s, 1H), 6.70 (d, 1H), 6.58 (t, 1H), 5.76 (s, 1H), 2.35 (s, 3H) ppm.Mass: 238(M+1)

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