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[$(C_3H_7)_3N$-SO_3H]Cl IONIC LIQUID CATALYZED SYNTHESIS OF 2,3-DIHYDROQUINOZOLINE-4(1*H*)-ONE DERIVATIVES

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ABSTRACT

Though the design and synthesis of N-heterocyclic motifs are extremely challenging and demanding, the involvement of toxic reagents and solvents often triggers environmental safety concerns. Herein, we have explored a simple, scalable, and benign method for the construction of 2,3-dihydroquinazolin-4(1H)-ones via the reaction between anthranilamide and aryl aldehydes in the presence of [$(C_3H_7)_3N$-SO_3H]Cl as a Bronsted acid ionic liquid (BAIL) catalyst in aqueous ethanolic medium at room temperature condition. Good to excellent yield of product, simple operational procedure, recovery and reusability of catalyst, and green reaction medium are the prime features of this protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Keywords: [$(C_3H_7)_3N$-SO_3H]Cl; Bronsted Acidic Ionic Liquid; 2,3-dihydroquinazolin-4(1H)-one; Reusability of Catalyst; Room Temperature.

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INTRODUCTION

In the modern era, heterocyclic compounds play a significant role in the pharmaceutical field due to their wide range of bioactivities.[1,2] More specifically, the design and synthesis of new nitrogen-containing heterocyclic scaffolds have always been a priority domain for synthetic organic chemists.[3,4] Among these, quinazolin-4(3H)-one and 2,3-Dihydroquinazolin-4-one (DHQ) form essential core structures within the quinazoline framework.[5] Their molecular structure consists of a quinazoline ring fused with a cyclohexanone ring.[6] The synthesis of these compounds is of great interest in medicinal chemistry due to their potential pharmacological properties, such as TRPM2 inhibitors,[7] fXa inhibitors,[8] cholinesterases inhibitors,[9] anticonvulsant agents,[10] etc. Some of the Marketed quinazoline drugs are depicted in Fig.-1.[11]

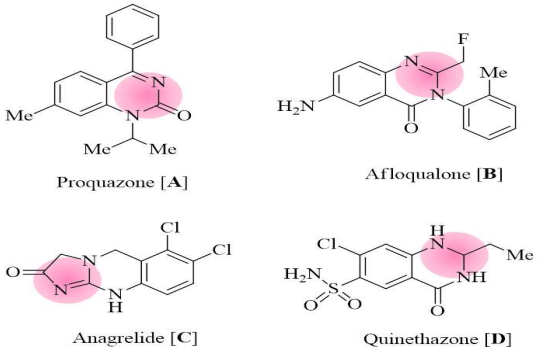

Fig.-1: Representative Biological Potent Marketed Quinazoline Drugs

To synthesize 2,3-dihydroquinazolin-4(1H)-ones, various distinct protocols have been developed for the construction of the DHQ core, the most common and simple synthetic route for the preparation of DHQs are $ZnFe_2O_4$@SiO_2–SO_3H,[12] *p*-TSA,[13] wang-OSO_3H,[14] ZrO_2-Al_2O_3 nanocatalyst,[15] Pd(II)/TPPMS,[16] L-Proline@Fe_3O_4[17] etc. However, the traditional methods are beneficial to some extent and some of these still facing some limitations, such as longer reaction times with unsatisfactory or inconsistent yields, use

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of expensive or complex reagents and catalysts, poor substrate tolerance, etc. However, with the growing concern of environmental contagions, there is an urgent need for the design and development of a simple, straightforward, and sustainable protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones (DHQ). Despite these, using green solvents and catalysis in organic synthesis is one of the many tactics to achieve greenness in the processes by eliminating the volatile organic components (VOC's).[18,19] In this regard, ionic liquids (ILs) have become a promising candidate to replace conventional solvents and catalysts due to their remarkable solubility, and potential recyclability, non-flammability, and non-volatility have made them more effective for synthetic conversions.[20,21] Among the diverse categories of ionic liquids, Brønsted acidic ionic liquids (BAILs) have gained considerable attention because of their adequate acidity and thermal stability, nontoxicity, and inertness toward air and water. It is non-corrosive than normal homogeneous acids.[22] The significant acidity of BAIL catalyst is mostly due to covalently bonded sulfonic acid (−SO_3H) moiety to the IL and such catalytic systems have gained widespread applications in synthetic transformations.[23] Also, the excellent miscibility of these BAIL catalysts with the reaction mixtures significantly enhances mass-transfer efficiency and improves the catalytic activity. With these considerations in mind, we would like to disclose a versatile procedure for the fabrication of 2,3-dihydroquinazolin-4(1H)-one (DHQ) derivatives from diversely substituted aromatic aldehydes and anthranilamide using $[(C_3H_7)_3N\text{-}SO_3H]Cl$ as a Bronsted acid catalyst in aqueous ethanolic medium under room temperature condition.

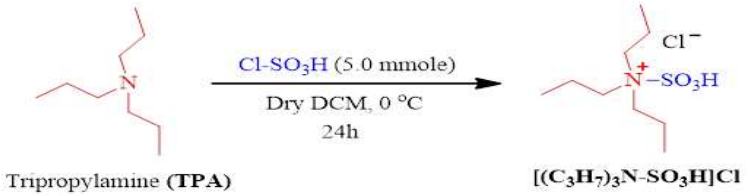
EXPERIMENTAL

Material and Methods

All Solvents, reagents, and chemicals were acquired from a local supplier and utilized without additional purification. The melting points of the purified compounds were measured using a DBK-programmed melting point apparatus with a temperature rise of 2 °C per minute. The progress of reactions was observed using thin-layer chromatography (TLC) on a silica gel-coated metal plate. Synthesized compounds were evaluated utilizing techniques such as FT-IR, ^1H and ^{13}C NMR, and mass spectrometry (MS).

Synthesis of $[(C_3H_7)_3N\text{-}SO_3H]Cl$ BAIL Catalyst

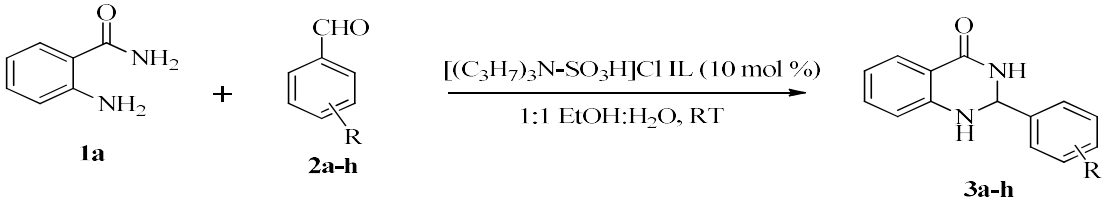
The $[(C_3H_7)_3N\text{-}SO_3H]Cl$ as Brønsted acidic ionic liquid (BAIL) was prepared according to our previously reported method.[24]



Scheme-1: Preparation of $[(C_3H_7)_3N\text{-}SO_3H]Cl$ BAIL Catalyst

General Procedure for the Preparation of 2,3-dihydroquinozoline-4(1*H*)-one Derivatives

To a mixture of anthranilamide (1 mmol) and substituted aromatic aldehyde (1 mmol), the 10 mol % $[(C_3H_7)_3N\text{-}SO_3H]Cl$ of BAIL was added and the mixture was stirred at room temperature till completion of the reaction. The reaction progress was monitored using thin-layer chromatography (TLC) with petroleum ether-ethyl acetate (7:3 v/v) as the eluent. Upon completion of the reaction, water was added to the reaction mixture. Then the product was filtered off and the BAIL catalyst was successfully recovered by evaporating the water and reused for a subsequent fresh batch of the reaction after reactivation. The crude product was further subjected to recrystallization in ethanol to purify the separated products (**3a-h**).

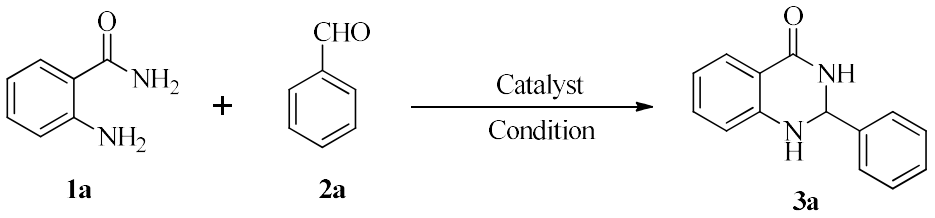


Scheme-2: Synthesis of 2,3-dihydroquinazoline-4(1*H*)-ones by using $[(C_3H_7)_3N\text{-}SO_3H]Cl$ IL as catalyst

RESULTS AND DISCUSSION

At the initial level of our study, the $[(C_3H_7)_3N\text{-}SO_3H]Cl$ BAIL catalyst was synthesized from tripropylamine and chloro-sulfonic acid ($Cl\text{-}SO_3H$) as per the reported method. The resulting $[(C_3H_7)_3N\text{-}SO_3H]Cl$ BAIL catalyst was separated, thoroughly washed with dry DCM and finally dried under vacuum and subsequently characterized using FT-IR, ^1H, and ^{13}C NMR, mass, and D_2O exchange analysis, as reported in our previous research work. We then initiated a preliminary study on the synthesis of 2,3-dihydroquinazolin-4(1H)-one via a prototype reaction between anthranilamide **1a** (1 mmol) and benzaldehyde **2a** (1 mmol) at ambient temperature in an aqueous medium under catalyst-free condition. The findings are shown in Table-1. It was observed that no significant progress occurred in the reaction mixture at room temperature, and even elevated temperatures were insufficient for generating the imine intermediate (Table-1, entries 1 and 2). Subsequently, we evaluated the synthetic potential of the BAIL catalyst in an aqueous medium at room temperature. A notable change was observed when 5 mol % and 10 mol % of the catalyst were used, affording a better yield (84%) of the desired product **3a** (Table-1, entries 3 and 4). The completion of the reaction was assessed by TLC (7:3 v/v, petroleum ether: ethyl acetate). Interestingly, when the reaction was conducted in an aqueous ethanolic medium (1:1 v/v EtOH: H_2O) using 10 mol % of the BAIL catalyst (Table-1, entry 5), a synergistic effect of the 1:1 EtOH: H_2O system was observed, leading to a significant improvement in yield, with the desired product obtained in 96 % yield. Employing a pure ethanolic system using 10 mol % of $[(C_3H_7)_3N\text{-}SO_3H]Cl$ catalyst was also less effective and afforded the desired product with 90 % yield, respectively (Table-1, entry 6). Increasing the catalyst loading to 20 mol % in the 1:1 EtOH: H_2O system did not improve the product yield (Table-1, entry 7). Finally, a solvent screening study was conducted using various organic solvents like MeOH, propane-2-ol, and glycerol (Table-1, entries 8-10). No product formation or only trace amounts of the desired product (**3a**) were observed in propane-2-ol and glycerol, respectively (Table-1, entries 9 and 10).

Table-1: Optimization of Catalyst Loading in Synthesis of 2, 3- dihydroquinazolin-4-(1*H*)-ones[a]



1a **2a** **3a**

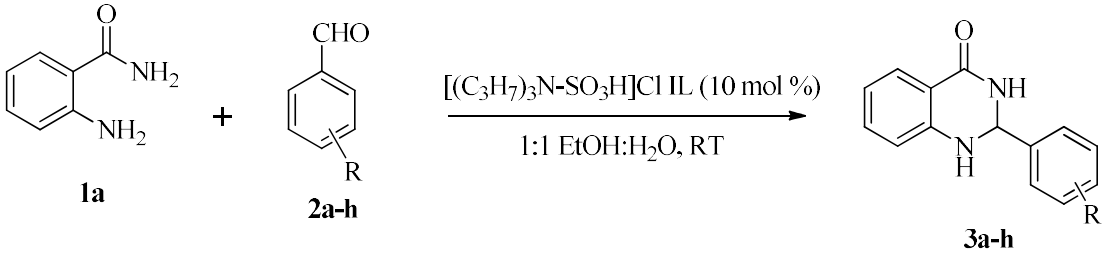
Entry	Catalyst (mol %)	Conditions	Time (min.)	Yield[b](%)
1	----	H_2O/ RT	--	--
2	----	H_2O/80 °C	--	--
3	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (05)	H_2O/ RT	26	84
4	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (10)	H_2O/ RT	25	84
5	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (10)	EtOH: H_2O (1:1)/ RT	15	96
6	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (10)	EtOH/ RT	15	90
7	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (20)	EtOH: H_2O (1:1)/ RT	10	95
8	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (10)	MeOH/ RT	45	53
9	$[(C_3H_7)_3N\text{-}SO_3H]cl$ (10)	Propane-2-ol/ RT	120	--
10	$[(C_3H_7)_3N\text{-}SO_3H]Cl$ (10)	Glycerol/ RT	60	14

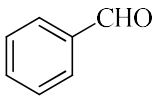
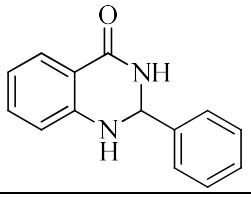
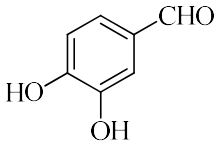
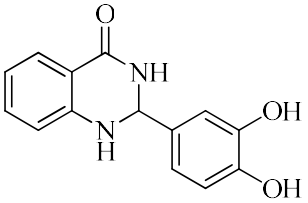
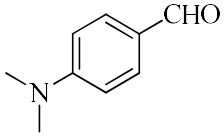
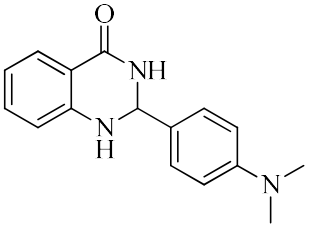
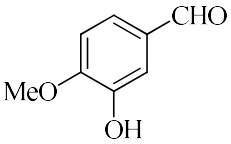
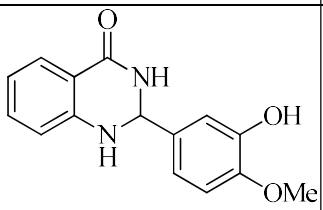
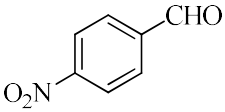
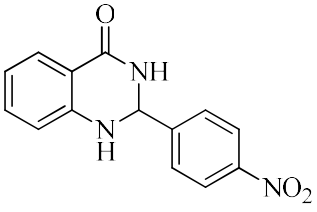
[a]Reaction condition: anthranilamide (1.0 mmol), benzaldehyde (1.0 mmol), and catalyst (entries 3 to 10) in 5 mL solvent; [b] Isolated yields.

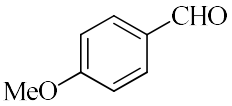
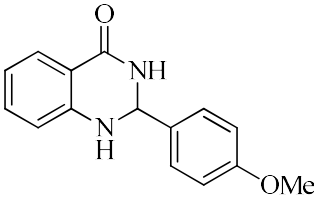
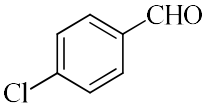
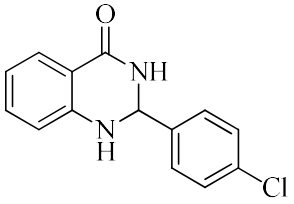
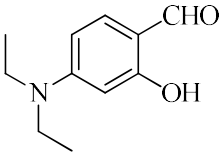
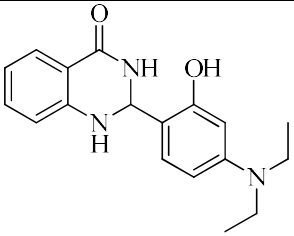
After getting the optimized reaction conditions in hand, numerous aryl aldehydes (**2a-h**) were introduced to react with anthranilamide (**1a**) to prove the general applicability of this protocol. The findings suggest

that the anthranilamide interacted well with the substituted aromatic aldehydes bearing both electron-rich and electron-deficient groups producing good to excellent yield of the resulting 2,3-dihydroquinazolin-4(1H)-ones (Table-2, entry **3a-h**). A moderate yield (84.47 %) of the intended quinozoline product was obtained from p-chlorobenzaldehyde, as anticipated (Table-2, entry **3g**).

Table-2: $[(C_3H_{21})_3N\text{-}SO_3H]Cl$ IL Catalyzed Synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones[a]



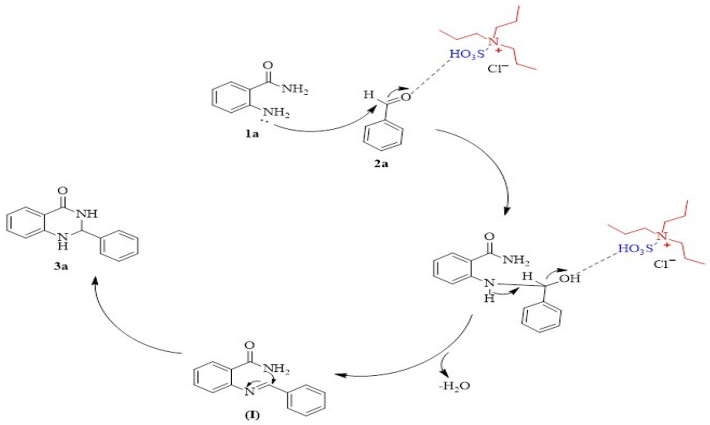
Entry	Aldehyde (2)	Product	Time(min.)	Yield[b](%)
3a			15	96.08
3b			16	90.34
3c			08	97.97
3d			16	88.86
3e			14	92.65

3f			14	96.06
3g			22	84.47
3h			18	89.24

[a]Reaction conditions: 1 mmol of **1a** and 1 mmol of **2** in presence of $[(C_3H_7)_3NSO_3H]Cl$ BAIL (10 mol %) at RT in EtOH:H_2O (5 mL, 1:1 v/v); [b]Isolated yields.

Reaction Mechanism

The proposed reaction pathway for the synthesis of 2,3-dihydroquinazolin-4(1H)-one, catalyzed by $[(C_3H_7)_3N\text{-}SO_3H]Cl$ IL is illustrated in Scheme-3.[25] The first step likely involves the activation of the carbonyl group of aldehyde (2a) by the acidic ionic liquid through coordination with the carbonyl oxygen. This activation enables the interaction of benzaldehyde (2a) with anthranilamide (1a), afforded the imine intermediate (I). Furthermore, the catalyst stimulates the imine group of (I), facilitating an intramolecular nucleophilic attack by the carboximidate nitrogen on the imine carbon, leading to the formation of the desired product (3a).



Scheme-3: Plausible Mechanism for the Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one using $[(C_3H_7)_3N\text{-}SO_3H]Cl$ IL

Inspired by the efficacy of the existing methodology, we evaluated the effectiveness of our synthesized ionic liquid catalyst in the synthesis of 2,3-dihydroquinazolin-4(1H)-one compared to previously documented catalysts for the specified reactions (Table-3, entries 1-6). The comparative results indicate that the $[(C_3H_7)_3NSO_3H]Cl$ IL catalyst offers multiple advantages over previously reported catalytic systems, including shorter reaction times, higher product yields, and more environmentally friendly solvent and temperature conditions.

Table-3: Comparative Evaluation for the Synthesis of 2,3-dihydroquinazolin-4(1*H*) one[a] with other Reported Methods

Entry	Catalyst	Reaction Conditions	Time	Yield (%)[a]
1	CuO (20 mg), HCl (5 mol %)	PEG/60 °C	--	95[26]
2	Fe_3O_4@EDTA/CuI (20 mg)	EtOH/reflux	20 min	97[27]
3	Hydroxyapatite NPs (100 mg)	H_2O, 110 °C	60 min	95[28]
4	KCC-1/Pr-SO_3H (05 mg)	EtOH, reflux	120 min	95[29]
5	$CoAl_2O_4$ spinel nanocrystal (8 mol %)	US, EtOH, 45 °C	15 min	96 [30]
6	$[(C_3H_7)_3N$-$SO_3H]Cl$ IL (10 mol %)	H_2O: EtOH/RT	15	96[Present work]

CONCLUSION

In summary, we have successfully demonstrated a greener protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by employing the $[(C_3H_7)_3N$-$SO_3H]Cl$ BAIL catalyst in an aqueous ethanolic medium under mild reaction conditions. In this approach, product formation was achieved effortlessly at room temperature. The notable advantages of the current protocol include reduced cost, operational simplicity, ease of product isolation and purification, use of easily accessible precursors, recyclability, and reusability of the BAIL catalyst. Additionally, all the products were obtained with good selectivity and yields ranging from 84 % to 97 %.

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CONFLICT OF INTERESTS

There is no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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[RJC-9169/2024]