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Cholinesulfuric acid ionic liquid catalyzed an eco-friendly synthesis of 2,3-dihydroquinazolin-4(1H)-one in aqueous media

Najmedin Azizi[1] · **Fatemeh Shirdel**[1]

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Abstract An efficient and straightforward approach to the synthesis of 2,3-dihydroquinazolin-4(1H)-one from 2-aminobenzamide and carbonyl compounds (aldehydes and ketones) using biocompatible choline sulfate-based acidic ionic liquid as a cheap and readily available catalyst in water has been developed. Various 2,3-dihydroquinazolin-4(1H)-one have been prepared using low-cost and environmental friendly solvent and catalyst in good to excellent yields in a shorter reaction time. The choline sulfate catalyst was prepared using a simple method from readily available starting material and was confirmed by ^{1}H NMR, FTIR, and TGA. The ease of the product separation without organic solvent and column chromatography and the reusability of the acidic ionic liquid catalyst makes this method economically affordable for large-scale synthesis.

Keywords Quinazolinone · Recyclable catalyst · Acidic ionic liquid · Green chemistry

Introduction

Sustainable and eco-friendly development of chemical processes is an important goal from an ecological point of view for chemists in both academia and industry [1, 2]. One approach to address this challenge involves the development of green solvents and biodegradable novel catalysts [3, 4]. In this context, organic reactions in water have proven to be highly popular and very attractive in recent years due to water's specific properties such as nontoxic,

✉ Najmedin Azizi
azizi@ccerci.ac.ir

[1] Chemistry & Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran

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nonflammable, inexpensive and friendliness to the environment [5, 6]. On the other hands, green catalysts have a big impact in today's society on the environmental acceptability of industrial processes in a facile and environmentally friendly manner [7, 8].

Choline sulfate (2-(trimethylammonio)ethyl sulfate) the sulfate ester of choline is a naturally-occurring osmolyte that is synthesized by plants, lichens, algae, fungi, and several bacterial species [9]. This neutral nonabsorbed zwitterion betaine appears to be a useful reservoir for sulfur in plants [10]. Choline sulfate also plays an important role in the microbial transformation of sulfur to the soil. Choline sulfate is particularly interesting in metabolic adaptations to stress in physiology and biochemistry [11]. However, the application of naturally-occurring choline sulfate hydrochloride in the field of dihydroquinazoline has not been reported [12, 13].

The quinazolineones scaffold is a central part of biologically active compounds with multiple pharmacophores, and is responsible for a wide range of bioactivities such as thymidylate synthase inhibition, antibiotic and antidefibrillatory effects and sedative effects [14]. Furthermore, 2,3-dihydroquinazolinones as well as the oxidized form, have been identified as synthetic building blocks as well as structural scaffolds in various natural products [15]. Based on this wide range of applications, numerous protocols for the preparation of 2,3-dihydroquinazolin-4(1H)-ones have been developed and reported in the literature [16–20]. The most popular and simple methods in the preparation of quinazolinones involve the condensation reaction of 2-aminobenzoicacid or its derivatives with aldehydes or ketones in the presence of catalysts or promoters [21–28]. A wide range of useful biological properties, as well as some marketed drugs based a 4-quiazolinone core (Fig. 1), have attracted researchers searching for new routes and strategies for the synthesis of quinazolinones that are operationally simpler and more compatible with the environment [29–43].

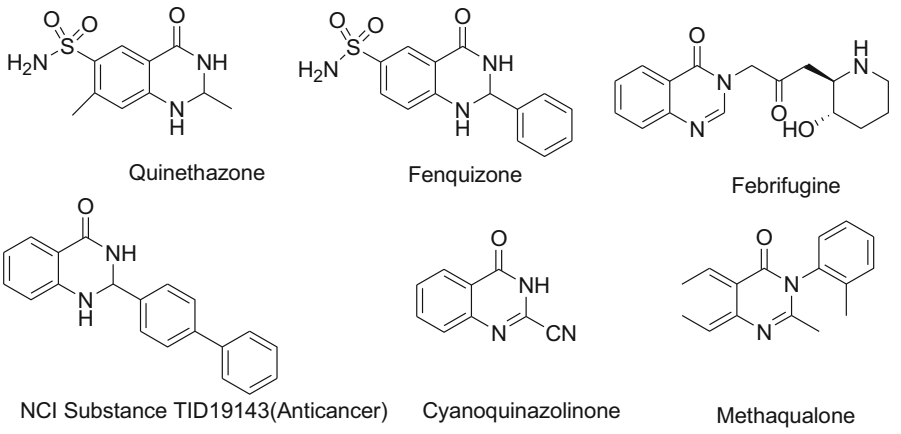


Fig. 1 Examples of the quinazolinones skeleton with pharmacological activities

Experimental

Materials and methods

All chemicals such as choline chloride, 2-aminobenzamide, carbonyl compounds (aldehydes and ketones) and chlorosoulfonic acid are commercially available. Solvents were distilled before use. All products were confirmed by ^{1}H NMR and FT-IR spectroscopy. ^{1}H NMR spectra were recorded on a 500 MHz spectrometer using DMSO-d_6 as a solvent, and chemical shifts have been expressed in (ppm) downfield from TMS. Melting points were recorded in a Buchi 535 melting point apparatus and are uncorrected. FT-IR spectra were determined on a Bruker Vector-22 infrared spectrometer using KBr disks. ^{1}H NMR spectra were recorded at room temperature on a FT-NMR Bruker Ultra Shield TM 500.

Preparation of the catalyst

To a magnetically stirred mixture of choline chloride (20 mmol, 2.79 g) in 30 mL of dichloromethane in a three-necked round-bottom flask equipped with a dropping funnel containing chlorosulfonic acid and a gas inlet tube for conducting HCl, chlorosulfonic acid (22 mmol, 1.43 mL) was added dropwise over a period of 60 min in an ice-bath. The resulting mixture was stirred for another 3 h at room temperature and then filtered to obtain a white solid which was washed with (2 × 25 mL) of ethyl acetate and dried at room temperature (Fig. 2).

General procedure

To a solution of the catalyst (10 mg) in H_2O (2 mL), 2-aminobenzamide (0.5 mmol) and carbonyl compounds (0.5 mmol) were added. The resulting mixture was stirred under room temperature for 20–120 min. After completion of the reaction, water (5 mL) was added and the precipitated products were filtered and then recrystallized from ethanol or ethyl actete to get the pure final product. The catalyst remaining in the water filter liquor could be used directly as a catalyst media for subsequent runs.

Results and discussion

Previously, we successfully used choline chloride-based deep eutectic solvents as a green reaction medium in the synthesis of biologically active nitrogen-based heterocycles [44–46]. As part of our ongoing efforts to explore novel catalyst sin

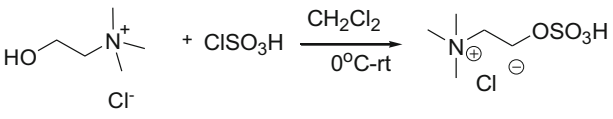


Fig. 2 Preparation of choline sulfate-based catalyst

water for heterocyclic synthesis, we report here a straightforward and eco-compatible procedure for the synthesis of 2,3-dihydroquinazolin-4 (1H)-one from 2-aminobenzamide and carbonyl compounds using a choline sulfate-based acidic ionic liquid catalyst in water (Fig. 2). The catalyst was prepared by treating commercially available choline chloride with chlorosulfonic acid in CH_2Cl_2 at room temperature under argon. The structure of the catalyst was characterized by various techniques such as Fourier transform infrared spectroscopy (FTIR), ^{1}H NMR, and TG–DTA, and the spectral data confirmed were the structures of the title catalyst. The FT-IR spectra of $ChSO_3HCl$ are presented in Fig. 3. The spectra of the catalyst exhibits major absorption bands at 1069 and 1229 cm^{-1} to confirm the presence of –SO_3H groups due to the S=O stretching vibrations in the catalyst. The stability and the weight loss patterns of the catalyst were investigated by thermal gravimetric (TG) analysis and are shown in Fig. 4, from wihch it can be seen that there is a negligible weight loss about 1.37% below 300 °C due to the removal of the physically adsorbed water, and a complete loss of weight occurs at above 300 °C. Furthermore, the DTG curve shows that the decomposition temperature of the catalyst was about 320–340 °C. The ^{1}H NMR spectra of the catalyst are given in Fig. 5. The ^{1}H NMR (D_2O) spectrum showed three signals and the proton of SO_3H was exchanged with D_2O.

Initially, we began our study with the reaction of 2-aminobenzamide **1** (0.5 mmol), benzaldehyde **2a** (0.5 mmol) in water (2 mL) in the presence of $ChSO_3HCl$ (10 mg) as a model reaction to explore the feasibility of the system using different solvents (Table 1). When the reaction mixture was stirred under solvent-free conditions at room temperature, the desired product **3a** was obtained in 45% isolated yield after 20 min (Table 1, entry 9). Although the reaction proceeds very rapidly, a longer reaction time did not improve the yield because of the massive solidification of the reaction mixture. The yield of the desired product was found to increase with the additionof the solvent. When polar solvents such as ethanol (Table 1, entry 1) or water (Table 1, entry 2) were used as solvents, complete

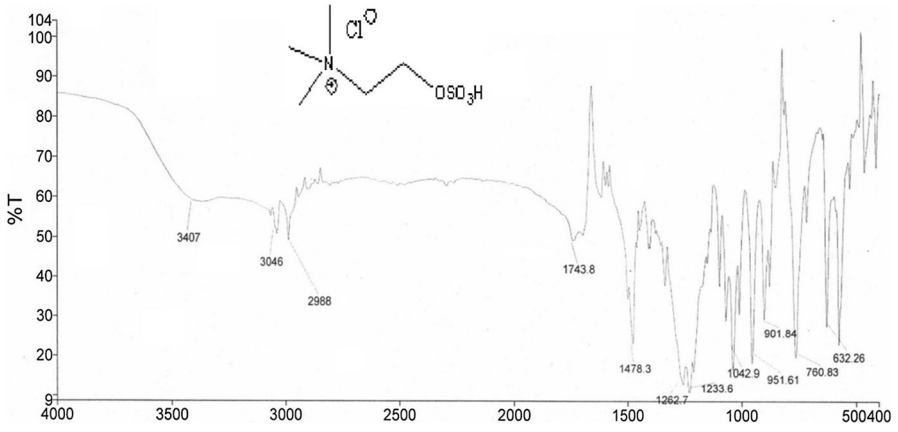


Fig. 3 FT-IR spectra of the catalyst

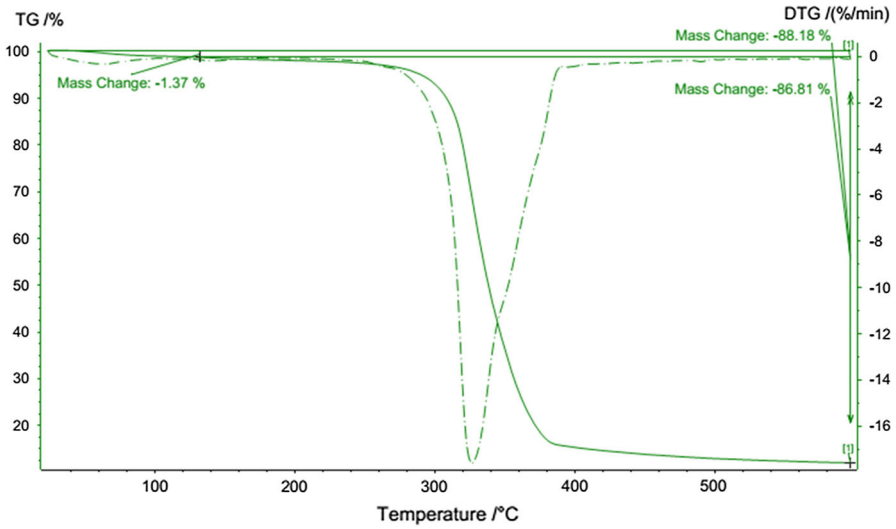


Fig. 4 TG–DTG curves of the catalyst

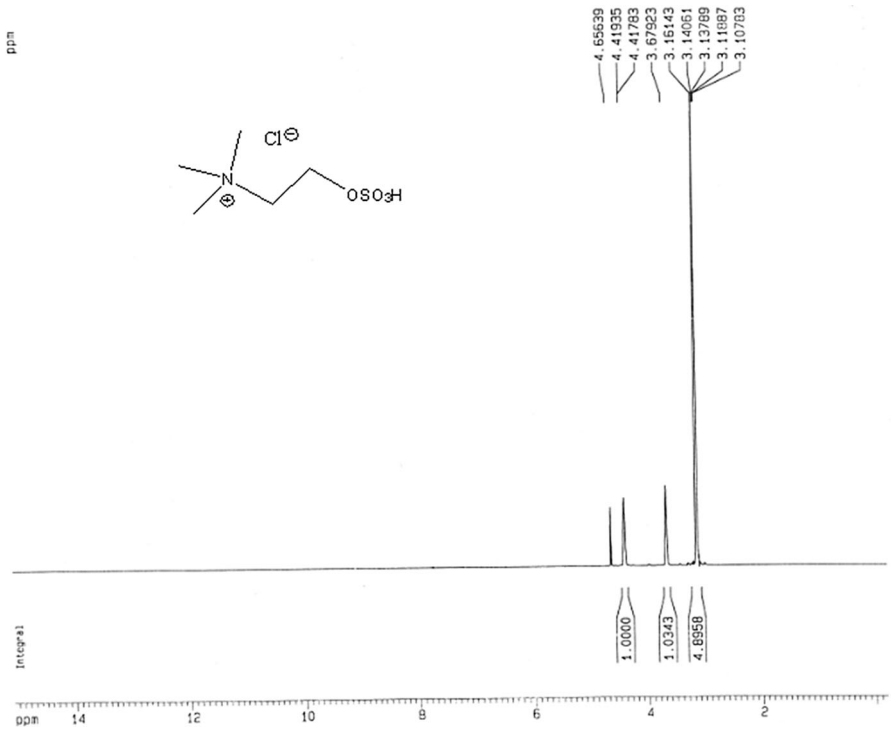
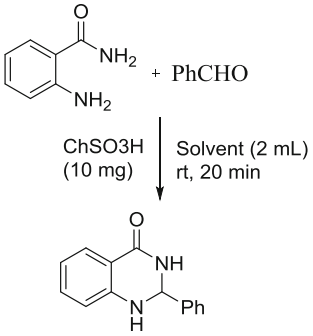


Fig. 5 ^{1}H NMR spectra of the catalyst

Table 1 Screening of various solvents



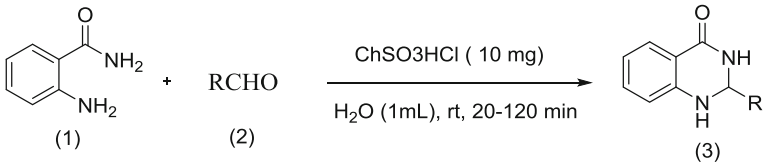
Entry	Solvent	Yield (%)
1	EtOH	92
2	H_2O	95
3	Toluene	25
4	CH_3CN	45
5	CH_2Cl_2	56
6	CH_3CO_2Et	38
7	THF	28
8	*n*-hexane	42
9	Without solvent	45

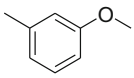
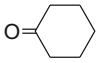
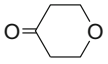
conversions of the starting materials were observed at 20 min. However, using toluene, *n*-hexane, dichloromethane, ethyl acetate and tetrahydrofuran as solvents, the corresponding products were isolated in moderate yields (Table 1, entries 3–8).

Furthermore, the effect of the catalyst amount on the reaction yields was investigated. When 5, 15 and 20 mg cholinesulfuric acid were used for the model reaction, this gave **3a** in 72, 95, and 95% yields, respectively. Therefore, it was concluded that cholinesulfuric acid (10 mg) was sufficient to catalyze the reaction at room temperature.

Using the optimized reaction conditions, (water, room temperature, 10 mg, catalyst), the diversity of our protocol was investigated by a wide range of aromatic aldehydes and 2-aminobenzamide and the results are shown in Table 2. A series of 2,3-dihydroquinazolin-4(1H)-ones were synthesized at room temperature within a few minutes in good to excellent yields under the optimized reaction conditions, and representative results are listed in Table 2. The reaction proceeded smoothly using differently-substituted electron-withdrawing or electron-donating substituents to the aldehyde core to give the corresponding products. Aromatic aldehydes bearing electron-donating groups (OMe) participated more rapidly in this protocol and gave better yields than those of aldehydes with alkyl groups (Me) or halogen-substituted (Br, Cl). For aldehydes carrying an electron-withdrawing group (NO_2, CO_2Me), the rate of the reaction was relatively slow and the yield of the product was also lower

Table 2 Synthesis of the diversified 2,3-dihydroquinazolinones derivatives



Entry	R (**2**)	Product (**3**)	Time (min.)	Yield (%)	M.p./°C	
					Found	Reported [Lit.]
1	Ph	**3a**	20	95	218–220	219–220 [19]
2	4-Cl-C_6H_4	**3b**	60	95	207–211	207–208 [33]
3	4-OMe-C_6H_4	**3c**	120	74	188–191	198–201 [18]
4	4-CO_2Me-C_6H_4	**3d**	70	72	217–219	218–220 [35]
5	3-NO_2-C_6H_4	**3e**	45	75	211–213	210–212 [17]
6	2,4-di OMe-C_6H_4	**3f**	80	72	224–227	187–188 [35]
7	2,4-di Cl-C_6H_4	**3g**	65	72	162–164	165–167 [17]
8	4-Me-C_6H_4	**3h**	40	82	225–227	229–231 [33]
9	4-Br-C_6H_4	**3i**	55	88	197–199	198–200 [33]
10	2-Cl-C_6H_4	**3j**	62	80	203–205	205–208 [39]
11		**3k**	50	76	144–146	142–144 [39]
12		**3l**	120	80	166–168	164–165 [19]
13		**3m**	120	78	166–168	169–171 [36]
14		**3n**	120	74	224–226	224–226 [34]
15		**3o**	120	70	196–198	200–202 [35]
16		**3p**	80	00	–	–
17		**3q**	80	00	–	–

due to the electron deficiency. Heterocyclic aldehydes gave the corresponding products in good yields. To further expand the scope of the green method ,we were keen to explore a variety of cyclic ketones like cyclohexanone and tetrahydro-4H-pyran-4-one in this reaction under the optimized reaction conditions and found the formation of desired products in good yield.

However, aliphatic aldehyde such as isobutyraldehyde and acetophenone as a linear ketone failed to give the corresponding products **3p** and **3q**, respectively,

Runs	1	2	3	4
Yield (%)	95	93	90	90

Fig. 6 Recyclability of the ionic catalyst in the model reaction

Table 3 Comparison of ionic catalyst with previous procedure

Entry	Solvent	Catalyst (×mol%)	Temp. (°C)	Time	Yield (%)	References
1	Chloroform	BINOL-phosphoric acid (10 mol %)	−15	24 h	96	[41]
2	Water	Cholin hydroxide (3.5 mL)	80	50 min	96	[47]
3	Water	β-Cyclodextrine-SO_3H (10 mol %)	25	25 min	95	[37]
4	Water	KOH	100	8 h	75	[16]
5	Ethanol	Poly(VPyPS)-PW (0.2 g)-ultrasound	25	6 min	95	[19]
6	Water	Wang-OSO_3H (10 mol%)	100	24 min	84	[18]
7	Water	–	120	16 h	100	[21]
8	Toluene	–	110	18 h	100	[22]
9	Water	Phosphatidylcholine (0.5 g)	80	15 min	97	[48]
10	Water	Cholinesulfuric acid (10 mg)	25	20	95	This work

under these conditions but led to a mixture of products that that it was impossible to separate.

Notably, from the viewpoint of green chemistry, not only did compound purification not require chromatography but there is also no need for the use of harmful organic solvents in the reaction or separation processes. After completion of the reaction, the crude product was filtered off and washed with water, then recrystallized from ethanol to yield the desired compounds **3a–3o** in 70–95% overall yields.

Finally, recycling experiments were carried out for the evaluation of the reusability of the catalyst which is highly important for economic considerations and environmental concerns. An attractive advantage of this procedure is its simple separation using filtration. To demonstrate this issue, the recycling efficiency of the catalyst was investigated for compound **3a** (Table 2, entry 1). The spent catalyst was completely water soluble and was recovered by simple filtration of the products from aqueous solutions containing the catalyst. The results shown in Fig. 6 reveal that the ionic catalyst can be recycled for at least 4 cycles without significant loss of its reactivity. Furthermore, no significant change in catalyst reactivity in either the yield or the time was observed, indicating that the recovered ionic catalyst was recoverable, which was confirmed by the FT-IR analysis of the reused ionic catalyst.

Finally, comparison of the cholinesulfuric acid ionic liquid-catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-one in water with a range of other methodologies demonstrated the high yields, short reaction times, low loading of the catalyst and eco-friendly nature of the protocol (Table 3).

Conclusion

In summary, we developed a simple and a straightforward procedure for the novel acidic ionic liquid-catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-ones in water. The most important features of this procedure are an environmentally benign catalyst and solvent, effective recovery and reusability of the catalyst, operational simplicity and short reaction times.

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