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Betaine hydrochloride (BHC) catalyzed synthesis of 4-thiazolidinones derivatives

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ABSTRACT

Betaine hydrochloride (BHC), as an ionic salt was found to be an efficient and recyclable catalyst for the one-pot synthesis of 4-thiazolidinediones. The methodology of study was achieved by one-pot condensation of aromatic aldehydes, aromatic amine and mercaptoacetic acid in the presence of betaine hydrochloride (BHC) at reflux temperature in ethanol as solvent. The efficiency of Betaine hydrochloride has been compared with all aspects of reaction conditions such as temperature, solvent and amount of the catalyst. This method excludes the use of heavy metal catalyst, tedious work-up and affords excellent yields of product. These advantages makes the technique greener and superior as compare to other reported methods.

Keywords: *Betaine hydrochloride (BHC), 4-Thiazolidinediones, Aromatic aldehydes, Aromatic amines, Mercaptoacetic acid.*

1. Introduction

In the era of green and sustainable chemistry, chemists have been trying to design the eco-friendly, metal free, waste minimizing and more economic and industrial scale production methodologies [1,2]. Multicomponent reactions (MCRs) are well-established approaches to design the product in a single operation from three or more reactant molecules with high yield of the product and multiple-bond-forming efficiency [3].

The nonvolatile replacement for hazardous volatile organic solvents to avoid the toxicity, is a part of this research. Recently, some green solvents materialized as inoffensive solvents, such as supercritical fluids, glycerol, water and derived solvents like deep eutectic solvents (DESs) based on choline chloride (ChCl) [4] and ionic liquids (ILs) [5-7]. In continuation of our work in the ionic liquid catalyzed reaction[8,9], we traced out the properties of betaine hydrochloride (BHC) to make use of such a potentially active bio-based based ionic salt.

Glycine betaine also known as N,N,N-trimethyl glycine, a metabolite of choline, is one of the main co-products produced in the carbohydrate industry.

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This glycine betaine has the zwitterionic form and is found in its acid form called betaine hydrochloride (BHC) which is solid in nature, easily available, cheap, biocompatible and biodegradable (Fig. 1). It is used to synthesize polar head groups containing more biodegradable cationic surfactants [10-12]. BHC was mixed with other chemicals such as glycerol, water, choline chloride or hydrogen peroxide to obtain liquid phase and used in an oxidative type of organic transformations [13-15]. These BHC-based media show similarities with the imidazolium based ionic liquids. Recently betainium based ionic liquids were also studied for the synthesis of acridinediones [16].

Nitrogen and sulfur containing heterocyclic compounds are widespread in nature and are very important due to their uses in pharmaceuticals and agrochemicals. Substituted 4-thiazolidinediones are one of the most important heterocyclic compounds with some macromolecules making them pseudo nucleotide; this enables them to exhibit interesting biological activities [17-21].

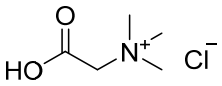


Fig. 1. Structure of Betaine Hydrochloride.

They are characterized by their therapeutic and medicinal activities such as COX-1 inhibition [22], anticonvulsant [23], anti-HIV [24], antimicrobial [25], anti-cancer [26], nematicidal [27] and immunostimulating activity [28].

Generally, thiazolidinones derivatives were synthesized by the condensation reaction of aromatic aldehydes, substituted anilines and mercaptoacetic acid. It is found that the removal of water during the cyclization of mercaptoacetic acid with imine is the most important rate determining process. Various efforts have taken to remove the water during the last step by using a different catalysts and solvent systems [29,30]. However, some dehydrating agents like N,N-dicyclohexylcarbodiimide (DCC) [31], molecular sieves [32], were used for synthesis of thiazolidinones. Different catalysts such as $Bi(SCH_2COOH)_3$ [33], polypropylene glycol (PPG)[34], Fly ash [35], Silica gel [36], Pd nanoparticle [37], β-cyclodextrin-SO_3H [38], anhydrous $ZnCl_2$ [39], $SnCl_2$ [40] were also reported. Surfactants such as HLE (home laundry effluent) [41] and p-dodecylbenzenesulfonic acid (DBSA) [42], biological catalysts like trypsin [43] and saccharomyces cerevisiae [44], ionic liquids such as triphenylphosphine and tetrabutylammonium bromide [45], diisopropylethyl ammonium acetate [46] were also reported for synthesis of thiazolidinones.

However, these methods have their own merits and demerits. Based on the protocols of green chemistry, to utilize simple, nontoxic, renewable feedstock, safer solvents and catalysts, herein we reported an efficient and novel method for the synthesis of 4-thiazolidinones (Scheme 1) by using BHC as a catalyst.

2. Experimental

All reagents were obtained from commercial sources Sigma Aldrich. The reaction is monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). Melting points were measured in open glass capillaries and may be incorrect. ^{1}HNMR was recorded at room temperature on a 300 MHz in acetone d_6 using TMS as an internal standard. The products were also characterized by comparison of their melting points with literature values.

2.1. General procedure for synthesis of 4-thiazolidinediones derivatives

A mixture of aromatic aldehydes (1 mmol), aromatic amines (1 mmol) and BHC 10 mol% was added to 10 mL of ethanol and the solution was stirred at reflux temperature. After 10-15 minutes of stirring, the solid was precipitated out indicating the formation of imine which is confirmed by disappearance of aldehyde and amine spots on TLC. To this reaction mass, mercaptoacetic acid (3 mmol) was added and refluxed for the specified time. Progress of the reaction was monitored by TLC using n-hexane: ethyl acetate (7:3) as an eluent; after completion of the reaction, the thick reaction mass obtained was cooled to room temperature, poured on crushed ice, filtered and washed with water. The obtained crude products were further purified by recrystallization using ethanol. The BHC was recovered from the filtrate layer and re-used for the next run to carry out the same experiment.

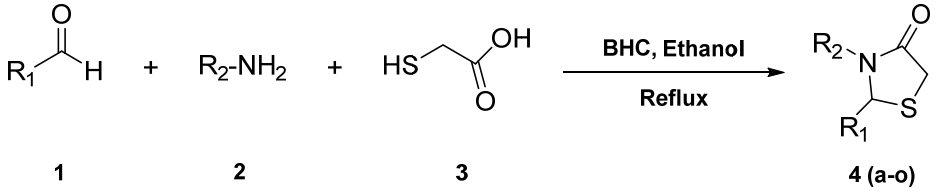
Spectral data of representative compound

*2-(4-Chlorophenyl)-3-phenylthiazolidine-4-one (**4d**):*

^{1}HNMR (300 MHz, acetone-d_6): δ= 7.49 (d, 2H, *J*= 8 Hz, ArH), 7.35 (d, 2H, *J*= 8 Hz, ArH), 7.30 (d, 2H, *J*= 8.4 Hz, ArH), 7.26 (d, 2H, *J*= 8.4 Hz, ArH), 7.15 (m, 1H, ArH), 6.47 (s, 1H, methine), 4.00 (d, *J*= 15.6 Hz, CH_2), 3.87(d, *J*= 15.6 Hz, CH_2) ppm. ^{13}CNMR (75 MHz acetone-d_6): δ= 171.22, 140.34, 139.04, 134.66, 130.53, 129.94, 129.67, 129.64, 129.31, 127.36, 126.54, 126.11, 64.51, 33.57 ppm. MS (ESI): m/z= 290.1 $[M+H]^+$.

3. Results and Discussion

To find the best reaction conditions, 4-chlorobenzaldehyde (1 mmol), aniline (1 mmol) and mercaptoacetic acid (3 mmol) in refluxed ethanol were used as a model reaction. The role of the catalyst was studied by applying all efficient categories of reaction enhancer additives. It was observed that reaction did not proceed in the absence of the catalyst. Inspiring from literature survey, we decided to use the surfactant type of catalyst, sodium lauryl sulfate which gave 48% yield of product.



Scheme 1. BHC catalyzed one-pot synthesis of 4-thiazolidinediones derivatives.

Table 1. Effect of catalysts for the synthesis of 4-thiazolidinediones.[a]

Entry	Catalyst	Time (h)	Yield (%)[b]	Ref.
1	Home laundry effluent (HLE)	12	54	[41]
2	Trypsin	4	96	[43]
3	[bmim][BF_4]	8	80	[47]
4	[bmim][PF_6]	5	90	[47]
5	Without catalyst	35	-	This work
6	Sodium lauryl sulfate	27	48	This work
7	Thiamine Hydrochloride	16	52	This work
8	Cellulose perchloric acid	20	50	This work
9	Glycine	10	60	This work
10	Betaine	12	62	This work
11	BHC	3	85	This work

[a]Reaction conditions: 4-Chlorobenzaldehyde (1 mmol), aniline (1 mmol), mercaptoacetic acid (3 mmol),catalyst (10 mol%) in 10 ml of Ethanol, reflux.
[b]Isolated yield.

The reaction in presence of thiamine hydrochloride and polymer supported acid, i.e. cellulose perchloric acid also provided a low yield up to 50 % while Glycine and betainegave rise to moderate yields of 60% and 62% respectively. It was observed that BHC affords excellent yield within short reaction time, hence the BHC was used as the reaction promoter.

To study the role of solvent and impacts of temperature, the model reaction was performed under polar and non-polar solvents at different temperatures. Different solvents such as non-polar solvents (toluene, cyclohexane), polar aprotic solvents (THF, Acetone, CH_3CN, DMF) and polar protic solvents (water, ethanol) were used at different temperatures. The best catalytic activity of BHC was found in ethanol. It was observed that the solubility of BHC catalyst in water and ethanol also played a very important role in catalyzing the reaction.

To evaluate the appropriate amount of the catalyst, the model reaction was carried out in the presence of 05, 10 and 15 mol% of BHT. The product was obtained in 70 and 85 and 87 % yield, respectively.

Table 2. Effects of solvents and Temperatures.[a]

Sr. No.	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	THF	Reflux	05	45
2	Acetone	Reflux	05	48
3	CH_3CN	Reflux	07	55
4	DMF	Reflux	05	60
5	Toluene	Reflux	04	40
6	Cyclohexane	Reflux	06	40
7	Water	Reflux	04	80
8	Ethanol	Reflux	03	85
9	Ethanol	80	05	72
10	Ethanol	60	06	60
11	Ethanol	RT	12	40

[a]Reaction conditions: 4-Chlorobenzaldehyde (1 mmol), aniline (1 mmol), mercaptoacetic acid (3 mmol) and BHC (10 mol%) in 10 ml of solvent.
[b]Isolated yield

This observation shows that 10 mol% of BHC is sufficient to carry out the reaction efficiently and any further increase in the amount of catalyst does not affect the reaction times and yield of products appreciably. Considering this result, a wide range of aromatic aldehydes and substituted anilines were incorporated to synthesize 4-thiazolidinediones by using BHC.

The BHC was recovered from the filtrate by evaporating the ethanol and re-used for the next run to carry out the same experiment. The results revealed that there was no change in its catalytic activity to afford the product up to three runs.

The possible reaction mechanism was proposed *via* the imine formation by condensation of an aldehyde and aniline, followed by the cyclization of mercaptoacetic acid to give the desired product (Scheme 2).

Selectivity of BHC for catalyzing this reaction was recognized by formation of anion and cation which act as acid and base. N,N,N-trimethyl glycinium is the cationic species which increases the electrophilic nature of aldehyde by protonating with carboxylic-OH to form the imine thereby increase the rate of reaction. To react with aromatic amine and Cl^- abstract, the H of mercaptoacetic acid enhances the nucleophilic character of thiol functionality and attack the imine species and undergo cyclization to afford the 4-thiazolidinediones. This ionic environment enhances the hydrophobic effect and increases the concentration of organic substrate in the reaction medium, this causes more and more collisions of reacting species and the mild viscous nature of reaction media increases the internal energy in favor of product formation. Three moles of mercaptoacetic acid was proved to be best stoichiometry for completing the reaction.

4. Conclusions

This illustrative approach has many advantages such as the efficient and trouble-free operation, improved yield, non-hazardous reaction conditions, the simple experimental and work up procedure and reusability of ionic salt. Also, in this strategy, safer reaction conditions and the biocompatible property of salty solvent avoid the use of Dean-Stark trap apparatus.

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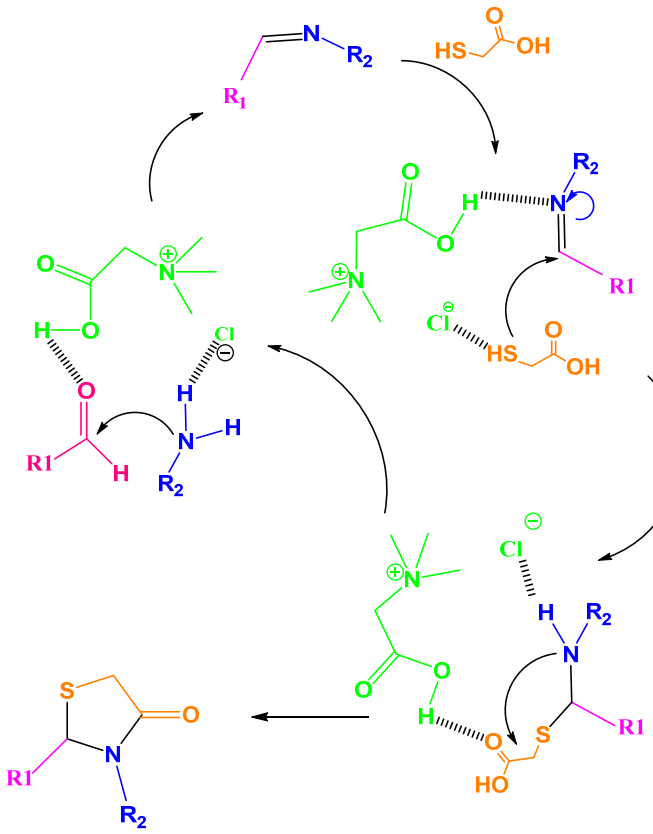
Table 3. BHC catalyzed one-pot synthesis of 4-thiazolidinediones derivatives.[a]

Sr. No.	R_1	R_2	Time (min)	Yield (%)[b]	m.p. (°C)		Ref.
					Found	Reported	
4a	Ph	Ph	70	85	106	105-107	[29]
4b	4-OCH_3-Ph	Ph	90	82	110	110-111	[29]
4c	4-OH-Ph	Ph	100	82	182	182-184	[29]
4d	4-Cl-Ph	Ph	180	85	130	130-132	[29]
4e	4-NO_2-Ph	Ph	120	75	108	105-107	[29]
4f	Ph	4-Cl-Ph	60	80	112	111-113	[29]
4g	4-OCH_3-Ph	4-Cl-Ph	50	85	158	158-160	[29]
4h	4-OH-Ph	4-Cl-Ph	45	80	160	158-160	[29]
4i	4-Cl-Ph	4-Cl-Ph	60	78	130	124-126	[29]
4j	4-NO_2-Ph	4-Cl-Ph	50	75	140	139-141	[29]
4k	Ph	4-CH_3-Ph	70	80	110	112-114	[29]
4l	4-OCH_3-Ph	4-CH_3-Ph	50	82	150	148-150	[29]
4m	4-OH-Ph	4-CH_3-Ph	75	80	210	210-211	[29]
4n	4-Cl-Ph	4-CH_3-Ph	55	80	160	169-171	[30]
4o	2-Cl-Ph	Ph	50	85	120	116-118	[30]
4p	2-Cl-Ph	3-CH_3-Ph	55	88	130	126-128	[30]

[a]Reaction conditions: aromatic aldehyde (1 mmol), substituted aniline (1mmol), mercaptoacetic acid (3mmol), BHC (10 mol%) in 10 ml of ethanol, reflux.
[b]Isolated yield.



Scheme 2. Possible mechanism for the synthesis of 4-thiazolidinediones derivatives.

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