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An Efficient Synthesis of 5-Arylidene-2,4-ThiazolidinedioneCatalyzed by Boric acid in Aqueous media under Ultrasound-Irradiation

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Abstract: Boric acid is an inexpensive, efficient and non-toxic catalyst used for the synthesis of 5-arylidine-2,4-thiazolidinediones by the Knoevenagel condensation of aromatic aldehydes with 2,4-thiazolidinedione in aqueous media under ultrasound at room temperature. Operational simplicity, use of economically an convenient catalyst, mild reaction conditions, high yield, short reaction times are the key features of this protocol.

Keywords: Knoevenagel condensation,boric acid, 2,4-thiazolidinedione, aromatic aldehyde,aqueous media

Introduction:

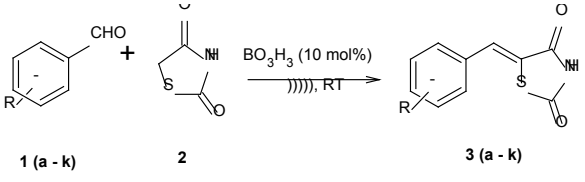
The steady growth of interest in heterocyclic compounds is connected with their raised biological activity and also with the fact that these compounds make possible the development of novel materials of unique properties. One very interesting and promising class of heterocycles is the thiazolidine ring system. Thiazolidinedione represents a class of chemical products with interesting pharmacological and biological activity including antibacterial, [1a]antidiabetic[1b], cardiotonic[1c] and anticonvulsant [1d]. In addition, thiazolidinedione based molecules have been popular as small molecule inhibitors such as aldose reductase[2]. Thus, the synthesis of thiazolidinedione derivatives is currently of much importance. It is well known that 5-arylidene-2,4-thiazolidinediones are generally synthesized by condensation of aromatic aldehydes with 2,4-thiazolidinedione in organic solvents, i.e. piperidine in EtOH[3a], $AlPO_4$-Zeolite in EtOH:H_2O [3b], polyethylene glycol [3c], L-tyrosine [3d], Phosphoryl Chloride [3e] and2-hydroxy ethylammonium acetate [3f]. Each of these methods have their own advantages but also be long reaction times, low to moderate yields, tedious work-up procedures,requirement of special apparatus, use of organic solvents, and requirement of excess of catalysts.Therefore, the development

of a simple, efficient and versatile method is still strongly desirable.

The Knoevenagel condensation is a basic reaction for C-C bond formation, which is of paramount importance in organic synthesis [4]. The Knoevenagel condensation reactions are classically catalyzed by base in liquid-phase systems; various catalysts are known to effect the reaction with different aldehydes and the active methylene group.

In recent years, many organic transformations have been carried out in water [5]. Water is a unique solvent due to it being readily available, inexpensive, non-toxic, safer and environmentally benign.

To the best of our knowledge, boric acid (BO_3H_3 or $B[OH]_3$) has not been used as a catalyst for the synthesis of 5-arylidene-2,4-thiazolidinediones and attracted our attention to investigate the application of boric acid as a catalyst.In recent years, boric acid have gained special attention as catalyst in organic synthesis because many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness and eco-friendly nature. Recently, several synthetically useful organic transformations using boric acid as a catalyst have been reported in the literature [6]. Ultrasound technique has increasingly been used in organic synthesis in the last three decades. It has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under ultrasound irradiation [7].



Scheme 1

Results and Discussion:

In continuation of our work on Knoevenagel condensations [8] and the development of green methodologies [9], herein, we would like to report a simple, efficient and rapid method for the synthesis of 5-arylidine-2,4-thiazolidinediones. As shown in Table **1**, benzaldehyde**1a** and 2,4-thiazolidinedion **2** were chosen as the model reaction to optimize reaction conditions including type of catalyst, concentration of catalyst and type of solvents. Other catalysts, L-prolineand oxalic acid were screened under ultrasound at room temperature (entries 1-2), and the results show that boric acid provided the highest yield (entry 3). Notably, a very slow reaction was observed when the catalytic amount of boric acid decreased from 10 mol% to 5 mol% (entry 4vs entry 5). With 15 mol% of boric acid there is no change in reaction rate as well as yield (entry 5). In addition, it was found that the solvent played a crucial role in this reaction (entry 3, and 7-9). Dichloromethane and ethanol as solvents were also able to facilate the Knoevenagel reaction. However, the use of water instead of dichloromethane and ethanol reduced the reaction time from 150-180 min to 50 min (entry 3 vs entries 7, 9).

To evaluate the effect of ultrasound for the model reaction, we first examined the reaction without ultrasound at room temperature. We found low yield (40%) with prolonged reaction time (180 min) and using ultrasound at room temperature amazingly we found excellent yield (95%) with short reaction time (50 min). Therefore, we chose this method to perform the synthesis of all derivatives of 5-arylidene-2,4-thiazolidinedione under ultrasound irradiation. With these optimal conditions in hand, we examined the scope of this Knoevenagel condensation reaction. Typical results are shown in Table **2**. These results suggest that water is the best solvent for synthesis of 5-arylidene-2,4-thiazolidinediones. It may be due to the

catalyst having greater solubility in water than in organic solvents.

Herein, we have developed an efficient methodology for the synthesis of 5-arylidene-2,4-thiazolidinedione using boric acid as a catalyst in aqueous mediumunder ultrasound at room temperatureas depicted in Scheme **1**. The methodology developed is simple with good to excellent yields. In this methodology, the products are isolated in pure form by simple filtration and as a result of which yield losses are avoided. To investigate the generality of the reaction various substituted and unsubstituted aldehydes were studied. Those include nitro, chloro, methoxy, methyl, and hydroxy groups, all of which undergo smooth reactions without any byproduct (Table **2**).

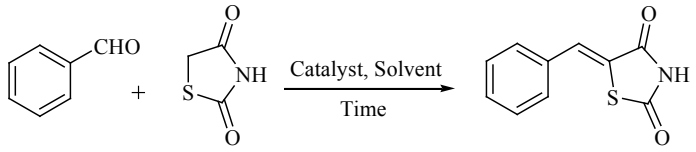
In Table **3**, our results are compared with results obtained by some other procedures for the synthesis of 5-arylidine-2,4-thiazolidinediones. The data presented in this table show the promising features of this method in terms of reaction time and yield of the product compared with those reported in the literature.

Experimental

All chemicals were purchased from Merck, Aldrich and Rankem chemical companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progress of the reactions was monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ /DMSO-d_6 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

The required starting material i.e. 2,4-thiazolidinedione [10] was prepared in an

Table 1. Standardized reaction condition for the synthesis of 5-benzylidene 2,4 thiazolidinedione **3a** under different solvents

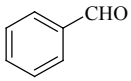
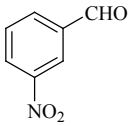
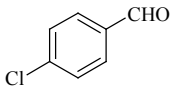
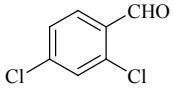
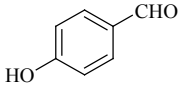
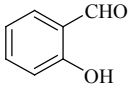
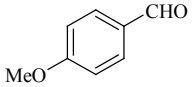
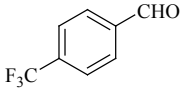
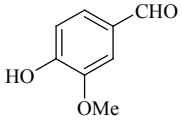
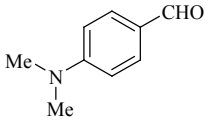
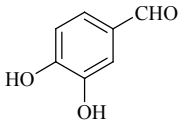


1a **2** **3a**

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)[a]
1	L-Proline (10)	H_2O	90	65
2	Oxalic acid (10)	H_2O	60	79
3	**Boric acid (10)**	**H_2O**	**50**	**95**
4	Boric acid (5)	H_2O	80	87
5	Boric acid (15)	H_2O	50	95
6	Boric acid (10)	H_2O	240	54
7	Boric acid(10)	CH_2Cl_2	180	75
8	Boric acid(10)	CH_3CN	150	65
9	Boric acid (10)	EtOH	70	85

[a]Isolated yield

Table 2. Synthesis of 5-arylidene-2,4-thiazolidinediones catalyzed by boric acid in water under ultrasound at room temperature

Compound	Aldehyde	Time (min)	Yield (%)[a]	Mp (°C)	
				Found	Literature
3a		50	95	242	240-242(3a)
3b		55	92	182	183-184(3b)
3c		50	92	270	267-268(3b)
3d		65	90	215	215-216(3b)
3e		80	92	280	282-285(3a)
3f		90	88	276	278-280(3a)
3g		90	88	236	235-238(3a)
3h		60	87	234	234-236(3a)
3i		80	86	194	194-196(3a)
3j		90	87	280	282-283(3b)
3k		70	85	268	266-268(3a)

[a]Isolated yields based upon starting aldehyde

Table 3. Comparison of results of other reported procedures with the present method[a].

Entry	Reagent	Reaction condition	Time	Yield (%)	References
1	Piperidine	EtOH/reflux	4 h	51-90	(3a)
2	$AlPO_4$-Zeolite	EtOH:H_2O/reflux	80-110 min	77-96	(3b)
3	PEG-300	130°C	3 h	75-84	(3c)
4	BO_3H_3	H_2O/))))), RT	50-90 min	85-95	Present

[a]Synthesis of 5-arylidine 2,4-thiazolidinediones.

eco-friendly way, by the reaction of thiourea with chloro acetic acid in water.

General procedure for the preparation of 5-aryilidene-2,4-thiazolidinediones 3(a-k)

A mixture of aromatic aldehyde (1 mmol), 2,4-thiazolidinedione (1 mmol) and water (10 mL) were taken in single neck round bottom flask and to this boric acid (10 mol%) was added. The flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at room temperature for the prescribed time (Table **2**). The progress of reaction was monitored by TLC using ethyl acetate: *n*-hexane (1:9) as a solvent system. After the completion of the reaction, the mixture was cooled to room temperature and poured into crushed ice, stirred and the solid product obtained, was separated *via*filtration and recrystallized from ethanol to get the corresponding 5-arylidene-2,4-thiazolidenedione **3**(**a-k**) in good to excellent yield.

Selected data of compound

(3a) IR (KBr) cm^{-1} : 3155 (NH), 3049, 879 (CH; aromatic), 2868 (CH; aliphatic), 1739, 1691 (C=O). ^{1}H NMR ($CDCl_3$/ DMSO-d_6): 8.27 (1H, s, NH), 7.86 (1H, s, CH), 7.26 (5H, m, aromatic protons). MS m/z (%): 206 (M+1).

(3b) ^{1}H NMR ($CDCl_3$/DMSO-d_6): 7.47 (m, 4H, aromatic protons). MS m/z (%): 251 (M+1).

(3g) ^{1}H NMR ($CDCl_3$/DMSO-d_6): 3.73 (3H, s, OCH_3), 7.26 (4H, m, aromatic protons). MS m/z (%): (236 (M+1).

(3h) ^{1}H NMR ($CDCl_3$/DMSO-d_6): 7.77 (4H, m, aromatic protons). MS m/z (%): 274 (M+1).

(3i) ^{1}H NMR ($CDCl_3$/DMSO-d_6): 3.73 (3H, s, OCH_3), 6.68 (3H, m, aromatic protons). MS m/z (%): 252 (M+1).

(3j) ^{1}H NMR ($CDCl_3$/DMSO-d_6): 2.85 (6H, s, CH_3), 7.26 (4H, m, aromatic protons). MS m/z (%): 249 (M+1).

(3k) ^{1}H NMR ($CDCl_3$/DMSO-d_6): 3.78 (3H, s, OCH_3), 7.52-7.06 (4H, m, aromatic protons). MS m/z (%): 238 (M+1).

Conclusion:

In conclusion, we have developed an ultrasound-assisted, efficient and convenient method for the synthesis of 5-arylidene-2,4-thiazolidinedione derivatives by Knoevenagel condensation of different aromatic aldehydes with 2,4-thiazolidinedione using cheap and readily available boric acid as a catalyst. Moreover, the catalyst used is easily available, inexpensive, non-toxic, eco-friendly, and water was chosen as a unique solvent, which makes

the reaction convenient, more economic and environmentally benign. The notable merits offered by this methodology are shorter reactions time without phase transfer catalyst (PTC), mild reaction conditions, easy work up procedures and good to excellent yields.

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