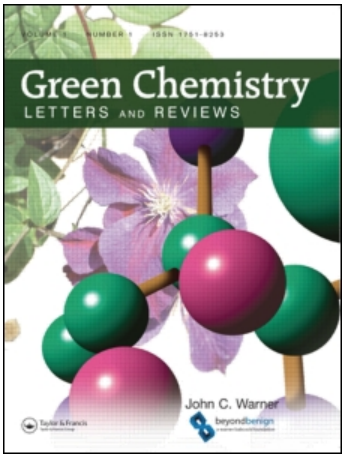

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Alum catalyzed simple and efficient synthesis of 5-arylidene-2,4-thiazolidinedione in aqueous media

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RESEARCH LETTER

Alum catalyzed simple and efficient synthesis of 5-arylidene-2,4-thiazolidinedione in aqueous media

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Alum ($KAl(SO_4)_2{\cdot}12H_2O$) 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 at 90°C. This method affords the 5-arylidine-2,4-thiazolidinediones in short reaction times, high yields, and green aspects by avoiding toxic catalysts and hazardous solvents.

Keywords: Knoevenagel condensation; alum; 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 (*1*), antidiabetic (*2*), cardiotonic (*3*), and anticonvulsant (*4*). In addition, thiazolidinedione based molecules have been popular as small molecule inhibitors such as aldose reductase (*5*). 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 (*6*), $AlPO_4$–Zeolite in EtOH:H_2O (*7*), and polyethylene glycol (*8*). However, above reported methods suffered from one or more drawbacks such as prolonged reaction times (*6*) with frequently low yields (*8*). 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 (*9*). 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 (*10–13*). Water is a unique solvent due to it being readily available, inexpensive, non-toxic, safer, and environmentally benign.

Alum ($KAl(SO_4)_2{\cdot}12H_2O$) has previously been reported to be effective in the synthesis of *cis*-isoquinolic acids (*14*), mono and disubstituted 2,3-dihydroquinazolin-4 (1*H*)-ones (*15*), dihydropyrimidine via Biginelli reaction (*16*), coumarins (*17*), 1,3,4-oxadiazoles (*18*), dibenzoxanthenes (*19*), 1,5-benzodiazepines (*20*), and trisubstituted imidazoles (*21*). Alum has continued to be exploited in organic synthesis because it is a non-toxic, inexpensive, eco-friendly, and easy handling catalyst. We investigated alum as a catalyst for the synthesis of 5-arylidine-2,4-thiazolidinediones. It was found that alum is an effective promoter in the synthesis of 5-arylidine-2,4-thiazolidinediones by the Knoevenagel condensation of aldehydes with 2,4-thiazolidinedione (Scheme 1).

Results and discussion

In continuation of our work on Knoevenagel condensations (*22–26*) and the development of green methodologies (*27–29*), herein, we would like to report a simple, efficient, and rapid method for the synthesis of 5-arylidine-2,4-thiazolidinediones.

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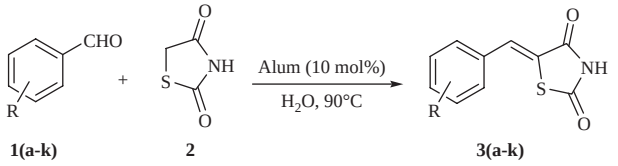


Scheme 1. Synthesis of 5-arylidene-2,4-thiazolidinediones.

As shown in Table 1, benzaldehyde **1a** and 2,4-thiazolidinedion **2** were chosen as the model substrate to optimize reaction conditions including type of catalyst, concentration of catalyst, and type of solvents. Other catalysts, l-proline, boric acid, and oxalic acid, were screened at 90°C (entries 1–3), and the results show that alum provided the highest yield (entry 4). Notably, a very slow reaction was observed when the catalytic amount of alum decreased from 10 to 5 mol% (entry 5 vs. entry 4). With 15 mol% of alum there is no change in reaction rate as well as yield (entry 6). In addition, it was found that the solvent played a crucial role in this reaction (entry 4, and 8–10). 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 to 50 min (entry 4 vs. entries 8, 10). Very little reaction is observed when the reaction is carried out at 25°C (entry 7).

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.

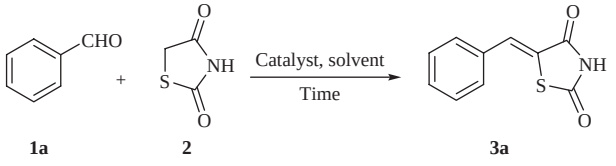
Herein, we have developed an efficient methodology for the synthesis of 5-arylidene-2,4-thiazolidinedione using alum as a catalyst in water at 90°C as depicted in Scheme 1. The methodology developed is simple with good to excellent yields. In this methodology, the products are isolated in pure form by 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 shows 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

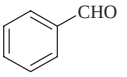
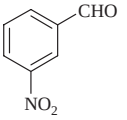
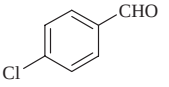
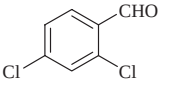
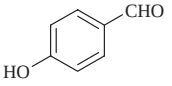
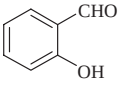
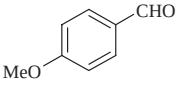
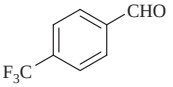
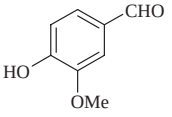
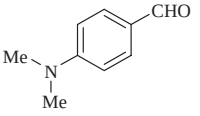
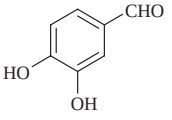
Table 1. Standardized reaction condition for the synthesis of 5-benzylidene 2,4 thiazolidinedione **3a** under different solvents.



Entry	Catalyst (mol%)	Solvent/Temperature (°C)	Time (min)	Yield (%)[a]
1	l-proline (10)	H_2O/90	90	65
2	Boric acid (10)	H_2O/90	60	72
3	Oxalic acid (10)	H_2O/90	60	79
4	**Alum (10)**	**H_2O/90**	**50**	**95**
5	Alum (5)	H_2O/90	80	87
6	Alum (15)	H_2O/90	50	95
7	Alum (10)	H_2O/25	240	54
8	Alum (10)	CH_2Cl_2/40	180	75
9	Alum (10)	CH_3CN/82	150	65
10	Alum (10)	EtOH/78	70	85

[a]Isolated yield.
Note: Entry in bold signifies best result.

Table 2. Synthesis of 5-arylidene-2,4-thiazolidinediones catalyzed by alum in water at 90°C.

Compound	Aldehyde	Time (min)	Yield (%)[a]	M.P. (°C)	
				Found	Literature
3a		50	95	240	240–242 (*6*)
3b		60	93	180	183–184 (*7*)
3c		50	92	270	267–268 (*7*)
3d		70	90	215	215–216 (*7*)
3e		80	92	281	282–285 (*6*)
3f		90	88	276	278–280 (*6*)
3g		90	88	235	235–238 (*6*)
3h		70	87	234	234–236 (*6*)
3i		80	86	194	194–196 (*6*)
3j		90	87	281	282–283 (*7*)
3k		70	85	267	266–268 (*6*)

[a]Isolated yields based upon starting aldehyde.

paraffin bath. The progress of the reactions was monitored by thin layer chromatography (TLC). 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 (*30*) was prepared in an 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 alum (10 mol%) was added. The reaction mixture was stirred at 90°C in a water bath for the appropriate time given in 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

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	(*6*)
2	$AlPO_4$–Zeolite	EtOH:H_2O/reflux	80–110 min	77–96	(*7*)
3	PEG-300	130°C	3 h	75–84	(*8*)
4	$KAl(SO_4)_2{\cdot}12H_2O$	H_2O/90°C	50–90 min	85–95	Present

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

product obtained, was separated via filtration, and recrystallized from ethanol to give pure 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). ^1H 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) ^1H NMR ($CDCl_3$/DMSO-d_6): 7.47 (m, 4H, aromatic protons). MS *m*/*z* (%): 251 (M + 1).

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

(3i) ^1H 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) ^1H 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) ^1H 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 described a simple, efficient, and cleaner methodology for the synthesis of 5-arylidene-2,4-thiazolidinedione derivatives by Knoevenagel condensation of different aromatic aldehydes with 2,4-thiazolidinedione in presence of alum in water at 90°C. 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 remarkable advantages of the present method are shorter reaction times without phase transfer catalyst (PTC), easy work up procedures, and good to excellent yields.

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