Research Article

A Solvent-Free Protocol for the Green Synthesis of 5-Arylidene-2,4-thiazolidinediones Using Ethylenediamine Diacetate as Catalyst

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Received 11 March 2012; Accepted 28 May 2012

Academic Editor: William N. Setzer

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A simple and efficient synthesis of 5-arylidene-2,4-thiazolidinediones by the Knoevenagel condensation of aromatic aldehydes with 2,4-thiazolidinedione catalyzed by ethylenediamine diacetate under solvent-free conditions is described. The major advantages of this method are simple experimental and work-up procedures, solvent-free reaction conditions, small amount of catalyst, short reaction time, high yields, and utilization of an inexpensive and reusable catalyst.

1. Introduction

2,4-Thiazolidinedione and its derivatives exhibit a variety of pharmacological activities [1–3]. 5-Arylidene derivatives of 4-thiazolidinones have been found to be better fungistatic agents than the parent 4-thiazolidinones [4]. It was reported that 5-arylidene-2,4-thiazolidinediones can act as potentially promising aldose reductase inhibitors [5] and 15-hydroxyprostaglandin dehydrogenase inhibitors [6]. There is a great interest in 5-benzylidenethiazolidine-2,4-dione derivatives as promising inhibitors of MurD ligase [7]. Thus, the synthesis of 5-arylidene-2,4-thiazolidinediones is currently of much importance. There are several methods reported in the literature for the synthesis of 5-arylidene-2,4-thiazolidinediones such as sodium acetate in acetic acid under reflux conditions [8], sodium acetate in acetic acid under microwave irradiation [9], piperidine in ethanol under reflux conditions [5, 10–12], piperidinium acetate in toluene under reflux conditions [6, 13], piperidinium acetate in ethanol under microwave irradiation [7], piperidinium acetate in DMF under microwave irradiation [14], glycine and sodium carbonate in H₂O under reflux conditions [15], grinding with ammonium acetate in the absence of solvents [16], KAl(SO₄)₂·12H₂O in H₂O at 90°C [17], baker's yeast

[18], KF·Al₂O₃ under microwave irradiation [19], glycine under microwave irradiation [20], and polyethylene glycol-300 at 100–120°C [21]. Recently, ionic liquids ([bmim]Cl, C₃[min]₂·2[Br[−]]) catalyzed synthesis of 5-arylidene-2,4-thiazolidinediones have also been reported [22, 23]. Each of these methods have their own advantages but also suffer from one or more disadvantages such as long reaction times, low to moderate yields, tedious work-up procedures, requirement of special apparatus, use of organic solvents, requirement of excess of catalysts, and difficulty in recovery and reusability of the catalysts. Researches are still in progress to improve the preparation methods of 5-arylidene-2,4-thiazolidinediones.

In recent past, ethylenediamine diacetate (EDDA) has emerged as an inexpensive and effective Brønsted acid-base combined salt catalyst in various organic transformations [24–27]. To the best of our knowledge, EDDA 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 EDDA as a catalyst. The solvent-free reaction has many advantages: reduced pollution, low costs, and simplicity in process and handling [28]. Herein, we reported a simple and efficient synthesis of 5-arylidene-2,4-thiazolidinediones by the Knoevenagel condensation

TABLE 1: Effect of different reaction conditions on EDDA catalyzed synthesis of 5-benzylidene-2,4-thiazolidinedione^a.

Entry	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield ^b (%)
1	30	10	150	63
2	40	10	85	77
3	50	10	35	82
4	60	10	15	80
5	70	10	7	90
6	80	10	3	91
7	90	10	3	89
8	80	—	3	—
9	80	3	3	76
10	80	5	3	91
11	80	20	3	88

^a Reaction condition: benzaldehyde (10 mmol), 2,4-thiazolidinedione (10 mmol), in presence of EDDA under solvent-free conditions.^b Isolated yield.

SCHEME 1: EDDA catalyzed synthesis of 5-arylidene-2,4-thiazolidinediones.

of aromatic aldehydes with 2,4-thiazolidinedione in the presence of EDDA under solvent-free conditions (Scheme 1).

2. Results and Discussion

Initially, benzaldehyde was selected as a probe aldehyde to optimize the reaction conditions, and the results are listed in Table 1. Obviously, the temperature and the amount of catalyst had important effects on the reaction. The mixture was stirred under solvent-free conditions at different temperatures ranging from 30 to 90°C, with an increment of 10°C each time. The yield of 5-benzylidene-2,4-thiazolidinedione was increased and the reaction rate was improved as the reaction temperature was raised from 30 to 80°C (Table 1, entries 1–6). However, raising the reaction temperature from 80 to 90°C did not increase the yield and also did not improve the reaction rate (Table 1, entries 6–7). Therefore, 80°C was chosen as the reaction temperature for all further reactions. The optimum amount of EDDA was found to be 5 mol% relative to reactants (2,4-thiazolidinedione, 10 mmol and benzaldehyde, 10 mmol). When the amount of the catalyst decreased to 3 mol% from 5 mol% relative to the substrates, the yield of 5-benzylidene-2,4-thiazolidinedione was reduced (Table 1, entries 9 and 10). However, the use of 10 mol% of the catalyst showed the same yield and the same time was required (Table 1, entries 6 and 10). It is noteworthy that in the absence of a catalyst under the reaction conditions, no product formation was observed after 3 min (Table 1, entry 8). This result indicates that the catalyst exhibits a high catalytic activity in this transformation.

TABLE 2: Recycling of the EDDA for the synthesis of 5-benzylidene-2,4-thiazolidinedione^a.

Run	Time (min)	Yield ^b (%)
1	3	91
2	3	90
3	6	87
4	9	86
5	14	84

^a Reaction condition: benzaldehyde (20 mmol), 2,4-thiazolidinedione (20 mmol), EDDA (1 mmol) at 80°C under solvent-free conditions.^b Isolated yield.

From the perspective of green chemistry, it is highly desirable that the catalyst can be recycled. We have also examined the recyclability of EDDA as catalyst by stirring 2,4-thiazolidinedione, benzaldehyde and EDDA under solvent-free conditions at 80°C (Table 2). After the completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature and diluted with water. The separated solid was suction filtered, washed with water, and recrystallized from hot ethanol to obtain the pure product. The water containing the EDDA was then evaporated to dryness under reduced pressure and the resulting catalyst was reused directly for the next run. The recovered EDDA can be reused at least four additional times in subsequent reactions without a considerable decrease in catalytic activity.

With these results in hand, we next examined the generality of these conditions to other substrates using several aromatic aldehydes. The results are summarized in Table 3. Several functionalities present in aromatic aldehydes such as halogen, hydroxyl group, methyl group, methoxy, and nitro group were tolerated. In all cases the corresponding 5-arylidene-2,4-thiazolidinediones were obtained in high yields. Cinnamaldehyde and furfural were also successfully converted to corresponding products in high yields. All products obtained are known compounds and were identified by comparing their physical and spectra data with the reported ones.

TABLE 3: EDDA catalyzed synthesis of 5-arylidene-2,4-thiazolidinediones^a.

Entry	Aldehyde	Product	Time (min)	Yield ^b (%)	M.p. (°C)	
					Found	Literature
1			3	91	241–242	241–242 [23]
2			3	88	230–232	225–226 [23]
3			4	91	218–220	218–219 [23]
4			7	89	224–225	220–221 [19]
5			7	84	192–194	187–190 [5]
6			8	79	281–282	281 [17]
7			40	70	187–189	185–190 [19]
8			22	91	195–197	194 [17]
9			8	82	226–228	223–224 [19]
10			65 (20°)	79 (90°)	213–215	215 [17]
11			50 (15°)	74 (85°)	260–262	261–263 [9]

TABLE 3: Continued.

Entry	Aldehyde	Product	Time (min)	Yield ^b (%)	M.p. (°C)	
					Found	Literature
12			75	89	228–230	225–226 [19]
13			15	85	309–310	310–312 [23]
14			30	80	219–221	218–220 [19]
15			2	81	231–233	230–233 [19]

^a Reaction condition: aldehyde (10 mmol), 2,4-thiazolidinedione (10 mmol), EDDA (0.5 mmol) at 80°C under solvent-free conditions.

^b Isolated yield.

^c Reactions were carried out at 90°C.

3. Conclusion

In conclusion, we have described a simple and efficient synthesis of 5-arylidene-2,4-thiazolidinediones by the Knoevenagel condensation of aromatic aldehydes with 2,4-thiazolidinedione in the presence of ethylenediamine diacetate under solvent-free conditions. The major advantages of this method are simple experimental and work-up procedures, solvent-free reaction conditions, small amount of catalyst, short reaction time, high yields, and utilization of an inexpensive and reusable catalyst.

4. Experimental

FT-IR spectra were obtained on a Nexus 470 spectrophotometer. ¹H NMR spectra were recorded on a Bruker Avance 400 with TMS as internal standard. Melting points were determined on a melting point apparatus and uncorrected. Thin layer chromatography (TLC) was performed on silica gel F254 plates using a 254 nm UV lamp or/and iodine vapor to visualize the compounds. 2,4-Thiazolidinedione was prepared according to the literature method [11].

General Procedure for the Preparation of 5-Arylidene-2,4-thiazolidinediones. A mixture of 2,4-thiazolidinedione (10 mmol), aldehyde (10 mmol), and EDDA (0.5 mmol) was stirred at 80°C in an oil bath for the appropriate time given in Table 3. The progress of the reaction was monitored by TLC using ethyl acetate/pet ether (1/3) as an eluent. After completion of reaction, the reaction mixture was

cooled to room temperature and diluted with water. The separated solid was suction filtered, washed with water, and recrystallized from hot ethanol to obtain the pure product.

Acknowledgment

The authors thank the Natural Science Foundation of Hubei Province (Grant no. 2007ABA291) for financial support.

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