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$AlPO_4$-modified natural zeolite catalyzed facile synthesis of 5-arylidene-2,4-thiazolidinediones

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ABSTRACT

A simple and efficient procedure for the synthesis of substituted 5-benzylidene-2,4-thiazolidinedione derivatives through a condensation of 2,4-thiazolidineone and aromatic aldehydes in the presence of modified zeolite in aqueous alcohol medium is described. Worldwide availability, non-toxicity, reusability of catalyst, high yield and simple work-up procedure are the advantages of presented work.

KEYWORDS

Knoevenagel condensation;
2,4-Thiazolidinedione (2,4-TZD);
$AlPO_4$- zeolite.

INTRODUCTION

The presence of thiazolidine ring in penicillin's and related derivatives was first recognition of its occurrence in nature[1]. Thiazolidine derivatives are reported to show variety of biological activities depending on the substituents, this heterocycle can induce different pharmacological properties such as antibacterial, antifungal[2], antidiabetic[3], cardiotonic[4], anticonvulsant[5], cyclooxygenase and lipoxygenase inhibitory[6]. It has been established that introduction of arylidene moieties at different positions of the thiazolidine ring enhanced antimicrobial activity[2,7]. Also, 2,4-TZD and its derivatives has remarkable anti-proliferative effect on vascular smooth muscle[8]. 2,4-TZD have active methylene group and are more reactive[9], hence many molecules are build at 5th position (i. e. methylene group) of 2,4-TZD having great importance in pharmacological aspect. A series of 5-benzylidene-2,4-TZDs are under clinical trials as potential phospholipase A_2 inhibitor, dual COX-2/5-LOX inhibitor and inflammatory agents[10].

As a result of their importance from a pharmacological, industrial and synthetic point of view, there has been increasing interest in the development of efficient methodologies for the synthesis of 5-benzylidene-2,4-Thiazolidinediones. Generally, 5-arylidene-2,4-TZDs were prepared by condensation of aromatic aldehydes with 2,4-TZD in organic solvent. i.e. piperidine in EtOH[11], NaOAc in DMF-AcOH[12], ethylenediammo nium acetate in MeOH[13], piperidine and acetic acid in toluene[14], morpholine in AcOH[15], polyethylene glycol[16] etc. many of these methods have several drawbacks such as low yields, large reaction times, use of environmentally unfavorable solvents and tedious work-up procedure. However, the search continues for the mild, efficient and versatile method for the synthesis of 5-arylidene-2,4-TZDs.

Increasingly, stringent environmental legislation has generated a pressing need for cleaner methods of chemical production. For instance, technologies that reduce or preferably, eliminate the generation of waste and avoid the use of toxic and/or hazardous reagents and solvents[17-20] this trend toward green chemistry[21-23]. Necessitates a paradigm shift from the traditional concept of process efficiency that focuses exclusively on chemical yield, to one that assigns economic value to eliminate waste. Solid catalysts such as clays and zeolites, are also used in synthetic transformation, rendering them eco-friendly[24].

The zeolite material are naturally available can act as catalyst[25] and can be modified to enhance their catalytic properties for particular applications. It has been previously observed that treatment or addition of either phosphorus or aluminum phosphate separately produced a small improvement in certain zeolite catalysts[26].

We have previously reported the activation of natural zeolite and its application in the synthesis of fine chemicals[25,27]. In continuation of our work on the applications of $AlPO_4$-modified natural zeolite[27] as a catalyst in organic reactions, herein, we report the synthesis of 5-arylidene-2,4-TZDs by Knoevenagel condensation of 2,4-TZD and substituted aldehydes in the presence of catalyst.

EXPERIMENTAL

Apparatus and reagents

All the reagents and aromatic aldehydes were obtained from S. D. Fine Ltd (Mumbai) and were used as such. Melting points were determined in open capillaries apparatus and are uncorrected. The reactions were monitored by TLC. IR spectra were recorded on a matrix of KBr with FTIR-4100 (Jasco, Japan) spectrometer. ^{1}H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (200 MHz) and the chemical shifts are given in ppm relative to TMS as an internal standard.

General procedure for the synthesis of 5-arylidene-2,4-thiazolidinediones (3a-j)

For each reaction, aromatic aldehydes **(1)** (5 mmol) and 2,4-thiazolidinedione **(2)** (5 mmol) and catalyst (0.2 gm) were mixed in 10 ml equimolar quantity of absolute ethanol and water in a 50 ml round bottom flask. Loosely capped and was heated in an oil bath with a temperature of 75^{0}C for the time specified in TABLE 1 progress of reaction was monitored by TLC[hexane: ethyl acetate (7:3)] after the reaction was completed, the solvent was evaporated to give crude product, which was purified by recrystallization.

TABLE 1: Synthesis of 5-arylidene-2,4-thiazolidinediones catalyzed by $AlPO_4$-natural zeolite in aqueous alcohol at 75^{0}C

Compd.	R	Time (min)	Yield^a (%)	Mp (^{o}C)
(3a)	H	90	96	242
(3b)	2-OH	110	84	279-280
(3c)	4-OH	100	89	283-285
(3d)	4-OCH_3	85	92	238-239
(3e)	4-Cl	90	96	267-268
(3f)	4-$N(CH_3)_2$	80	94	282-283
(3g)	3-NO_2	95	92	183-184
(3h)	4-OH,3-OCH_3	80	89	198-200
(3i)	3-OH, 4-OH	110	79	263-264
(3j)	2-Cl, 4-Cl	95	77	215-216

[a] All the products were characterized by IR, ^{1}H NMR, mass spectra and comparisons of their physical characteristics with those of authentic compounds[11]

The required starting material i.e. 2,4-thiazolidine dione[28] was prepared in an eco-friendly way, by the reaction of thiourea with monochloroacetic acid in water

RESULT AND DISCUSSION

In order to find the optimum reaction conditions for ecofriendly synthesis of 5-arylidene-2,4-thiazolidine diones, we have selected condensation of 4-chloro benzaldehyde (TABLE 1, Entry 3e) and 2,4-thiazolidine dione as a model reaction in presence of modified natural zeolite, the reaction was carried out using 1:1 molar ratio of reactants in ethanol : water medium and the results of this synthetic route are found to be inspiring. In a similar fashion, a variety of substituted 5-arylidene-2,4-thiazolidinediones were synthesized using different aldehydes and in each case it is observed that the time period for condensation was reduced considerably and the yield of the products changed to excellent yields (TABLE 1). This indicates that the present catalyst efficiently makes the condensation reaction much faster with increased yields.

To determine the role catalyst, the same reaction was carried out in the absence of catalyst. The desired product was not observed after 50 minutes, this indicates that catalyst exhibits a high catalytic activity in this transformation.

The best solvent is no solvent, and if a solvent is needed, it should be water, which is non-toxic, nonin flammable, inexpensive and abundantly available. But use of water in this reaction gave only moderate yield

TABLE 2: Effect of solvent in the reaction of 4-chlorobenzaldehyde and 2,4-thiazolidinedione (3e)

Entry	Solvent	Reaction time	Yield[a] (%)
1	EtOH	120	70
2	CH_3CN	120	67
3	H_2O	120	73
4	CH_2Cl_2	120	60
5	EtOH : H_2O	70	87
6	CH_3CN : H_2O	70	80
7	CH_2Cl_2 : H_2O	70	72

[a]Yield refers to isolated product after recrystallization

TABLE 3: Recovery and reuse of catalyst in the reaction of 4-chlorobenzaldehyde and 2,4-thiazolidinedione

Run no.	Yield[a] (%)
1	96
2	94
3	94
4	93
5	94

[a]Yield refers to isolated product

of products (73%) (TABLE 2, entry 3). So we studied the effect of different solvents on synthesis of 5-arylidene-2,4-thiazolidinediones and results are summarized in TABLE 2. Among them EtOH: H_2O (1:1) was found to be the most efficient with respect to short reaction times and maximum yield of products. Aldehyde compounds, which have electron donating or electron withdrawing groups were used and as expected, in all the cases 5-arylidene-2,4-thiazolidinedione derivatives obtained in good to excellent yield.

The reusability of the catalyst is important for the large scale operation and industrial point of view. Therefore the recovery and reusability of catalyst was examined. The catalyst was separated and reused after washing it with n-hexane and drying at 70^0C. The reusability of the catalyst was investigated in the reaction of 4-chlorobenzaldehyde with 2,4-thiazolidinedione (TABLE 1, entry 3e) in the presence of catalyst. The results illustrated in TABLE 3 showed that the catalyst can be used five times without much loss in activity.

In conclusion, we have described a simple and efficient method for the synthesis of 5-arylidene-2,4-thiazolidinediones. The easy work-up procedure, non-toxic cost efficiency providing recyclability of the catalyst, excellent yields make this method a valid contribution to the existing methodologies.

Spectral data of selected compound

3a : IR (KBr) : 3155 (NH), 3049, 879 (CH: aromatic), 2868 (CH: aliphatic), 1739, 1691 cm^{-1}(C= O). ^{1}HNMR ($CDCl_3$/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).

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

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

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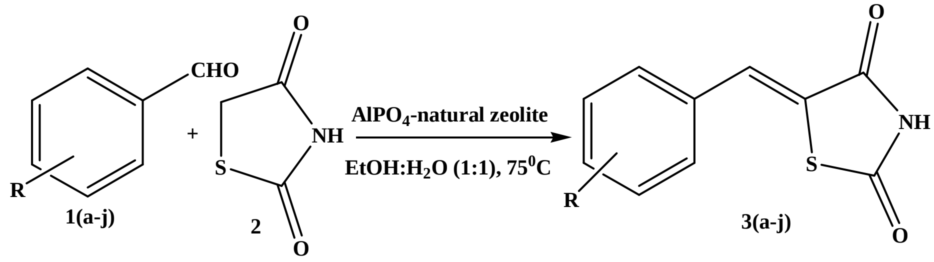

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