Glutamic Acid as an Efficient Catalyst Used for the Synthesis of 5-Arylidene-2, 4-Thiazolidinediones

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ABSTRACT
Knoevenagel condensation of aromatic aldehydes and active methylene compounds catalyzed by glutamic acid was performed. The developed protocol was found to be applicable for the preparation of 5-arylidene-2,4-thiazolidinediones using glutamic acid as an efficient catalyst in ethanol solvent under reflux conditions.

Keywords: Glutamic acid, Thiazolidine-2, 4-diones; 5-Arylidene-2, 4-Thiazolidinediones, Knoevenagel condensation.

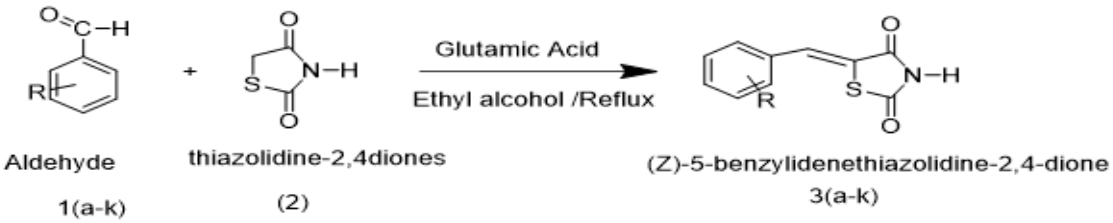
I. INTRODUCTION

Knoevenagel-catalyzed glutamic acid condensation of aromatic aldehydes and active methylene compounds (thiazolidine-2,4-diones) was performed. Knoevenagel condensation is a multicomponent reaction leading to the formation of new C–C bonds. The reaction is applicable for the synthesis of substituted alkenes, α, β-unsaturated cyanide, acid,esters, dyes and polymers.[1-4]

Glutamic acid is an α-amino acid used by almost all living things in protein biosynthesis. Glutamic acid is non-essential Amino acid. In the last year, glutamic acid has received considerable attention as an effective corrosion inhibitor for aluminum in HCl solution [21]. Glutamic acid occurs naturally in many foods, the flavor contributions of glutamic acid and other amino acids were only scientifically discovered in the early twentieth century. The substance was discovered and identified in 1866 by the German chemist Karl Heinrich Ritthausen [22]. When glutamic acid is dissolved in water, the amino group (-NH2) may gain a proton (H+) and/or the carboxyl groups may lose protons, depending on the acidity of the medium [23-25]. By considering this activity of glutamic acid, we have described an efficient way to use glutamic acid as an efficient catalyst for the synthesis of 2,4,5-triaryl-1H-imidazoles.

The condensation of 2,4-thiazolidinediones with aldehydes is of considerable interest. 5-Arylidene-2,4-thiazolidinediones products are important structural elements in medicinal chemistry and have been found to have significant hypoglycemic,[5] anti-inflammatory,[6] antitumor,[7] antifungal, [8] antidiabetic,[9]] and antimicrobial [10]activities. Several methods have been reported in the literature for the synthesis of benzylidenethiazolidine-2,4-dione derivatives, such as baker's yeast, [11] piperidine in ethanol under reflux conditions [12], piperidinium acetate in DMF under microwave irradiation, [13] milling with ammonium acetate in absence of solvents, [14] sodium acetate in acetic acid under microwave irradiation [15] , KAl(SO4)2·12H2O in H2O at 90 C, [16] polyethylene glycol-300 at 100–120 °C, [17] L- proline,[18] thiourea,[19] sodium acetate in acetic acid under reflux conditions, [20] hydrochloric acid,[21] without glycine/solvent under microwave irradiation, [22] (DABCO) in aqueous medium, [23] ethylene diamine acetate, [24] without catalyst/water as green solvent under microwave irradiation, [25] L-tyrosine/water [26] acidic ionic liquid, [27] calcium hydroxide, [28] tungstic acid, [29].

However, most of the reported methodologies still have some limitations, such as expensive catalysts, solvent toxicity, limitations for large-scale applications, critical product isolation procedures, difficulties in obtaining high-boiling solvents, excessive amounts of catalysts. It would therefore be highly desirable to develop a simple and efficient method for the synthesis of 5-arylidene-2,4-thiazolidinediones derivatives.



Scheme 1: Synthesis of substituted Benzylidenethiazolidine-2,4-dione derivatives.

II. RESULTS AND DISCUSSION

During the reaction conditions and optimization of the solvent, it is achieved that the reaction does not take place at room temperature or at 50 °C, but at 100 °C in ethyl alcohol, the reaction is faster and takes less time. Other solvents such as water, DMF, DMSO effluent, ethyl alcohol: water.

Table1: Optimization of different solvents for the synthesis of the 3c model product

Sr.No	Solvent	Time (Hrs)	Yield (%)
1	Ethyl alcohol	10	86
2	Ethyl alcohol:Water	26	55
3	Water	20	30
4	DMF	19	60
5	DMSO	18	64
6	Solvent less	24	62

To determine the exact concentration of the catalyst, model reactions were investigated at 2.5, 5, 7.5, 10, 12.5 mol% glutamic acid in ethyl alcohol at reflux temperature. The products were obtained in 24, 50, 60, 86 and 86%, respectively. This shows that the reaction can be accelerated with only (10 mol %) glutamic acid **(Table 2)**.

Table 2: Effect on catalyst concentration[a]

Entry	Concentration of catalyst in Mole (%)	Time (hr)	Yield [b]
1	2.5	16	24
2	5	14	50
3	7.5	12	60
4	10	10	86
5	12.5	10	86

[a]Reaction conditions: 1 (1 mmol), 2a (1 mmol), 3 (2 mmol) and (10 mol%) Glutamic acid reflux temperature. [b]Isolated yields.

Table 3: Glutamic acid catalyzed synthesis of 5-arylidene-2,4-thiazolidinediones derivatives in ethyl alcohol.

Sr.No	Product	Aldehyde	Time (Hours)	Yield(%)	M.P (ºC)	M.P Lit. (ºC)
1	3a	C_6H_5-	30	80	240	240-241[26]
2	3b	2-(Cl)C_6H_4-	28	77	209	210-212[29]
3	3c	4-(Cl)C_6H_4-	24	76	110	109[23]
4	3d	3-(NO2)C6H4-	28	79	187	186-188[26]
5	3e	4-(NO2)C6H4-	30	74	182	182-183[26]
6	3f	3-(OH)C_6H_4-	26	70	116	118-120[23]
7	3g	4-(OH)C_6H_4-	18	63	112	111-113[23]
8	3h	4-(OCH3)C6H4-	19	68	236	235-237[26]
9	3i	Furan-2-CHO	20	70	241	240-242[29]
10	3j	Thiophene-2-CHO	21	74	225	-----
11	3k	Pyridine-3-CHO	23	78	218	-----

III. EXPERIMENTAL

All chemical compounds used had been purchased from industrial providers and used without purification. The reaction was monitored by TLC on ethyl acetate and n-hexane mobile phases. Melting points are recorded by the open capillary method and are uncorrected.

3.1. General Procedure for the Synthesis of Benzylidenethiazolidine-2,4-Dione Derivatives:

A mixture of substituted aromatic aldehyde (1 mmol), active methylene compound (thiazolidine-2,4-dione) (1 mmol) and ethanol (10 ml) was stirred at reflux temperature for a predetermined time in the presence of a Glutamic acid catalyst. The development of this reaction turned into monitored with the aid of TLC After completion of the reaction, the reaction mixture was cooled to room temperature and ice-cold water was added. The solid product was filtered, washed with cold water and recrystallized from ethanol to give a pure benzilidenethiazolidine-2,4-dione derivative.

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