

Ionic liquid mediated synthesis of 5-arylidene-2,4-thiazolidinediones and antibacterial evaluation

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Abstract: Knoevenagel condensation of various aromatic aldehydes with 2,4-thiazolidinedione has been carried out in ionic liquid 4-methyl pyridinium tosylate as a eco-friendly medium. The isolation procedure is very simple with better yields. A series of 5-arylidene-2,4-thiazolidinediones derivatives (3a-3j) were evaluated for antibacterial activity. Derivatives 3b and 3c show good activity 3a, 3d and 3j show moderate activity against *S. aureus* whereas 3d and 3j show moderate activity against *B. subtilis*.

Key words: 2,4-Thiazolidinedione, Ionic Liquid, Knoevenagel Condensation, Antibacterial Activity.

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I. Introduction:

In recent years, the chemistry of 2,4-thiazolidinediones (TZDs) nucleus has captured attention of commercial market as these compounds have been found to exhibit several biological activities, such as antimalarial¹ antimicrobial² antiinflammatory³ antioxidant⁴ euglycemic⁵ antitumor⁶ antihyperglycemic⁷ PPAR agonist⁸ cytotoxic⁹ antiproliferative¹⁰ activator of dual PPAR α /c¹¹ inhibitor of Glycogen synthase kinase (GSK) 3¹² free radical scavenger¹³ inhibitor of aldose reductase¹⁴ inhibitor of LDL oxidation¹⁵ inhibitor of cholesterol esterase¹⁶ inhibitor of bacterial arylamine N-Acetyltransferases (NATs)¹⁷ inhibitor of 1,5-hydroxyprostaglandin dehydrogenase (15-PGDH)¹⁸ ERK and the PI3K/Akt signaling pathways¹⁹ human β_3 agonist²⁰ inhibitor of monoamine oxidase B (MAO-B)²¹ chymase inhibitor²² P2X7 receptor antagonist²³ inhibitor of MurD ligase²⁴ thyroid hormone receptor antagonist²⁵ neuroprotective²⁶ dual inhibitor of the Raf/MEK/serine/threonine & protein kinases Pim-1 and Pim-2²⁷ G-protein coupled receptor 40 (GPR40) agonist²⁸ PTP1B inhibitor²⁹ inhibitor of Raf/MEK/Extracellular signal regulated kinase (ERK1/2)³⁰ inhibitor of human PTP1B and LMW-PTP³¹ In view of the above pharmacological significance of 2,4-thiazolidinedione ring, synthetic chemists have paid considerable attention towards the designing construction of new 2,4-thiazolidinedione derivatives by developing various synthetic routes.

As described by Momose *et al.*³² and Bruno *et al.*³³ 2,4-thiazolidinedione can undergo a Knoevenagel condensation with a variety of substituted aldehydes to produce 5-arylidene-2,4-thiazolidinediones. There are several methods reported in the literature for the synthesis of 5-arylidene-2,4-thiazolidinediones such as piperidine in EtOH^{34a} NaOAc in DMF-AcOH^{34b} ethylenediammonium diacetate in MeOH^{34c} morpholine in AcOH^{34d} polyethylene glycol (PEG)^{34e} etc. However, above reported methods suffer from one or more drawbacks like prolonged reaction times, use of environmentally unfavorable solvents and frequently low yields. Therefore, the development of mild, efficient and versatile method is still strongly desirable. In recent years, applications of ionic liquids (ILs) in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, non-inflammability, negligible vapor pressure, easy of recycling, high thermal stability and rate enhancers³⁵. Also IL is environmentally benign media for catalytic processes, much attention has currently been focused on organic reaction catalyzed by ILs have been reported with high performance.³⁶ They have attracted quite justifiable enormous attention as media for green synthesis and hence several reviews have been appeared.³⁷⁻³⁹ Following is a brief literature survey covering history, synthetic aspects and applications of ionic liquids in organic transformations.

Ionic liquids have been described as a designer solvents⁴⁰ this means their properties can be adjusted to suit the requirements of particular process. Properties such as melting point, viscosity, density, hydrophobicity can be varied by simple changes to the structure of the ions. Another important property that changes with structure is the miscibility in water. This behavior can be of substantial benefit when carrying out solvent extraction or product separations. As a result, ionic liquids are receiving increasing attention in last few decades that resulted into development of different classes of ionic liquids.

II. Results And Discussion:

In comparison of the research work studied on Knoevenagel condensation and development of novel synthetic methodologies herein, we have reported a simple, efficient and rapid method for the synthesis of 5-arylidine-2,4-thiazolidinediones. In search for an efficient ionic liquid, the reaction of benzaldehyde and 2,4-thiazolidinedione in different reaction media is carried out as mentioned in **Table 1**. We have developed a newer route for the condensation of substituted aromatic aldehydes with 2,4-thiazolidinedione in an IL-4-methyl pyridinium tosylate at 120°C. The liberated water during the reaction was absorbed by the IL and hence the reactions proceed well. The synthetic route for the preparation of compounds **3a-j** has been illustrated in **Scheme 1**. The ionic liquid 4-methyl pyridinium tosylate was synthesized and used to carry out one pot synthesis of 5-substituted 2,4-thiazolidinediones. It was observed that generally cyclocondensation found to undergo completion at 120°C temperature using the freshly prepared ionic liquid within 2.5-3 hr. resulting in to high yields of the derivatives of 2,4-thiazolidinediones.

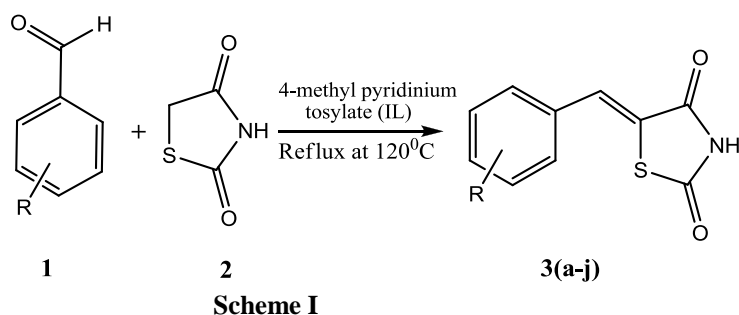


Table 1: Comparisons of results of different media for the present reaction

Sr. no.	Reaction medium	Time	Yield %	Reaction Condition
1	Choline chloride	6 hr	70	Reflux at 150
2	Diutectic solvent	3 hr	78	Shaking
3	4-methyl pyridinium tosylate	1.5 hr	80	Reflux at 120

Pharmacology:

Wide spread resistance to many commercially available antibiotics is emerging and resistance to these agents will only increase day by day⁴¹. Bacterial infections can cause some of the most serious diseases and widespread epidemics in the world. With the increase in resistance of bacteria to antibiotic treatment, it is essential to develop novel approaches and new antibacterial agents as alternatives to various existing antimicrobial therapies⁴². Although a large number of antibiotics and chemotherapeutics are available for medical use, the emergence of old and new antibiotic resistant bacterial strains in the last few decades constitute a substantial need for the new classes of antibacterial agents⁴³.

Antibacterial activity:

The antibacterial activity was determined using disc diffusion method by measuring zone of inhibition in mm⁴⁴. All the compounds **3a-j** were screened in-vitro at a concentration of 100 µg/disc for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* NCIM 2672 and *Bacillus subtilis* NCIM 2010) and two Gram-negative strains (*Escherichia coli* NCIM 5051 and *Pseudomonas aeruginosa* NCIM 2074). The Bacterial Culture were procured from NCCS, Pune. Standard antibacterial drug Streptomycin was also tested under similar conditions against these organisms. Each experiment was carried out in triplicate and the average diameter of zone of inhibition was calculated. The antibacterial activity was classified as highly active (≥26 mm), good to moderately active (11-25 mm) least active (<11 mm). The results of antibacterial activities were expressed in terms of zone of inhibition and presented in **Table 3**. Few of the tested compounds exhibited good antibacterial activity against Gram-positive bacteria. However, none of the compounds showed activity against Gram-negative bacteria.

Table 3: In vitro antibacterial activity of compound

Compounds Code	Diameter of the of zone of inhibition (mm)			
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
a	15.6	13.3	9.3	10.3
b	16.5	14.5	9.5	8.5
c	16.5	13.2	10.2	9.2
d	15.5	15.0	10.0	9.0
e	13.3	13.0	9.0	8.0

f	14.1	14.0	9.0	8.0
g	12.8	13.0	10.0	10.0
h	14.7	13.8	8.8	9.8
i	13.4	13.2	10.2	8.2
j	15.7	15.7	8.7	10.7

III. Conclusion:

In conclusion, we have mentioned a simple but efficient methodology for the synthesis of 5-arylidine 2,4-thiazolidinedione derivatives mentioned in **Table 2** by Knoevenagel condensation with the reactant like different aromatic aldehydes and 2,4-thiazolidinedione in presence 4-methyl pyridinium tosylate ionic liquid at 120°C. The major advantages of the present method are much faster reaction, easy work up procedure and good yields. Here we have avoided hazardous organic solvent and toxic catalyst. All the compounds synthesized were characterized by spectral and elemental analytical data and evaluated for them in vitro antibacterial activities. Results of antibacterial activity were best observed for Gram-positive bacteria only, none of the compounds showed activity against Gram-negative bacteria.

Table 2: Synthesis of 5-arylidine-2,4-thiazolidinediones using 4-methyl pyridinium tosylate

Entry	R	Product	Yield	MP(°C)
1	Phenyl	a	89	241—242
2	2-Chlorophenyl	b	80	200-204
3	4-fluorophenyl	c	82	219—220
4	2-phenyl -4-methyl thiazolyl	d	85	118-120
5	4-Methoxyphenyl	e	91	218—219
6	4-Hydroxyphenyl	f	87	311—312
7	4-Methylphenyl	g	90	225—226
8	3-Hydroxy-4-methoxyphenyl	h	85	195—196
9	3-Hydroxy-4-ethoxyphenyl	i	84	200—201
10	2-Chloroquinolynyl	j	86	220—221

Experimental:

The melting points were determined by open cup capillary method and are uncorrected. TLC analyses were performed on glass plates using silica gel G60 and spots were visualized either by ultraviolet light or by iodine vapours. IR spectra were recorded as KBr pellets, using JASCO 4100 FTIR spectrophotometer. ¹H-NMR were obtained with BRUKER AVANCE II 400 NMR spectrometer and are reported as parts per million (ppm) downfield to TMS. A mass spectrum was recorded on PRA-O-336 wiff Turbo Spray mass spectrometer. The required starting material i.e. 2,4-thiazolidinedione⁴⁵ was prepared in an eco-friendly way, by the reaction of thiourea with chloro acetic acid in water.2.1.

a) Synthesis of N-methyl pyridinium tosylate (Ionic liquid):

Pyridine (1.1 mole) was added to a methyl-4-toulene sulphonate (1 mole) at 0-10 °C. After completion of addition the reaction mass was stirred at room temperature for 1 hr the solid appeared N-methyl pyridinium tosylate was filtered and washed with ethyl acetate.

b) General procedure for the synthesis of 2,3-diaryl/heteryl 2,4-thiazolidindiones:(3a-j)

A mixture of benzaldehyde (10 mmol) and 2,4-thiazolidinedione (11 mmol) in N-methyl pyridinium tosylate ionic liquid (10 mmol) was refluxed at 120°C. The progress of the reaction was monitored by thin layer chromatography. After heating the reaction mass for 2-3h, the reaction mass was allowed to cool at room temperature and then to this ice cold water (50 mL) was added. The solid separated 5-arylidine-2,4-thiazolidinedione was filtered and dried. It was further purified by crystallization. Similarly, the other compounds of the series were prepared by using the same procedure.

Spectral data of representative compounds:

1)5-(Benzylidene)-1,3-thiazolidine-2, 4-dione:Half white solid;m.p. 241—242°C IR ¹H NMR (DMSO-d₆): δ 12.62 (s, 1H, NH), δ 7.7 (s, 1H, =CH), δ 7.4-7.6 (m, 5H, Ar). MS: m/z 205 (M⁺)

2)5-(4-Fluorobenzylidene) thiazolidine-2,4-dione

Yellow solid; m.p. 219—220 °C; ¹H NMR (DMSO-d₆, 300 MHz) δ: 12.63 (br s, 1H, NH, exchangeable with D₂O, 2,4-TZD), 7.79 (s, 1H, olefenic proton), 7.34—7.74 (m, 4H, ArH); DART-MS (ESI⁺) m/z: 224 (M⁺).

3)5-(4-Methoxybenzylidene) thiazolidine-2,4-dione

Yellow solid; m.p. 218—219°C; ¹H NMR (DMSO-d₆, 300 MHz) δ: 12.60 (br s, 1H, NH, ex-changeable with D₂O, 2,4-TZD), 7.75 (s, 1H, olefenic proton), 7.57 (d, J=9.0 Hz, 2H, ArH), 7.10 (d, J=9.0 Hz, 2H, ArH), 3.83 (s, 3H, OCH₃); DART-MS (ESI⁺) m/z: 266 (M⁺).

4) 5-(4-Ethoxy-3-hydroxybenzylidene) thiazolidine-

2,4-dione Yellow solid; m.p. 200—201 °C; ¹H NMR (DMSO-d₆, 300 MHz) δ: 12.21 (br s, 1H, NH, exchangeable with D₂O, 2,4-TZD), 7.93 (s, 1H, olefinic proton), 6.84—6.96 (m, 3H, ArH), 4.03 (q, 2H, CH₂), 1.39 (t, 3H, CH₃); DART-MS (ESI⁺) m/z: 268 (M⁺).

5)5-[(2-Chloroquinolin-3-yl) methylene] thia-zolidine-2,4-dione Yellow solid; m.p. 220—221° C; ¹H NMR (DMSO-d₆, 300 MHz) δ: 12.19 (br s, 1H, NH, exchangeable with D₂O, 2,4-TZD), 8.15 (s, 1H, olefinic proton), 7.25—7.67 (m, 4H, ArH); DART-MS (ESI⁺) m/z: 291 (M⁺), 293 (M⁺ + 2)

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