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SOLID-SUPPORTED CATALYSED GREEN SYNTHESIS OF THIAZOLIDINEDIONE DERIVATIVES AND ITS BIOLOGICAL SCREENING

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ABSTRACT

A new green synthesis of thiazolidinedione derivatives have been reported by reacting thiazolidinedione and variety of aldehydes using solid-supported catalyst in good yields. The thiazolidine-2,4-diones synthesized, have been biologically screened for their anti-microbial activities.

Keywords: Thiazolidine-2,4-diones, solid-supported catalyst, recycling, anti-microbial

INTRODUCTION

Green Chemistry is the utilization of set of principles that reduces or eliminates the use or generation of hazardous substances, in the design, manufacture and application of chemical products. Green chemistry relies on a set of 12 principles that can be used in designing or re-designing of molecules, materials used in chemistry.[1] Using green chemistry to prevent pollution provides a more efficient approach for making human health and the environment more sustainable. Thus, for an organic chemist, working within the framework of green chemistry to develop biologically active compounds is a challenging task. Thiazolidinediones, also known as glitazones, are an important group of compounds used for the treatment of type-II diabetes. They are five-membered heterocyclic compounds introduced in the late 1990s. They contain a functional group in which thiazolidine serves as a dione. The only approved use of the thiazolidinediones is in diabetes mellitus type 2.[2] Besides, thiazolidine-2,4-diones form an important pharmacophoric group[3] having wide range o biological activities, such as anti-HIV,[4] anti-fungal,[5] anti-diabetic,[6] anti-cancer,[7] anti-bacterial,[8] anti-inflammatory[9], anti-tubercular[10] etc. Pyrazolyl thiazoline-2,4-diones have been synthesized and evaluated for their antibacterial and antifungal activity.[11] Benzoxazole containing thiazolidinediones have also been found to exhibit bioactivity.[12] PEG-600 mediated synthesis of quinolidinyl thiazolidinedione as potential anti-hyperglycemic agents have been reported.[13] Commonly known derivatives of thiazolidinediones have been its knoevenagel condensation product, which have been biologically evaluated for varied activities.[14]

The commonly known conventional method for the knoevenagel condensation of thiazolidinedione has been equimolar amounts of thiazolidinedione and aromatic aldehyde in toluene refluxing conditions.[8] However, this method suffers from drawbacks such as high temperature, longer reaction time and not so easy separation of the product. In literature, there are several methods known for knoevenagel condensation, that include microwave,[15] ultrasonication in presence of ionic liquids[16] etc, there is a report on one-pot multi-component synthesis of quinolidinyl thiazolidine-2,4-diones.[17] Besides, there are methods known for knoevenagel condensation of aromatic aldehydes with malononitrile using silica-Pr-SO_3H,[18] calcined egg shell,[19], visible-light induced[20] and silica-supported ammonium acetate.[21] However , the

method which drew our attention was one-pot synthesis of polysubstituted aniline, where iodine/potassium carbonate was used.[22] Since, this synthesis goes via knoevenagel condensation, we thought of modifying this for the synthesis of thiazolidine-2,4-diones Nowadays, the use of solid-acid or solid-base catalyst in organic synthesis has created a lot of interest in the pharmaceutical sector. Owing to several advantages, use of solid-supported catalyst in organic synthesis[23] has been known for more than a decade. Solid-supported catalyst are greener and cleaner in a way that they are non-toxic, easy to handle, involves no problem of purification, easy filtration and can be recycled. In view of synthesizing greener products via greener process, we visualized using silica-supported iodine and potassium carbonate to catalyze knoevenagel condensation of thiazolidinediones. Thus, our objective was to demonstrate, role of solid-supported catalyst, its greenness, towards synthesis of biologically active thiazolidinediones.

MATERIALS AND METHODS

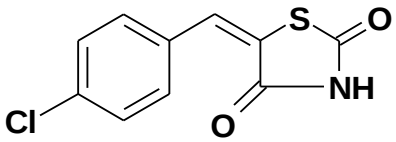
All chemicals are purchased from S. D. fine Chemicals Pvt Ltd, Loba Chemie and Avra Synthesis Pvt Ltd and are used after purification. The parent thiazolidinedione[9] and silica-supported iodine[24] was prepared using literature known procedure. Thin layer chromatography was performed on Merck-precoated silicagel 60-F_{254} plates. The IR spectra of the synthesized compounds were recorded on a Shimadzu FTIR spectrophotometer using DRS method. The ^{1}HNMR were recorded on Bruker Avance II 400 NMR Spectrometer. Chemical shifts (δ) are reported in ppm.

Typical experimental procedure for the synthesis of thiazolidinedione (1): In a 50 ml round bottom flask, a solution of chloroacetic acid (0.02 mol) in water (2 ml), was added to a solution of thiourea (0.02 mol) dissolved in water (2 ml) with stirring. The mixture was stirred for 15 minutes to form a white precipitate, and then considerably cooled. To the contents of flask was then added slowly concentrated HCl (2 ml) drop wise, the flask was then connected with a reflux condenser and gentle heat applied to effect complete dissolution, after which the reaction mixture was stirred and refluxed for 10-15 hrs at 100-110ºC. On cooling, the content of the flask solidified to a cluster of white needles. The product was filtered and washed with cold water to remove traces of HCl and dried. It was purified by recrystallisation from ethanol, white crystals were obtained 43.09% yield, and melting point was 123-125ºC.

Typical general experimental procedure for the green synthesis of thiazolidinedione derivatives (2). In a 50 ml conical flask, a solution of substituted benzaldehyde (0.001mol) and thiazolidine dione (0.001mol) was mixed with I_2-Silica (10 mol%) and K_2CO_3 (10 mol%). The reaction mixture was heated on sand bath at **70**-80ºC, with intermittent mixing. After monitoring by tlc, the product was obtained by filtering off the catalyst and washing the catalyst with ethanol. On evaporation of ethanol, the product was obtained in good yield and was confirmed by its melting point and spectroscopic data.

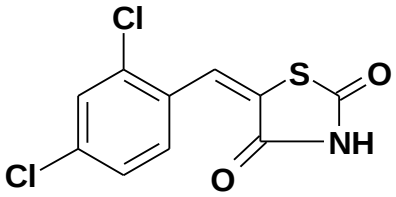
Spectroscopic data of Thiazolidine-2,4-dione derivatives (2)

5-(4'-chlorobenzylidene) thiazolidine-2,4-dione (2a)[25]



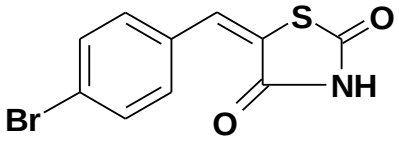
Cream solid, m.p.225-227^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.25(s, 1H, NH), 7.75 (d, 2H, C-2'and C-6' Hs), 7.72 (s, 1H, =CH), 7.53 (d, 2H, C-3' and C-5' Hs); IR (DRS method-KBr): cm^{-1} 3500, 3000, 1750, 1680, 1590, 770, 700.

5-(2',4'-dichlorobenzylidene)thiazolidine-2,4-dione (2b)[25]



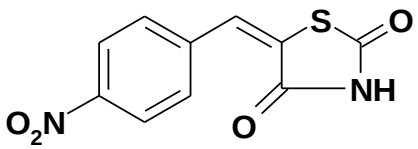
Yellow solid, m.p.190-192^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.5(s, 1H, NH), 7.86 (s, 1H, =CH), 7.42 (d, 1H, C-6'H), 7.34 (d, 1H, C-5' H); 7.32 (s, 1H, C-6' H); IR (DRS method-KBr): cm^{-1} 3500, 3000, 1700, 1680, 1600, 777, 760, 700.

5-(4'-bromobenzylidene) thiazolidine-2,4-dione (2c)



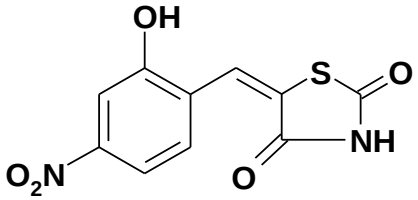
Light brown solid, m.p.228-230^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.6 (s, 1H, NH), 7.74 (d, 2H, C-2'and C-6' Hs), 7.65 (s, 1H, =CH), 7.45 (d, 2H, C-3' and C-5' Hs); IR (DRS method-KBr): cm^{-1} 3500, 3000, 1730, 1680, 1600, 840, 700.

5-(4'-nitrobenzylidene) thiazolidine-2,4-dione (2d)[25]



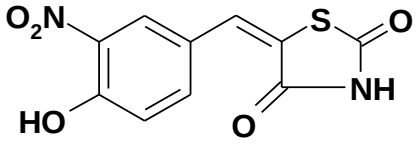
Yellow solid, m.p.260-262^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.5 (s, 1H, NH), 8.3 (s, 1H, =CH), 8.20 (d, 2H, C-3'and C-5' Hs), 7.91 (d, 2H, C-2' and C-6' Hs); IR (DRS method-KBr): cm^{-1} 3525, 3050, 1725, 1700, 1600, 1501, 700.

5-(2'-hydroxy-4'-nitrobenzylidene) thiazolidine-2,4-dione (2e)



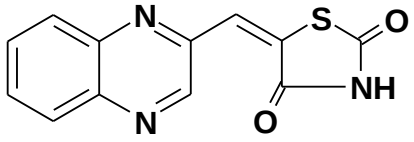
Yellow solid, m.p.275-278^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.6 (s, 1H, NH), 9.5 (brs, OH), 8.2 (s, 1H, =CH), 7.6 (s, 1H, C-3'H), 7.5 (d, 1H, C-5'H), 7.4 (d, 1H, C-6'H); IR (DRS method-KBr): cm^{-1} 3520, 3440, 2960, 1700, 1680, 1590, 1540, 625.

5-(4'-hydroxy-3'-nitrobenzylidene) thiazolidine-2,4-dione (2f)[26]



Yellow solid, m.p.260-263^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.4 (s, 1H, NH), 9.8 (brs, OH), 8.7 (s, 1H, C-2'H), 7.9 (s, 1H, =CH), 7.7 (d, 1H, C-6'H), 7.1 (d, 1H, C-5'H); IR (DRS method-KBr): cm^{-1} 3520, 3280, 3040, 1700, 1660, 1590, 1520, 640.

5 (2'-quinoxalinylbenzylidene)thiazoline-2,4-dione (2g)



Brown solid, m.p.250-252^{0}C. ^{1}H NMR (400MHz, DMSO) δ ppm: 12.8 (s, 1H, NH), 9.3 (s, 1H, =CH), 7.8-8.2 (m, 4H, Ar-H), 7.4 (s, 1H, C-3'H); IR (DRS method-KBr): cm^{-1} 3500, 3050, 1750, 1720, 1625, 1500, 625.

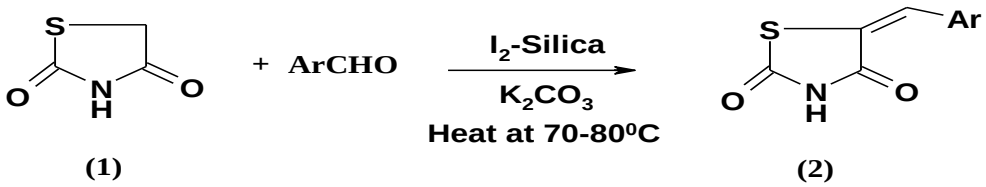
Typical procedure for the recycling of the silica-supported iodine catalyst to obtain thiazolidinedione derivatives (2b): In a 50 ml conical flask, 2,4-Dichlorobenzaldehyde (0.001 mol) was taken and it was mixed with thiazolidinedione (0.001 mol) using I_2-silica as a catalyst and potassium carbonate as a base (10mol%). The mixture was heated on a sand bath maintaining the temperature between **70**-80^{o}C.The solid mass was mixed well. The completion of reaction was monitored by TLC. The product was obtained by filtering off the catalyst and washing of catalyst using ethanol. On evaporation of ethanol on water-bath, the product was obtained in good yield. The catalyst was dried and reused for the next cycle.

RESULTS AND DISCUSSION

As reported, the knoevenagel condensation of thiazolidine-2,4-diones have been carried out in a conventional synthesis. We initially synthesized four such derivatives via conventional method. As, we were interested in using solid-supported catalyst, silica-supported iodine along with base was used for knoevenagel condensation. Following scheme was visualized (Scheme 1).

Initially, we tried the reaction of equimolar amount of thiazolidine-2,4-dione and p-chlorobenzaldehyde with 10mol% of catalyst, neat heat without solvent at 70-80^{0}C on sand bath. After 30 minutes, once the TLC showed completion of the reaction, ethanol was added to the solid mass, with stirring and the catalyst was filtered off. The residue was then washed with ethanol. The filtrate was evaporated on water bath and then under vacuum, to afford the product in 66% yield. In all, we prepared seven thiazolidine-2,4-diones in good yields. The product 2 was obtained in quick time by neat heating. (Table 1)

Scheme 1:



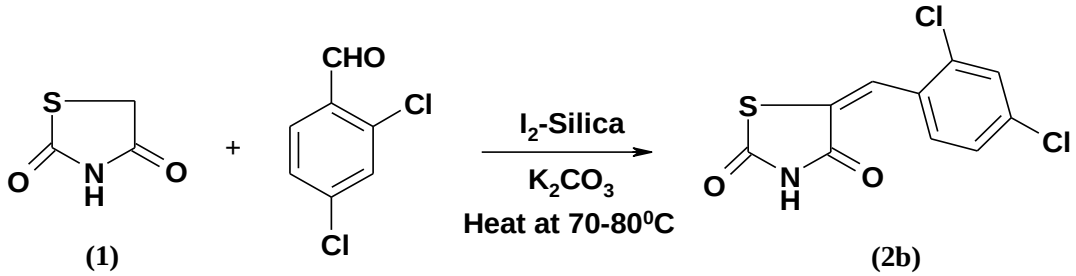
(1) **(2)**

Table 1: Synthesis of thiazolidinediones (2a-g) using green methodology

Compound	Ar	Time (mins)	% Yield	M.P ^{0}C
2a	4-Chlorophenyl	30	66	225-227
2b	2,4-Dichlorophenyl	25	61	190-192
2c	4-Bromophenyl	35	73	228-230
2d	4-Nitrophenyl	35	88	260-262
2e	2-Hydroxy-4-nitrophenyl	30	70	215-218
2f	4-Hydroxy-3-nitrophenyl	25	75	210-212
2g	2'-quinoxalinyl	40	67	260-264

As solid-supported catalyst holds an advantage of the ability to get recycled, the recycling of the catalyst was effected for reaction leading to compound (2b) (Scheme 2).

Scheme 2



The reaction between thiazolidine-2,4-dione and 2,4-dichlorobenzaldehyde gave the product (2b), till the 4th recycle. (Table 2)

Table 2: Synthesis of thiazolidinediones (2b) by recycling of catalyst

Reactions	**Time**	**% yield**	**Melting point**
Reaction	25 min	84.17	193-194^{o}C
Recycle 1	30 min	68.73	195-197^{o}C
Recycle 2	40 min	62.86	193-194^{o}C
Recycle 3	45 min	35.87	194-196^{o}C
Recycle 4	50 min	29.5	194-196^{o}C

Biological Evaluation

The thiazolidine-2,4-diones (2) synthesized were evaluated for their antibacterial and anti-fungal activities.

Anti-bacterial activity (Table 3): The thiazolidine-2,4-diones were screened for antibacterial property against pathogenic strains Gram positive *staphylococcus aureus* and gram negative *escherichia coli* by agar well diffusion method. Media used for this procedure is brain heart infusion agar. Agar plates were brought to room temperature. For inoculums preparation, colonies were transferred to the plates using a loop or swab. Turbidity was then adjusted to equal that of a 0.5 McFarland turbidity standard. Alternatively the suspension was standardized with a photometric device. Within 15 min of adjusting the inoculums to a McFarland 0.5 turbidity standard a sterile cotton swab was dipped into the inoculums and were rotated against the wall of the tube above the liquid to remove excess inoculums. The entire surface of agar plate was swabbed three times by rotating plates approximately 60^{o}C between streaking. The inoculated plate was allowed to stand for at least 3 minutes but not longer than 15 min before making wells. A hollow tube of 5mm diameter was heated and pressed above the inoculated agar plate and was removed immediately

by making a well in the plate. Five wells were made on each plate and 75µL, 50µL, 25µL, 10µL and 5µL of compound were added into the respective wells. Within 15 min of compound application plates were incubated. Plates were incubated for 18- 24 hrs at 37ºC in incubator. Diameter of inhibition zone to nearest whole millimeter was measured by holding the measuring device.

NOTE: **(Table-3)**

- In anti-fungal disc diffusion method, Sabouraud agar medium was used instead of Brain heart infusion agar.
- For Facultative anaerobes, plates were incubated in the CO_2 Jar and the jar was kept in the incubator at 37 ºC.
- For Anaerobic organisms, plates were incubated in the anaerobic jar and the jar was kept in the incubator at 37 ºC.

Table 3: Antibacterial activity of compounds (2a-g) against E.Coli

E. Coli	75µg/ml	50 µg/ml	25 µg/ml	10 µg/ml	5 µg/ml
2a	14mm	12mm	10mm	R	R
2b	14mm	12mm	R	R	R
2c	15mm	12mm	10mm	R	R
2d	15mm	12mm	10mm	R	R
2e	14mm	10mm	R	R	R
2f	14mm	12mm	8mm	R	R
2g	18mm	12mm	R	R	R

Standard : Ciprofloxacin 32mm

Table 4: Antibacterial activity of compounds (2a-g) against S. Aureus

S. Aureus	**75 µg/ml**	**50 µg/ml**	**25 µg/ml**	**10 µg/ml**	**5 µg/ml**
2a	14mm	12mm	10mm	R	R
2b	32mm	25mm	18mm	R	R
2c	24mm	22mm	20mm	10mm	R
2d	26mm	22mm	18mm	R	R
2e	R	R	R	R	R
2f	28mm	26mm	22mm	R	R
2g	12mm	10mm	R	R	R

Standard : Ciprofloxacin 26mm

Table 5: Antifungal activity of compounds (2a-g)

C.Albicans	**75 µg/ml**	**50 µg/ml**	**25 µg/ml**	**10 µg/ml**	**5 µg/ml**
2a	30mm	25mm	22mm	15mm	R
2b	30mm	25mm	23mm	R	R
2c	18mm	15mm	10mm	R	R
2d	28mm	25mm	24mm	12mm	R
2e	30mm	26mm	20mm	R	R
2f	14mm	12mm	8mm	R	R

Standard : Fluconazole 32mm

CONCLUSION

In conclusion, we have developed a new, simple and convenient green synthesis of thiazolidine-2,4-dione derivatives in good yields. The role of solid-supported catalyst as a green catalyst has been well demonstrated. The advantages of our method include solvent-free synthesis, time-saving, recycling of catalyst, avoiding high temperature. The methodology works well for variety of monosubstituted, disubstituted and heterocyclic aromatic aldehydes. The anti-microbial screening indicated that the synthesized compounds showed significant antibacterial and antifungal activity. The substituted thiazolidinediones can be excellent lead compounds for the development of new drug scaffolds.

ACKNOWLEDGEMENTS

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