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Green Synthesis of 5-Arylidene-2,4-Thiazolidinedione derivatives Catalyzed by Titanium Dioxide under Microwave Irradiation

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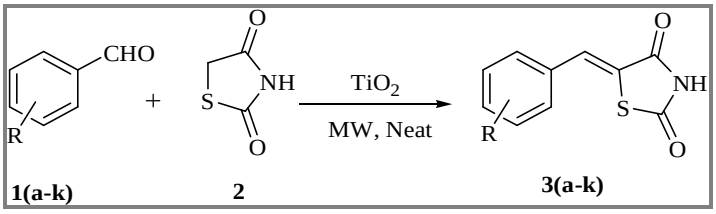
ABSTRACT

Green synthesis, simple, eco-friendly approach for the synthesis of 5-arylidene-2,4thiazolidinedione derivatives by Knoevenagel condensation of aromatic aldehydes with 2,4-thiazolidinedione catalyzed by titanium dioxide in solvent free condition under microwave irradiation has been performed. Effective simplicity, use of inexpensive catalyst, mild reaction conditions, high yield, short reaction time and green aspects by avoiding toxic catalysts and hazardous solvents are the key characteristics of this approach.

Graphical Abstract:



Synthesis of 5-arylidine-2,4-thiazolidinediones

Keywords: Knoevenagel condensation, Titanium dioxide, 2,4-Thiazolidinedione, Aromatic aldehydes.

INTRODUCTION

Heterocycles are present in a broad range of drugs, a large portion of the vitamins, natural products, biomolecules and biologically active compounds including antitumor, anti-inflammatory, antidepressant, antimalarial, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal and insecticidal agents [1]. The steady growth in interest in heterocyclic compounds is basically connected with their raised biological activity and also with the fact that they enable the development of novel materials with unique biological properties. One especially attractive and

promising class of heterocyclic compounds is nitrogen-containing heterocycles with a sulfur atom signify an important class of compounds in medicinal chemistry. Thiazole has involved progressing interest over the decades because of its different biological activities: antibacterial [2], antiviral [3], and antifungal [4]. Thiazolidinediones (TZDs) have been the subject of wide range of research since of their connection in the regulation of different physiological pathways. Thiazolidinediones like as pioglitazone and rosiglitazone, inferior plasma glucose levels by acting as ligands for the gamma peroxisome proliferator-activated receptors (PPARs). Chemical modification on this heterocycles form a class of compounds that have a number of other potentially useful effects counting improvement in lipid outline, blood pressure lowering, antitumor activity, anti-inflammatory effects [5], antibacterial, and antifungal properties [6]. TZDs targeted vascular cells and macrophages / monocytes to slow down the production of pro-inflammatory cytokines [7] as well as the improvement of oxidative stress and cell adhesion molecules [8]. In addition, thiazolidinedione based derivatives have been shows popular as small molecule inhibitors such as aldose reductase activities [9].

The Knoevenagel reaction is generally utilized in organic chemistry for C=C bond formation [10]. The product formed is α,β-unsaturated compound which is chiefly utilized as intermediate in the synthesis of therapeutic agents [11], natural products [12], polymers having different functional groups [13], adequate chemicals [14], insecticides and pesticides. It is typically done in organic solvents and catalyzed by organic bases such as pyridine or piperidine [15]. Along these outline, the synthesis of thiazolidinedione derivatives is at present of much significance. It is well known that 5-arylidene-2,4-thiazolidinediones are by condensation of aromaticaldehydes with 2,4-thiazolidinedione in organic solvents, for example piperidine in EtOH [9], $AlPO_4$Zeolite in EtOH:H_2O [16], and PEG-300 [17]. But the above literature approach experienced from one or more limitation such as delayed reaction times with as often as possible low yields. Therefore, the development of a simple, efficient, eco-friendly and versatile approach is still strongly demand.

The utilization of microwave irradiation in organic synthesis has gotten progressively main stream inside the pharmaceutical and academic fields, since it is another empowering innovation for drug discovery and development this approach feasible better desired yield and higher purity, energy saving, uniform and selective heating, green synthesis, reproducibility [18].

Titanium dioxide (TiO_2) has gotten progressively main stream as a catalyst. It is extremely helpful because of its chemical stability, non-toxicity, low cost, easily available and other advantages. It has been generally utilized in paint as white coloring pigments, food coloring, cosmetics, photovoltaic cells, solar cells, and photo applications. Numerous specialty applications have additionally been investigated particularly in biomedical fields, for example cancer therapies, stent placement, orthopaedic surgery, bactericides, and protein separation [19]. TiO_2 is a capable reducible oxide catalyst for green organic approach for example, in hydrogenation, esterification, transesterification, deoxygenation, the WGS reaction, visible light-induced organic transformation etc. This catalyst can be modified by a range of metal or non-metal dopants to raise the textural properties and thermal stability of TiO_2, in that way enhancing the catalytic stability and activity [20].

MATERIALS AND METHODS

Reagents and analysis: All aldehyde were purchased from Aldrich, Merck and Rankem chemical companies and used without further purification. The melting points of compounds were taken in an open capillary in a paraffin bath and it is uncorrected. The reactions progress was monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ /DMSO-d_6 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

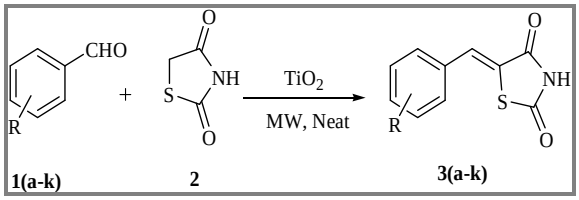
General procedure for the preparation of 5-aryilidene-2,4-thiazolidinediones3(a-k): A mixture of aromatic aldehyde (1 mmol), 2,4-thiazolidinedione (1 mmol) and TiO_2 (10 mol%) were taken in a beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod. The total period of microwave irradiation (180W) was 3-6 min. The progress of reaction was monitored by TLC. After completion of reaction, the reaction content cooled to room temperature and extracted with diethyl ether (2×20 mL) and the insoluble TiO_2 directly recycled in subsequent runs. The organic layer washed by brine (2×10 mL) and dried over $NaSO_4$ and solvent removed on rotary evaporator under reduced pressure. The crude product was recrystallized from ethanol to get pure product.

Spectral data of representative compounds:

Compound 3a: IR (KBr): 3155 (NH), 3049, 879 (CH; aromatic), 2868 (CH; aliphatic), 1739, 1691 (C=O) cm^{-1}, ^1H NMR ($CDCl_3$/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).
Compound 3b: ^1H NMR ($CDCl_3$/DMSO-d_6): 7.47 (m, 4H, aromatic protons). MS m/z (%): 251 (M+1).
Compound 3g: ^1H NMR ($CDCl_3$/DMSO-d_6): 3.73 (3H, s, OCH_3), 7.26 (4H, m, aromatic protons). MS m/z (%): (236 (M+1).
Compound 3h: ^1H NMR ($CDCl_3$/DMSO-d_6): 7.77 (4H, m, aromatic protons). MS m/z (%): 274 (M+1).
Compound 3i: ^1H NMR ($CDCl_3$/DMSO-d_6): 3.73 (3H, s, OCH_3), 6.68 (3H, m, aromatic protons). MS m/z (%): 252 (M+1).
Compound 3j: ^1H NMR ($CDCl_3$/DMSO-d_6): 2.85 (6H, s, CH_3), 7.26 (4H, m, aromatic protons). MS m/z (%): 249 (M+1).

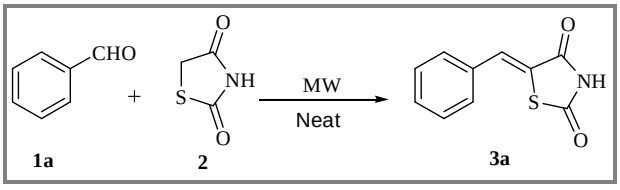
RESULTS AND DISCUSSION

In extension of our work going on Knoevenagel condensations [21] and the advancement of green synthetic methodologies [22], herein, we report a simple, efficient, rapid and eco-friendly microwave assisted root for the synthesis of 5-arylidine-2,4-thiazolidinediones in solvent free condition (Scheme 1).



Scheme 1. Synthesis of 5-arylidine-2,4-thiazolidinediones

In search for the best experimental condition, the solvent free reaction of benzaldehyde and 2,4-thiazolidinedion in presence/absence of catalytic amount of titanium dioxide under microwave irradiation has been considered as the typical model reaction(Scheme 2). Initially we studied the catalytic efficiency of titanium dioxide using in different mol%. Particularly, a very slow reaction was observed when the absence of catalyst (Table 1, entry 1). After that catalytic amount of titanium



Scheme 2. Model reaction for synthesis of 5-benzylidine-2,4-thiazolidinedione

dioxide was decreased from 10 mol% to 5 mol% (Table 1, entry 3 vs entry 2),with 15 mol% of titanium dioxide there is no change in reaction rate as well as yield (Table 1, entry 4). By using, 10mol% titanium dioxide the desired product was obtained in satisfactory yield.

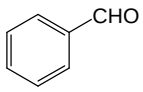
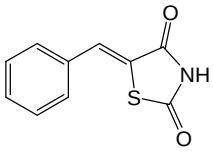
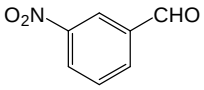
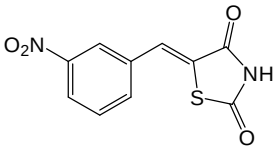
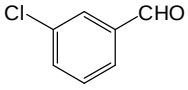
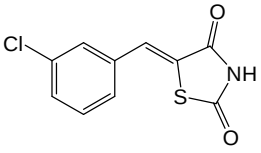
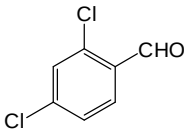
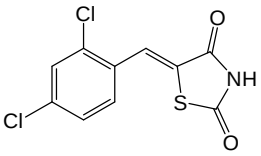
Table 1. Effect of different mol% of titanium dioxide as a catalyst for synthesis of 5-benzylidene-2,4-thiazolidinedione (**3a)**

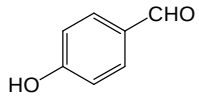
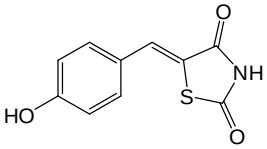
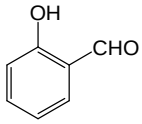
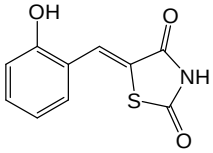
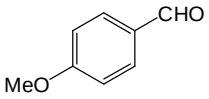
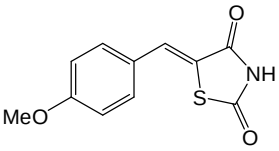
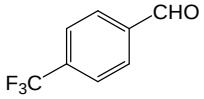
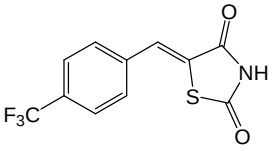
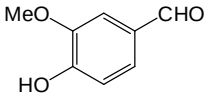
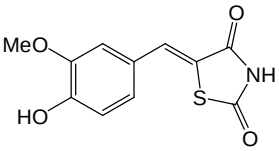
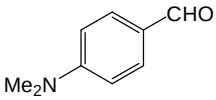
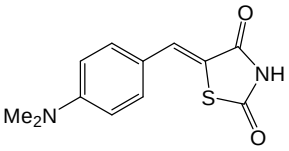
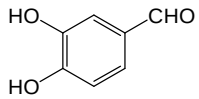
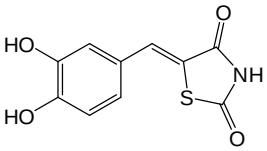
S.No.	Catalyst (mol %)	Time (min)	Yield (%)[a]
1	-	20	10
2	5	5	89
3	**10**	**3**	**96**
4	15	3	96

[a] Isolated Yield

The condensations with various aldehydes took place in solvent free condition to synthesized compounds **3(a-k)** (Table 2) in the presence of titanium dioxide under microwave irradiation. The electronic effects of the different substituted aldehydes have been investigated. The aldehyde bearing electron withdrawing groups ie, -NO_2 and -Cl on ortho position are less favorable and give less yield as compare to groups on meta position. In the same way aldehyde bearing electron donating groups ie, -OCH_3 on meta position are less favorable and give less yield as compare to groups on ortho positions shown in table 2. The purity of the compounds was confirmed by TLC. All the structures was confirm by their spectral (IR, ^{1}HNMR, Mass Spectra) data. The IR spectra exhibited characteristic absorption bands at 1739 cm^{-1} and 1691 cm^{-1} due to the two (C=O), 3155 due to (NH), 3049, 879 due to (CH; aromatic), 2868 due to (CH; aliphatic) from the TZD heterocycle. The ^{1}H NMR spectra showed characteristic singlets 8.27 due to (NH), singlets 7.86 due to (CH), and multiplet 7.26 due to (aromatic protons).

Table 2. Synthesis of 5-arylidene-2,4-thiazolidinedione derivatives catalyzed by titanium dioxide in solvent free condition under microwave irradiation

Entry	Aldehydes	Products[a]	Time (min)	Yield (%)[b]	M.P. (°C)
3a			3	96	242
3b			4	93	180
3c			4	92	270
3d			5	88	216

3e			4	92	280
3f			4	88	276
3g			5	88	235
3h			4	85	234
3i			4	86	194
3j			6	82	280
3k			5	84	266

[a]All compounds are known compounds, which were characterized by IR, and [1]H NMR spectral data and melting points compared with literature procedure[5, 8d]. [b]Isolated yields based upon starting aldehyde.

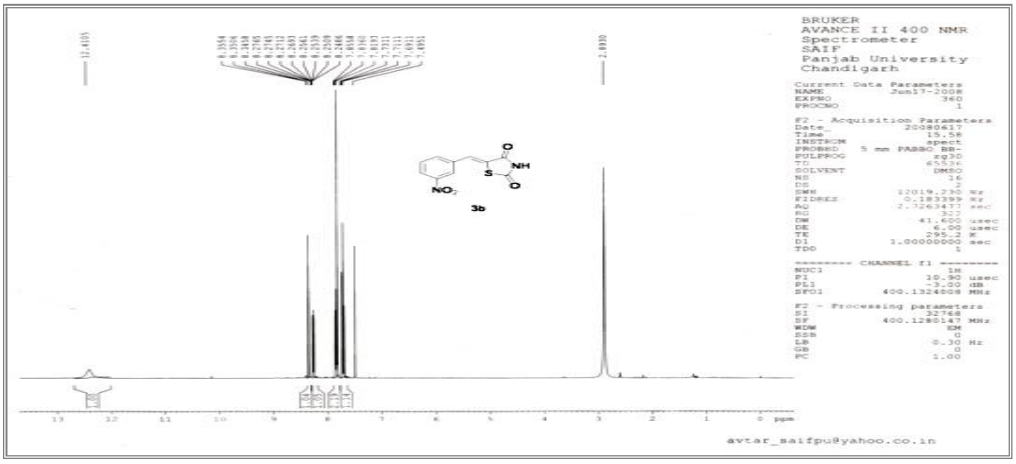


Figure 1. [1]H NMR spectra of (*Z*)-5-(3-nitrobenzylidene)thiazolidine-2,4-dione (**3b**).

Further we carry examination on the reusability of catalyst is significant for the large-scale process and industrial point of view. In this manner, the recovery and reusability of titanium dioxide was investigated for the model reaction. The results outlined in table 3 indicated that the recovered titanium dioxide can be reused at least four additional times in subsequent reactions with no significant decrease in catalytic activity.

In table 4, we compared our result with result obtained by a reported procedure for the synthesis of 5-benzylidene-2,4-thiazolidinedione (Table 2, entry 3a**)**. The data presented in this table show the promising feature of this method in terms of reaction rate and the yield of product compared with reported in the literature.

Table 3.Recycling of the titanium dioxide for the synthesis of 5-benzylidene-2,4-thiazolidinedione (**3a)**

Entry	1	2	3	4
Cycle	First	Second	Third	Fourth
[a]Yield	96	94	92	92

[a] Isolated Yield

Table 4. Comparison data with the present method catalyst for synthesis of 5-benzylidene-2,4-thiazolidinedione (**3a)**

Entry	Reagent	Reaction condition	Time	Yield (%)[a]	Reference
1	Piperidine	EtOH/reflux	4 h	51-90	[3c]
2	$AlPO_4$-Zeolite	EtOH:H_2O/reflux	80 min	77-96	[5a]
3	PEG-300	130°C	3 h	75-84	[5b]
4	BO_3H	H_2O/Sonication, RT	50 min	85-95	[8d]
5	TiO_2	Solvent free/MW	3 min	96	**Present**

[a]Isolated Yield

APPLICATION

The present method is highly useful for Knoevenagel condensations of variety of aromatic aldehydes and 2,4-thiazolidinedione under solvent free conditions. This is simple and eco-friendly approach for the synthesis of 5-arylidene-2,4thiazolidinedione derivatives catalyzed by titanium dioxide under microwave irradiation.

CONCLUSION

In conclusion, we have developed a simple and efficient methodology for the synthesis of 5-arylidene-2,4-thiazolidinediones by the Knoevenagel condensation of aromatic aldehydes with 2,4thiazolidinedione in the presence of titanium dioxide under solvent-free conditions in microwave irradiation. The major advantages of this method are simple experimental and work-up procedures, solvent-free reaction conditions, required small amount of catalyst, short reaction time, high desired yields, and utilization of an inexpensive easily available and reusable catalyst and eco-friendly approach.

Conflict of Interest: The authors confirm that this article content has no conflict of interest.

REFERENCES

[1] A. Khalifi-nezhad, Selenocysteine-Mediated Native Chemical Ligation, *Helv. Chim. Acta.*, **2001**, 90, 730-737.

[2] H. S. Sader, D. M. Johnson, R. N. Jones, In Vitro Activities of the Novel Cephalosporin LB 11058 against Multidrug-Resistant Staphylococci and Streptococci, *Antimicrob. Agents and Chemother*., **2004**, 48, 53-62.
[3] F. C. Spector, L. Liang, H. Giordano, M. Sivaraja, M. G. Peterson, Inhibition of Herpes Simplex Virus Replication by a 2-Amino Thiazole via Interactions with the Helicase Component of the UL5-UL8-UL52 Complex, *J. Virol.*,**1998**, 72(9), 6979-6987.
[4] A. DeLogu, M. Saddi, M. C. Cardia, R. Borgna, C. Sanna, B. Saddi, E. Maccioni, In vitro activity of 2-cyclohexylidenhydrazo-4-phenyl-thiazole compared with those of amphotericin B and fluconazole against clinical isolates of Candida spp. and fluconazole-resistant Candida albicans, *J. Antimicrob. Chemother*., **2005**, 55, 692-698.
[5] (a) V. Patil, K. Tilekar, S. Mehendale-Munj, R. Mohan, C. S. Rama, Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione derivatives, *Eur. J. Med. Chem*., **2010**, 45(10), 4539-4544. (b) J. D. Browning, J. D. Horton, Molecular Mediators of Hepatic Steatosis and Liver Injury, *J. Clin. Invest*., **2004**, 114, 147-152.
[6] G. Chinetti, J. C. Fruchart, B. Staels, Synthesis of New N-Substituted 5-Arylidene-2,4-thiazolidinediones as Anti-Inflammatory and Antimicrobial Agents, *Inflamm. Res*., **2000**, 49, 497-505.
[7] A. A. Abdin, A. A. Baalash, H. E. Hamooda, Effects of rosiglitazone and aspirin on experimental model of induced type 2 diabetes in rats: focus on insulin resistance and inflammatory markers, *J. Diabetes Complicat*, **2010**, 24, 168-178.
[8] M. C. Unlusoy, O. Dundar, N. Altanlar, R. Ertan, Synthesis and antimicrobial activity of some new 3-substituted benzyl-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene) -thiazolidine-2, 4-dione derivatives, Turk, *J. Chem*., **2006**, 30, 355-360.
[9] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, C. K. Glass, The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation, *Nature*, **1998**, 391, 79-82.
[10] C. Jiang, A. T. Ting, B. Seed, PPAR-γ agonists inhibit production of monocyte inflammatory cytokines, *Nature*, **1998**, 391, 82-86.
[11] N. Sachan, S. S Kadam, V. M. Kulkarni, Synthesis, antihyperglycemic activity and QSAR of 5-benzylidene-2,4-thiazolidinediones, *Ind. J. Hetro. Chem*., **2007**, 17, 57-62.
[12] R. S. Mahalle, P. D. Netankar, S. P. Bondge, R. A. Mane, An efficient method for Knoevenagel condensation: a facile synthesis of 5-arylidenyl 2,4-thiazolidinedione, *Green Chem. Lett. Rev*., **2008**, 1, 103-106.
[13] M. C. A. DeLima, D. L. B Costa, A. J. S. Goes, S. L. Galdino, I. R. Pitta, C. Luu-Duc, Synthesis and antimicrobial activity of some novel 4-oxo-1,3-thiazolidines tethered to phthalimido moiety, *Pharmazie*., **1992**, 47, 182-184.
[14] M. Strumvoll, H. U. Haring, Synthesis and Antimicrobial Activity of Some New 3-Substituted Benzyl-5-(4-chloro-2-piperidin-1ylthiazole-5-yl-methylene)-thiazolidine-2,4-dione Derivatives, *Ann. Med*., **2002**, 34, 217-222.
[15] A. Andreani, M. Rambaldi, A. Locatelli, R. Leoni, M. Bossa, I. Chiericozzi, G. Alatulas, A. Salvatore, Synthesis of lactams with potential cardiotonic activity, *Eur. J. Med. Chem*., **1993**, 28, 825-829.
[16] A. Gumieniczek, Effect of the new thiazolidinedione-pioglitazone on the development of oxidative stress in liver and kidney of diabetic rabbits, *Life. Sci*., **2003**, 19, 553-562.
[17] K. Seno, N. Okuna, K. Hishi, Y. Murakami, F. Watanable, T. Matsuura, M. Wada, M. Yamada, T. Ogawa, T. Okada, H. H. Zume, S. K. H. Hagishita, Pyrrolidine Inhibitors of Human Cytosolic Phospholipase A2, *J. Med. Chem*., **2000**, 43, 1041-1044.
[18] (a) P. Lidström, J. Tierney, B. Wathey, J. Westman, Microwave assisted organic synthesis: a review, Tetrahedron, 2001, 57, 9225. (b) L. Perreux, A. Loupy, A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations, *Tetrahedron*, **2001**, 57, 9199. (c) M. R. Ezhilarasi, B. Prabha, S. Prabakaran, Pyrimidine Derivatives, *J. Applicable Chem.*,**2014**, 3(5), 1929. (d) R. Gupta, Y. Madan, E. Menghani, Microwave Assisted ZnO Nanocatalysed biginelli Synthesis of Pyrazolopyrimidione Derivatives and Evaluation of Their Bioactivity, *J. Applicable Chem.*, **2014**, 3(5), 1955-1966.

[19] K. M. Kummer, E. Taylor, T. J. Webster, Biological applications of anodized TiO2 nanostructures: a review from orthopedic to stent applications, *Nanosci. Nanotechnol. Lett*., **2012**, 4, 483-493.

[20] Q. Bu, H. Lei, A. H. Zacher, L. Wang, S. Ren, J. Liang, Y. Wei, Y. Liu, J. Tang, Q. Zhang, R. Ruan, A Review of Catalytic Hydrodeoxygenation of Lignin-Derived Phenols From Biomass Pyrolysis, *Bioresour. Technol*., **2012**, 124, 470-477.

[21] (a) K. F. Shelke, B. R. Madje, S. B. Sapkal, B. B. Shingate, M. S. Shingare, An efficient ionic liquid promoted Knoevenagel condensation of 4-oxo-4H-benzopyran-3- carbaldehyde with Meldrum's acid, *Green Chem. Lett. Rev*., **2009**, 2, 3-7. (b) K. F. Shelke, R. E. Khadse, Ultrasound assisted an efficient Knoevenagel reaction catalyzed by ionic Liquid, *J. Applicable Chem*., **2015**, 4(6), 1804-1810. (c) K. F. Shelke, R. E. Khadse, Ionic liquid is an efficient catalyst for Knoevenagel condensation under grinding method, *Der.Pharma Chemica*., **2015**, 7(1), 191-196. (d) K. F. Shelke, A. D. Badar, J. B. Devhade, Ultrasound Assisted An Efficient Synthesis of Azlactone Derivatives Catalyzed by Ionic Liquid, *Chem.Bio. Inter.*, **2016**,6(6), 410-415.

[22] (a) K. F. Shelke, S. B. Sapkal, M. S. Shingare, Ultrasound assisted one-pot synthesis of 2, 4, 5-triarylimidazole derivatives catalyzed by ceric (IV) ammonium nitrate in aqueous media, *Chin. Chem. Lett*., **2009**, 20, 283-287. (b) S. B. Sapkal, K. F. Shelke, M. S. Shingare, Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions, *Tetrahedron Lett*., **2009**, 50, 1754-1756. (c) K. F. Shelke, S. B. Sapkal, S. S. Sonar, B. R. Madje, B. B. Shingate, M. S. Shingare, An efficient synthesis of 2, 4, 5-triaryl-1H-imidazole derivatives catalyzed by boric acid in aqueous media under ultrasound-irradiation, *Bull. Korean Chem. Soc*., **2009**, 30, 1057-1060. (d) K. F. Shelke, A. D. Badar, J. B. Devhade, Ultrasound assisted an efficient synthesis of Azalactone derivatives catalysed by ionic liquid, *Chem.Bio. Inter*., **2016**, 6(3), 157-161. (e) K. F. Shelke, J. V. Gholave, Microwave Assisted Synthesis of 14- aryl- 14H-dibenzo [a, j] xanthenes Catalyzed by Oxalic acid, *J. Applicable Chem*., **2019**, 8(5), 2213-2216.