

Research Article



Synthesis of Some 5-(Substituted Benzylidene)-3-Phenyl-2-Phenylimino-1,3-Thiazolidin-4-Ones Under Ultrasound Irradiation

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ABSTRACT

Recently, we have synthesized environmental benign one pot synthesis of 5-(Substituted Benzylidene)-3-Phenyl-2-Phenylimino-1,3-Thiazolidin-4-Ones (a-f) under Ultrasound irradiation by cyclization of 1,3 -diphenylthiourea with a-halo acids in presence of sodium acetate in absolute ethanol for 10-15 minute. The crude compound was purified by silica gel column chromatography using n-hexane and ethyl acetate as solvent system and recrystallised from ethanol. The synthesized compounds have been screened in vitro for their antimicrobial activity against *S. aureus* and *E.coli* as compare with standard drug Streptomycin. Some of the compounds displayed pronounced biological activity. The resulting products were characterized by IR, ¹H NMR and ¹³C NMR spectroscopic method.

Keywords: Ultrasonication, Thiazolidine, 1,3-diphenylthiourea, Antimicrobial activity.

INTRODUCTION

Thiazolidin-4-one, the saturated form of thiazole has been considered a magic moiety which displays a broad spectrum of biological activities. Nearly, all the positions of 4-thiazolidinone have been explored to improve its physiological activities such as antiinflammatory¹, antimicrobial², antitubercular³, anti-hepatitis C virus⁴, antitumor⁵, antidiabetes⁶, antioxidant⁷, and anti-HIV⁸. We have focused on the synthesis of 2-imino-thiazolidine-4-ones as target compounds and to study their relevance in the biological responses.

It has been observed in the literature that several strategies, conventional as well as modern, can be used for the synthesis of thiazolidines. Ultrasound⁹⁻¹³ is one such technique that has been utilized to accelerate a number of synthetically useful reactions, especially in the synthesis of heterocycles.

All these facts cited above and our interest in the synthesis of new biologically active heterocyclic compounds containing 5-(substituted benzylidene)3-phenyl-2-phenylimino-1,3-thiazolidine-4-ones prompted us to prepare them by employing simple technique of ultrasonication and study their biological activities.

MATERIALS AND METHODS

All chemicals were of synthetic grade (S.D. Fine. Chem. Ltd. Mumbai, India). Melting points were determined by open capillary method and are uncorrected. Products were recrystallized from ethanol as a solvent. The purity of compound checked by the TLC plate method (Pet ether:

Ethyl acetate, 9:1, v/v). The compounds were characterized by using IR, ¹H NMR and C¹³ spectral analysis. The IR spectra were recorded on Perkin –Elmer

spectrum in form of KBr pellet. ¹H NMR was recorded in CDCl₃ on Perkin Elmer R-32 spectrum using TMS as internal standard. All the compounds were analyzed for C, H and N on Carlo-Erba elemental analyzer. The synthesized samples were purified by using Column chromatography (Pet ether and Ethyl acetate system) and recrystallized from ethanol.

Synthesis of 5-(substituted benzylidene)-3-phenyl-2-phenylimino-1, 3-thiazolidine-4-ones:

Imino-thiazolidinones are generally synthesized by cyclization of thioureas with a-halo acids or esters in the presence of an inorganic base like sodium acetate in polar solvents such as acetic acid or ethyl alcohol. Hence, we had carried out cyclization – condensation by adding equimolar quantities of 1,3 -diphenylthiourea (1 mmol), substituted benzaldehyde (1mmol) and chloro acetic acid (2.2 mmol) in presence of sodium acetate (3 m mol) and 10 ml of absolute ethanol in an ultra-sonicator. Initially, the mixture was sonicated for 15 minute. The progress of reactions and the purity of compounds were monitored by thin layer chromatography. Depending on need, the mixture was further sonicated for some more time (5-10 min.). The crude compound was purified by silica gel column chromatography using n-hexane and ethyl acetate as solvent system and recrystallised from ethanol.

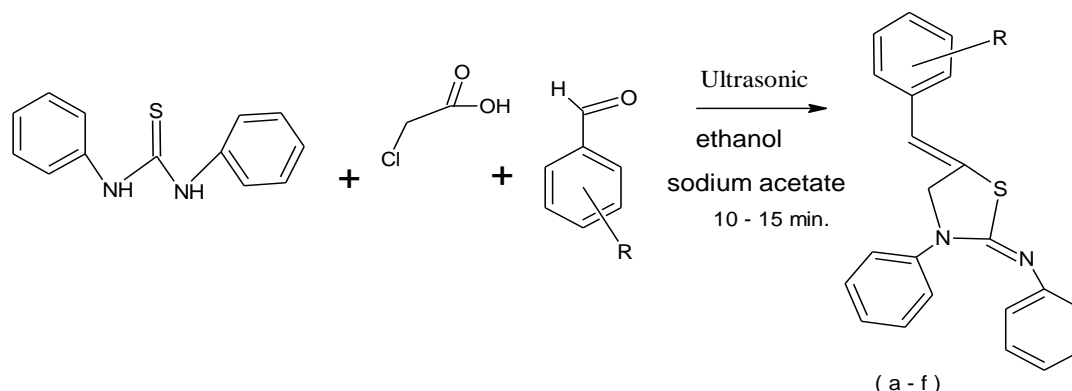
RESULTS AND DISCUSSION

4-Thiazolidinone containing substituents at all positions exhibit anti-microbial activities to varying degree and hence are important for pharmaceutical industry. While going through the literature, it is observed in drug design, that introduction of arylidene group at C-5 and presence of halogen atoms improve penetration through lipid membranes and tissue,. So, we prepared some 3 and 5



substituted-2 imino thiazolidine-4-one derivatives by employing very simple and efficient technique of ultrasonication to reduce reaction time and enhance the yield of the desired compounds. The N substituted thio-urea, chloroacetic acid and substituted benzaldehyde were sonicated in presence of ethanol and sodium acetate for 15 minute and the progress of consumption of reagents was monitored by TLC. The mixture was sonicated for 10-

15 minute depending upon the need. The resulting products were purified by column chromatography using n-hexane and ethyl acetate as solvent system and recrystallised from methanol. Synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR and elemental analysis and were screened for antimicrobial activities against *E. Coli* as Gram negative bacteria and *S. Aureus* as Gram positive bacteria. [**Scheme**]



Scheme

- a] R = 2-Cl b] R = 2-NO₂ c] R = 2-OH
 d] R = H e] R = 4-NO₂ f] R = 4-Br

The synthetic route to the targeted compounds is depicted in the scheme. N-substituted thiourea required for the synthesis of the desired compounds was prepared by refluxing aniline and carbon disulfide in 10 % NaOH solution at 60° C for about 6 h. This afforded very good yield (90%) of it. The synthesis of thiazolidinone in good yield was achieved by the condensation- cyclization reaction of N-substituted thiourea, substituted aromatic aldehydes and chloro acetic acid in ethyl alcohol in the presence of sodium acetate. The products so formed were purified by column chromatography using n-hexane and ethyl acetate as solvent system and recrystallised from methanol. All the synthesised compounds were characterized by IR, ^1H NMR, Mass spectroscopic method and elemental analysis. The yield of the synthesised derivatives by this methodology were quite better (70-88 %). Formation of the products was confirmed from spectral data. The $>\text{C}=\text{O}$ (amido) frequency was observed to around 1670 cm^{-1} . The C-H stretching frequency in IR and chemical shift at 7.8 ppm , appearance of multiplet due to presence of aromatic protons suggested the formation of the products. All the synthesised compounds were screened for their activities. Two products viz. a and f , containing strong electron withdrawing substituents and also the arylidene moiety, exhibited better responses against *S. aureus* while b and e showed moderate activities and other two were very poor in that regards. To put the result in nutshell, it is observed that some of the synthesised 4-thiazolidinones carrying substituents at 2,3 and 5 positions [2- phenylimino, 3-phenyl and 5- substituted benzylidene] exhibited better antibacterial responses.

Table 1: Physical and Analytical data of 5-(substituted benzylidene)-3-phenyl-2-phenylimino-1,3-thiazolidine-4-ones (a-f)

Compound No.	-R	M.P. °C	Yield %	Spectral Analysis
a	2-Cl	175	84	IR (KBr) ; 3097 (C-H), 1670 (C= O), 1640 (C= N) cm^{-1} . ^1H -NMR (CDCl ₃); δ : 7.1 (s, 1H, CH), 7.3-8.0 (m, 15H) ppm. ^{13}C -NMR (CDCl ₃) δ : 171.19, 160.21, 150.61, 139.32, 136.21, 136.16, 131.40, 129.51, 129.25, 129.05, 128.38, 127.16, 124.17, 118.67.
b	2-NO ₂	216	79	IR (KBr) ;3080 (C-H), 1670 (>C=O),1640 (C=N) cm^{-1} . ^1H -NMR (CDCl ₃); δ : 6.8 (s, 1H, CH), 7.1-7.4 (m, 14H, Ar-H) ppm. ^{13}C -NMR (CDCl ₃) δ : 171.19, 160.21, 150.61, 139.32, 136.21, 136.16, 131.40, 129.51, 129.25, 129.05, 128.38, 127.16,

				124.17, 118.67.
c	2-OH	256	72	IR (KBr) ; 3222 (O-H), 3080 (C-H), 1670 (>C=O),1640 (C =N) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 6.8 (s, 1H, CH), 7.1-7.4 (m, 14H, Ar-H) ppm. $^{13}\text{C-NMR}$ (CDCl_3); δ : 171.36, 164.18, 151.55, 147.72, 138.83, 137.89, 137.82, 130.38, 130.30, 129.37, 129.19, 127.21, 123.96, 123.93.
d	H	204	70	IR (KBr); 3080 (C-H), 1670 (>C=O),1640 (C =N) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3); δ : 6.8 (s, 1H, CH), 7.1-7.4 (m, 15H, Ar-H) ppm. $^{13}\text{C-NMR}$ (CDCl_3); δ : 171.36, 164.18, 151.55, 147.72, 138.83, 137.89, 137.82, 130.38, 130.30, 129.37, 129.19, 127.21, 123.96, 123.93.
e	4-NO ₂	195	80	IR (KBr); 3080 (C-H), 1670 (>C=O),1640 (C =N), cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) ; δ : 6.8 (s, 1H, CH), 7.1-7.4 (m, 14H, Ar-H) ppm. $^{13}\text{C-NMR}$ (CDCl_3); δ : 171.19, 160.21, 150.61, 139.32, 136.21, 136.16, 131.40, 129.51, 129.25, 129.05, 128.38, 127.16, 124.17, 118.67,
f	4-Br	182	88	IR(KBr); 3097 (C-H), 1670 (C= O), 1640 (C= N). cm^{-1} . $^1\text{H-NMR}$ (CDCl_3); δ : 7.1 (s, 1H, CH), 7.3-8.0 (m, 15H) ppm. $^{13}\text{C-NMR}$ (CDCl_3); δ : 171.19, 160.21, 150.61, 139.32, 136.21, 136.16, 131.40, 129.51, 129.25, 129.05, 128.38, 127.16, 124.17, 118.67,

Table 2: Antibacterial activity of Synthesized Compounds (a-f)

Comp. (100 $\mu\text{g/ml}$)	Antibacterial activity(mm)	
	<i>S.aureus</i>	<i>E.coli</i>
a	20	14
b	16	08
c	12	06
d	06	08
e	14	10
f	18	12
Streptomycin	23	22

CONCLUSION

We have carried out the synthesis of some 1,3-Thiazolidin-4-One derivatives by modern techniques.

The merits of the current protocols are,

1. One pot synthesis
2. Environmental benign methodology i.e. Ultrasonication
3. Shorter reaction time
4. Operationally simple and efficient technique
5. Atom economy
6. Good antibacterial activity

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