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Der Chemica Sinica, 2015, 6(10):7-12

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis of thiazolidinone compounds: Part-II[§]. Synthesis of thiazolidin-4-one from schiff bases derived from 5-chloro-2-hydroxy-4-methyl-acetophenone

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ABSTRACT

*A series of new 2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-2-methyl-3-phenyl-thiazolidin-4-one derivatives (**MT-I to MT-VII**) were synthesized from novel schiff base of 4-Chloro-5-methyl-2-(1-phenylimino-ethyl)-phenol (**M-I to M-VII**) with thioglycolic acid in presence of anhydrous zinc chloride. The chemical structures of these compounds were confirmed by colour, physical constant and various spectral techniques viz, UV-Vis, FTIR spectral data and elemental analysis. These newly synthesized compounds were screened in vitro for their antimicrobial activity against varieties of fungal strain Saccharomyce cerevisiae, Candida albicans, Penicillum notatum, Alternaria alternate, Aspergillus niger at 500 and 1000 µg/mL. The 2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-2-methyl-3-(4-methyl-2-nitro-phenyl)-thiazolidin-4-one, **MT-IV** and 2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-3-(4-hydroxy-2-nitro-phenyl)-2-methyl-thiazolidin-4-one, **MT-V**, derivatives are showing marked activity against Saccharomyce cerevisiae, Candida albicans, as compare to the other derivatives.*

Keywords: 5-Chloro-2-hydroxy-4-methyl-acetophenone, Schiff bases, Substituted-Thiazolidin-4-one and Antifungal activity.

INTRODUCTION

Thiazolidin-4-one, a saturated form of thiazole with carbonyl group on fourth carbon posses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities.

The structure and property is exerted by the various group which are attached to the carbon atom in aniline part, which is found to be biologically interesting substance as reported in the literature since from many years. Since bulky substitution at all positions of 4-Thiazolidin-4-ones were reported and known to possess antitubercular, antimicrobial and cytotoxic activities

[§]**Part-1**, refer. Ref. 16.

The aromatic derivatives of thiazolidin-4-one nucleus have occupied a specified place in the field of medicinal chemistry because of wide range of biological activities like anticancer, anticonvulsant, antibacterial[1], antifungal[2] and antitubercular[3-5].

Among pharmacologically important heterocyclic compounds, thiazolidin-4-one derivatives have been known to possess a wide range of biological properties such as anti-inflammatory, analgesic [6-12], cytotoxic[13]. anticonvulsant[14], anti-HIV[15], Recently we have reported[16] synthesis of Schiff bases, azetidino-2-one and Thiazolidin-4-ones from the Schiff bases of 2-Aminobenzothiazole and their antifungal activity.

Looking to the glimpses of the literature done, we have proposed to synthesized the Thiazolidin-4-ones from the earlier reported Schiff bases[17].

MATERIALS AND METHODS

The raw materials Schiff bases, were used as prepared in our earlier work[17] were used for synthesis of Thiazolidin-4-ones. The solvents toluene and ethylacetate used for synthesis and in analysis, TLC and UV-Vis spectra purpose were of the synthesis and spectroscopic grade. The physical constant(m.p.) were recorded on digital melting point apparatus, EQ-730(Model) of Equiptronics(Make). The reactions were monitored by employing the techniques such as TLC on aluminium plates coated with silica gel $60F_{254}$ (Merck) and colour by visual observation method. The elemental (CHN) analysis were also determined. UV-Vis monitored on Shimadzu-1800 spectrophotometer in alcohol. Stock solutions prepared in absolute ethanol and were of 0.01 M concentration. These solutions were used for the UV-Vis spectral determinations by making desired dilutions. The obtained products were purified by column chromatography on 60-120 Silica Gel and employing Toluene and Chloroform as eluent. The FTIR spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer (Model-IRAffinity-1) using sample mixed in powder form with KBr powder, the frequency values, 'ν', are in the range of 4000-350 cm^{-1}.

General procedure for the synthesis of Thiazolidin-4-ones:
This is the second step of the scheme and it is performed as per reported methods[16, 18-19]. The Schiff base, synthesized in step-I, 5-Chloro-2-hydroxy-4-methyl-acetophenoneanil (0.01 mole) was dissolved in THF or suitable solvents like dry Toluene or benzene in a conical flask (100 ml) with a pinch of anhydrous $ZnCl_2$ and thioglycolic acid or mercaptoacetic acid (0.01 mole) was added to the above solution in small instalments and with vigorous shaking was then refluxed, the reaction is monitored by TLC technique till to complete the reaction(about 22 hrs.), reaction mass was washed with sufficient water. The obtained $ZnCl_2$ free, residue was then dissolved in 1,4-dioxane-ethanol(1:1) and passed through a column of silica gel using eluent benzene: chloroform (8:2) mixture. Eluent was concentrated and the elution obtained was evaporated to product (thiazolidin-4-one) and the fine crystals if required is recrystallisze from ethanol, thiazolidin-4-one derivative, **MT-I**, was obtained. Record its physical constant and the dried weight to calculate the yield.

The remaining Thiazolidin-4-ones(**MT-II** to **MT-VII**) were prepared by the reaction of thioglycolic acid with the respective schiff bases by following the above procedure.

Anti-Fungal Study of the Thiazolidin-4-ones:
The antifungal studies are performed for all the Thiazolidin-4-ones for strains like *S. cerveace*, *P. nonatum*, *C. albicans* and *A. alternata* by disc diffusion method[17-18].

RESULTS AND DISCUSSION

In the present study, Thiazolidin-4-ones from Ketimines derived from 5-Chloro-2-hydroxy-4-methyl-acetophenone with Aniline, 3,4-Dimethyl-aniline, 2,4,5-Trichloro-aniline, 4-Methyl-2-nitro-aniline, 4-Methoxy-2-nitro-aniline, 2,3-Dichloro-aniline and 4-Chloro-2-nitro-aniline which were reported earlier[17]. The progress of reactions was monitored by Silica gel-G TLC $60F_{254}$ Merck, visualized by iodine vapour or UV cabinet. The obtained products were purified by column chromatography on 60-120 Silica Gel and employing Toluene and Ethyl acetate eluent. The purity of the compounds was ascertained by melting point determinations (open capillary method) and by Silica gel-G TLC. The structural assignment of the products was based on UV-Vis and FTIR spectral data and elemental (CHN) analyses. All compounds gave satisfactory elemental analysis. Values are in the close agreement with the values calculated for expected molecular formulae assigned to these compounds and are in 5 % in statistics. The physical constant and elemental analysis for synthesized Thiazolidin-4-ones are given in **Table-1**. The abbrivation of Thiazolidin-4-ones, melting point and elemental analysis of the Thiazolidin-4-ones were summarized in **Table-1**.

TABLE-1: Data for Melting Point and Elemental Analysis of the Synthesized Thiazolidin-4-ones, (MT-I to MT-VII) from Ketimines and thioglycolic acid

Sr. No.	Code No.	Code of Schiff Base Used	Melting Point °C*	Elemental Analysis of Schiff base					
				% C		% H		% N	
				obs.	cal.	obs.	cal.	obs.	cal.
01	**MT-I**	**M-I**	136-140	60.89	61.16	4.62	4.83	4.18	4.20
02	**MT-II**	**M-II**	159	60.00	60.06	5.41	5.57	3.65	3.87
03	**MT-III**	**M-III**	226	46.11	46.71	2.88	3.00	3.01	3.20
04	**MT-IV**	**M-IV**	57 – 60	54.95	55.03	4.18	4.36	7.02	7.13
05	**MT-V**	**M-V**	119	52.62	52.88	4.02	4.19	6.71	6.85
06	**MT-VI**	**M-VI**	68	50.64	50.70	3.39	3.50	3.38	3.48
07	**MT-VII**	**M-VII**	115	49.15	49.41	3.27	3.41	6.65	6.78

** These physical constants of these substances are decomposable.*

Analytical and Spectral Data Interpretation of thiazolidin-4-ones:

The above compounds were also analyzed by Colour and UV. The data obtain is shown in following **Table-2**. The typical UV spectra is depicted in the **Fig. 1.** The analytical results colour, and % yields for synthesized Thiazolidin-4-ones are given in **Table-2**.

Fig. 1. UV-Vis Spectra for 5-Chloro-2-hydroxy-4-methyl-acetohenoneanil (MT-I, $C_{17}H_{16}O_2NSCl$)

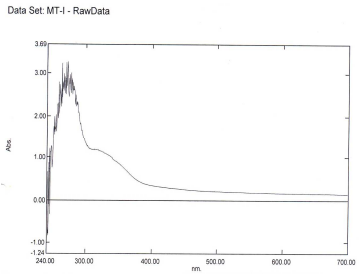


TABLE-2: Analytcal Data for Colour and UV-Vis Spectral of the Synthesized Thiazolidin-4-ones, MT-I to MT-VII

Sr. No.	Code No.	Colour	Mol. Wt.	UV ($\lambda_{max.}$)
01	MT-I	light Brown	332.5	310^{Ψ}, 271
02	MT-II	light Brown	360.5	321^{Ψ}, 263
03	MT-III	light Brown	436.0	320^{Ψ}, 278
04	MT-IV	Brown	391.5	433, 345, 275
05	MT-V	Dark Brown to black	407.5	425^{Ψ}, 375, 357, 275
06	MT-VI	Dark Brown to black	401.5	334, 258
07	MT-VII	Dark Brown to black	412.0	409, 342, 265

$^{\Psi}$ = shoulder peak

The above compounds were also analyzed for FTIR. The data obtain is shown in following **Table-3**. The FTIR spectra are reported in the **Fig. 2**.

Fig. 2. FTIR Spectra for 5-Chloro-2-hydroxy-4-methyl-acetohenoneanil (MT-I, $C_{17}H_{16}O_2NSCl$)

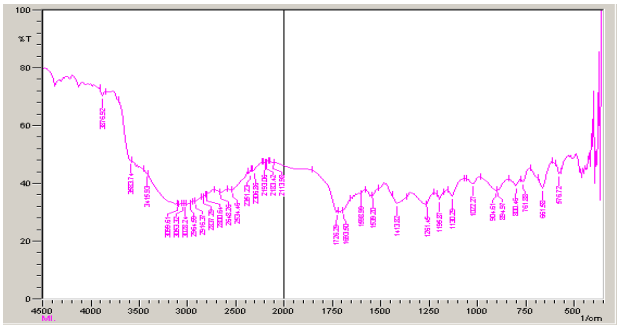


TABLE-3: FTIR Spectral Data of the Synthesized Thiazolidin-4-ones, MT-I to MT-VII

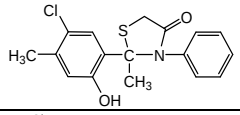
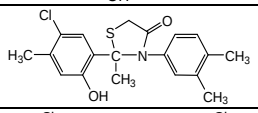
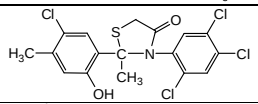
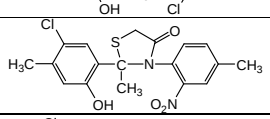
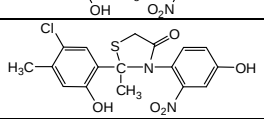
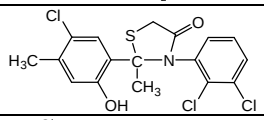
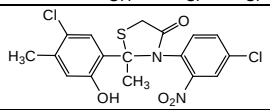
Sr. No.	Code No.	IR (in cm^{-1})								
		ν_{-OH}	ν_{Ar-H}	$\nu_{Ar-C-CH3}$	$\nu_{S-CH2-C=O-}$	ν_{-NO2}	*	$\nu_{>C-N-}$	ν_{-C-Cl}	ν_{S-CH2-}
01	**MT-I**	3416 (broad)	3028	2837	1693, 1726	-	-	1195, 1261	761, 800	661
02	**MT-II**	3445	2964	2881	1712	-	-	1172, 1224	725, 751	653
03	**MT-III**	3580	3010	2852	1724	-	-	1261	692, 798	661
04	**MT-IV**	3555	3082	2852	1612	1377	1564	1150	875	600
05	**MT-V**	3500	3030	2780	1690	1380	1570	1250	790	655
06	**MT-VI**	3510	2990	2980	1643	-	-	1172	650, 780	670
07	**MT-VII**	3550	3025	2840	1705	1380	1502	1288	810	707

* *2nd frequency due to –NO_2 group*

Structural Studies of Thiazolidin-4-one:

From all the characterization [viz. physical constant, analytical and spectral(UV-Vis and FTIR)] data one arrives at the detailed structures and they are as mentioned in below **Table-4**.

TABLE-4: Structural Formula, Name, Molecular Formula, Notation and of the Synthesized Thiazolidin-4-ones, MT-I to MT-VII

Sr. No.	Structural Formula	Name and MF and ID of Thiazolidin-4-ones
1		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-2-methyl-3-phenyl-thiazolidin-4-one ($C_{17}H_{16}O_2NSCl$) **MT-I**
2		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-3-(3,4-dimethyl-phenyl)-2-methyl-thiazolidin-4-one ($C_{19}H_{20}O_2NSCl$) **MT-II**
3		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-2-methyl-3-(2,4,5-trichloro-phenyl)-thiazolidin-4-one ($C_{17}H_{13}O_2NSCl_4$) **MT-III**
4		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-2-methyl-3-(4-methyl-2-nitro-phenyl)-thiazolidin-4-one ($C_{18}H_{17}O_4N_2SCl$) **MT-IV**
5		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-3-(4-hydroxy-2-nitro-phenyl)-2-methyl-thiazolidin-4-one ($C_{18}H_{17}O_5N_2SCl$) **MT-V**
6		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-3-(2,3-dichloro-phenyl)-2-methyl-thiazolidin-4-one ($C_{17}H_{14}O_2NSCl_3$) **MT-VI**
7		2-(5-Chloro-2-hydroxy-4-methyl-phenyl)-3-(4-chloro-2-nitro-phenyl)-2-methyl-thiazolidin-4-one ($C_{17}H_{14}O_4N_2SCl_2$) **MT-VII**

Anti-Fungal Study of the Thiazolidin-4-ones:

The antifungal studies are performed for all the Thiazolidin-4-ones for strains like *S. cerveace*, *P. nonatum*, *C. albicans* and *A. alternata* by disc diffusion method[18-19], and their results are depicted in Table-5.

Preparation of Solutions:

Experimental Procedure for antifungal activity:

To study the antifungal activity of Thiazolidin-4-ones synthesized from the Schiff bases, following setup will be required. The following experimental procedure will be adopted.

Newly synthesized compounds were screened for their antifungal activities against four strain of fungi out of *S. cerevisiae*, *C. albicans*, *Alternaria alternata*, *Aspergillus niger* and *Penicillum notatum* using diisk diffusion method [20-21. Activity of each compound was compared with that of control.

Before testing the test species were cultured on potato dextrose agar. Mature colonies were covered with sterile water (approx. 2.0 ml). The agar plates (saboured glucose agar 2 %) were inoculated by dipping a sterile cotton swab into the inoculum and evenly streaking the swab in three directions over the entire surface of the plates, which were then allowed to dry. The disks with compounds (500 and 1000 µg/disk) were applied into each inoculated plate and the plates were incubated at 37°C for yeasts and 25°C for filamentous fungi, with readings taken after 48 to 72 hours and 5 to 14 days respectively[22]. Inhibitory zone diameters for disks were measured in mm and compared with control disk (15 µg/disk) used as controls.

Table-5: The Antifungal activity screening for Synthesized Thiazolidin-4-ones, MT-I to MT-VII, derived from 5-Chloro-2-hydroxy-4-methyl-acetophenone in different strains after 72 hrs. (20/06/2015)

Comp. ID ↓	Concentration of Compound (µg/ml)↓	Name of Strain used				
		Saccharomyce cerevisiae	*Candida albicans*	*Penicillum notatum*	*Alternaria alternata*	*Aspergillus niger*
		Zone of Inhibition(mm)↓				
MT-I	500	-	-	-	-	-
	1000	-	-	-	-	-
MT-II	500	-	-	-	-	-
	1000	-	-	-	-	05
MT-III	500	05	-	-	-	05
	1000	11	-	-	-	06
MT-IV	500	-	06	-	-	05
	1000	-	07	-	-	-
MT-V	500	07	09	-	-	-
	1000	13	-	-	-	-
MT-VI	500	-	-	-	-	-
	1000	-	-	-	-	-
MT-VII	500	-	-	-	-	-
	1000	-	-	-	-	-
Positive Control (Ethanol)	-	-	-	-	-	-
Negative Control (Distilled Water)	-	-	-	-	-	-

Conclusions drawn from The Antifungal activities of the studied Thiazolidin-4-ones were as...
1) The Thiazolidinone, **MT-I** is not active for all the studied strains of the fungus.
2) The Thiazolidinone, **MT-II** is active for the *Aspergillus niger* (*1000* µg/ml).
3) The Thiazolidinone, **MT-III** is active for the *Saccharomyce cerevisiae and Aspergillus niger*. (500 and *1000* µg/ml).
4) The Thiazolidinone, **MT-IV** is active for the *Candida albicans (*500 and *1000* µg/ml) *and Aspergillus niger*. (500 µg/ml).
5) The Thiazolidinone, **MT-V** is active for the *Saccharomyce cerevisiae*(500 and *1000* µg/ml) *and Candida albicans (*500 µg/ml).
6) The Thiazolidinone, **MT-VI**, **MT-VII** is not active for all the studied strains of the fungus.
7) *Saccharomyce cerevisiae* is active for the Thiazolidinone, **MT-III** and **MT-V** (500 and 1000 µg/ml) only.
8) *Candida albicans*, is active for the Thiazolidinone, **MT-IV** and **MT-V** only.
9) *Penicillum notatum and Alternaria alternate* are not active for the studied Thiazolidin-4-ones.
10) *Aspergillus niger*, is active for the Thiazolidinone, **MT-II**, **MT-III** and **MT-IV** only.
11) The **MT-III** and **MT-V** were high activity against *Saccharomyce cerevisiae* and **MT-II** (*Aspergillus niger*) and **MT-IV** (*Candida albicans*) derivatives are showing low activity.

Acknowledgement
This work is supported by WRO-UGC, Pune by sanctioning the Minor Research Project File No.: 47-2048/11(WRO) dated 23-02-2012 to CAN and CJP. They are also thankful to the Management and Principal of their College for the permission of the present work.

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