International Journal of Theoretical & Applied Sciences, **1**(2)**:** 24-26(2009) **ISSN : 0975-1718**

Synthesis and antifungal activities of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-ones

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ABSTRACT : A new series of 2-ketophenyl-3-substituted aryl-1- thiazolidin-4-ones were synthesized by cyclocondensation of ketoazomethines and thioglycolic acid.Ketoazomethines was synthesized by condensation of phenyl glyoxal (prepared by partial oxidation of acetophenone) and various Para-substituted anilines. Their structure were elucidated by elemental analysis, IR and H^1NMR, they were screened for their antifungal activities against hazardous fungi namely Fusarium oxysporum, Pythium, Sclerotinia and Alternaria Brassicola.

Keywords : Synthesis, 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-ones, Antifungal activities

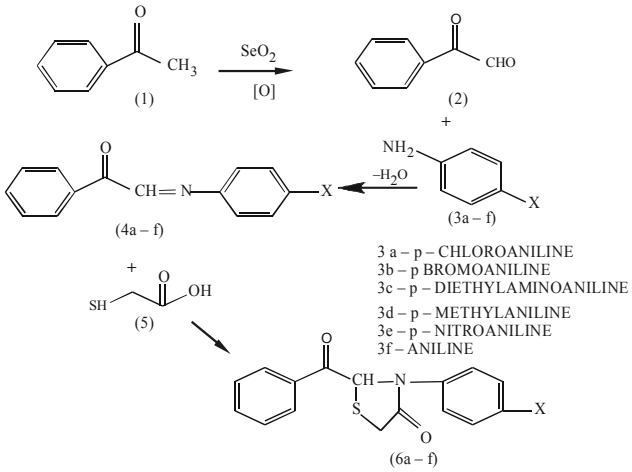
INTRODUCTION

4-Thiazolidinones are most popular, probably owing to their high versatility in exhibiting diverse potent biological properties viz., antiprotozoa [1], analgesic [2-5], anti inflammatory [6-9], anti-HIV [10], CFTR-inhibitor [11], anticonvulsant [12,13], antimicrobial [14-15], Nematicidal [16], fungicidal [17], SHP-2 inhibitors [18] etc. Although plenty of thiazolidinones and their derivatives have been synthesized by condensation of Schiff bases [19-21], Halo acetanilide [22], Thiosemicarbazone [23], Thiamide [24] with thiocyanates, halo fatty acid, aldehydes etc. This project includes synthesis of these compounds and their elemental, spectral studies and screening for antifungal activities against hazardous fungi *i.e.,* fusarium oxysporum, Alternaria Brasssicola, Sclerotium and Pythium which cause harm to crops like tomato, onion and cauliflower.

MATERIAL AND METHODS

All the chemicals used were either E-Merck or Qualigens. Melting points of all the compounds determined in open glass capillaries were uncorrected. Elemental analyses of samples were done on Euro EA Elemental Analyzer. Infrared spectra were recorded in KBr medium on Thermo Nicolet Nexus FT-IR spectrophotometer and 300MHz NMR spectra were recorded in dimethylsulphoxide medium on Varian C-13 NMR spectrometer using TMS as internal standard. Column chromatography was carried out using silica gel (finer than 200#). Characterization data are presented in Table 1 and spectral data in Table 2**.**

(l) Preparation of phenyl glyoxal. Phenyl glyoxal was prepared by the partial oxidation of acetophenone with selenium dioxide. Reaction mixture containing acetophenone (1, 0.2 mol) and selenium dioxide (0.4 mol) was taken in round bottom flask containing 300 ml of 95% ethyl alcohol and refluxed for 4-6 hrs. Orange yellow reaction mixture was decanted and concentrated over water bath and dissolved in ether to remove selenium from the product.



Scheme-l

General procedure for preparation of 4-thiazolidinones

(ll) Preparation of ketoazomethines(4a-f). Phenyl glyoxal(2, 0.2 mol) and aniline (3a-f, 0.2 mol) were taken in a round bottom flask containing 100 ml of ethanol and refluxed on water bath for 8hrs. Excess of ethanol was removed from reaction mixture and cooled at room temperature. Then it was poured in ice cold water and filtered. Solid obtained were collected and recrystallized with ethanol. Similarly other ketoazomethines of p-chloro, p-bromo, p-nitro, p-methyl, and p-diethylaminoaniline were prepared.

(lll) Preparation of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-one (6a-f) (scheme-l) ketoazomethines (0.2 mol, 4a-f) and thioglyciolic acid (0.3mol,5).were refluxed in dry benzene for ~ 15 hrs. The reaction mixture was concentrated to half of its volume over water bath and then neutralized with sodium bicarbonate solution. The contents were cooled and poured in ice cold water and filtered. The solid obtained was collected and purified with recrystallization.

Antifungal Activities

Preparation of medium and sample solutions :

For the preparation of PDA (Potato Dextrose Agar) medium 250 g. potato pieces boiled in water were filtered and filtrate was made up to 1 litre. To this solution 20 gm dextrose powder was added followed by heating to syrupy viscous consistency.Standard solutions of all the samples were prepared by dissolving known quantity of compounds in known volume of DMSO (dimethylsulphoxide).

Table 1 : Characterization data of compounds (6a-f)

Compound	m.f.	Colour	Yield %	m.p. (°C)	Elemental analysis (%) Cald.(found)			
					S	C	H	N
6a	$C_{16}H_{12}NO_2SCl$	Pink	67.4	223	7.6 (7.8)	60.37 (60.44)	3.77 (3.18)	4.40 (4.76)
6b	$C_{16}H_{12}NO_2SBr$	Yellow	78.5	245	9.2 (9.1)	53.35 (53.39)	3.31 (3.35)	3.86 (3.15)
6c	$C_{20}H_{22}N_2O_2S$	Light brown	63.6	235	8.0 (7.8)	67.79 (67.83)	6.21 (6.35)	7.90 (7.65)
6d	$C_{17}H_{15}NO_2S$	Brown	71.5	218	8.9 (9.1)	68.68 (68.65)	5.75 (5.86)	4.71 (4.23)
6e	$C_{16}H_{12}N_2O_4S$	Light green	65.6	228	8.6 (8.5)	58.53 (58.74)	3.65 (3.46)	8.53 (8.32)
6d	$C_{16}H_{13}NO_2S$	Orange	69.5	210	8.3 (8.4)	67.84 (67.73)	4.59 (4.13)	4.96 (4.12)

Method [25]

First of all PDA medium was sterilized in Autoclave and then poured into autoclaved Petri dishes near the gas flame, to avoid contamination and these plates were placed in Laminar Air Flow for an hour. There after filter paper discs dipped in sample solution were placed on medium in Petri dish and kept in Laminar Air Flow for half an hour. Fungus bit of 1mm diameter was put at a distance of 1 cm from paper disk wet in sample solution and Petri dishes were sealed with paraffin film and kept in incubator at 25-30°C for 72-96 hrs for growth of fungus.

Table 2 : IR, H^1 NMR Spectral data of the compounds (6a-f).

Compd.	IR (cm^{-1}) (KBr)	H^1 NMR (δ ppm)
6a	560, 700, 750, 818, 1241, 1324, 1486, 1542, 1605, 1651, 3061	7.48-7.50(6h,m), 6.89(4h,m), 5.11(1H,s), 3.98(2h,s)
6b	660, 752 , 822, 1326, 1489, 1549, 1609, 1648, 3066	7.51-7.72(6H,m), 6.78(4H,m), 5.15(1H,s), 3.82(2H,s)
6c	692, 778, 1407, 1594, 1680, 1684, 2970, 3032	7.56-7.73(6H,m),7.11(2H,d) 6.92(2H,d), 3.89(2H,s), 2.75(3H,m), 5.21(1H,s)
6d	694, 756, 1238, 1316, 1496, 1543, 1595, 1670, 3052	7.48-7.51(6H,m), 4.02(2H,s), 4.31(2H,s), 2.75(3H,s,Ar-CH_3), 5.43(1H,s)
6e	683, 771, 888, 1286, 1569, 1652, 1713, 3045	7.33-7.36(6H,m), 4.05(2H,S), 4.28(2H,s), 5.34(1H,s)
6f	648, 700, 748, 813, 1257, 1458, 1515, 1682, 1726, 3056	7.35-7.54(5H,m), 7.51-7.64(4H,m), 4.25(2H,s), 5.32(1H,s)

Fungal growth was measured as the mean of distances from inoculation point of fungus to its maximum growth in three directions. Three replicates were used for each fungus.

The synthesized thiazolidinones were screened for their antifungal activity against hazardous fungi namely Fusarium oxysporum, Pythium, Alternaria brassicola and Sclerotium using Diethane-M45 as reference fungicide and incubation periods of 72 hrs for the growth of fungi were measured in triplicates and the results of inhibition were noted in Table 3.

Table 3 : Antifungal activity of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-one.

Compound	M.F.	Incb. Time (days)	Sc.	Py.	F.O.	A.B.
6a	$C_{16}H_{12}NO_2SCl$	3	++	++	+	++
6b	$C_{16}H_{12}NO_2SBr$	3	++	++	++	++
6c	$C_{20}H_{22}N_2O_2S$	3	–	+	–	–
6d	$C_{17}H_{15}NO_2S$	3	–	+	–	+
6e	$C_{16}H_{22}N_2O_4S$	3	++	–	–	+
6f	$C_{16}H_{13}NO_2S$	3	++	–	–	++
Ref.	Diethane-M45	3	+	++	–	++

Sample 10 mg/ml, Sc-*Sclerotium*, Py-*Pythium*, F.O.-*Fusarium oxysporum*, AB- *Alternaria brassicola*
-ve=1-7mm, +ve= 10-15mm, ++ve=15-18mm,

RESULTS AND DISCUSSION

The antifungal studies of the compounds were tested by paper bit method against hazardous fungi namely *Fusarium oxysporum, Alternaria brassicola, Pythium* and *Sclerotium* and were compared with reference fungicidal Diethane-M45, 2-ketophenyl-3-(4-bromoaryl)-1-thiazoldin-4-one(6b) and 2-ketophenyl-3-(4-chloroaryl)-1-thiazolidin-4-one(6a) showed highest inhibition against *Fusarium oxysporum, Alternaria brassicola, Sclerotium* and *Pythium*. 2-ketophenyl-3-(4-nitroaryl)-1-thiazolidin-4-one (6e) showed highest inhibition against *Sclerotinia*, 2-ketophenyl-3-aryl-1-thiazolidin-4-one (6f**)** was effective against *Alternaria brassicola* and *Sclerotium*. Therefore, from the results it is evident that compounds having electronegative groups are responsible for antifungal activity.

ACKNOWLEDGEMENT

We are grateful to Mrs. Prathibha Sharma (Principal Scientist) and the staff of Plant Pathology department of Indian Agricultural Research Institute. New Delhi, staff of IIT Roorkee for their immense support.

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