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Synthesis and Antifungal Activities of 5-Substituted-arylimino-2-N-substituted-phenyl-3-oxo-1,2,4-thiadiazolidines

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5-Substituted-arylimino-2-N-substituted-phenyl-3-oxo-1,2,4-thiadiazolidines **(IVa–e)** have been synthesized by oxidative debenzylation and cyclization with molecular bromine in moistened chloroform from the corresponding 1-substituted-aryl-5-substituted-phenyl-2-S-benzyliso-4-biurets **(IIIa–e)** in moderate yield. Biurets, in turn, were prepared by the condensation of 1-substituted-aryl-2-S-benzylisocarbamides **(IIa–e)** and substituted-phenyl-isocyanate. These thiadiazolidines have been characterized by element analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra. Anti-fungal screening of the title compounds against ten fungi have been carried out by glass slides method and their comparative findings have been critically examined and reported. The compound possessing methoxy group at *p*-position in one aryl ring and dichloro group in another aryl ring **(IVe)** has shown maximum inhibition (99.5%) against *Aspergilus pisi* at 1000 g/mL concentration.

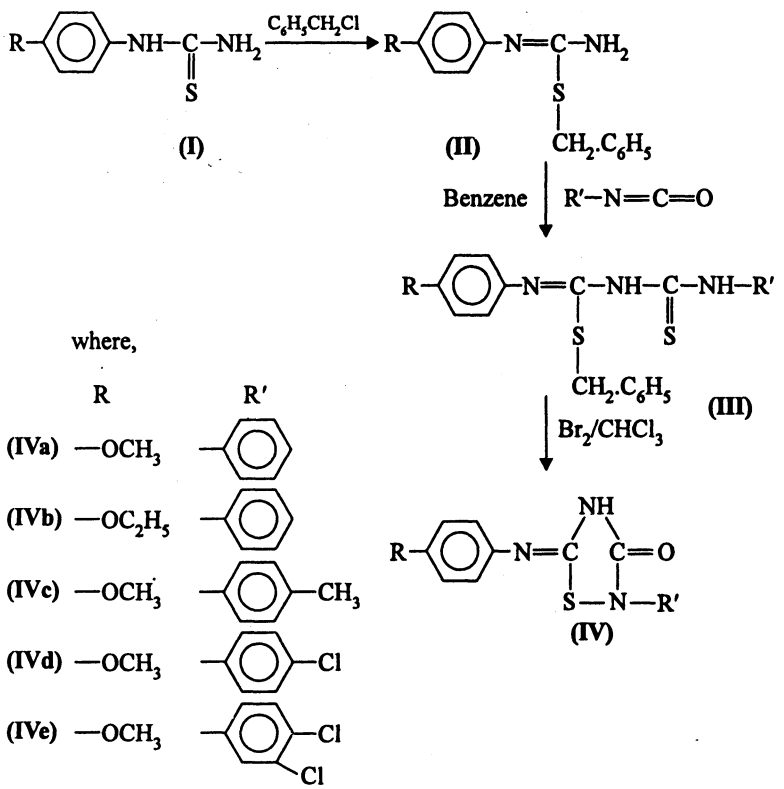
Key Words: Synthesis, 1,2,4-thiadiazolidine derivatives, Characterization, Anti-fungal.

INTRODUCTION

The chemistry of thiazolidinone and thiazolidindiones, the oxo derivatives of tetrahydrothiazole, have drawn considerable attention of a number of investigations due to their varied biological and physiological activities, *e.g.*, anti-fungal[1], anti-bacterial[2], anti-tubercular[3] and local anaesthetic[4] activities. 1,3,4-Thiadiazole, derivatives have also been shown to possess anti-microbial[5], anti-convulsant[6], carbonic anhydrase inhibitors[7] and tumour associated isozyme IX inhibition[7] activities. 3-Oxo-1,2,4-thiadizolidines have been shown to possess promising anti-fungal[8], anti-bacterial[8] and plant growth regulator[9] activities. 1,2,4-Triazole derivatives have been shown to possess promising eosinophilia inhibitor[10] activities. The oxidative debenzylation and cyclization[11–14] technique has been reported as a standard technique for the synthesis of N and S containing 1,2,4-thiadiazolidines. A perusal of the synthetic routes followed by earlier workers[15, 16] for the synthesis of 1,2,4-thiadiazolidines, oxidative dealkylation and

cyclization of isodithiobiurets and related systems showed, enhanced anti-fungal activities[8] associated with certain 3-oxo-1,2,4-thiadiazolidines[8]. This prompted us to synthesize newer 1,2,4-thiadiazolidines by employing oxidative debenzylation technique and study their biological activities.

Keeping the above facts in view an effort has been made to extend the work to synthesis of 5-substituted-arylimino-2-N-substituted-phenyl-3-oxo-1,2,4-thiadiazolidines **(IVa–e)** **(Scheme-1)** from the related 1-substituted-aryl-5-substituted-phenyl-2-S-benzyliso-4-biurets **(IIIa–e)** by oxidative debenzylation technique[4–7] and further study their anti-fungal activities by glass slides method[17]. The preparation of compounds 1-substituted-aryl-5-substituted-phenyl-2-S-benzyliso-4-biurets **(IIIa–e)** was achieved[13, 15] by the condensation of related S-benzylisocarbamides **(IIa–e)** and substituted-phenylisocyanate in benzene medium at its refluxing temperature for 6 h. The structure of compounds **(IVa–e)** was confirmed by element analyses, IR[18, 19], ^{1}H-NMR[19], ^{13}C-NMR[19] and mass spectra[19].



Scheme-1

EXPERIMENTAL

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) and different isocyanates were obtained from Sigma-Aldrich Chemicals (USA).

Penicillin, streptomycin, RPM 1–1640 medium and fetal bovine serum (FBS) were obtained from Life Technologies. TNF was obtained from Peprotech (New Jersey, USA). Benzene, ethanol, bromine, chloroform, benzylchloride were obtained from E. Merck. All the melting points were determined using Kofler hot stage apparatus by open capillary tube method and are uncorrected. IR spectra were recorded in Nujol on JASCO FTIR-5300 spectrophotometer and ^{1}H-NMR and ^{13}C-NMR spectra (in DMSO-d_6) on JEOL FX 90Q spectrometer (90 MHz-instrument). The microanalyses were carried out using a Coleman carbon-hydrogen and nitrogen analyzer. All the precursors were prepared in conformity with the methods described in literature. A single spot on TLC plate confirmed the purity of the compounds. S-Benzylisocarbamide **(IIa–e)** was prepared by benzylation[20] of 1-substituted-arylthiocarbamides with benzyl chloride.

1-(4-Methoxyaryl)-5-phenyl-2-S-benzyliso-4-biurets (IIIa): A mixture of 1-(4-methoxyaryl)-2-S-benzylisocarbamides **(IIa)** (5.44 g; 0.02 mol) and phenylisocyanate (2.38 g; sp. gr. 1.13; 2.10 mL; 0.02 mol) in 50 mL benzene was refluxed for 6 h. The excess of solvent was removed under vacuum over rotary evaporator and the semi-solid residue was repeatedly washed with petroleum ether (40–60°C) followed by addition of a little ethanol. The crude 1-(4-methoxyaryl)-5-phenyl-2-S-benzyliso-4-biurets **(IIIa)** thus obtained was recrystallized from ethanol. Purity of the compound was checked by TLC **(IIIa)**; yield 4.8480 g (61.9%); m.p. 235°C. $C_{22}H_{21}N_3O_2S$ (391) (%), Found: C 67.45, H 5.45, N 10.66, S 8.05; Calcd. C 67.51, H 5.37, N 10.74, S 8.18. IR (KBr, cm^{-1}): 3295 ν(NH), 1696 ν(C=O), 1590 ν(C=N), 1416 ν(CH_2—S); ^{1}H-NMR (DMSO-d_6)/ppm: 3.60 (3H, OCH_3), 4.30 (2H, S—CH_2), 7.54 (2H, NH), 7.79 (14H, Ar—H).

Compounds **(IIIb–c)** were prepared similarly and their characterization data are given below:

1-(4-Ethoxyaryl)-5-phenyl-2-S-benzyliso-4-biurets (IIIb): Yield (64%); m.p. 188°C. $C_{23}H_{23}N_3O_2S$ (405) (%), Found: C 68.25, H 5.79, N 10.44, S 7.78; Calcd. C 68.14, H 5.67, N 10.37, S 7.90. IR (KBr, cm^{-1}): 3290 ν(NH), 1640 ν(C=O), 1585 ν(C=N), 1418 ν(CH_2—S); ^{1}H-NMR (DMSO-d_6)/ppm: 1.52 (t, 3H, CH_3), 4.18 (2H, S—CH_2), 4.48 (q, 2H, OCH_2), 7.48 (2H, NH), 7.66 (14H, Ar—H)

1-(4-Methoxyaryl)-5-(4-methylphenyl)-2-S-benzyliso-4-biurets(IIIc): Yield 60.9%; m.p. 244°C. $C_{23}H_{23}N_3O_2S$ (405) (%), Found: C 68.22, H 5.59, N 10.24; Calcd. C 68.14, H 5.67, N 10.37. IR (KBr, cm^{-1}): 3306 ν(NH), 1689 ν(C=O), 1597 ν(C=N), 1410 (CH_2—S); ^{1}H-NMR (DMSO-d_6)/ppm: 2.48 (3H, Ar—CH_3), 3.36 (3H, OCH_3), 4.20 (2H, S—CH_2), 7.42 (2H, NH), 7.78 (13H, Ar—H)

1-(4-Methoxyaryl)-5-(4-chlorophenyl)-2-S-benzyliso-4-biurets (IIId): Yield (66.9%); m.p. 288°C. $C_{22}H_{20}O_2SCl$ (425.5) (%), Found: C 62.18, H 4.63, N 9.78; Calcd.: C 62.04, H 4.70, N 9.87; IR (KBr), cm^{-1}): 3300 ν(NH), 1648 ν(C=O), 1595 ν(C=N), 1420 ν(CH_2—S), 670 (C—Cl); ^{1}H-NMR (DMSO-d_6)/ppm: 3.66 (3H, OCH_3), 4.36 (2H, S—CH_2), 7.66 (2H, NH), 7.72 (13H, Ar—H).

1-(4-Methoxyaryl)-5-(3,4-dichlorophenyl)-2-S-benzyliso-4-biurets (IIIe): Yield (59%); m.p. 222°C. $C_{22}H_{19}N_3O_2SCl_2$ (460) (%), Found: C 57.49, H 4.01, N 9.20, S 6.88; Calcd.: C 57.39, H 4.13, N 9.13, S 6.95. IR (KBr), cm^{-1}): 3370

ν(NH), 1680 ν(C=O), 1585 ν(C=N), 1450 ν(CH_2—S), 672 ν(C—Cl); ^{1}H-NMR (in DMSO-d_6)/ppm: 3.42 (3H, OCH_3), 4.40 (2H, S—CH_2), 7.36 (2H, NH), 7.86 (12H, Ar—H).

5-(4-Methoxyarylimino)-2-N-phenyl-3-oxo-1,2,4-thiadiazolidines (IVa): 5-(4-Methoxyarylimino)-2-N-phenyl-3-oxo-1,2,4-thiadiazolidines **(IVa)** are prepared by oxidative debenzylation technique[4-7] of 1-(4-methoxyaryl)-5-phenyl-2-S-benzyliso-4-biurets **(IIIa).**

1-(4-Methoxyaryl)-5-phenyl-2-S-benzyliso-4-biurets **(IIIa)** (3.91 g, 0.01 mol) was made into a paste with chloroform and treated with molecular bromine, with vigorous and continuous stirring, till the colour of bromine persisted. Reaction mixture warmed up considerably, evolving lachrymatory fumes of benzyl bromide. The mixture was allowed to stand for 1 h and then repeatedly washed with ether. On addition of a little ethanol, the hydro bromide of 5-(4-methoxyarylimino)-2-N-phenyl-3-oxo-1,2,4-thiadiazolidines **(IVa)** separated out as a solid mass which was treated with liquor ammonia solution to obtain the free base, **(IVa)** which was then filtered and purified by recrystallization from ethanol; yield 2.0930 g (70%); m.p. 241 °C. $C_{15}H_{13}N_3O_2S$ (299) (%), Found: C 60.14, H 4.39, N 14.16, S 10.78; Calcd.: C 60.20, H 4.34, N 14.04, S 10.70; IR (KBr, cm^{-1}): 3296 ν(NH), 1649 ν(C=O), 1583 ν(C=N); ^{1}H-NMR (DMSO-d_6)/ppm: 3.54 (3H, OCH_3), 7.48 (1H, NH), 7.84 (9H, Ar—H); ^{13}C-NMR (DMSO-d_6)/ppm: 167.80 (C=N), 163.54 (C=O), 120.16–137.55 (aromatic carbon), 55.37 (OCH_3); mass spectra (m/z): 299 (M^+); m.p. of DNP derivative: 290°C.

Compounds **(IVb–e)** were similarly prepared by oxidative debenzylation to their corresponding **(IIIb–e)** and their characterization data are given below.

5-(4-Ethoxyarylimino)-2-N-phenyl-3-oxo-1,2,4-thiadiazolidines (IVb): Yield (69.9%), m.p. 210°C. $C_{16}H_{15}N_3O_2S$ (313) (%), Found: C 61.24, H 4.68, N 13.44, S 10.32; Calcd.: C 61.34, H 4.79, N 13.41, S 10.22; IR (KBr, cm^{-1}): 3298 ν(NH), 1656 ν(C=O), 1583 ν(C=N); ^{1}H-NMR (DMSO-d_6)/ppm: 1.54 (t, 3H, CH_3), 4.42 (q, 2H, O—CH_2), 7.52 (1H, NH), 7.72 (9H, Ar—H); m.p. of DNP derivative: 305°C.

5-(4-Methoxyarylimino)-2-N-(4-methylphenyl)-3-oxo-1,2,4-thiadiazolidines (IVc): Yield (71.9%), m.p. 190°C. $C_{16}H_{15}N_3O_2S$ (313) (%), Found: C 61.26, H 4.86, N 13.29, S 10.30; Calcd.: C 61.34, H 4.79, N 13.41, S 10.22; IR (KBr, cm^{-1}): 3294 ν(NH), 1660 ν(C=O), 1581 ν(C=N), ^{1}H-NMR (DMSO-d_6)/ppm: 2.42 (3H, Ar—CH_3), 3.42 (3H, OCH_3), 7.36 (1H, NH), 7.84 (8H, Ar—H); ^{13}C-NMR (DMSO-d_6)/ppm: 167.76 (C=N), 163.50 (C=O), 119.56–139.50 (aromatic carbon), 55.44 (OCH_3); m.p. of DNP derivative: 260°C

5-(4-Methoxyarylimino)-2-N-(4-chlorophenyl)-3-oxo-1,2,4-thiadiazolidines (IVd): Yield (73.8%), m.p. 250°C. $C_{15}H_{12}N_3O_2SCl$ (333.5) (%), Found: C 53.86, H 3.72, N 12.44, S 9.53; Calcd.: C 53.97, H 3.59, N 12.59, S 9.59. IR (KBr, cm^{-1}): 3296 ν(NH), 1672 ν(C=O), 1583 ν(C=N), 680 ν(C—Cl); ^{1}H-NMR (DMSO-d_6)/ppm: 3.60 (3H, OCH_3), 7.60 (1H, NH), 7.78 (8H, Ar—H); Mass spectra, (m/z): 333 (M^+); m.p. of DNP derivative: 330°C.

5-(4-Methoxyarylimino)-2-N-(3,4-dichlorophenyl)-3-oxo-1,2,4-thiadiazolidines (IVe): Yield 70.4%, m.p. 265°C. $C_{15}H_{11}N_3O_2SCl_2$ (368) (%), Found: C 49.85, H 2.83, N 11.37, S 8.74; Calcd.: C 48.91, H 2.98, N 11.41, S 8.69; IR (KBr, cm^{-1}): 3292 ν(NH), 1682 ν(C=O), 1577 ν(C=N), 660 ν(C—Cl); ^{1}H-NMR (DMSO-d_6)/ppm: 3.36 (3H, OCH_3), 7.30 (1H, NH), 7.78 (7H, Ar—H); ^{13}C-NMR (DMSO-d_6)/ppm: 168.82 (C=N), 163.76 (C=O), 119.84–138.31 (aromatic carbon), 56.51 (OCH_3); mass spectra (m/z): 368 (M^+); m.p. of DNP derivative: 370°C.

RESULTS AND DISCUSSION

The oxidative debenzylation of 1-substitutedaryl-5-substituted-phenyl-2-S-benzyliso-4-biurets with bromine in chloroform afforded the corresponding 1,2,4-thiadiazolidines as the main products.

The position of the substituents at 1 and 5 did not appear to have any marked effect on this mode of reaction.

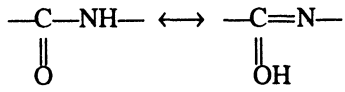
The rate of benzyl group substituted at the sulphur atom in 1-substituted-aryl-5-substituted-phenyl-2-S-benzyliso-4-biurets seems to be an important determination of the reaction route. The benzyl group could only be eliminated when bromine was the oxidant. However, iodine failed to bring about the required reaction.

In the oxidative debenzylation, the role of the solvent appears to be an important factor. The oxidative debenzylation and cyclization of related 2-S-benzyliso-4-biurets to the corresponding 1,2,4-thiadiazolidines using chloroform and benzene as solvents was successfully observed. Such a type of oxidation in ethanol could not eliminate the benzyl group and did not form the expected compounds. It may, therefore, be concluded that the polarity of the solvent has some relevant effect on the oxidative debenzylation and cyclization reaction that with decrease in polarity of the solvent, the oxidative debenzylation is favoured and with increase in polarity, it is not favoured.

Temperature is also a vital factor and plays an important role. At room temperature (30°C) the oxidative debenzylation and cyclization could be easily affected. At lower temperatures (around 10°C), however, the expected reaction leading to the formation of the corresponding 1,2,4-thiadiazolidines did not take place. Thus, the nature of the solvent, temperature and oxidant appear to be important factors in the reaction for synthesis of compounds from **II–IV** (**Scheme-1**).

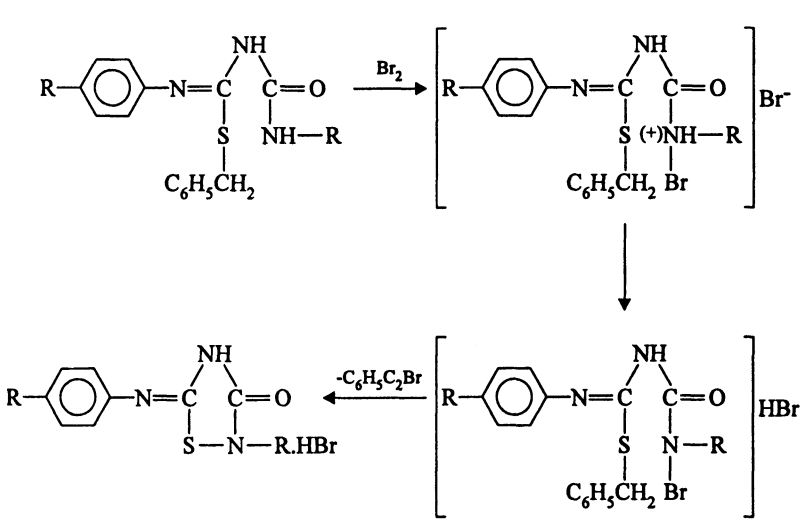
5-Substituted-arylimino-2-N-substituted-phenyl-3-oxo-1,2,4-thiadiazolidines (**IVa–e**) have been studied for their structure with the help of IR, ^{1}H-NMR and ^{13}C-NMR spectra and their important bonds (signals) and their assignments are given in experimental section. Out of the two groups, either —CO, NH— or —CN·NH—, may exist in two tautomeric forms. But, due to greater electronegativity of oxygen atom of carbonyl group (C=O) than nitrogen atoms of imino

group (C=N—), there is a greater only probability for —CO·NH to exist in the tautomeric form i.e.



But, from the IR spectra[18,19], presence of ν(C=O) at 1649 **(IVa)**, 1656 **(IVb)**, 1660 **(IVc)**, 1672 **(IVd)**, 1682 **(IVe)**, firmly rule out the existence of tautomeric enol forms. Similarly, from ^{1}H-NMR[19], the signals of —NH at 7.48 **(IVa)**, 7.52 **(IVb)**, 7.36 **(IVc)**, 7.60 **(IVd)**, 7.30 **(IVe)** and from ^{13}C-NMR[19], the signals of C=O at 163.59 **(IVa)**, 163.50 **(IVc)**, 163.76 **(IVe)**, rule out the existence of tautomerism in the compound.

The 2,4-dinitorophenylhydrazone (DNP) derivatives of carbonyl group in the final products indicates the presence of free C=O group. The expected mechanism of the oxidative debenzylation and cyclization may be given as follows:



The antifungal activity of compounds **IVa–e** was done by glass-slides method[17] against ten typical pathogenic agricultural fungi, namely, *A. alternata*, *A. tenuissima*, *A. solani*, *C. lunata*, *Colletotrichum* sp. *Fusarium ecceni*, *F. udum*, *E. pisi*, *Trichoderma* sp. *and A. pisi*, which cause serious plant diseases in India. The effect of these compounds on the spore germination of plant pathogenic fungi were carried out at different concentrations (500, 1000 and 1500 μg/mL) at 25 ± °C for 24 h of incubation. Each tested compound has shown maximum inhibition only at 1000 μg/mL. Amongst the compounds tested for potential fungicidal activity by spore germination method, the compound **IVe** shows maximum inhibitory effect (99.5%) against *A. pisi* at 1000 μg/mL concentration. This compound also showed maximum inhibitory effect against all the fungi,

i.e., > 90.0%. The compound **IVd** has shown remarkable inhibitory effect (96.8%) against *Colletotrichum* sp. However, all the other fungi have exhibited more than 87.1% effect on the same concentration. The compound **IVc** showed maximum inhibitory effect (92.3%) in the case of *E. pisi*, while all the other fungi exhibited more than 83.1% inhibition on the same concentration. The compound **IVb** showed maximum inhibitory effect (89.2%) in the case of *F. udum* and all the other fungi exhibited more than 77.3% inhibition on the same concentration. The compound **IVa** showed maximum inhibitory effect (79.1%) against *A. alternata* but all the other fungi exhibited more than 60.1% inhibition on the same concentration. From such observation, it may be concluded that the order of inhibitory effect against all the tested fungi is influenced by the type of the substituent, *i.e.*, the order of activities of compounds is **IVe > IVd > IVc > IVb > IVa** (Table-1). However, the effect(s) of these compounds on the host plant and their mode of action on targeted organisms still remain to be studied.

TABLE-1
PERCENTAGE INHIBITION AT 1000 μg/mL OF THE COMPOUNDS **IVa–e**

Sl.No.	Fungi	Compounds				
		IVa	**IVb**	**IVc**	**IVd**	**IVe**
1	*Alternaria alternata*	79.1	77.3	90.3	89.2	90.0
2	*A.tenuissima*	74.5	87.2	89.2	90.1	94.3
3	*Alternaria solani*	68.1	79.0	88.1	93.2	92.1
4	*Curvularia lunata*	60.1	84.5	89.1	87.1	90.2
5	*Colletotrichum* sp.	74.5	87.3	86.0	96.8	97.6
6	*Fusarium ecceni*	73.2	79.1	87.1	88.0	93.1
7	*F. udum*	78.7	89.2	90.1	96.2	94.5
8	*Erysiphe pisi.*	70.2	87.1	92.3	90.2	90.8
9	*Trichoderma* sp.	68.0	84.1	83.1	91.3	91.3
10	*Aspergillus pisi*	64.2	83.2	89.3	88.1	99.5

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