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Synthesis and Fungicidal Activities of Some 1,3,4-Oxadiazolo-[3,2-d]-1,3,4-Thiadiazine

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Abstract: 2,5-Diaryl-1,3,4-oxadiazolo-[3,2-d]-1,3,4-thiadiazine(**4**) have been conventionally prepared from 5-aryl-1,3,4-oxadiazol-2-yl-methyl-N-aryldithiocarbamate(**3**) by treating with thionyl chloride. The 5-aryl-1,3,4-oxadiazol-2-yl-methyl-N-aryldithiocarbamate(**3**) are synthesized by general method from 5-aryl-2-chloromethyl-1,3,4-oxadiazole(**1**) with ammonium-N-aryldithiocarbamate(**2**) in presence of anhydrous sodium acetate. All the title compounds have been tested in vitro for their antifungal activity against two fungal species *Colletotrichum falcatum* and *Fusarium oxysporum*. All the title compounds are characterized by elemental analysis, IR and HNMR spectral data.
Key Words: Fungicide, *Colletotrichum falcatum*, HNMR, IR.

INTRODUCTION

The dithiocarbamates like maneb, zineb, nabem and vapam are amongst the most important commercial fungicides for controlling plant diseases. Rhodanine incorporating dithiocarbamate moiety is highly toxic to micro-organisms and they have evoked considerable attention [1-3]. Similarly, it has been observed that 1,3,4-oxadiazole nucleus is associated with broad spectrum of biological activity like bactericidal [4-6], fungicidal [7-8], herbicidal [9-11] and insecticidal [12-13]. Therefore, it was anticipated that combination of the two moieties 1,3,4-oxadiazole **1** and dithio - carbamate **2** may produce title compound **3** with enhanced fungicidal and other biological activity.

Further, thiadiazine derivative have been reported to be toxic to bacteria and fungi [14-21]. In view of above fact, it prompted us to design a system which may fuse these biolabile rings together in a molecular framework to observe the additive effect towards antifungal activity. The compound (**3**) was transformed into (**4**) with the object to compare their fungicidal activity. The investigation further appeared interesting because compactness and planarity of such ring system may

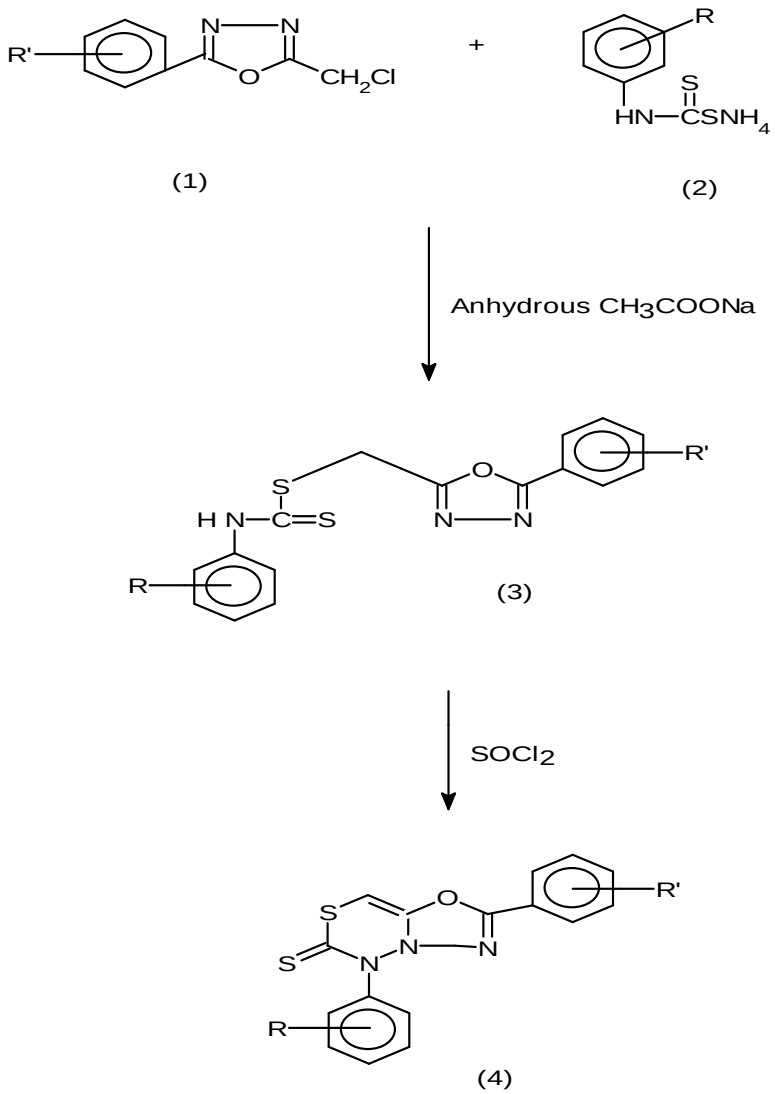
be an additional factor for enhancing the biological activity.

MATERIALS AND METHODS

In this communication, the title compound (**4**a-h) were synthesized in 54-69 % yield by refluxing 5-aryl-1,3,4-oxadiazol-2-yl-methyl-N-aryldithiocarbamate **3** with thionyl chloride. The compound (**3)** were synthesized by refluxing 5-aryl-2-chloromethyl-1,3,4-oxadiazole(**1)** and ammonium -N-aryldithiocarbamate(**2)** by conventional method. The starting material 5-aryl-2-chloromethyl-1,3,4-oxadiazole(**1)** were synthesized according to the method of Vakula and Srinivasan [22].

The compound (**4**a-h) was characterized by elemental analysis, IR and ^{1}HNMR spectral data. The cyclization of compound (**3)** furnished the title compound (**4)**. The absence of N-H peak in IR and ^{1}HNMR spectra of compound (**4)** revealed that cyclization has taken place **(scheme 1).**

SCHEME – I



Fungicidal Screening

The fungicidal activities were evaluated against *Colletotrichum falcatum* and *Fusarium oxysporum* by usual agar-plate technique [23] at 1000, 100 and 10 ppm concentration using Dithane M-45, a commercial fungicide, as standard. The number of replications in each case was three. After 96 hr the diameter of fungal growth zone was measured. The results were expressed in terms of the percentage growth inhibition, by comparing with growth on control. The, Percentage inhibition is given by-

$$\frac{(C - T) \times 100}{C}$$

Where

C = Diameter (in mm) of the fungal colony in control plate.

T = Diameter (in mm) of the fungal colony in treated plate.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 881 infrared spectrophotometer (ν_{max} cm^{-1}); and ^{1}HNMR spectra in DMSO-d_6 were recorded on a Varian EM-360L (200 MHz) spectrometer using TMS as internal reference.

5-Aryl-2-chloromethyl-1,3,4-oxadiazole(1)

These compounds were prepared by heating chloroacetyl chloride (0.1mol) and derivative of benzoic acid hydrazide (0.1mol) on oil bath at the m.p. of acid hydrazide until the evolution of HCl has ceased following the method reported in literature [22].

Ammonium-N-aryldithiocarbamate(2)

These compounds were prepared by the method given in literature [28]. This has been prepared by the reaction of CS_2 (0.25 mol) into the mixture of substituted aniline (0.2 mol) and ammonium solution in ice bath.

5-Aryl-1,3,4-oxadiazol-2-yl-methyl-N-aryldithiocarbamate(3)

These compounds were prepared by refluxing the mixture of 1(0.08 mol), 2(0.08mol) in absolutel alcohol for 2 hrs. The desired product thus precipitated was filtered and washed with water and crystallized from ethanol.

2,5-Diaryl-1,3,4-oxadiazolo-[3,2-d]-1,3,4-thiadiazine(4)

These compounds were prepared by refluxing the mixture of 5-aryl-1,3,4-oxadiazol-2-yl-methyl-N-aryldithiocarbamate (0.02 mol) and thionyl chloride (0.025 mol) in pyridine for 6-8 hrs. Pyridine was evaporated and the residue was washed with water and crystallized from ethanol. The characterization data, m.p., yield and molecular formula are recorded in table 1 and table 2 shows the spectral data of compound (4) while the fungicidal screening is shown in table 3**.**

RESULTS AND DISCUSSION

The fungicidal data indicates that all the tested compounds showed strong to moderate activities. It is interesting to mention from antifungal data that all the tested compounds (**4**a-h) displayed significant fungicidal activity at 1000 ppm against both the test fungi *Colletotrichum falcatum* and *Fusarium oxysporum* but their activity decreases at lower concentration i.e. 100 ppm and 10 ppm. It is important to mention that presence of more electronegative toxophores Cl, OCH_3, NO_2 in the title compound enhanced the antifungal activity. The title compound (**4)** also contain >C=S group responsible for enhanced activity. This is in conformity with earlier observation that >C=O and >C=S group induces fungi toxicity [24]. These data are in accordance with the fact that combination of some modified bioactive nitrogen heterocyclic like oxadiazole and thiadiazine have given more potent compound.

Although the dithiocarbamates **3**a-h have a pre-formed open chain skeleton of 1,3,4-diazine ring these were considerably less toxic than their cyclized product (**4**a-h) where chain is closed resulting in more compact and planar system. This is in conformity with the observation that the compact size and planarity of the molecule often enhance its fungicidal activity [25-27]. The compactness and planarity of title compound may be increased on complexation with essential metals required for different metabolic activity of the test fungi. Presumably these compounds interfere in the cell wall of fungi and thus inhibit different metabolic activity of fungi and cause inhibition in the fungal cell growth.

Table - 1 Physical data

Compound	R	R`	% Yield	m. p. (^{0}C)	Mol. formula	Found (Calcd.)		
						C	H	N
3a	4-Cl	4-Cl	58	169	$C_{16}H_{11}Cl_2N_3OS_2$	48.53 (48.48)	2.78(2.80)	10.66(10.60)
3b	4-Cl	4-CH_3	69	177	$C_{17}H_{14}ClN_3OS_2$	54.55 (54.61)	3.71(3.74)	11.28(11.24)
3c	4-OCH_3	4-Cl	62	173	$C_{17}H_{14}ClN_3O_2S_2$	51.8 (52.1)	3.51(3.57)	10.69(10.73)
3d	4-OCH_3	4-CH_3	73	176	$C_{18}S_{17}N_3O_2S_2$	58.24 (58.22)	4.61(4.58)	11.29(11.32)
3e	4-NO_2	4-Cl	67	170	$C_{16}H_{11}ClN_4O_3S_2$	47.21(47.23)	2.65(2.70)	13.71(13.77)
3f	4-NO_2	4-CH_3	61	158	$C_{17}H_{14}N_4O_3S_2$	52.81 (52.84)	3.58(3.62)	14.46(14.51)
3g	2,4-Cl_2	4-Cl	65	183	$C_{16}H_{10}Cl_3N_3OS_2$	44.66 (44.60)	2.26(2.32)	9.71(9.75)
3h	2,4-Cl_2	4-CH_3	71	168	$C_{17}H_{13}Cl_2N_3OS_2$	49.77 (49.75)	3.14(3.17)	10.22(10.24)
4a	4-Cl	4-Cl	54	224	$C_{16}H_9Cl_2N_3\ OS_2$	48.68 (48.73)	2.26(2.30)	10.75(10.70)
4b	4-Cl	4-CH_3	56	227	$C_{17}H_{12}ClN_3OS_2$	54.58 (54.61)	3.26(3.21)	11.2(11.24)
4c	4-OCH_3	4-Cl	61	216	$C_{17}H_{12}ClN_3O_2S_2$	52.31 (52.37)	3.04(3.08)	10.74(10.78)
4d	4-OCH_3	4-CH_3	69	221	$C_{18}S_{15}N_3O_2S_2$	58.48 (58.53)	4.01(4.06)	11.36(11.38)
4e	4-NO_2	4-Cl	68	209	$C_{16}H_9ClN_4O_3S_2$	57.41(57.46)	2.18(2.22)	13.79(13.84)
4f	4-NO_2	4-CH_3	61	219	$C_{17}H_{12}N_4O_3S_2$	53.08(53.12)	3.16(3.12)	14.51(14.58)
4g	2,4-Cl_2	4-Cl	62	229	$C_{16}H_8Cl_3N_3OS_2$	44.75(44.80)	1.81(1.86)	9.85(9.80)
4h	2,4-Cl_2	4-CH_3	67	218	$C_{17}H_{11}Cl_2N_3OS_2$	49.97(50.00)	2.75(2.69)	10.33(10.29)

Table - 2 Spectral data of compound 4

IR	**Cyclic C=N 1625 cm^{-1}, C=N 1090 cm^{-1}**	
^{1}HNMR (DMSO-d_6) (δ-ppm)	4a	7.12-7.98 (m, 9H, Ar-H & =CH)
	4b	7.16-7.98 (m, 9H, Ar-H & =CH), 2.26 (s, 3H, CH_3)
	4c	7.12-7.98 (m, 9H, Ar-H & =CH), 3.85 (s, 3H,-OCH_3)
	4d	7.22-7.92 (m, 9H, Ar-H & =CH), 2.26 (s, 3H, CH_3), 3.85 (s, 3H,-OCH_3)
	4e	7.12-7.98 (m, 9H, Ar-H & =CH)
	4f	7.12-7.98 (m, 9H, Ar-H & =CH), 2.22 (s, 3H, CH_3)
	4g	7.12-7.98 (m, 8H, Ar-H & =CH)
	4h	7.12-7.98 (m, 8H, Ar-H & =CH), 2.21 (s, 3H, CH_3)

Table - 3 Fungicidal screening

Compound	**Average percentage inhibition against**					
	C. falcatum			***F. oxysporum***		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
3a	55	47	24	53	46	22
3b	48	36	21	49	34	20
3c	53	23	42	50	36	21
3d	52	41	22	48	34	19
3e	51	44	19	52	42	18
3f	51	43	20	53	43	22
3g	58	51	25	59	48	25
3h	56	49	24	58	46	24
4a	97	72	52	98	69	53
4b	81	58	40	79	53	33
4c	93	69	51	91	70	52
4d	88	53	43	87	55	41
4e	83	51	46	86	53	49
4f	79	52	43	82	53	39
4g	99	73	54	98	69	50
4h	92	79	47	93	76	49
Dithiane M45	100	88	65	100	86	68

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