Studies on Biologically Active Heterocycles. Part I. Synthesis and Antifungal Activity of Some New Aroyl Hydrazones and 2,5-Disubstituted-1,3,4-oxadiazoles

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A series of new 1-(2,4-dichlorobenzoyl) hydrazones and 2-aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazoles have been synthesized from 2,4-dichlorobenzoylhydrazine and different aldehydes. Subsequent ring closure of the substituted aroyl hydrazones yielded the 1,3,4-oxadiazoles. All the compounds were characterized by their sharp melting point, microanalysis, ir, ^{1}H nmr and mass spectra and screened for their fungitoxic properties against *Alternaria tenuis* and *Curvularia verruciformis*. A few of the compounds showed good activity.

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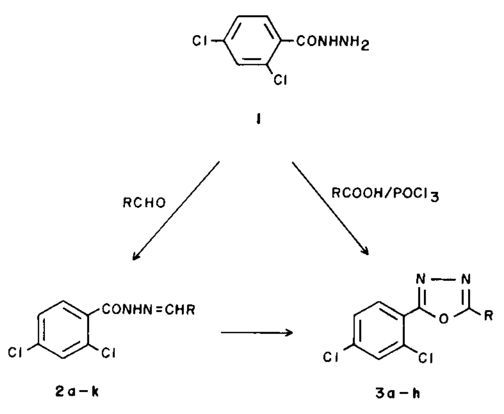
During the course of our extensive program directed towards the synthesis of novel heterocycles of potential biological application, a variety of new 1,2,4-triazoles, 1,3,4-oxadiazoles, mercaptotriazoles and fused heterocyclic systems were synthesized and screened for biological activities [1-5].

Earlier reports reveal that several hydrazones of substituted aroylhydrazine exhibit bacteriostatic [6], antiparasite [6], psychotropic [7] and antifungal [6,8,9] activities. It has been shown [8] that the biological activity associated with these hydrazones was attributed to the presence of -CONHN=C- moiety. The 1,3,4-oxadiazoles have been reported to be biologically versatile compounds having bactericidal, fungicidal, herbicidal, analgesic, antiproteolytic, hypoglycemic, antiinflammatory, tranquilizing and CNS depressant [10-16] properties. The above observations created the interest for the synthesis of the previously unreported series of aroyl hydrazones **2a-k** and 2,5-disubstituted-1,3,4-oxadiazoles **3a-h** containing a 2,4-dichlorophenyl moiety and to study their fungicidal properties. The synthesis of the title compounds **2a-k** and **3a-h** was accomplished in accordance with the sequence of reactions depicted in the Scheme 1.

Scheme I



Following the method of Yale *et al* [17], 1-(2,4-dichlorobenzyol)hydrazine (**1**) was obtained by refluxing ethyl 2,4-dichlorobenzoate and hydrazine hydrate (99%) in absolute ethanol. Condensation of this hydrazine **1** with appropriate alkyl/aryl/aralkylaldehydes yielded the corresponding hydrazones **2a-k**. The hydrazones **2a-k** on oxidative cyclization in presence of either Ferric chloride [18] or Lead dioxide [19] gave 1,3,4-oxadiazoles **3a-h**. These methods gave low yield and the products were not easily isolable and in certain cases no reaction took place. Following another method [20], 2,5-disubstituted-1,3,4-oxadiazoles **3a-h** were synthesized by a route in which hydrazine **1** was condensed with appropriate aliphatic or aromatic acids in presence of phosphorus oxychloride (Scheme 1).

The products were identified by elemental analysis, (Table 1 and 2), ir, ^{1}H nmr and mass spectra. In the ir spectra the hydrazones **2a-k** showed the bands (ν cm^{-1}), 3190-3160 (NH), 1675-1650 (-CONH-), 1615-1580 (C=N). The spectra of 1,3,4-oxadiazoles **3a-h** on the other hand lacked the C=O absorption bands. The ^{1}H nmr spectra of the hydrazones **2a-k** showed peaks at δ 10.2-10.6 ppm (-CONH-) and 8.2-8.4 ppm (-CH=N-). The ^{1}H nmr spectra of 1,3,4-oxadiazoles **3a-h** showed the characteristic peaks. The fragmentation of these compounds under electron impact was generally found to follow the general pattern anticipated for oxadiazoles [21].

Determination of Fungitoxic Activity.

The new synthetic compounds were screened for fungitoxic properties. The method of the American Phytopathological Society [22] modified by Horsfall and Rich [23] was used for screening on two test organisms *Curvularia verruciformis*-Agarwal and Sahni and *Alternaria tenuis*-Nees. The screening result is shown in Table 3. No activity was exhibited by 1,3,4-oxadiazoles **3a-h**. Only three acyl hydrazones having phenolic hydroxyl group (**2f**, **2h** and **2j**) showed activity against both the organisims.

Table 1

Physical Data of 2,4-Dichlorobenzoyl Hydrazones **2a-k**

Compound No.	R	Yield	Mp (°C)	Molecular formula	Analysis (%) Found (Calcd.) C	H	N
2a	$-CH_3$	79	146	$C_9H_8Cl_2ON_2$	46.68 (46.75	3.42 3.46	12.25 12.12)
2b	-*iso*-C_3H_7	93	162	$C_{11}H_{12}Cl_2ON_2$	50.90 (50.96	4.59 4.63	10.75 10.81)
2c	$-CH=CHCH_3$	87	197	$C_{11}H_{10}Cl_2ON_2$	51.40 (51.36	3.83 3.89	10.80 10.89)
2d	2-Furyl	90	202	$C_{12}H_8Cl_2O_2N_2$	50.92 (50.88	2.91 2.82	9.85 9.89)
2e	$-C_6H_5$	88	170	$C_{14}H_{10}Cl_2ON_2$	57.39 (57.33	3.50 3.41	9.69 9.55)
2f	2-OHC_6H_4	82	145	$C_{14}H_{10}Cl_2O_2N_2$	54.40 (54.36	3.30 3.23	9.19 9.06)
2g	4-$OCH_3C_6H_4$	94	170	$C_{15}H_{12}Cl_2O_2N_2$	55.69 (55.72	3.72 3.71	8.59 8.66)
2h	2,4-di-(OH)C_6H_3	93	235	$C_{14}H_{10}Cl_2O_3N_2$	51.72 (51.69	3.10 3.07	8.52 8.61)
2i	$-CH=CH-C_6H_5$	92	209	$C_{16}H_{12}Cl_2ON_2$	60.20 (60.19	3.78 3.76	8.75 8.77)
2j	3,4-(OCH_3)(OH)C_6H_3	80	193	$C_{15}H_{12}Cl_2O_3N_2$	53.10 (53.09	3.58 3.53	8.30 8.25)
2k	4-$N(CH_3)_2C_6H_4$	92	214	$C_{16}H_{15}Cl_2ON_3$	57.20 (57.14	4.49 4.46	12.48 12.50)

Table 2

Physical Data of 2-Aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-Oxadiazoles **3a-h**

Compound No.	R	Yield	Mp (°C)	Molecular formula	Analysis (%) Found (Calcd.) C	H	N
3a	$-C_6H_5$	86	113	$C_{14}H_8Cl_2ON_2$	57.62 (57.73	2.81 2.74	9.65 9.62)
3b	4-$OCH_3C_6H_4$	85	145	$C_{15}H_{10}Cl_2O_2N_2$	56.12 (56.07	3.20 3.11	8.71 8.72)
3c	4-$N(CH_3)_2C_6H_4$	82	208	$C_{16}H_{13}Cl_2ON_3$	57.42 (57.48	3.79 3.89	12.59 12.57)
3d	$-CH=CH-C_6H_5$	82	148	$C_{16}H_{10}Cl_2ON_2$	60.55 (60.56	3.18 3.15	8.80 8.83)
3e	3,4-di-ClC_6H_3	89	187	$C_{14}H_6Cl_2ON_2$	46.52 (46.66	1.72 1.66	7.70 7.77)
3f	$-(CH_2)_2C_6H_5$	84	183	$C_{16}H_{12}Cl_2ON_2$	60.20 (60.18	3.75 3.76	8.72 8.77)
3g	2-Cl-C_6H_4	91	153	$C_{14}H_7Cl_2ON_2$	51.59 (51.61	2.20 2.15	8.69 8.60)
3h	2-OH-C_6H_4	82	141	$C_{14}H_8Cl_2O_2N_2$	54.78 (54.72	2.65 2.60	9.02 9.12)

EXPERIMENTAL

Melting points were determined with a Büchi oil heated apparatus in open capillaries and are uncorrected. Infrared (ir) spectra were recorded with a Perkin-Elmer 237B spectrophotometer using potassium bromide discs, unless otherwise stated (ν max in cm^{-1}). Nuclear magnetic resonance (^1H nmr) spectra were recorded in solutions stated with TMS as the internal reference in 60 MHz on a Varian T-60 spectrometer (Chemical shift in δ ppm) and mass spectra were recorded on an AEIMS-30 instrument at 70 ev. 2,4-Dichlorobenzhydrazide (**1**) was prepared from ethyl 2,4-dichlorobenzoate following the method of Yale *et al* [17] yield 63%, mp 163°.

Table 3

Percentage Inhibition of Conidial Germination in the Test Solutions

Compound No.	Test Organisms *Curvularia verruciformis*	*Alternaria tenuis*
2a	–	–
2b	–	–
2c	–	–
2d	–	–
2e	–	–
2f	+	+ +
2g	–	–
2h	+ + +	+ + +
2i	–	–
2j	+ +	+ +
2k	–	–

– = No inhibition, + = 0-25%, + + = 26-50%, + + + = 51-75% and + + + + = 76-100% inhibition.

1-(2,4-Dichlorobenzoyl) Hydrazones **2a-k**.

General Procedure.

To a hot ethanolic solution of 2,4-dichlorobenzhydrazide (**1**) (0.01 mole), a solution of corresponding aldehyde (0.01 mole) in 10 ml ethanol was added and the reaction mixture was refluxed for 2-3 hours. On cooling the separated solid was filtered and recrystallized from ethanol to yield the hydrazones **2a-k**; ir, 3190-3160 (NH), 1673-1650 (-CONH-), 1615-1580 (C=N); ^{1}H nmr (deuteriochloroform/DMSO-d_6): 10.2-10.6 (-CONH-), 8.2-8.4 (-CH=N-). The physical properties and yields for the compounds are given in Table 1.

2-Aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazoles **3a-h**. Method A [18].

Hydrazone **2** (0.01 mole) were dissolved in 25 ml glacial acetic acid and a solution of ferric chloride (15 g) in water was added to it with shaking. The mixture was then stirred for 1 hour and diluted with water (200 ml) and kept at room temperature for 2 days. The separated solid **3** was filtered, washed with water, dried and crystallized to give the pure product.

Method B [19].

To a solution of hydrazone **2** (0.01 mole) in 40 ml glacial acetic acid 2.39 g (0.01 mole) lead dioxide was added. Then the mixture was stirred at 25° for 1 hour and diluted with 200 g ice and 100 ml water. The precipitate was then filtered, washed with water and dried and recrystallized from ethanol.

Method C [21].

A mixture of 2,4-dichlorobenzhydrazide (**1**) (0.01 mole) appropriate monocarboxylic acids (0.01 mole) and phosphorus oxychloride (5 ml) was refluxed for 3-5 hours. The cold reaction mixture was poured into ice water and made basic by adding sodium bicarbonate solution. The resulting solid was filtered, dried and recrystallized from chloroform to give the desired oxadiazoles **3a-h**. The physical properties and yields for the compounds are given in Table 2; ir: 1645-1600 (C=N), 1250-1245 (C-O-C); ^{1}H nmr (deuteriochloroform/DMSO-d_6): 7.0-7.4 (m, Aromatic-H).

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