[Chem. Pharm. Bull. 22(12)2778—2783(1974)]

UDC 547.792.057 : 547.498.04

Synthesis of 5-Membered Heterocycles and Related Compounds

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(Received February 19, 1974)

Some 1-(2,4-dichlorophenoxy and 2,4,5-trichlorophenoxy) acetyl-4-arylthiosemicarbazides were prepared from corresponding chlorophenoxyacetohydrazide. The resulting thiosemicarbazides were cyclised into 1,3,4-thiadiazoles and 5-mercapto-1,2,4-triazoles under different reaction conditions. The mercapto compounds were converted into sulphides and sulphones. N′-arylidene (2,4-dichlorophenoxy)acetohydrazides and 5-substituted-1,3,4-oxadiazole-2-thiones were also prepared from (2,4-dichlorophenoxy and 2,4,5-trichlorophenoxy)acetohydrazides separately and were subjected to Mannich reaction. Some of these compounds were evaluated as fungicides against *Aspergillus niger*.

Various 1-acyl-4-substituted thiosemicarbazides are known to posses interestings biol ogical properties like antitubercular,[2] antifungal[3] and hypoglycemic[4] activities. Heterocycles derived from these thiosemicarbazides such as oxadiazoles, thiadiazoles and triazoles are important chemotherapeutic agents and have been reported to exhibit antitubercular,[5] bacteriostatic[6] hypoglycemic,[7,8] antiviral,[9] antifungal,[10] antithyroid,[11] carcinostatic[12,13] and strong herbicidal[14] action. Madne, *et al.*[15] have reported that tuberculotherapeutic activity of 1,2,4-triazoles is the function of their basicity and the active hydrogen in triazole ring. Since the Mycobacteria and fungi are phytogenetically related substances,[16] so compounds acting as antitubercular agents are likely to show antifungal properties. Recently Greenfield, *et al.*[17] have reported that 5-mercapto-1,2,4-triazoles and related compounds were active against cereal rust. As chlorophenoxy acetic acids and its derivatives are known to have strong herbicidal action, some cyclic and noncyclic compounds with 2,4-dichlorophenoxy and 2,4,5-trichlorophenoxy methyl moiety were thought to prepare which might be useful as herbicide and fungicide.

1-Chlorophenoxyacetyl-4-aryl-thiosemicarbazides (II) were prepared by reacting chlorophenoxyaceto-hydrazide (I) with different aryl isothiocyanates in alcoholic medium and some of these were converted[18] in to corresponding 3-(2,4-dichlorophenoxy)methyl-4-aryl-5-

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mercapto-1,2,4-triazoles (III) by refluxing with aqueous sodium hydroxide (4%). Mercapto triazoles (III) on reaction with alkyl/aralkyl halide in presence of ethanolic sodium hydroxide (10%) furnished 3-(2,4-dichlorophenoxy)methyl-4-aryl-5-alkyl/aralkylthio-1,2,4-triazole (IV) which was oxidised with acidic potassium permanganate, in to 3-(2,4-dichlorophenoxy)methyl-4-aryl-5-alkyl/aralkylsulphonyl-1,2,4-triazole (V). Cyclodehydration[19] of (II) with concentrated sulphuric acid gave 2-amino-5-(2,4-dichlorophenoxy)methyl-1,3,4-thiadiazole (VI). N'-arylidene-(2,4-Dichlorophenoxy)acetohydrazides (VII) were prepared by the condensation of hydrazide (I) with different aryl aldehydes. 5-Substituted 1,3,4-oxadiazole-2-thiones (VIII) were prepared by following the method of Young and Wood[20] and were subjected to Mannich reaction by condensing with formaldehyde and a primary or secondary amine in ethanolic medium to give 3-aryl-aminomethyl-5-substituted-1,3,4-oxadiazole-2-thione (IX). The structure of triazoles (III and IV) were confirmed by nuclear magnetic resonance (NMR) studies of two representative compounds, (i) 3-(2,4-dichlorophenoxy)methyl-4-(*p*-)tolyl-5-mercapto-1,2,4-triazole and (ii) 3-(2,4-dichlorophenoxy) methyl-4-(*p*-) iodophenyl-5-benzylthio-1,2,4-triazole.

Spectrum of the compound (i) showed two high field singlets and a low field multiplet. The signal at highest field (τ=7.55) can be assigned to the methyl group and other singlet (τ=5.0) to the methylene group. The ratio of the areas under aromatic multiplet and the methylene signal seem to be in accordance with the structure. The signal corresponding to the –SH group seems to have been superimposed on the methyl signal fortutiously as they have been reported to lie in the same region.

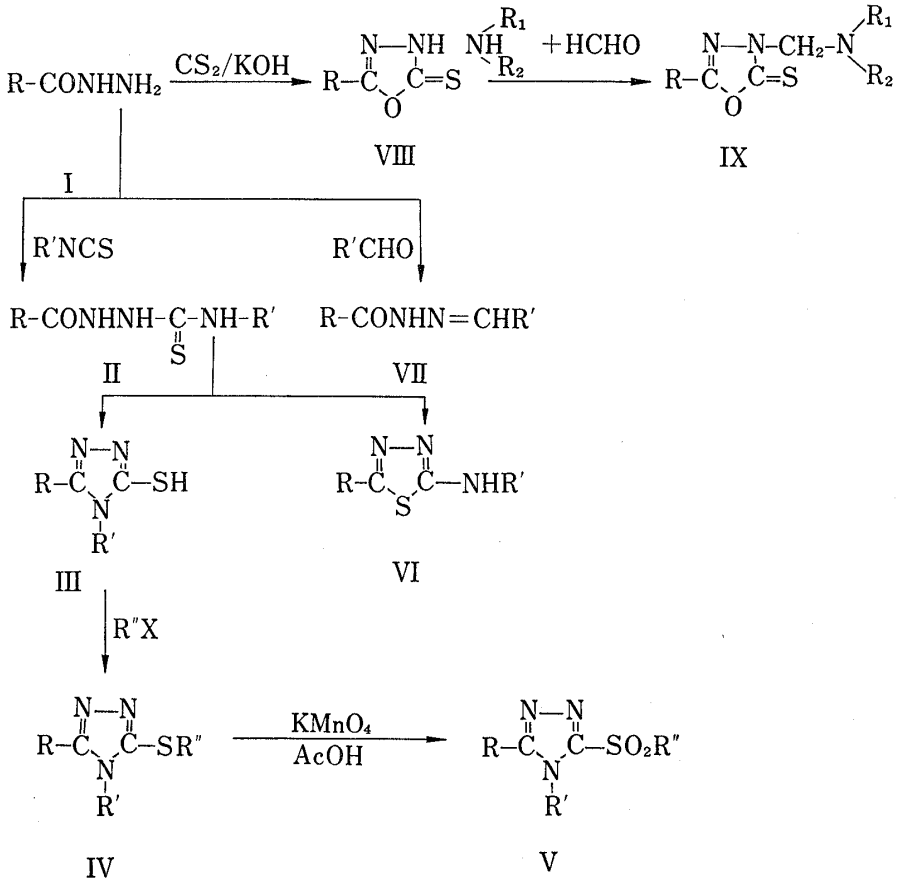

Chart of the Reactions

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Spectrum of the compound (ii) showed two singlets on the high field side and a multiplet on the low field side. The two singlets on the high field side can be assigned to the two methylene groups *viz.* $C_6H_5OCH_2$–$\overset{\overset{\|}{S}}{C}$–($\tau$=4.8) and $C_6H_5CH_2$–S–$\overset{\overset{\|}{S}}{C}$–($\tau$=5.47) in accordance with the structure of the compound and the multiplet to the non-equivalent aromatic protons. The two methylene groups will obviously be non-equivalent and the signal at the low field (τ=4.8) will correspond to the –OCH_2-methylene group in view of the greater electrophilic character of oxygen as compared to sulphur. This assignment is further supported by the area measurements. If the area under a methylene singlet is taken to correspond to 2 protons, the total area under the aromatic multiplets corresponds to about 12 protons.

Experimental[21]

2,4-Dichlorophenoxyacetohydrazide——It was prepared by refluxing methyl ester of 2,4-dichlorophenoxyacetic acid (11.6 g, 0.05 mole) with hydrazine-hydrate (10 ml, 80%) for 2 hr in EtOH (10 ml). The excess of EtOH was evaporated. Residue thus obtained was filtered, washed with cold EtOH and crystallised with dilute EtOH, mp 155°, yield 8.3 g (80%).

2,4,5-Trichlorophenoxyacetohydrazide——The compound was prepared from methyl 2,4,5-trichlorophenoxyacetate by the procedure described above in yield 75% mp 200°.

General Method for the Preparation of 1-Chlorophenoxyacetyl-4-Substituted Thiosemicarbazides (II)——To a suspension of chlorophenoxyacetohydrazide (1.1 g, 0.005 mole) in EtOH (10 ml) was added the appropriate isothiocyanate (0.005 mole) and the mixture heated under reflux on water bath for 2 hr. The solid obtained was filtered, washed with EtOH and crystallized with boiling EtOH. The compounds thus prepared are listed in Table I.

Table I. 1,4-Disubstituted Thiosemicarbazides

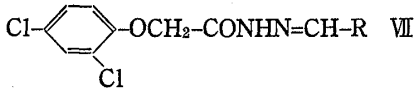
R–CONHNH–$\overset{\overset{\|}{S}}{C}$–NH–R′ II

Ent. No.	R	R′	mp. (°C)	Formula	Analysis N% Calcd.	Found
1	2,4-dichlorophenoxymethyl	*o*-tolyl	165	$C_{16}H_{15}O_2N_3Cl_2S$	10.93	11.2
2	2,4-dichlorophenoxymethyl	*m*-tolyl	160	$C_{16}H_{15}O_2N_3Cl_2S$	10.93	11.4
3	2,4-dichlorophenoxymethyl	*p*-tolyl	175	$C_{16}H_{15}O_2N_3Cl_2S$	10.93	11.1
4	2,4-dichlorophenoxymethyl	*p*-iodophenyl	176	$C_{15}H_{12}O_2N_3Cl_2IS$	8.4	8.9
5	2,4-dichlorophenoxymethyl	*p*-phenetyl	150	$C_{17}H_{17}O_3N_3Cl_2S$	10.14	10.3
6	2,4-dichlorophenoxymethyl	*p*-chlorophenyl	165	$C_{15}H_{12}O_2N_3Cl_3S$	10.38	10.6
7	2,4-dichlorophenoxymethyl	*p*-bromophenyl	170	$C_{15}H_{12}O_2N_3BrCl_2S$	9.3	9.1
8	2,4,5-trichlorophenoxymethyl	*m*-tolyl	180	$C_{16}H_{14}O_2N_3Cl_3S$	10.03	10.4
9	2,4,5-trichlorophenoxymethyl	*p*-bromophenyl	185	$C_{15}H_{11}O_2N_3BrCl_3S$	8.68	9.1
10	2,4-dihydroxyphenyl	*p*-chlorophenyl	200	$C_{14}H_{12}O_3N_3ClS$	12.44	12.6

N′-Arylidene(2,4-dichlorophenoxy)acetohydrazides (VII)——These were prepared by refluxing 2,4-dichlorophenoxyacetohydrazide (0.001 mole) and appropriate aldehyde (0.001 mole) in EtOH (10 ml) for 2 hr. After cooling a white solid obtained, which was filtered and crystallized with EtOH, yield in each case was quantitative. Compounds thus prepared are recorded in Table II.

21) All melting points are uncorrected.

Table II. N′-Arylidene-(2,4-dichlorophenoxy)acetohydrazides



Ent. No.	R	mp. (°C)	Formula	Analysis N% Calcd.	Found
1	4-hydroxy-3-methoxyphenyl	140[a]	$C_{16}H_{14}O_4N_2Cl_2$	7.59	7.3
2	*p*-dimethylaminophenyl	185[a]	$C_{17}H_{17}O_2N_3Cl_2$	11.47	10.8
3	*o*-hydroxyphenyl	195	$C_{15}H_{12}O_3N_2Cl_2$	8.23	8.6
4	*p*-anisyl	180	$C_{16}H_{14}O_3N_2Cl_2$	7.91	8.5
5	2-furyl	145	$C_{13}H_{10}O_3N_2Cl_2$	8.94	9.3

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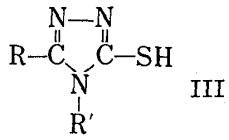
3-(2,4-Dichlorophenoxy)methyl-4-aryl-5-mercapto-1,2,4-triazole (III)——Thiosemicarbazide (II, 0.01 mole) was dissolved in 4% NaOH solution (30 ml) and refluxed gently for 2 hr. The resulting solution was cooled, treated with charcoal and filtered. The filtrate on acidification with dil. HCl afforded white solid which was filtered off, washed with water and crystallized with dil. EtOH. The analyses, mp and other relevant data are listed in Table III.

Table III. 3,4-Disubstituted-5-mercapto-1,2,4-triazoles



III

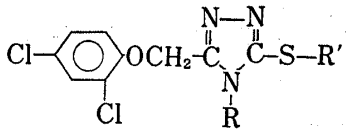
Ent. No.	R	R′	mp. (°C)	Formula	Analysis N% Calcd.	Found
1	*p*-hydroxyphenyl	*p*-chlorophenyl	260	$C_{14}H_{10}ON_3ClS$	13.83	14.1
2	2,4-dihydroxyphenyl	*p*-chlorophenyl	215	$C_{14}H_{10}O_2N_3ClS$	13.14	13.5
3	2,4-dichloro-phenoxymethyl	*p*-bromophenyl	190	$C_{15}H_{10}ON_3BrCl_2S$	9.7	10.3
4	2,4-dichloro-phenoxymethyl	*p*-chlorophenyl	185	$C_{15}H_{10}ON_3Cl_3S$	10.87	10.5
5	2,4-dichloro-phenoxymethyl	*p*-iodophenyl	210	$C_{15}H_{10}ON_3Cl_2IS$	8.8	8.5
6	2,4-dichloro-phenoxymethyl	*p*-phenetyl	115	$C_{17}H_{15}O_2N_3Cl_2S$	10.60	10.3

3-(2,4-Dichlorophenoxy)methyl-4-aryl-5-alkyl/aralkylthio-1,2,4-triazole (IV)——Mercapto triazole (III, 0.001 mole) was dissolved in alcoholic NaOH (10 ml, 10%) and to this solution alkyl halide (0.001 mole) was added and the whole mixture was gently refluxed for 2 hr. Reaction content was poured into cold water, cooled and filtered. Product on crystallization with dil. EtOH afforded analytical sample. Physical properties and analytical data are recorded in Table IV.

3-(2,4-Dichlorophenoxy)methyl-4-(*o*-)tolyl-5-ethylsulphonyl-1,2,4-triazole (V)——A solution of 3-(2,4-dichlorophenoxy)methyl-4-(*o*-)tolyl-5-ethylthio-1,2,4-triazole (0.001 mole) in glacial AcOH was treated with $KMnO_4$ aq. till colour persisted. Upon cooling residue was filtered and washed with water and crystallized with dilute acetic acid, mp 160°. *Anal.* Calcd. for $C_{18}H_{17}O_3N_3Cl_2S$: N, 9.86. Found: N, 9.86.

2-Amino-5-(2,4-dichlorophenoxy methyl-1,3,4-thiadiazole (VI)——1-(2,4-Dichlorophenoxy)acetylthiosemicarbazide (2.0 g) was added portion-wise to conc. H_2SO_4 (20 g) with cooling and left to stand for 0.5 hr. The solution was poured on ice and neutralized with NH_4OH. A white solid obtained, was filtered and washed with distilled water. The crude product, was crystallized with dimethylformamide, mp 195°, yield 70%. *Anal.* Calcd. for $C_9H_7ON_3Cl_2S$: N, 15.22. Found: N, 15.5.

Table IV. 3-(2,4-Dichlorophenoxy)methyl-4-aryl-5-mercapto-1,2,4-triazoles



IV

Ent. No.	R	R′	mp. (°C)	Formula	Analysis N% Calcd.	Found
1	*o*-tolyl	ethyl	105	$C_{18}H_{17}ON_3Cl_2S$	10.66	10.2
2	*o*-tolyl	*n*-propyl	85	$C_{19}H_{19}ON_3Cl_2S$	10.2	9.6
3	*o*-tolyl	benzyl	120	$C_{23}H_{19}ON_3Cl_2S$	9.21	9.1
4	*m*-tolyl	ethyl	78	$C_{18}H_{17}ON_3Cl_2S$	10.66	10.8
5	*m*-tolyl	*n*-propyl	175	$C_{19}H_{19}ON_3Cl_2S$	10.29	9.8
6	*m*-tolyl	benzyl	110	$C_{23}H_{19}ON_3Cl_2S$	9.21	9.5
7	*p*-tolyl	ethyl	105	$C_{18}H_{17}ON_3Cl_2S$	10.66	10.9
8	*p*-tolyl	benzyl	125	$C_{23}H_{19}ON_3Cl_2S$	9.21	9.5
9	*p*-iodophenyl	benzyl	155	$C_{22}H_{16}ON_3Cl_2IS$	7.4	7.8
10	*p*-phenetyl	ethyl	80	$C_{19}H_{19}O_2N_3Cl_2S$	9.9	10.4

5-(2,4-Dichlorophenoxy)methyl-1,3,4-oxadiazole-2-thione (VIII)——It was prepared by following the method of Young and Wood[20] from 2,4-dichlorophenoxyacetohydrazide in 62% yield, mp 128°. *Anal.* Calcd. for $C_9H_6O_2N_2Cl_2S$: N, 10.11. Found: N, 10.3.

5-(2,4,5-Trichlorophenoxy)methyl-1,3,4-oxadiazole-2-thione——It was prepared by the procedure described above in 40% yield, mp 205°. *Anal.* Calcd. for $C_9H_5O_2N_2Cl_3S$: N, 9.0. Found: N, 8.9.

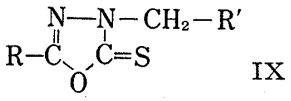
N,N′-Bis[5-(2,4,5-trichlorophenoxy)methyl-3-methyleno-1,3,4-oxadiazole-2-thione]benzidine——5-(2,4,5-Trichlorophenoxy)methyl-1,3,4-oxadiazole-2-thione (0.002 mole) was dissolved in abs. EtOH and treated with formaldehyde (0.002 mole). To this mixture, a solution of benzidine (0.001 mole) in EtOH was added slowly with swirling and reaction mixture was left in refrigerator for 2 hr with occasional shaking. Mannich base thus obtained was collected and crystallized with EtOH, mp 220°. *Anal.* Calcd. for $C_{32}H_{22}O_4N_6Cl_6S_2$: N, 10.11. Found: N, 10.4.

N,N′-Bis[5-(2,4,5-trichlorophenoxy)methyl-3-methyleno-1,3,4-oxadiazole-2-thione]piperazine——5-(2,4,5-Trichlorophenoxy)methyl-1,3,4-oxadiazole-2-thione (0.002 mole) was dissolved in abs. EtOH and treated with formaldehyde (0.002 mole). To this mixture a solution of piperazine (0.001 mole) was added dropwise with occasional shaking and left the reaction mixture in freeze for 2.5 hr, white solid thus obtained was filtered and crystallized with EtOH, mp 210°. *Anal.* Calcd. for $C_{24}H_{20}O_4N_6Cl_6S_2$: N, 11.46. Found: N, 11.6.

Fungicidal Test: The compounds were tested as fungicide on *Aspergillus niger* by taking the dry weight of mycelium at three different concentrations namely 1: 10000, 1: 1000 and 1: 100000.

The standard Czapek's solution was sterilized and 10 ml of this solution was distributed in each conical flask. The homogeneous suspension of fungus was prepared from fresh culture. One ml of culture suspension

Table V. 3-Arylaminomethyl-5-substituted-1,3,4-oxadiazole-2-thiones



IX

Ent. No.	R	R′	mp. (°C)	Formula	Analysis N% Calcd.	Found
1	2,4-dichlorophenoxymethyl	*p*-chlorophenylamino	135	$C_{16}H_{12}O_2N_3Cl_3S$	10.08	9.9
2	2,4-dichlorophenoxymethyl	2-pyridylamino	138	$C_{15}H_{12}O_2N_4Cl_2S$	14.62	14.4
3	2,4,5-trichlorophenoxymethyl	*p*-acetylphenylamino	145	$C_{18}H_{14}O_3N_3Cl_3S$	9.16	9.4
4	2,4,5-trichlorophenoxymethyl	diphenylamino	95	$C_{22}H_{16}O_2N_3Cl_3S$	8.53	8.2

Table VI. Antifungal and Seed Germination Activity

Ent. No.	Compound	Dry weight of mycelium[a] concentrations used (mg)				Seed germination activity: Germination percentage after 10 days at 100 ppm concentration	
		1:1000	1:10000	1:100000	Control	Seeds soaked in solution of chemicals for 24 hr	Seeds soaked in solvent for 24 hr (control)
1	1-D-acetyl-4-(*o*-)tolyl Th	225	250	308	400	5	96
2	1-D-acetyl-4-(*m*-)tolyl Th	215	260	305	400	10	96
3	1-D-acetyl-4-(*p*-)tolyl Th	210	290	305	400	20	96
4	1-D-acetyl-4-(*p*-) phenetyl Th	240	350	390	450	15	96
5	1-D-acetyl-4-(*p*-) iodophenyl Th	196	206	300	390	45	96
6	3-D-methyl-4-(*o*-) tolyl-5-mercapto T	210	240	260	380	00	96
7	3-D-methyl-4-(*m*-) tolyl-5-mercapto T	210	290	300	300	15	96
8	3-D-methyl-4-(*p*-) tolyl-5-mercapto T	230	300	305	350	20	96
9	3-D-methyl-4-(*p*-) tolyl-5-benzylthio T	250	360	400	450	30	96
10	3-D-methyl-4-(*p*-)tolyl-5-ethylthio T	180	210	350	400	25	96
11	3-(*p*-)chlorophenylamino-methyl-5-D-methyl-1,3,4-oxadiazole-2-thione	190	210	230	400	20	96
12	3-(α-)pyridylamino-methyl-5-D-1,3,4-oxadiazole-2-thione	210	250	350	450	15	96

D=2,4-dichlorophenoxy, Th=thiosemicarbazide, T=1,2,4-triazole.
a) No. of replications for each concentration=3

and 1 ml of test chemical (in acetone) of any one concentrations were transferred to each conical flask containing media. The conical flasks were incubated at 25±2° for 10 days. At the close of incubation period mycelial felt was filtered and dried at 100° overnight and weighed.

The blank experiments were performed in the similar way using culture, media and solvent (acetone) only. The results of this screening are recorded in Table VI. As it is evident from the results that some of the compounds (**5**, **10**, **11**, and **12**) exhibit a good fungicidal action.

Seed Germination Activity: The compounds screened as fungicides were also tested for seed germination activity on *Pisum-sativum* at 22.3° and 100 ppm concentration in diffused day light and their effects were observed. As it is clear from the data recorded in Table VI that compound **6** inhibited the germination completely whereas compound No. **9** showed 30% germination.

Acknowledgement The authors are thankful to Prof. R.P. Rastogi, Dean and Head, Chemistry Department, University of Gorakhpur for encouragement and Dr. Kamal, Department of Botany for fungicidal screening. Authors are also grateful to Shri B. Upadhyay, Reader and Head, Chemistry Department, S.C. College, Ballia for his assistance and Dr. J.R. Merchant, Institute of Science, Madam Cama Road, Bombay for micro-analyses.