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Synthesis and Fungicidal Activities of Some 2-Furano-3-[(5-aryloxy Methyl)-1,3,4-thiadiazo-2-yl]-thiazolidin-4-ones

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A series of new 2-furano-3-[5-aryloxy methyl)-1,3,4-thiadiazo-2-yl]-thiazolidin-4-ones (IIIa–f) have been synthesized. All the compounds have been screened for their activities against seven samples of fungi namely *Aspergillus niger*, *Aspergillus flavus*, *Mucor spp*, *Trichophyton Mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum* and *cryptococcus neoformans*.

INTRODUCTION

A thiazolidinone ring, by virtue of incorporating —N=C—S linkage and a cyclic >C=O function in five membered ring, is associated with diverse biological activities[1,2]. Similarly 1,3,4-thiadiazole derivatives are well known for their herbicidal[3], fungicidal[4] and bactericidal[5] activities. It has been shown that when a thiadiazole ring is coupled with another heterocyclic system, compounds of better biological activities are obtained[6+7]. With this view in mind and in continuation of our work on heterocyclic compounds[8,9], we undertook the coupling of 1,3,4-thiadiazole system with 4-thiazolidinone to get compounds of better biological activity. The presence of furan ring[10] at position 2 would be an additional factor to enhance their fungicidal activities.

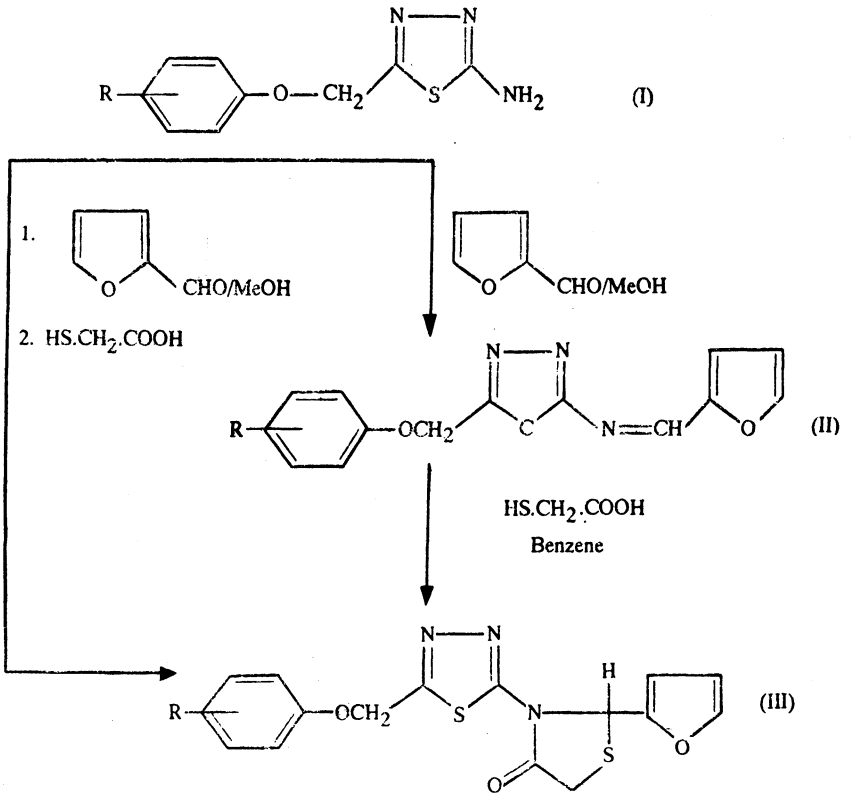
RESULTS AND DISCUSSION

The required 2-amino-5-aryloxy-methyl-1,3,4-thiadiazole (Ia–g) were prepared by the method of Maffii *et al*[11]. The title compounds (IIIa–f) were prepared by two methods.

Firstly, 2-amino thiadiazole and furfural were refluxed in methanol to give crystalline Schiff's base (IIa–f). This on cycloaddition reaction with mercapto acetic acid in methanol furnishes the desired product.

In another method the title compounds were prepared without the isolation of Schiff's bases. A mixture of 2-amino-1,3,4-thiadiazoles, aromatic aldehyde and mercapto acetic acid, in methanol were refluxed. The removal of solvent and treatment of residue with sodium bicarbonate gave the desired compound. The yield of the product (III) from this method was superior (80%) as compared to the first (60–65%). Hence all the compounds except one were prepared by latter method (Scheme I).

SCHEME I



The structural assignment of these products were based on elemental analysis and IR and PMR spectral data.

Fungicidal Activity*

The antifungal activity was determined against seven fungi namely *A. niger*, *A. flavus*, *Mucor spp.*, *T. mentagrophytes*, *T. rubrum*, *M. gypseum*, and *C. neoformans* at three different concentrations of 1.0, 0.1 and 0.01 mg/ml, following Horsefall and Rich[11] procedure with modifications[9]. All the compounds exhibited considerable antifungal activity except against *A. flavus*, *Mucor spp* and *cryptococcus spp.* Among all the compounds significant activity was exhibited by compounds numbers 5 and 6 on *A. niger*, 2 and 4 on *T. mentagrophytes*. All the compounds on *T. rubrum*, and 1, 2 and 5 on *M. gypseum*. It was observed that compounds 2 and 5 were active on 3 fungi and all the compounds were active on *T. rubrum*. Hence further screening of this compound on wider range of fungi as well as at more dilution is desirable.

*Details of the result can be obtained from the author on request.

Bactericidal Activity*

The antibacterial activity was determined by following the methods of Bauer *et al.*[12] against one strain each of *Staphylococcus aureus*, *Escherichia Coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Klebsiella pneumoniae* at 10 μg and 100 μg per disc concentrations. None of the compounds showed any notable activity.

EXPERIMENTAL

Procedure for one typical case for each step has been described. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer-157 spectrophotometer in KBr pellets (ν_{max} in cm^{-1}) and PMR in DMSO–d_6 on a Perkin-Elmer R–32 spectrometer at 90 MHz (chemical shifts in δ_{ppm} down field from TMS internal standard). The characterization data of the various compounds prepared are given in Table 1.

5-(2,4-Dichlorophenoxymethyl)-2-(Furylidenimino)-1,3,4-Thiadiazole(IIf)

A mixture of 2-amino-5 (2,4-dichlorophenoxymethyl)-1,3,4-thiadiazole (If; 0.01 mol) and furfuraldehyde (0.01 mol) in methanol was refluxed for 1½ hr. On coolling fine crystals separated out. It was recrystallised from ethanol to give IIf yield 74.2%, M.pt. 137°C (Found : C, 47.3; H, 2.5; N, 11.8). $C_{14}H_9H_3O_2SCl_2$ requires C, 47.4; H, 2.54; N, 11.8%; IR (KBr : 1690 (C=N), 1490 (C–H, aromatic), 1230 and 1020 cm^{-1} (C–O–C); PMR : 6.6–8.1 (m, 6H, aromatic and furan proton), 4.9 (s, 2H, $-OCH_2$) and 3.5 (s, 1H, N=CH).

Other compounds thus prepared are recorded in Table 1.

3-[5-(4-Methyl Phenoxymethyl)-2 Furano-1,3,4-Thiadiazo-2-yl]-Thiadiazolidin-4-Ones(III)

Method 1. 2 Furylidenimino-5-(4-methyl phenoxymethyl)-1,3,4-thiadiazole (0.01 M) and thioglycollic acid (0.011 M) was dissolved in methanol (60 ml) and the mixture was refluxed for 4 hrs. Excess methanol was evaporated and the solid mass neutralized with dilute sodium bicarbonate solution. The precipitate was filtered, washed and recrystallized with aq. methanol. Yield 62%, M.pt. 145°C (Found : C, 54.6; H, 3.9; N, 11.1, $C_{17}H_{15}N_3O_3S_2$ requires C, 54.7; H, 4.02; N, 11.3%).

Method 2. The same compound was prepared without isolating the Schiff base (II). A mixture of 2-amino-5-(2,4-dichlorophenoxymethyl)-1,3, 4-thiadiazole (0.01 M) and furfuraldehyde (0.01 M) and mercaptoacetic acid (0.011 M) in methanol (65 ml) was refluxed for 3–4 hrs. The solvent was removed and the residue was poured into water. It was neutralised with sodium bicarbonate solution. The solid mass was crystallised from aq. methanol. Yield 86%, M.pt. 145°C. (Found : C, 54.5; H, 3.8; N, 11.0 $C_{17}H_{15}N_3O_3S_2$ requires C, 54.7; H, 4.0; N, 11.3%).

TABLE 1

CHARACTERISATION DATA OF VARIOUS COMPOUNDS PREPARED

Compound	R	m.pt.	Yield	Mol Form.		Analysis %	
						Found	Calc.
IIa	2-Cl	169	76	$C_{14}H_{10}N_3O_2SCl$	C	52.3	52.6
					H	3.0	3.1
					N	13.0	13.1
IIb	4-Cl	131	70	$C_{14}H_{10}N_3O_2SCl$	C	52.4	52.6
					H	3.1	3.1
					N	13.0	13.1
IIc	2-CH_3	175	68	$C_{15}H_{13}N_3O_2S$	C	60.0	60.2
					H	4.2	4.3
					N	14.0	14.0
IId	4-CH_3	157	75	$C_{15}H_{13}N_3O_2S$	C	60.1	60.2
					H	4.2	4.3
					N	13.9	14.0
IIe	3-CH_3,4-Cl	178	72	$C_{15}H_{12}N_3O_2SCl$	C	53.8	53.9
					H	3.3	3.6
					N	12.4	12.6
IIf	2,4-diCl	137	74	$C_{14}H_9N_3O_2SCl_2$	C	47.3	47.4
					H	2.5	2.5
					N	11.8	11.9
IIIa	2-Cl	164	85	$C_{16}H_{12}N_3O_3S_2Cl$	C	48.6	48.8
					H	2.9	3.0
					N	10.4	10.6
IIIb	4-Cl	118	83	$C_{16}H_{12}N_3O_3S_2Cl$	C	48.6	48.8
					H	2.9	3.0
					N	10.5	10.7
IIIc	2-CH_3	163	88	$C_{17}H_{15}N_3O_3S_2$	C	54.5	54.7
					H	4.0	4.0
					N	11.1	11.2
IIId	4-CH_3	145	86	$C_{17}H_{15}N_3O_3S_2$	C	54.5	54.7
					H	3.8	4.0
					N	11.0	11.2
IIIe	3-CH_3,4-Cl	158	84	$C_{17}H_{14}N_3O_3S_2Cl$	C	50.1	50.0
					H	3.5	3.4
					N	10.2	10.3
IIIf	2,4-diCl	147	86	$C_{16}H_{10}N_3O_3S_2Cl_2$	C	44.7	44.8
					H	2.2	2.3
					N	9.7	9.8

The same compounds, prepared by abovetwo methods, have superimposible IR and PMR spectra which are as follows. IR (KBr) : 1710 (C=O), 1670 (C=N) 1230 and 1020 cm^{-1} (C–O–C); PMR : 6.9–7.3 (m, 7H, aromatic), 4.7 (s, 2H, $-OCH_2$), 4.1 (s, 2H, $C-\underset{\underset{O}{\|}}{C}H_2$), 3.6 (s, 1H, N–CH), 2.4 (s, 3H, $-CH_3$).

Other compounds prepared by this method are recorded in Table 1.

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