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Synthesis and Antifungal Activity of Some 2-Arylimino-3-Phthalimidoacetyl-4-Thiazolidinones and Their 5-Arylidine Derivatives

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Some 2-arylimino-3-phthalimidoacetyl-4-thiazolidinones and their 5-arylidine derivatives were synthesised and screened for their antifungal activity against *Fusarium moniliforme*, *Aspergillus flavus* and *Alternaria alternata*.

INTRODUCTION

A variety of N-substituted phthalimides[1-3] have been reported to possess promising fungicidal activity. On the other hand, thiazolidinone derivatives exhibit a variety of pharmacological activities[4-7]. The presence of –N–C–S linkage has been postulated to account for the antifungal activity of 4-thiazolidinones[8]. Attempts were made earlier to enhance the fungitoxicity of thiazolidinone derivatives by introducing different substituents either at 2-, 3-, or 5-position in the thiazolidinone ring[9-14]. On the basis of these observations the synthesis of 1-phthalimidoacetyl-3-aryl thiocarbamides (III) was undertaken, which on cyclisation with monochloroacetic acid were converted to 2-arylimino-3-phthalimidoacetyl-4-thiazolidinones (IV) and then to their corresponding 2-arylimino-3-phthalimidoacetyl-5-arylidino-4-thiazolidinones (V) by aldol condensation with aryl aldehydes. The steps involved in the synthesis are shown in Scheme 1.

All these compounds III, IV and V were screened for their antifungal activity against *Fusarium moniliforme*, *Aspergillus flavus* and *Alternaria alternata* as the test fungi.

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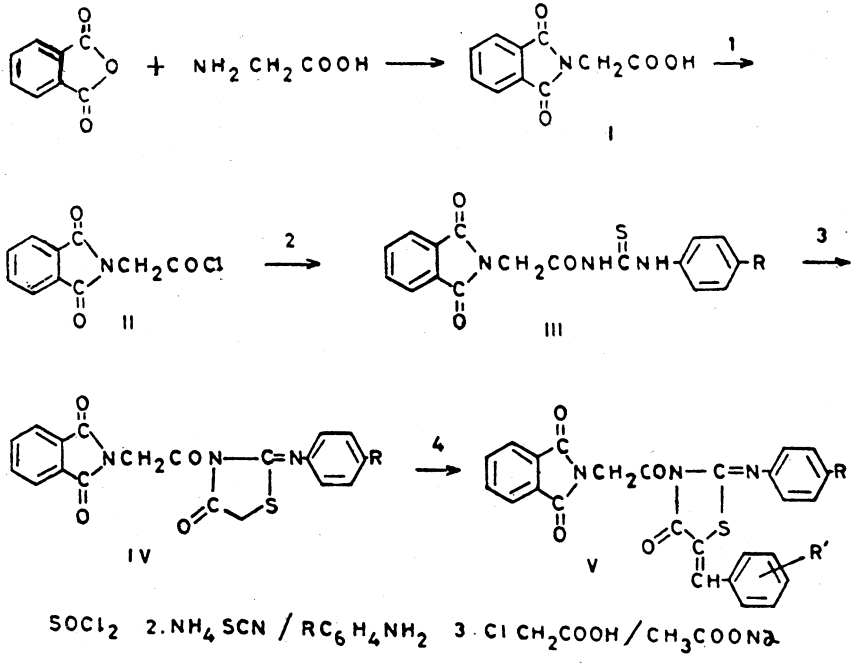
SCHEME 1



EXPERIMENTAL

Melting points were taken in open capillaries in sulphuric acid bath and are uncorrected. Infrared spectra in KBr pellets were recorded on a Perkin-Elmer spectrophotometer (ν_{max} in cm^{-1}) and pmr spectra on a 60 MHz EM-360 NMR spectrometer using TMS as internal standard. Phthalimidoacetic acid (I) and phthalimidoacetyl chloride (II) were prepared by the known procedures[15, 16].

1-Phthalimidoacetyl-3-aryl thiocarbamides (III):

A mixture of ammonium thiocyanate (0.11 mole) and acetone (50 ml) was placed in a flask and a solution of phthalimidoacetyl chloride (0.1 mole) in acetone (50 ml) was added through a dropping funnel with stirring. Arylamine (0.1 mole) in acetone (50 ml) was then added to the reaction mixture in small portions. When the addition was over, the reaction mixture was refluxed for 2 hr, cooled and poured into ice-cold water. The resulting precipitate was filtered, washed with water and crystallised from ethanol. Analytical and spectral data of these compounds are recorded in Table 1.

TABLE 1

ANALYTICAL AND SPECTRAL DATA OF 1-PHTHALIMIDOACETYL-3-ARYL THIOCARBAMIDES (III) AND 2-ARYLIMINO-3-PHTHALIMIDO-ACETYL-4-THIAZOLIDINONES (IV)

Compd. No.	R	M.P. °C	Yield %	Molecular formula	Analysis: Found/(Calculated)	
					N	S
IIIa	H	215	78	$C_{17}H_{13}N_3O_3S$	12.55 (12.39)	9.60 (9.44)
IIIb	CH_3	205	76	$C_{18}H_{15}N_3O_3S$	12.46 (11.89)	9.41 (9.06)
IIIc	OCH_3	180	75	$C_{18}H_{15}N_3O_4S$	11.25 (11.38)	8.50 (8.67)
IIId	Cl	197	72	$C_{17}H_{12}ClN_3O_3S$	11.46 (11.24)	9.00 (8.56)
IIIe	Br	201	70	$C_{17}H_{12}BrN_3O_3S$	10.30 (10.04)	7.48 (7.65)
IVa	H	195	66	$C_{19}H_{13}N_3O_4S$	11.40 (11.08)	8.62 (8.44)
IVb	CH_3	260	68	$C_{20}H_{15}N_3O_4S$	11.22 (10.68)	8.50 (8.14)
IVc	OCH_3	194	62	$C_{20}H_{15}N_3O_5S$	10.05 (10.26)	8.05 (7.82)
IVd	Cl	215	65	$C_{19}H_{12}ClN_3O_4S$	10.36 (10.15)	8.00 (7.73)
IVe	Br	220	63	$C_{19}H_{12}BrN_3O_4S$	9.52 (9.17)	7.20 (6.98)

IIIa: ν_{max}(KBr): 3200 (N–H, stretch), 1770, 1720 (C=O, endocyclic), 1700 (CONH), 1590 (C=C, aromatic), 1465, 1445 (C–N, stretch), 1410 (CH_2CO), 1320 (NHCSNH) and 760 (monosubstituted benzene ring) cm^{-1}

$\delta(CDCl_3)$: 4.55 (2H, s, NCH_2CO), 7.2–8.0 (9H, m, ArH), 9.6 (1H, s, $-CSNHC_6H_5$).

IVa: ν_{max}(KBr): 1770, 1720 (C=O, endocyclic), 1595 (C=C, aromatic), 1550, 1525 (C=N, stretch), 1410 (CH_2CO), 1320, 1250 (C–S–C, thiazolidinone), and 760 (monosubstituted benzene ring) cm^{-1}

$\delta(CDCl_3)$: 3.75 (2H, s, $-NCH_2CO$), 4.15 (3H, s, OCH_3), 4.9 (2H, s, $-CH_2-$) and 7.2–8.2 (8H, m, ArH).

TABLE 2
ANALYTICAL, SPECTRAL AND ANTIFUNGAL ACTIVITY DATA OF 2-ARYLIMINO-3-PHTHALIMIDOACETYL-5-ARYLIDINO-4-THIAZOLIDINONES (V)

Compd No.	R	R′	M.P. °C	Molecular formula*	Inhibition zone diameter† (mm) of fungi at concentrations (%, w/v)					
					FM		AF		AA	
					2.0	0.2	2.0	0.2	2.0	0.2
Va	H	H	178	$C_{26}H_{17}N_3O_4S$	—	—	—	—	—	—
Vb	H	p-NO_2	205	$C_{26}H_{16}N_4O_6S$	16	—	15	—	18	—
Vc	H	p-OCH_3	173–5	$C_{27}H_{19}N_3O_5S$	—	—	—	—	—	—
Vd	H	p-CH_3	202	$C_{27}H_{19}N_3O_4S$	—	—	—	—	—	—
Ve	H	o-OH	193	$C_{26}H_{17}N_3O_5S$	—	—	—	—	—	—
Vf	CH_3	H	215	$C_{27}H_{19}N_3O_4S$	—	—	—	—	—	—
Vg	CH_3	p-NO_2	178	$C_{27}H_{18}N_4O_6S$	19	—	16.5	—	21	—
Vh	CH_3	p-OCH_3	235	$C_{28}H_{21}N_3O_5S$	18	—	17	—	16.5	—
Vi	CH_3	p-CH_3	240	$C_{28}H_{21}N_3O_4S$	—	—	—	—	—	—
Vj	CH_3	o-OH	243	$C_{27}H_{19}N_3O_5S$	—	—	—	—	—	—
Vk	OCH_3	H	>250	$C_{27}H_{19}N_3O_5S$	—	—	—	—	—	—
Vl	OCH_3	p-NO_2	210	$C_{27}H_{18}N_4O_7S$	23	—	22.5	—	24	—
Vm	OCH_3	p-OCH_3	>250	$C_{28}H_{21}N_3O_6S$	18.5	—	17	—	19	—
Vn	OCH_3	p-CH_3	>250	$C_{28}H_{21}N_3O_5S$	16	—	18	—	16	—
Vo	OCH_3	o-OH	>250	$C_{27}H_{19}N_3O_6S$	—	—	—	—	—	—
Vp	Cl	H	212	$C_{26}H_{16}ClN_3O_4S$	—	—	—	—	—	—
Vq	Cl	p-NO_2	213	$C_{26}H_{15}ClN_4O_6S$	16.5	—	19	—	17	—
Vr	Cl	p-OCH_3	209	$C_{27}H_{18}ClN_3O_5S$	17	—	17.5	—	18.5	—
Vs	Cl	p-CH_3	219	$C_{27}H_{18}ClN_3O_4S$	—	—	—	—	—	—
Vt	Cl	o-OH	217	$C_{26}H_{16}ClN_3O_5S$	—	—	—	—	—	—
Vu	Br	H	228	$C_{26}H_{16}BrN_3O_4S$	—	—	—	—	—	—
Vv	Br	p-NO_2	206	$C_{26}H_{15}BrN_4O_6S$	22	—	26	—	24	—
Vw	Br	p-OCH_3	216	$C_{27}H_{16}BrN_3O_5S$	—	—	—	—	—	—
Vx	Br	p-CH_3	210	$C_{27}H_{18}BrN_3O_4S$	18	—	16	—	15	—
Vy	Br	o-OH	208	$C_{26}H_{16}BrN_3O_5S$	—	—	—	—	—	—
‡Thiram 75W					28	25	30	20	40	30

Vp: ν_{max}(KBr): 1770, 1700 (C=O, endocyclic), 1605, 1590 (C=C, aromatic), 1530 (C=N, stretch), 1425, 1405 (CH_2CO), 1345, 1240 (C-S-C, thiazolidinone), 835 (1,4-disubstituted benzene ring) and 725, 680 (monosubstituted benzene ring) cm^{-1}.

$\delta(CDCl_3)$: 4.7 (2H, s, NCH_2CO), 7.4–8.3 (14H, m, 13 ArH+ −C=CH).

*Analysis for C, H and N found within ±0.5%. The yields ranged from 43–52%.

†Three replicates averaged.

‡Reference fungicide.

— No inhibition.

Fm: *Fusarium moniliforme*; AF: *Aspergillus flavus*; AA: *Alternaria alternata*.

2-Arylimino-3-phthalimidoacetyl-4-thiazolidinones (IV):

A mixture of 1-phthalimidoacetyl-3-aryl thiocarbamide (0.01 mole), monochloroacetic acid (0.01 mole) and anhydrous sodium acetate (0.01 mole) was refluxed in glacial acetic acid (50 ml) for 6 hr. The reaction mixture was cooled, poured into ice-cold water and kept overnight. The precipitate thus obtained was filtered, dried and crystallised from acetic acid-water. Analytical and spectral data of these compounds are recorded in Table 1.

2-Arylimino-3-phthalimidoacetyl-5-arylidino-4-thiazolidinones (V):

A mixture of 2-arylimino-3-phthalimidoacetyl-4-thiazolidinone (0.01 mole), aryl aldehyde (0.01 mole) and anhydrous sodium acetate (0.01 mole) in glacial acetic acid (40 ml) was refluxed for 6 hr till a clear solution was obtained. The excess solvent was removed by distillation under reduced pressure and the residue obtained was washed with cold water, dried and crystallised from ethanol. Analytical and spectral data of these compounds are recorded in Table 2.

Screening for antifungal activity:

Compounds III, IV and V were screened for their antifungal activity against *Fusarium moniliforme*, *Aspergillus flavus* and *alternaria alternata* as the test fungi by paper-disc plate method[17] at concentration levels of 2 and 0.2% (w/v) in dimethylformamide. Standard PDA medium was used. Filter paper discs of diameter 12 mm were used and the diameter of zones of inhibitation formed around each disc after incubating for a period of 48 hr at 25–28°C were recorded. Results were compared with a reference fungicide, thiram 75W. Compounds III and IV were found to be completely inactive against all the test fungi. Antifungal activity of compounds V is recorded in Table 2.

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