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Fungitoxicity of 2-aryl, 7-alkyl/aryl-1,3,4-Thiadiazolo [3,2-a], [1,3,5]-Triazine Derivatives

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Abstract

Ten 2-aryl, 7-alkyl/aryl-5-hydro 1,3,4-thiadiazolo [3,2-a], [1,3,5]-triazine (IIIa-j), 2-aryl, 7-alkyl/aryl 1,3,4-thiadiazolo [3,2-a] [1,3,5]-triazine 5-ones (IVa-j) and their thiones (Va-j) each, have been synthesized by chemoselective cyclization of corresponding 2-amidino-5-aryl 1,3,4-thiadiazole (IIa-j) with HCHO/Toluene, ClCOOEt. and CS_2/KOH respectively. The required amidines (IIa-j) were prepared by reacting 2-amino, 5-aryl 1,3,4-thiadiazole (Ia-e) either by reaction of alkyl cynide or aryl cynide (R-CN). Above compounds were evaluated for fungitoxicity against two fungal species, viz. *Alternaria solanai* and *Puccinia graminia tritici* and the screening results correlated with structural features of the tested compounds.

Key words : *Alternaria solani*, *Puccinia graminis tritici*, Fungitoxicity, Agar Plate technique & spectral analysis.

Introduction

A number of 1,3,5-triazines are associated with a broad pesticidal activity. Various s-triazine derivatives have been patented as fungicides[1-2] bactercide[3], herbicides[4] and insectides[5-6]. 1,3,4-thiadiazole nucleus is also associated with useful pesticidal activity. The presence of >C=S group is also known to enhance the fungicidal activity of heterocyclic compounds[7-8]. In view of these facts efforts were made to combine the 1,3,4-thiadizole and 1,3,5 -triazine nuclei and to probe how far this combination could enhanced the fungicidal action.

Experimental

Synthesis : The reaction sequence leading to the formation of III-IV-V (a-j) is

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outlined in the Scheme-I. Melting points were taken in open glass capillaries and are uncorrected. IR spectra as KBr pellets were recorded on a Perkin-Elmer model 156 spectrophotometer and ^{1}H-NMR on Perkin Elmer R-34 spectrometer in $CDCl_3$ with tetramethyl silane (TMS) as internal standard. Chemical shifts are expressed in δ ppm.

2-Amino-5 aryl-1,3,4-thiadiazoles (Ia-e) :

These compounds were prepared by cyclodehydration of benzoyl thiosemicarbazide with conc. H_2SO_4 as follows method of Maffi *et al*[9]. N^1-benzoylthiosemicarbazide (10.5g, 0.05 ml) was treated with concentrated H_2SO_4 (10 ml.) with (below 15^0C). The reaction mixture was cooled and poured on crushed ice and neutralized with Ammonium hydroxide. The precipitated product was filtered washed with water and recrystallised from ethanol, m.p. 298-299^{0}C (reported m.p. 300^{0}C)[10], yield 6.5g (68%) of theory.

2-Amino-5-(4-chlorophenyl)-1,3,4-thiadiazole, m.p. 207^{0}C (reported m.p. 208^{0}C), yield 70% and 2-amino-5-(4-methyl phenoxy methyl)-1,3,4-thidiazole, m.p. 208^{0}C (reported m.p. 209^{0}C)[11], yield 71% were similarly prepared.

2-Amidino-5 aryl-1,3,4-thiadiazoles (IIa-j):

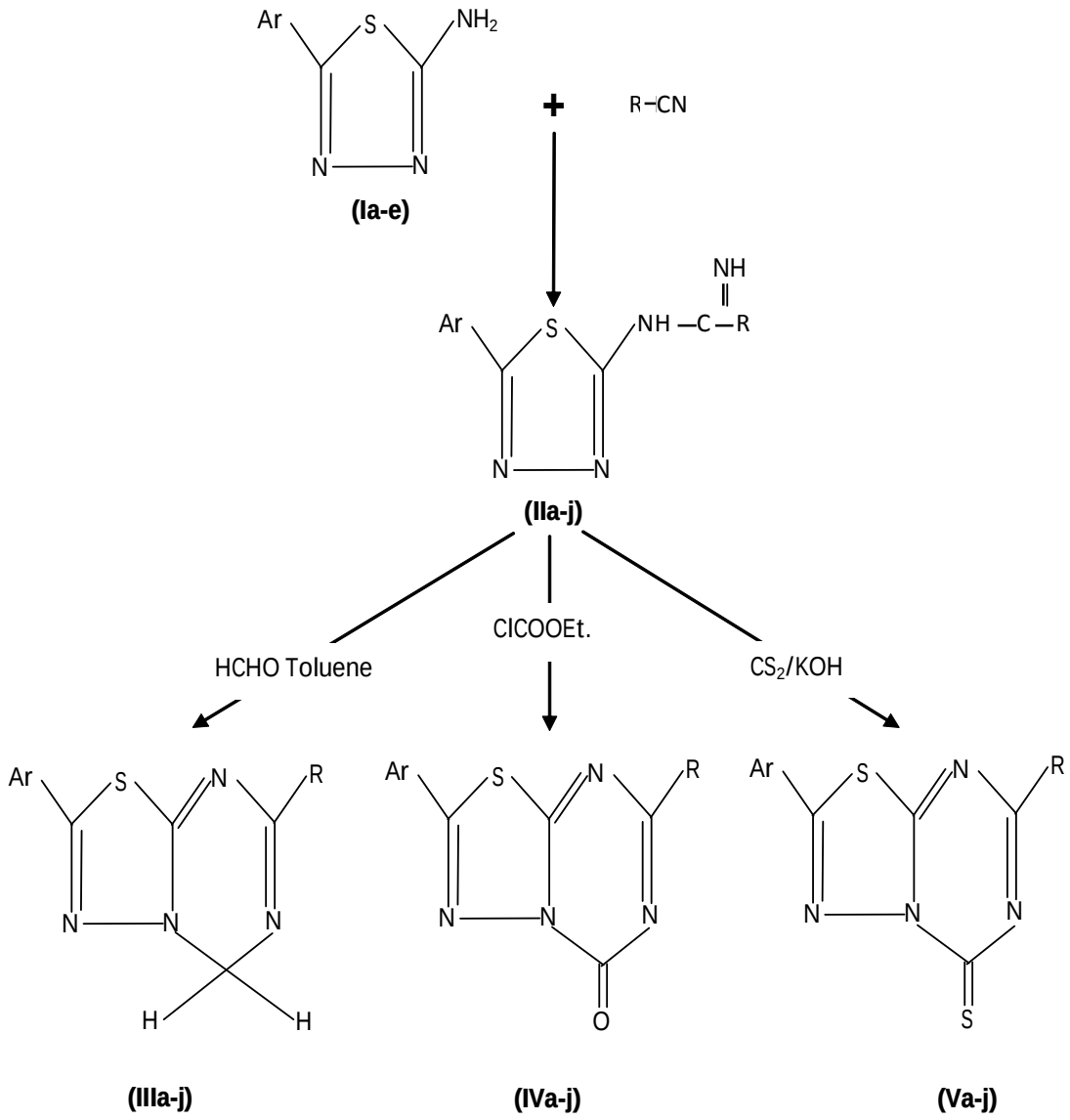
A mixture of 2-amino-5-aryl-1,3,4-thiadiazoles (0.01 mole) and alkyl or aryl cynide (1.0mole) was heated in an oil bath keeping the temperature (155^0-165^{0}C) for 2 hours, the content were cooled and then the product was decomposed using ice cold HCl acid. The residue was basified with aq. ammonia and filtered. The product was recrystallized from ethanol and the synthesized 2-amidino-5-aryl-1,3,4-thiadiazole were characterized (Table 1).

Table 1. Physicochemical properties of 2-amidino-5-aryl-1,3,4 thiadiazole (IIa-j)

Compd.	Ar.	R	Molecular Formula	M.P. (^{0}C)	Yield (%)	Analysis % Found (Calcd.)	
						N	S
IIa*	C_6H_5	CH_3	$C_{10}H_{10}N_4S$	152	75	25.63 (25.68)	14.64 (14.67)
b	4-$CH_3C_6H_4$	CH_3	$C_{11}H_{12}N_4S$	149	73	24.10 (24.13)	13.75 (13.79)
c	2-ClC_6H_4	CH_3	$C_{10}H_9ClN_4S$	146	74	22.14 (22.17)	12.64 (12.67)
d	4-ClC_6H_4	CH_3	$C_{10}H_9ClN_4S$	156	78	22.13 (22.17)	12.62 (12.67)
e	4-BrC_6H_4	CH_3	$C_{10}H_9BrN_4S$	188	84	18.83 (18.85)	10.75 (10.77)
f**	C_6H_5	C_6H_5	$C_{15}H_{12}N_4S$	154	72	19.94 (20.00)	11.41 (11.42)
g	4-$CH_3C_6H_4$	C_6H_5	$C_{16}H_{14}N_4S$	146	71	19.02 (19.04)	10.86 (10.88)
h	2-ClC_6H_4	C_6H_5	$C_{15}H_{11}ClN_4S$	148	77	17.76 (17.80)	10.14 (10.17)
i	4-ClC_6H_4	C_6H_5	$C_{15}H_{11}ClN_4S$	158	76	17.75 (17.80)	10.12 (10.17)
j	4-BrC_6H_4	C_6H_5	$C_{15}H_{11}BrN_4S$	186	80	15.57 (15.59)	08.90 (08.91)

* IR(KBr) : 1625 (Cyclic>C=N), 1665 (Exocyclic>C=N) Cm^{-1}

** IR(KBr) : 1620 (Cyclic>C=N), 1660 (Exocyclic>C=N) Cm^{-1}



Ar ; a = C_6H_5 , b = 4–$CH_3C_6H_4$, c = 2–ClC_6H_4 ,
d = 4–ClC_4H_4 , e = 4–BrC_6H_4
R = a–e = CH_3
Ar = f–j = C_6H_5

SCHEME – I

Table 2. Physicochemical properties of 2-aryl-7-alkyl/aryl-1,3,4-thiadiazolo [3,2-a] [1,3,5]-triazine-5-hydro, ones and their thiones (III, IV, Va-j)

Compd.	Ar.	R	Molecular Farmula	M.P. (^{0}C)	Yield (%)	IR	NMR
IIIa*	C_6H_5	CH_3	$C_{11}H_{10}N_4S$	208	66	* IR (KBr) : 1375 (C-H),	^{1}H-NMR ($CDCl_3$) δ : 2.1 (2H,s,>CH_2),
b	4-$CH_3C_6H_4$	CH_3	$C_{12}H_{12}N_4S$	218	72	1620 (Cyclic>C=N) Cm^{-1}	2.4 (2H,s,CH_3),
c	2-ClC_6H_4	CH_3	$C_{11}H_9ClN_4S$	214	76		6.00-7.20 (5H,m,Ar-H)
d	4-ClC_6H_4	CH_3	$C_{11}H_9ClN_4S$	190	80		
e	4-BrC_6H_4	CH_3	$C_{11}H_9BrN_4S$	225	78		
f**	C_6H_5	C_6H_5	$C_{16}H_{12}N_4S$	205	72	** IR (KBr) : 1380 (C-H),	^{1}H-NMR ($CDCl_3$) δ : 2.2 (2H,s,>CH_2),
g	4-$CH_3C_6H_4$	C_6H_5	$C_{17}H_{14}N_4S$	215	71	1625 (Cyclic>C=N) Cm^{-1}	6.20-7.50 (10H,m,Ar-H)
h	2-ClC_6H_4	C_6H_5	$C_{16}H_{11}ClN_4S$	208	68		
i	4-ClC_6H_4	C_6H_5	$C_{16}H_{11}ClN_4S$	245	75		
j	4-BrC_6H_4	C_6H_5	$C_{16}H_{11}BrN_4S$	232	68		
IVa***	C_6H_5	CH_3	$C_{11}H_8N_4OS$	189	72	*** IR (KBr) : 1700 (>C=O),	^{1}H-NMR ($CDCl_3$) δ : 2.3 (3H,s,CH_3),
b	4-$CH_3C_6H_4$	CH_3	$C_{12}H_{10}N_4OS$	205	71	1620 (Cyclic>C=N) Cm^{-1}	6.20-7.00 (5H,m,Ar-H)
c	2-ClC_6H_4	CH_3	$C_{11}H_7ClN_4OS$	208	68		
d	4-ClC_6H_4	CH_3	$C_{11}H_7ClN_4OS$	189	76		
e	4-BrC_6H_4	CH_3	$C_{11}H_7BrN_4OS$	202	71		
f****	C_6H_5	C_6H_5	$C_{16}H_{10}N_4OS$	211	62	**** IR (KBr) : 1700 (>C=O),	^{1}H-NMR ($CDCl_3$)δ:6.00-7.20 (10H,m,Ar-H)

g	4-$CH_3C_6H_4$	C_6H_5	$C_{17}H_{12}N_4OS$	209	67	1625 (Cyclic>C=N) Cm^{-1}	
h	2-ClC_6H_4	C_6H_5	$C_{16}H_9ClN_4OS$	188	76		
i	4-ClC_6H_4	C_6H_5	$C_{16}H_9ClN_4OS$	225	78		
j	4-BrC_6H_4	C_6H_5	$C_{16}H_9BrN_4OS$	238	88		
Va******	C_6H_5	CH_3	$C_{11}H_8N_4S_2$	236	76	****** IR (KBr) : 1055 (>C=S), 1625 (Cyclic>C=N) Cm^{-1}	^{1}H-NMR ($CDCl_3$) δ : 2.00 (3H,s,CH_3), 6.30-7.40 (5H,m,Ar-H)
b	4-$CH_3C_6H_4$	CH_3	$C_{12}H_{10}N_4S_2$	250	80		
c	2-ClC_6H_4	CH_3	$C_{11}H_7ClN_4S_2$	185	70		
d	4-ClC_6H_4	CH_3	$C_{11}H_7ClN_4S_2$	245	75		
e	4-BrC_6H_4	CH_3	$C_{11}H_7BrN_4S_2$	235	80		
f*******	C_6H_5	C_6H_5	$C_{16}H_{10}N_4S_2$	232	75	******* IR (KBr) : 1060 (>C=S), 1625 (Cyclic>C=N) Cm^{-1}	^{1}H-NMR ($CDCl_3$) δ : 6.10-7.50 (10H,m,Ar-H)
g	4-$CH_3C_6H_4$	C_6H_5	$C_{17}H_{12}N_4S_2$	242	73		
h	2-ClC_6H_4	C_6H_5	$C_{16}H_9ClN_4S_2$	250	78		
i	4-ClC_6H_4	C_6H_5	$C_{16}H_9ClN_4S_2$	248	72		
j	4-BrC_6H_4	C_6H_5	$C_{16}H_9BrN_4S_2$	244	80		

Note : Elemental analysis was in agreement with proposed molecular formula.

2-Aryl, 7-alkyl/aryl-5-hydro-1,3,4-thiadiazole [3,2-a], [1,3,5-]-triazines(IIIa-j):

An equimolar mixture of compound (II) and appropriate formaldehyde was refluxed for 4-6 hours in dry toluene and the solvent was distilled off under reduce pressure. The residue was washed with small amount of ethanol followed by ice water, and the product was recrystallized from ethanol as shining yellowish needles, yields, melting points, molecular formula and spectral data of these compounds (IIIa-j) thus synthesized are recorded in (Table 2).

2-Aryl, 7-alkyl/aryl-1,3,4-thiadiazolo [3,2-a] [1,3,5]-triazine-5-ones (IVa-j):

A solution of 2-amidine-5-aryl-1,3,4-thiadiazole (0.1 mole) in pyridine (42 ml) was added ethyl chloroformate in an ice bath. The reaction mixture was is tired at room temperature for 3 hours, then refluxed for 1 hours. The contains were heated with 1-N KOH (40 ml.) and thus product precipitated out and recrystallized from ethanol. The physicochemical properties of these compounds are reported in Table 2.

2-Aryl, 7-alkyl/aryl-1,3,4-thiadiazalo[3,2-a][1,3,5]-triazine-5-thiones (Va-j):

A mixture of compound (II) (0.01mole) ethanol (40 ml) KOH (0.2 mole) and carbondisulphide (2.0 gm.) (0.2 mole) was refluxed for 6 hours and concentrated to a small volume. The contains were poured into ice cold water and acidify with dil. HCl to give the desire product which was recrystallized from ethanol. These compounds are reported in Table 2 with their characterization data.

Fungicidal Activity :

Test fungi *Alternaria Solani* and *Puccinia graminis tritici* were obtained from the division of mycology and plant pathology. Indian Agricultural Research Institute, Delhi and maintained on agar. Compounds (IIIa-j), (IVa-j) and (Va-j) were screened in vitro by agar-plate technique[12], using Czapek's agar medium against *A. Solani* and *P. graminis tritici* at different concentrations (1000, 100 and 10 ppm) Indofil M-45, a Commercial fungicide was also tested under similar conditions for comparing the results.

Result and Discussion

The titled compounds (**III, IV** and **Va-j**) have been synthesized by the chemo selective heterocyclisation of **IIa-j** with HCHO/Toluene, ClCOOEt, and CS_2/KOH respectively. The structure of compound **IIIa-j** are based on their elemental analysis and IR spectra (1375 and 1620 cm^{-1} attributed to >C-H and cyclic C=N, respectively). Compounds **IVa-j** were also characterized by their elemental analysis and IR spectra (1700 and 1625 cm^{-1} attributed to >C=O and cyclic C=N, respectively). And the compounds **Va-j** are based on their elemental analysis and IR spectra (1060 and 1625 cm^{-1} attributed to > C=S and cyclic C=N, respectively). Results of the fungicidal activity are summarized in Table 3. It is evident from the data that most of the compounds were significantly toxic to both the test fungi at 1000 ppm but their toxicity decreased considerably at lower concentrations (100 and 10 ppm).

Table 3. Fungitoxicity of 2-aryl-7-alkyl/aryl [1,3,4]-thiadiazolo [3,2-a] [1,3,5]-triazine- 5-hydro, ones and their thiones.

Compd.	Average inhibition (%)					
	A. Solani Dose (ppm)			*P. graminis tritici* Dose (ppm)		
	1000	100	10	1000	100	10
IIIa	60	30	11	59	28	12
b	62	32	13	64	34	16
c	98	62	45	99	63	46
d	97	32	44	98	62	45
e	65	36	18	68	36	16
f	67	35	20	70	35	17
g	68	38	19	69	31	19
h	66	37	17	63	30	20
i	70	33	15	61	33	23
j	69	40	12	69	29	21
IVa	70	42	24	70	39	25
b	78	46	30	74	46	26
c	95	45	29	88	49	27
d	93	41	33	92	52	29
e	89	48	38	75	56	30
f	76	51	35	78	58	36
g	85	58	36	80	60	39
h	77	56	39	83	64	40
i	82	44	40	82	63	44
j	83	45	43	86	67	46
Va	86	58	51	88	72	49
b	88	54	39	78	76	52
c	98	66	44	96	59	50
d	94	64	48	93	65	58
e	79	68	54	88	74	62
f	88	72	58	87	78	66
g	87	75	60	92	67	61
h	98	68	56	98	79	58
i	94	63	52	86	68	67
j	89	76	46	89	76	47
Indofil M-45	100	82	67	100	85	70

Conclusion

Although the compounds IIIc, IIId and Vc exhibited fungicidal activity of the order of Indofil M-45 at 1000 ppm and inhibited 44-50% growth of both the fungal species even at 10 ppm, the over all results are not so encouraging as one would expect from the combined performance of the fused biolabile nuclei *i.e.* 1,3,4-thiadiazole with 1,3,5-triazine. This might be attributed to the partial saturation in the triazine and thiadiazole nucleus, resulting in the loss of planarity of the thiadiazole and 1,3,5 - triazine ring system. It is however, note worthy that the introduction of chloro and methyl group in the phenyl moiety of these compounds tend to increase the fungitoxicity and that introduction of 2-chloro group increased the activity than 4-chlorogroup. Fungicidal activity varied marginally with the fungal species.

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