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SYNTHESIS OF 2-SUBSTITUTED-1, 3, 4-THIADIAZOLO (2, 3-b)-6, 7-DIALKYLTHIENO [3, 2-e]-PYRIMIDINE-5-(4H)-ONES AS POTENTIAL FUNGICIDES

R.M. MISHRA

Department of Chemistry, Harishchandra Post Graduate College, Maidagin, Varanasi-221001 (U.P.), India

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2-Substituted-1,3,4-thiadiazolo (2,3-b)-6,7-dialkylthieno [3,2-e]-pyrimidine -5-(4H)-ones (IVa-l) have been synthesized by treating 2-amino-3-carbethoxy-4,3-dialkyl thiophene (Ia-b) with carbonisulphide and dimethyl sulphate in diimethyl sulphoxide to give mthyl N-(3-carbethoxy-4,5-dimethyl thienyl)-dithiocarbamate (IIa-b). Which on refluxing with hydrazinehydrate in ethanol yielded corresponding 3-amino-2-mercapto-5,6-dimethylthieno [2,3-d] pyrimidine-4-(3H)-ones (IIIa-b). Which in turn were treated with suitable isothiocynates and a pinch of anhydrous potassium carbonate in DMF solvent to yield the title compounds (IVa-l). The structure of the synthesized compound have been established on the basis of elemental analysis, molecular formula, IR spectra and ^{1}H-NMR spectra data. Fungicidal activity was evaluated against *Helminthosporium oryzae* and *Phytophthora infestans*. Screening data have been correlated with the structural feature of the tested compounds.

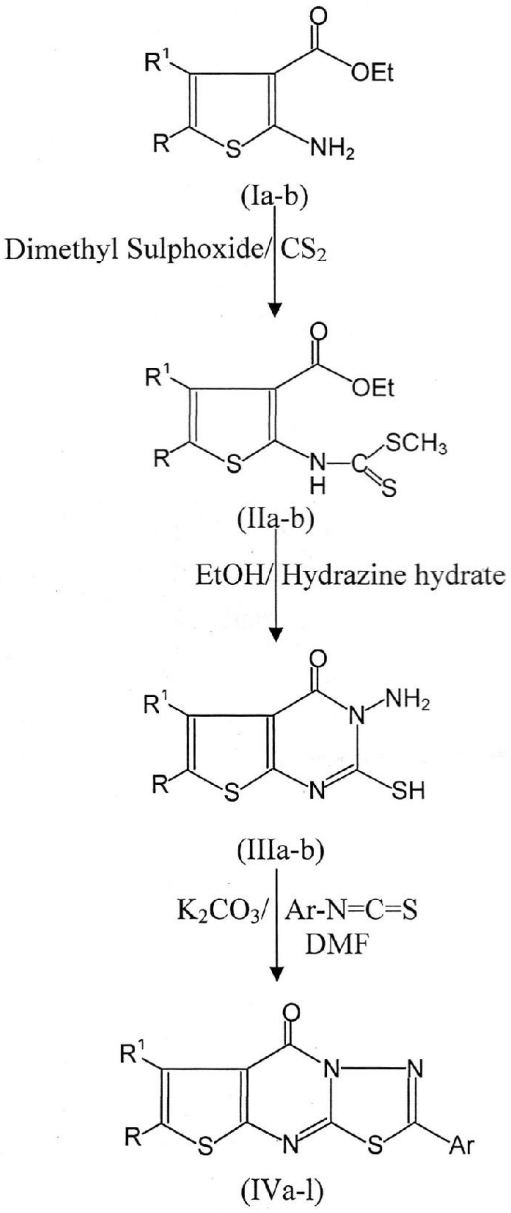
KEY WORDS : Thiadiazoles, Dithane M-45, hydrazinehydrate.

INTRODUCTION

1, 3, 4-Thiadiazole nucleus is associated with a broad spectrum of biocidal activity for *e.g.* fungicides [1, 2], insecticides [3, 4], bactericides [5, 6] and herbicides [7, 8]. Possibly by virtue of incorporating $>N-\underset{|}{\overset{|}{C}}-S-$ moiety. The toxophoric importance of which has been well stressed in many pesticides [9, 10]. The pyrimidines are of great importance in fundamental metabolism for uracil, thiamine and cytosine are three of the six bases found in the nuclueotide [11]. Similarly pesticidal activities [12-15]. Therefore in continuation of our research work on synthesis of fungicidal heterocyclic compounds I have fused the biolabile nuclei 1, 3, 4-oxadiazole & pyrimidines nucleus to prove how for this combination enhanced the fungicidal action. The reaction sequence leading to the formation of title compound is given in the Scheme-I and fungicidal screening data are given in the experimental section.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. The IR Spectra in KBr were recorded either on Perkin-Elmer 157 or Hitachi 295 Infrared spectrophotometer. ^{1}HNMR spectra were recorded on a EM 360L (60MHz) NMR spectrometer in $CDCl_3$ or $DMSOd_6$ with TMS as internal reference. Chemical shifts are expressed in δ ppm.



R : (a-f) = CH_3; (g-l) = C_2H_5

R^1 : (a-l) = CH_3

Ar : (a, g) = – NH (4-$OCH_3C_6H_4$; (b,h) = CH_3;

(c, i) = – CH_2-CH_2-CH_3; (d,j) = –$NHCH_3$;

(e, k) = – $NHCH_2$-CH=CH_2; (f,l) = –NHC_6H_5

(i) Methyl N-(3-carbethoxy-4, 5-dimethylthienyl)-dithiocarbamate (II*a-b*).

To a vigorously stirred solution of 2-amino-3-carbe-thoxy-4, 5-dimethyl thiophene (4.18 g, 0.02 mol) in dimethyl sulphoxide (10 ml) at room temperature, carbon disulphide (1.98 g, 0.26 mol) were added dropwise. After 30 minute dimethyl sulphate (2.5 g, 0.02 mol) was added dropwise under cooling in on ice bath. Stirring was continued for 3 hours and then the reaction mixture was poured in ice water. The precipitated product was filtered, dried and recrystalized from ethanol (95%).

M.P. 110°C; Yield 3.5 gm (89% of theory)

Analysis : Found C, 45.66; H, 5.20; N, 4.83; S, 33.22

Molecular formula ($C_{11}H_{15}NS_3O_2$)

Requires : C, 45.67; H, 5.19; N, 4.84; S, 33.21%

IR (KBr) : 3200 (NH), 1680 (>C=O), 1060 (>C=S) cm^{-1}

^{1}HNMR ($CDCl_3$) δ : 1.95 (3H, 1,2-$COOCH_2CH_3$), 2.20 (3H, s, 4-CH_3)

2.30 (3H, s, 6-CH_3), 4.20 (2H, q, 2-$COOCH_2CH_3$)

4.30 (3H, s, 1-CH_3), 7.00 (1H, s, 1-$NHCSSCH_3$)

Similarly, Methyl N-(3-carbethoxy-5-ethyl-4-methyl thienyldithiocarbamate were prepared and recrystallized from ethanol.

M.P. 112°C; Yield 3.9 gm (90% of theory)

Analysis : Found C, 47.54; H, 5.62; N, 4.61; S, 31.67

Molecular formula ($C_{12}H_{17}NS_3O_2$)

Requires : C, 47.52; H 5.61; N, 4.62; S, 31.68%

IR (KBr) : 3250 (NH), 1660 (>C=O), 1050 (>C=S) cm^{-1}

^{1}NHMR ($CDCl_3$) δ : 1.82 (3H, 1, 2-$COOCH_2CH_3$), 2.30 (3H, s, 4-CH_3)

2.40 (3H, s, 6-CH_3), 4.30 (2H, q, 2-$COOCH_2CH_3$)

4.20 (3H, s, 1-CH_3), 7.20 (1H, s, 1-$NHCSSCH_3$)

(ii) 3-Amino-2-mercapto-5, 6-dimethylthieno (2, 3-d)-pyrimidine-4-(3H)-one (III*a-b*).

A solution of methyl-N-(3-carbethoxy-4,5-dimethyl-thienyl dithio-carbamate (3.15g, 0.01 mol) in ethanol 30 ml (95%) was treated with hydrazine hydrate (4.3g, 0.1 mol) and refluxed on a water bath until the methyl mercaptan evolution ceased (6 hours). After cooling the solid obtained was filtered, dried and recrystalized from ethanol (95%) acetone mixture.

M.P. 269°C; Yield 2.4 gm (80% of theory)

Analysis : Found C, 42.30; H, 3.97; S, 28.20; N, 18.51

Molecular formula ($C_8H_9S_2N_3O$)

Requires : C, 42.29; H, 3.96; S, 28.19; N, 18.50%.

IR (KBr) : 3330, 3240 (NH_2), 1680 (>C=O) cm^{-1}

^{1}HNMR (DMSO-d_6) δ : 2.12(3H, s, 5-CH_3), 2.19 (3H, s, 6-CH_3)

3.10 (1H, s, 2-SH), 5.20 (2H, s, 3-NH_2)

Similarly 3-amino-2-mercapto-6-ethyl-5-methylthieno (2, 3-d)-pyrimidine-4-(3H)-one was prepared & recrystallized from ethanol.

M.P. 2710C; Yield 2.8 gm (82% of theory)

Analysis : Found C, 44.82; H, 4.58; S, 26.53; N, 17.43;

Molecular formula ($C_9H_{11}S_2N_3O$)

Requires: C, 44.81; H, 4.56; O, 6.63; S, 26.55; N, 17.42

IR (KBr) : 3350, 3260 (NH_2), 1660 (>C=O) cm^{-1}

^{1}HNMR (DMSO-d_6) δ : 2.14 (3H, s, 5-CH_3), 2.20 (3H, s, 6-CH_3),

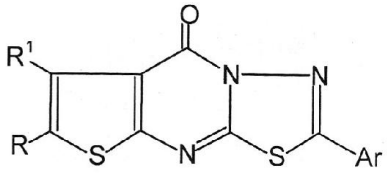
3.14 (1H, s, 2-SH), 5.23 (2H, s, 3-NH_2)

(iii) 2-Substituted-1, 3, 4-thiadiazolo (2, 3-b)-6, 7-dialkylthieno [3, 2-e]-pyrimidine -5-(4H)-ones (IV*a-l*).

A mixture of 3-amino-2-mercapto-5, 6-alkylthieno (2, 3-d)- pyrimidine-4-(3H)-ones (0.02 mol) and a pinch of potassium carbonate (anhydrous) and suitable isothiocynate (0.02 mol) in DMF (20 mol) was refluxed in oil bath maintaining the temperature at 150°C for 36 hours. The solvent was removed by distillation under reduced pressure. The solid was obtained and recrystallized from ethanol (99%).

Similarly following other title compounds were prepared and recorded in the **Table-1** with their characterization data, M.P., yield, elemental analysis, IR and ^{1}HNMR spectral data.

Table 1. Characterization data of 2-substituted-1, 3, 4-thiadiazolo (2, 3-b)-6, 7-dialkylthieno [3, 2-e]-pyrimidine-5(4H)-ones (IV*a-l*).



Comp. No.	R	R^1	Ar	Molecular formula	M.P. (°C)	Yield (%)	Analysis Found (Calculated)%		
							C	N	S
a*	CH_3	CH_3	-NH(4-$OCH_3C_6H_4$)	$C_{16}H_{14}N_4O_2S_2$	235-237	66	53.65 (53.63)	15.62 (15.64)	17.90 (17.87)
b	CH_3	CH_3	-CH_3	$C_{10}H_9N_3OS_2$	194-196	80	47.82 (47.80)	16.71 (16.73)	25.51 (25.49)
c	CH_3	CH_3	-CH_2-CH_2-CH_3	$C_{12}H_{13}N_3OS_2$	165	88	51.63 (51.61)	15.15 (15.05)	22.95 (22.93)
d	CH_3	CH_3	-$NHCH_3$	$C_{10}H_{10}N_4OS_2$	250	40	45.15 (45.11)	21.01 (21.05)	24.10 (24.06)
e**	CH_3	CH_3	-NH-CH_2-CH=CH_2	$C_{12}H_{12}N_4OS_2$	255-257	62	49.33 (49.31)	19.19 (19.17)	21.93 (21.91)
f	CH_3	CH_3	-NHC_6H_5	$C_{15}H_{12}N_4OS_2$	300	73	60.64 (60.61)	18.89 (18.91)	21.63 (21.62)
g	C_2H_5	CH_3	-NH(4-$OCH_3C_6H_4$)	$C_{17}H_{16}N_4O_2S_2$	238-240	68	54.85 (54.83)	15.08 (15.05)	17.22 (17.20)
h	C_2H_5	CH_3	-CH_3	$C_{11}H_{11}N_3OS_2$	196-198	82	49.84	15.83	24.16

Comp. No.	R	R^1	Ar	Molecular formula	M.P. (°C)	Yield (%)	Analysis Found (Calculated)%		
							C	N	S
							(49.81)	(15.84)	(24.15)
i	C_2H_5	CH_3	$-CH_2-CH_2-CH_3$	$C_{13}H_{15}N_3OS_2$	168	86	53.25 (53.24)	14.35 (14.33)	21.86 (21.84)
j	C_2H_5	CH_3	$-NHCH_3$	$C_{11}H_{12}N_4OS_2$	258-260	41	47.16 (47.14)	20.05 (20.00)	22.86 (22.85)
k	C_2H_5	CH_3	$-NH-CH_2-CH=CH_2$	$C_{13}H_{14}N_4OS_2$	257-259	64	51.33 (51.31)	18.31 (18.30)	20.89 (20.91)
l	C_2H_5	CH_3	$-NHC_6H_5$	$C_{16}H_{14}N_4OS_2$	302	70	57.29 (57.30)	16.38 (16.37)	18.72 (18.71)

* IR (KBr) : 3280 (NH); 1700 (>C=O); 1610 (cyclic C=N) cm^{-1}

^{1}HNMR ($CDCl_3$) δ : 1.30 (6H, s, CH_3), 3.62 (3H, s, OCH_3), 4.00 (1H, s, NH), 7.00 – 8.00 (4H, m, Ar-H)

** IR (KBr) : 3260 (NH); 1690 (>C=O); 1615 (cyclic C=N) cm^{-1}

^{1}HNMR ($CDCl_3$) δ : 1.40 (6H, s, CH_3), 2.10 (5H, m, CH_2–$CH=CH_2$), 4.10 (1H, s, NH)

Fungicidal Activity

The fungicidal activity of such 12 compounds (IV*a-l*) were evaluated against *Helminthosporium oryzae* and *Phytophthora infestans* at 1000, 100 & 10 ppm concentration following the Agar Plate Technique [16] and the results are summarized in **Table-2**.

Table 2. Fungicidal screening data of 2-substituted-1, 3, 4-thiadiazolo [2, 3-b]-6, 7-dialkylthieno [3, 2-e]-pyrimidine-5-(4H)-ones (IVa-l).

Compd. No.	Average % inhibition against.					
	Helminthosporium oryzae at			Phytophthora infestans at		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
IVa	98	65	35	97	62	32
b	92	58	31	90	56	34
c	94	60	38	92	58	35
d	88	55	32	86	52	30
e	96	52	35	94	55	38
f	95	53	30	93	55	32
g	96	51	32	95	53	33
h	91	56	30	90	54	31
i	95	61	40	93	57	34
j	86	52	29	85	50	32
k	94	48	28	92	47	29
l	91	45	27	90	44	28
Dithane M-45	100	81	67	100	82	66

Results and discussion

Survey of screening data clearly indicates that all the screened compounds inhibited the growth of both the fungal species *Phytophthora infestans* and *Helminthosporium oryzae* to some extent. Therefore they are fungicides. All the tested compounds are more active at 1000 ppm concentration but their toxicity decreased considerably at lower concentrations (100, 10 ppm). Out of these compounds IV*a;*, IV*e* & IV*g* exhibited fungitoxicity nearly the order of **Dithane M-45** at 1000 ppm against both the test fungi, and also inhibited the mycelial growth of both the test fungi up to 32-38% even at 10 ppm concentration.

Conclusions

The comparison of antifungal activity of the title compounds IV*a-l* with their precursors clearly shows that the former incorporating different toxophoric groups are more active. The screening data **(Table-2)** clearly indicates that there was significant alteration in the fungitoxicity with the change of the toxophoric group. For example 4-methoxyphenylamino and alylamino group were more toxic than the aminophenyl, methyl, aminomethyl and propyl group, overall results are not show encouraging as one would aspect from the title compounds.

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