Ultra Chemistry Vol. 8(2), 211-217 (2012).

Synthesis and fungitoxicity of 1,3,4-Oxadiazolo [3,2-a] -s-triazine-5,7-diones and their thione analogues

ATMA RAM MISHRA, PRINCE KUMAR RAI* and CHHAVI RAJ SINGH

Department of Chemistry, Shri Durga Ji Post Graduate College, Chandeshwar, Azamgarh, U.P. (INDIA)

(Acceptance Date 15th May, 2012)

Abstract

1,3,4-oxadiazolo [3,2-a]-s-triazine-5-7-diones (Va-l) and their thione (VIa-l) were synthesized from their corresponding N^1-(5-aryl-1,3,4-oxadiazolo-2,-yl)-N^3-(4-substituted phenyl) ureas (IVa-l) by cyclising with ethyl chloro formate and carbon disulphide respectively. Requisite N^1-(5-aryl-1,3,4-oxadiozol-2yl)-N^3-(4-subsituted phenyl) ureas were obtained from ethyl-N-(5-aryl-1,3,4-oxadiazole-2yl) carbamate (IIIa-d) by treating it with aromatic amine in ethanol solution. Ethyl-N-5-aryl-1,3,4-oxadizole-2yl) carbamate (IIIa-d) were prepared from starting material 2-amino-5-aryl-1,3,4-oxadiazoles as shown in scheme-I. Fungitoxicity of the synthesise compounds were evaluated for their fungitoxicity against *Helminsthosporium oryzae* and *Phytophtora infestans*. Structure, activity, relationship of the different substituents on phenyl ring with antifungal activity have been discussed.

Key words: Dithane M-45, oxadiazole, Triazine, *Helminthosporium oryzae* and *Phytophtora infestans*.

Introduction

A number of condensed ring system incorporating 1,3,4-oxadiazole nucleus is reported as potential fungicides[1-3], bactericides[4,5], herbicides[6] and antimicrobial activity[7-9]. Triazing ring is also associated with various pesticidal activities[10-13]. In continuous of our works on heterocyclic pesticides and perusal of the above reports we have synthesized the title compounds 1,3,4-oxadiazole [3,2-a]-s-triazine-5,7-diones and their thiones analogues which have both the biolabile nuclei i.e. 1,3,4-oxadiazole and s-triazine which might be fungicides of enhanced potency.

Corresponding Author Address-Vaishno Nagar Colony, P.O. Bramhasthan Sadar, Distt.-Azamgarh (U.P.)

Experimental

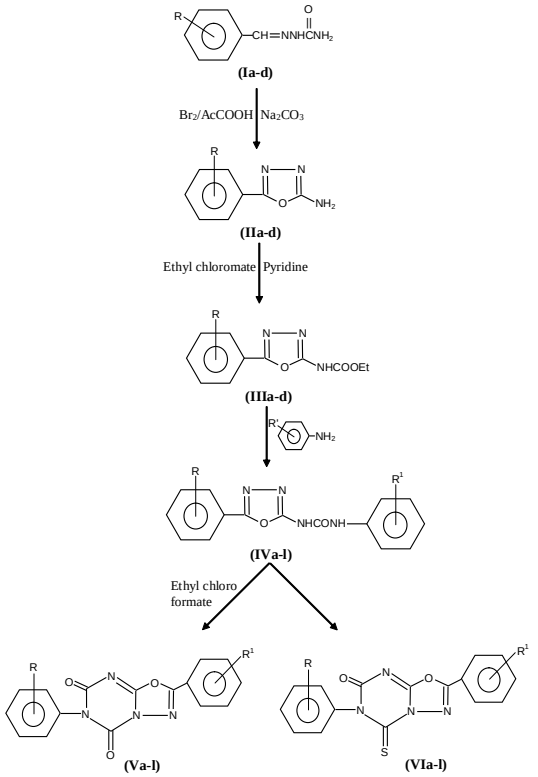
Melting points were determined in open capillaries and are uncorrected. The IR spectra in KBr were recorded on a Jesco FT/ IR-460 Fourier Transform infrared spectrometer. ^{1}HNMR spectra were scanned on a bruker ultraspec 500 MHz/AMX 400 MHz spectrometer using DMSO-d_6 as solvent. Chemical shift are expressed in δ ppm.

(i) 2-Amino-5-substituted aryl-1,3,4-thiadiazoles (IIa-d) :

This was prepared by oxidative cyclisation of semicarbazone of appropriate aromatic aldehyde following the method of Gibson[14]. Thus, bromine (0.1 mol) in glacial acetic acid (15 ml) was added slowly to stirred slurry of semicabazone (0.1 mol) and powedered anhydrous sodium acetate 40g in glacial acetic acid (120 ml). The solids dissolved giving in red solution after 15 minutes, it was poured into water and recrystallized from ethanol.

According to above procedure following 2-amino-5-substituted aryl-1,3,4-oxadiazole were synthesized.

(a) 2-Amino-5-phenyl-1,3,4-oxadiazole, M.P. 240^{0}C, (reported[14] M.P. 243^{0}C) Yield 88% of theory.
(b) 2-Amino-5-(4-chlorophenyl)-1,3,4-oxadiazole, M.P. 273^{0}C, (reported[15] M.P. 274^{0}C) Yield 85% of theory.
(c) 2-Amino-5-(4-methoxyphenyl)-1,3-4-thiadiazole M.P. 247^{0}C, (reported[15] M.P. 249^{0}C) Yield 82% of theory.
(d) 2-Amino-5-(2-methoxylphenyl)-1,3,4-oxadiazole, M.P. 176^{0}C (reported[15] M.P. 178^{0}C) Yield 80% of theory.



(I to VI) R ; a=H, b=4-Cl, c=4-OCH_3, d=2-OCH_3

(IV to VI) R^1 ; a=H, b=4-Cl, c=2-Cl

(Scheme-I)

(ii) Ethyl-N-(5-substituted aryl-1,3,4-oxadiazoles-2yl) carbamate (IIIa-d) :

A solution of 2-amino-5-substituted-aryl-1,3,4-oxadizole (0.04 ml) in pyridine (160 ml) was added ethyl chloroformate (0.044 mol) and triethylamine (10 ml) and the mixture was refluxed for 1 hour. It was poured into dil. hydrochloric acid and the carbamate, thus obtained was recrystallized from ethanol.

According to above procedure following

Table 1. Characterization data of N^1-(5-substituted aryl-1,3,4-oxadiazole-2yl)-N^3 (4-substituted phenyl) ureas (IVa-l).

Comp. No.	R	R^1	Molecular Formula	M.P. (^{0}C)	Yield (%)	Analysis Found (Calculated %)		
						C	N	S
IVa*	H	H	$C_{15}H_{12}N_4O$	224	61	68.03 (68.18)	4.20 (4.50)	21.32 (21.21)
b	4-Cl	H	$C_{15}H_{11}N_4OCl$	229	60	64.12 (60.40)	3.52 (3.69)	18.65 (18.79)
c	4-OCH_3	H	$C_{16}H_{14}N_4O_2$	250	62	65.54 (65.30)	4.34 (4.76)	19.21 (19.04)
d	2-OCH_3	H	$C_{16}H_{14}N_4O_2$	248	66	65.45 (65.30)	4.14 (4.76)	19.31 (19.04)
e	H	4-Cl	$C_{15}H_{11}N_4OCl$	226	64	60.22 (60.40)	3.51 (3.69)	18.80 (18.79)
f**	4-Cl	4-Cl	$C_{15}H_{10}N_4OCl_2$	230	65	54.16 (54.21)	3.21 (3.01)	16.56 (16.86)
g	4-OCH_3	4-Cl	$C_{16}H_{13}N_4O_2Cl$	248	66	58.61 (58.53)	3.90 (3.96)	17.01 (17.07)
h	2-OCH_3	4-Cl	$C_{16}H_{13}N_4O_2Cl$	246	68	58.42 (58.53)	3.86 (3.96)	17.21 (17.07)
i	H	2-Cl	$C_{15}H_{11}N_4OCl$	222	64	60.42 (60.40)	3.56 (3.69)	18.56 (18.79)
j	4-Cl	2-Cl	$C_{15}H_{10}N_4OCl_2$	228	68	54.31 (54.21)	3.21 (3.01)	11.61 (16.86)
k	4-OCH_3	2-Cl	$C_{16}H_{13}N_4O_2Cl$	248	66	58.42 (58.53)	3.86 (3.96)	17.21 (17.07)
l	2-OCH_3	2-Cl	$C_{16}H_{13}N_2O_2Cl$	250	64	58.62 (58.53)	3.69 (3.96)	17.17 (17.07)

* IR (KBr) : 3280 (N-H), 1665 (C=O), 1620 (cyclic C=N)

** IR (KBr) : 3285 (N-H), 1660 (C=O), 1615 (cyclic C=N)

Table 2.Characterization data of 2,6-substituted aryl-1,3,4-oxadiazolo-[3,2-a]-s-triazine-5,7-diones (Va-l)

Comp. No.	R	R^1	Molecular Formula	M.P. (^{0}C)	Yield (%)	Analysis Found (Calculated %)		
						C	N	S
Va	H	H	$C_{16}H_{10}N_4O_3$	241	65	62.52 (62.74)	3.42 (3.26)	18.21 (18.30)
b	4-Cl	H	$C_{16}H_9N_4O_3Cl$	240	69	56.64 (56.47)	2.29 (2.64)	16.51 (16.47)
c*	4-OCH_3	H	$C_{17}H_{12}N_4O_4$	248	72	60.69 (60.71)	3.61 (3.57)	16.65 (16.66)
d	2-OCH_3	H	$C_{17}H_{12}N_4O_4$	250	71	60.82 (60.71)	3.65 (3.57)	16.80 (16.66)
e	H	4-Cl	$C_{16}H_9N_4O_3Cl$	249	76	56.54 (56.47)	2.82 (2.64)	16.51 (16.47)
f**	4-Cl	4-Cl	$C_{16}H_8N_4O_3Cl_2$	251	79	51.47 (51.33)	2.32 (2.13)	14.80 (14.97)
g	4-OCH_3	4-Cl	$C_{17}H_{11}N_4O_4Cl$	248	78	55.40 (55.13)	2.79 (2.97)	15.31 (15.13)
h	2-OCH_3	4-Cl	$C_{17}H_{11}N_4O_4Cl$	250	76	55.41 (55.13)	2.82 (2.97)	15.43 (15.13)
i	H	2-Cl	$C_{16}H_9N_4O_3Cl$	242	66	56.31 (56.47)	2.74 (2.64)	16.51 (16.47)
j	4-Cl	2-Cl	$C_{16}H_8N_4O_3Cl_2$	244	70	51.42 (51.33)	2.41 (2.13)	14.87 (14.97)
k	4-OCH_3	2-Cl	$C_{17}H_{11}N_4O_4Cl$	246	73	55.23 (55.13)	2.81 (2.97)	15.43 (15.13)
l	2-OCH_3	2-Cl	$C_{17}H_{11}N_4O_4Cl$	245	72	55.41 (55.13)	2.90 (2.97)	15.35 (15.13)

* IR (KBr) : 1710 (C=O), 1625 (cyclic C=N) cm^{-1}

^{1}HNMR (DMSO-d_6) d : 3.80 (3H, s, OC<u>H</u>$_3$), 7.00 - 8.12 (9H, m, Ar-<u>H</u>)

** IR (KBr) : 1715 (C=O), 1620 (cyclic C=N) cm^{-1}

^{1}HNMR (DMSO-d_6) d : 7.29 - 8.28 (8H, m, Ar-<u>H</u>)

Table 3. Characterization data of 2,6-substituted aryl-5-thiaoxo-1,3,4-oxadiazolo-[3,2-a]-s-triazine-7-ones (VIa-l).

Comp. No.	R	R^1	Molecular Formula	M.P. (^{0}C)	Yield (%)	Analysis Found (Calculated %)		
						C	N	S
VIa	H	H	$C_{16}H_{10}N_4O_2S$	210	75	59.71 (59.62)	3.21 (3.10)	17.51 (17.39)
b	4-Cl	H	$C_{16}H_9N_4O_2SCl$	217	77	53.99 (53.93)	02.71 (2.52)	15.92 (15.73)
c*	4-OCH_3	H	$C_{17}H_{12}N_4O_3S$	225	82	53.80 (57.95)	3.70 (3.40)	15.98 (15.90)
d	2-OCH_3	H	$C_{17}H_{12}N_4O_3S$	227	83	57.65 (57.95)	3.21 (3.40)	15.63 (15.90)
e	H	4-Cl	$C_{16}H_9N_4O_2SCl$	220	75	53.82 (53.93)	2.42 (2.52)	15.53 (15.73)
f**	4-Cl	4-Cl	$C_{16}H_8N_4O_2SCl_2$	199	81	49.42 (49.23)	2.35 (2.05)	14.05 (14.35)
g	4-OCH_3	4-Cl	$C_{17}H_{11}N_4O_3SCl$	230	85	52.54 (52.84)	02.94 (2.84)	14.82 (14.50)
h	2-OCH_3	4-Cl	$C_{17}H_{11}N_4O_3SCl$	228	83	52.93 (52.84)	2.92 (2.84)	14.73 (14.50)
i	H	2-Cl	$C_{16}H_9N_4O_2SCl$	215	76	53.80 (53.93)	2.71 (2.52)	15.82 (15.73)
j	4-Cl	2-Cl	$C_{16}H_8N_4O_2SCl_2$	200	80	49.52 (49.23)	2.15 (2.05)	14.45 (14.35)
k	4-OCH_3	2-Cl	$C_{17}H_{11}N_4O_3SCl$	227	83	52.71 (52.84)	2.51 (2.84)	14.61 (14.50)
l	2-OCH_3	2-Cl	$C_{17}H_{11}N_4O_3SCl$	229	84	52.51 (52.84)	2.53 (2.84)	14.75 (14.50)

* IR (KBr) : 1700 (C=O), 1080 (C=S) cm^1

^{1}HNMR (DMSO-d_6) d : 3.78 (3H, s, OC<u>H</u>$_3$), 7.14 - 8.14 (9H, m, Ar-<u>H</u>)

** IR (KBr) : 1705 (C=O), 1084 (C=S) cm^1

^{1}HNMR (DMSO-d_6) d : 7.24 - 8.25 (9H, m, Ar-<u>H</u>)

Ethyl-N-(5-substituted aryl-1,3,4-oxadiazole-2yl) carbamate were synthesized.

(a) Ethyl-N-(5-phenyl-1,3,4-oxadiazole-2yl)carbamate, M.P. 205^{0}C, (reported M.P. 207^{0}C) Yield 75% of theory.
(b) Ethyl-N-5(4-chlorophenyl-1,3,4-oxadiazole-2yl) carbamate, M. P. 206^{0}C, (reported M.P. 208^{0}C) Yield 81% of theory.
(c) Ethyl-N-5(4-methoxyphenyl-1,3,4-oxadiazole-2yl) carbamate, M.P. 235^{0}C, (reported M.P. 237^{0}C) Yield 84% of theory.
(d) Ethyl-N-5(2-methoxyphenyl-1,3,4-oxadiazole-2yl) carbamate, M. P. 168^{0}C (reported, M.P. 170^{0}C) Yield 82% of theory.

(iii) *N^1-(5-substituted aryl-1,3,4-oxadiazole-2yl)-N^3-(4-substituted phenyl) ureas(IVa-l):*

A mixture of ethyl-N-(5-substituted aryl-1,3,4-oxadiazole-2yl) carbamate (.01 mol) and aromatic amine (0.01 mol) in ethanol was refluxed for 16 hrs. and the solvent was distilled off. The residue thus obtained was washed with water and recrystallized from ethanol to furnish the desired product.

According to above procedure following twelve N^1-(5-substituted aryl-1,3,4-oxadiazole-2yl)-N^3-(4-substituted phenyl) ureas were prepared, which are recorded in the Table-1 with their characterization data, molecular formula, elemental analysis, M.P., Yield and spectral data as foot-note.

(iv) 2,6-Substituted aryl-1,3,4-oxadiazolo-[3,2-a]-s-triazine-5,7-diones (Va-l) :

A solution of N^1-(5-substituted aryl-1,3,4-oxadiazole-2yl)-N^3-(4-substituted phenyl) urea (0.01 mol), pyridine (40 ml) was added ethyl chloroformate in an ice bath. The reaction mixture was stirred at room temperature for 2 hrs., then refluxed for 1 hr. The contents were treated with 1N KOH (40 ml) and the product thus precipitated was recrystallized from ethanol, which are recorded in the Table 2 with their characterization data.

(v) 2,6-Substituted aryl-5-thiaoxo-1,3,4-oxadiazolo-[3,2-a]-s-triazine-7-ones (VIa-l):

A mixture of N^1-(5-substituted aryl-1,3,4-oxadiazole-2yl)-N^3-(4-substituted phenyl) urea (0.01 mol), ethanol (40 ml) and carbon disulphide (0.02 mol) was refluxed for 6 hrs. and concentrated to a small volume. the contents were poured into ice-cold water and acidified with dil. HCl to give the desired product which are recrystallized from ethanol, which are recorded in the Table-3 with their characterization data.

Antifungal activity :

The compound (IVa-l) (Va-l) and (VIa-l) were screened for their antifungal activity against *Helminthosporium oryzae* and *Phytophtora infestans* at 1000, 100 and 10 ppm concentration following the Agar Plate Technique[16]. It is appeared from screening data that all the compounds were more active against *Helminthosporium oryzae* as compared with *Phytophtora infestans* but their difference was marginal. Most of the compound showed the significance antifungal activity at 1000 ppm against markedly at lower concentration (100 and 10 ppm). The compound (IVj and VIf), exhibited fungitoxicity of the order of Dithane

M-45 at 1000 ppm against both the fungi. It was noted that the introduction of chloro group *i.e.* more effective than that of methoxy group. The overall results are not so encouraging performance of the fused biolabile *i.e.* 1,3,4-oxadiazole and 1,3,5-triazine ring.

Acknowledgement

The authors express their deep gratitude to the Principal and HOD, Department of Chemistry of the institution for their constant research encouragement and providing necessary research facilities.

References

1. R.P. Singh, C. R. Singh *et al*., *Indian J. of Heterocyclic Chemistry*, *15*, 345-348 (2006).
2. Mohd. A. Bakht *et al*., *Indian J. of Hterocyclic Chemistry*, *15*, 297-298 (2006).
3. D.S. Tripathi, A.R. Mishra *et al*., *Indian J. of Hterocyclic Chemistry*, *16*, 239-242 (2007).
4. C.S. Androtra *et al*., *Indian J. Pharma. Sci*., *55(1)*, 19-22 (1993), Chem. Abstr., (1993), 119, 271079f.
5. A.K. Gadad *et al*., *Indian Hterocyclic Chemistry*, *2(2)*, 125-8 (1992), *Chem. Abstr.*, (1993), 118, 233962k.
6. K. Hiraki *et al*., *Sagamichemicla Research Centre*; Karen Pharmaceutical Ltd., Chem. Abstr., (1998), 128, 217380v.
7. S.R. Dhol, A.S. Bhimani, R.C. Khunt and A.R. Parikh, *Indian J. of Hterocyclic Chemistry*, *15*, 63-64 (2005).
8. V.H. Bhaskar, Prasanth Francis *et al*., *Indian J. of Hterocyclic Chemistry*, *15*, 409-410 (2006).
9. K.R. Alagawadi *et al*., *Indian J. of Hterocyclic Chemistry*, *14*, 315-318, (2005).
10. M. Majid Heavi, Mohd. Rahimizadeh *et al*., *Indian J. of Hterocyclic Chemistry*, *16*, 387-388 (2006).
11. D.S. Tripathi, A.R. Mishra *et al*., *Indian J. of Hterocyclic Chemistry*, *16*, 117-120, (2006).
12. A.K. Rai, A.R. Mishra et al, *Indian J. of Hterocyclic Chemistry*, *16*, 121-124 (2006).
13. A.J. Zahra *et al*., *Jpn Kokkai Koho JP*, (2006), 241, 120, Chem. Abstr., (2006), 145, 315028g.
14. M.S. Gibson, *Tetrahedron*, *18*, 1377 (1962).
15. H. Gehlen, K. Moeckel, *Ann. 651*, 133 (1962), Chem. Abstr., 57, 34241 (1962).
16. Horsfall, J.G., *Bot. Rev.*, *11*, 357 (1945).