HL ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
http://heteroletters.org Vol. 2: (2), 2012, 174-180

SYNTHESIS, CHARACTERIZATION AND BIOCIDAL ACTIVITY OF NOVEL HALOGENATED - 4-[(SUBSTITUTED-BENZOTHIAZOL-2-YL) HYDRAZONO]-2-(SUBSTITUTED-PHENYL)-5-METHYL /ETHOXY -2,4-DIHYDRO-PYRAZOL-3-ONE DERIVATIVES

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ABSTRACT

Some new 4-[(substituted-benzothiazol-2-yl)hydrazono]-2-(substituted-phenyl)-5-methyl/ethoxy-2,4-dihydro-pyrazol-3-one(4) have been synthesized by reacting substituted 2-amino benzothiazol (1) with acetoacetic ester and malonic ester (2). 2-[(substituted-benzothiazol-2-yl)hydrazono]-3-oxo-butyric acid ethyl ester and 2-[(substituted-benzothiazol-2-yl)hydrazono]- malonic acid diethyl ester (3) react with different hydrazines to give the title compounds(4). These compounds are evaluated for their antifungal and insecticidal activity. The structures of all these compounds have been confirmed by IR, ^{1}H NMR, mass spectra and elemental analysis data.

KEYWORDS

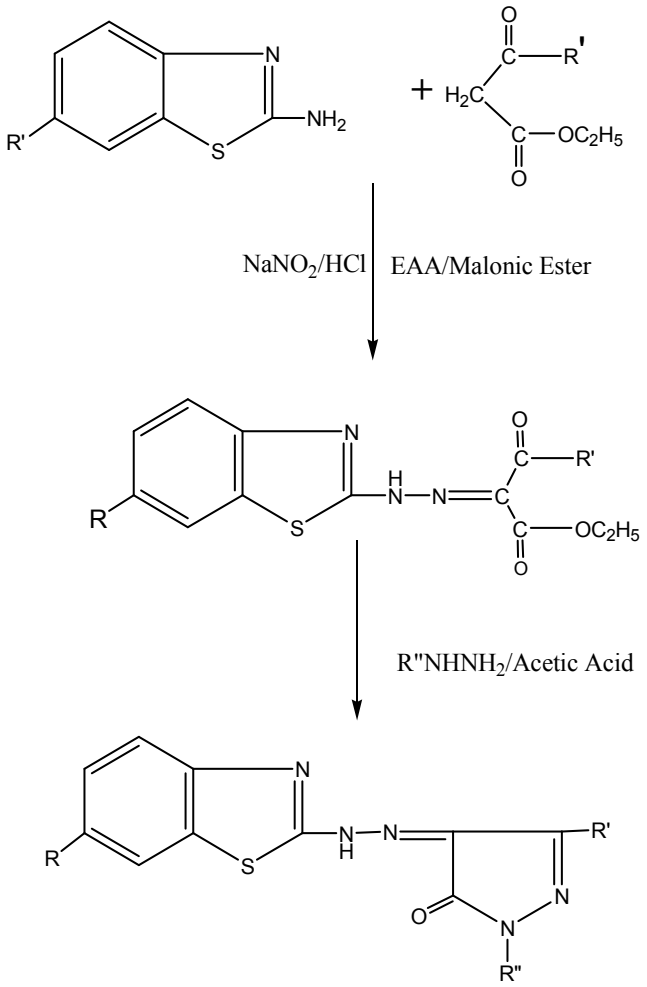
4-[(substituted-benzothiazol-2-yl)hydrazono]-2-(substituted-phenyl)-5-methyl/ethoxy-2,4-dihydro-pyrazol-3-one, fungicidal activity, insecticidal activity.

INTRODUCTION

Many five membered heterocycles including pyrazoles[1] are considered as an important class of heterocyclic compounds possessing interesting biological[2] and pharmacological properties as anti-inflammatory[3], anticancer[4], antibacterial[5], antiviral[6], antidiabetic[7], antimicrobial[8] and antifungal[9] activities. Some pyrazoles possess agrochemical[10] activity and have applications as pesticides and insecticides[11-13].

On the other hand heterocycles containing thiazole rings are associated with a wide range of biological properties, such as inflammation inhibitors[14], antitumor[15], herbicidal[16], antimicrobial[17], antiviral[18] due to toxophoric –N=C–S– group.

In view of all these findings and in continuation of our work on heterocyclic compounds[19-21], we have synthesized some new derivatives of halogenated 4-[(substituted-benzothiazol-2-yl)-hydrazono]-2-(substituted-phenyl)-5-methyl/ethoxy-2, 4-dihydro-pyrazol-3-one.(SCHEME –1)



4a-n

3a : R = 5-Cl, R’ = CH_3; 3b: R = 4-Cl, R’ = CH_3; 3c: R = 6-F, R’ = CH_3 ; 3d : R = 4-F, R’ = CH_3; 3e : R = 6-F, R’ = OC_2H_5 ; 3f : R = 4-Cl, R’ = OC_2H_5

4a : R = 5-Cl, R’ = CH_3 , R”= $CSNH_2$; 4b : R = 5-Cl, R’ = CH_3 , R”= CH_2=CH-CH_2NH-CS ; 4c : R = 4-Cl, R’ = CH_3 , R”= $CSNH_2$; 4d : R = 4-Cl, R’ = CH_3 , R”= CH_2=CH-CH_2NH-CS ; 4e : R = 6-F, R’ = CH_3 , R”= $CSNH_2$; 4f : R = 6-F, R’ = CH_3
,R”= CH_2=CH-CH_2NH-CS ; 4g : R = 4-F, R’ = CH_3 , R”= $CSNH_2$; 4h : R = 4-F, R’ = CH_3 ,R”=CH_2=CH-CH_2NH-CS ; 4i : R = 6-F, R’ = OC_2H_5 , R”=C_6H_5; 4j : R = 6-F, R’ = OC_2H_5, R”=2,4-di$NO_2C_6H_5$; 4k : R = 6-F, R’ = OC_2H_5, R”= $CSNH_2$; 4l : R = 4-Cl, R’ = OC_2H_5, R”= C_6H_5 ; 4m : R = 4-Cl, R’ = OC_2H_5, R”= 2,4-di$NO_2C_6H_5$; 4n : R = 4-Cl, R’ = OC_2H_5, R”= $CSNH_2$

SCHEME-1

RESULT AND DISCUSSION

2-[(substituted benzothiazol-2-yl)-hydrazono]-3-oxo-butyric acid ethyl ester and 2-[(substituted-benzothiazol-2-yl)-hydrazono]-malonic acid diethyl ester (3) have been synthesized by diazotization of substituted 2- amino benzothiazole with acetoacetic ester and malonic ester at 0-5 ^{0}C with continuous stirring for 2 ½ hours. The diazotized form has been reacted with different hydrazines in presence of acetic acid on water bath for 4-5
hours to yield hydrazono pyrazol-3-one(4).

Compound (3) showed the presence of >NH group in IR spectrum at 3375 cm^{-1} and showed a singlet at δ 8.6 ppm. In ^{1}H NMR spectrum .IR spectra of compound (4)showed peak at: 3360 (>NH), 1645 (>C=O), 3040(Aromatic), 1510 (>NHN=C), 1040-1050 (>C=S) and 3480 (–NH_2)cm^{-1}.^{1}H NMR showed characteristic peaks at δ 9.2 (s, H, >NHN=C), δ 2.5 (s, 3H, –CH_3), δ 7.2-7.8 (m, Ar-H), δ 1.63 (t, 3H,–CH_3), and δ 3.9 (q, 2H, OCH_2) ppm.

Fungicidal activity was evaluated against Alternaria burnsii and Macrophomina phaseolina and insectcidal activity against Corcyra cephalonica. All the compounds showed good inhibition of growth due to presence of thiazole nucleus along with pyrazole ring.

ACTIVITY OF SYNTHESIZED COMPOUNDS

The synthesized compounds were evaluated for their antifungal and insecticidal activity against plant pathogens.

FUNGICIDAL ACTIVITY

The synthesized compounds were evaluated for their antifungal activities against two plant pathogenic fungi v.i.z. Alternaria burnsii causing blight in cumin and Macrophomina phaseolina (Tassi) Goid, Pure culture of fungi raised on potato dextrose agar medium and activity of compounds were tested adopting food poison technique and measurement of radial growth. Each fungus was tested at two dosages (100ppm and 500ppm) with each dose replicated thrice. The radial growth fungal colony was measured for 7 days. The % inhibition of fungal growth of compounds was calculated using following formula:

% inhibition = DC-DT/ DC *100
where DC= Diameter of radial growth in untreated petri plate, DT= Diameter of radial growth in treated (Compound mixed in fungal medium) petri plate
All the compounds showed moderate level of antifungal activity. All fourteen tested compounds were found more effective(higher % inhibition) against . Alternaria burnsii as compared to Macrophomina phaseolina (80.33-86.43% inhibition at 500 ppm dose) was found in compound 4e and 4l followed by compounds 4f and 4j (74.43 –76.13 % inhibition at 500 ppm dose). The remaining compounds showed relatively moderate level of antifungal activity (60.66-69.57% inhibition at 500 ppm dose).

INSECTICIDAL ACTIVITY

Each compound was tested at a single higher dose of 1000 ppm.the test compound was dissolved in alcohol and to this required amount of sterile water (containing 0.625% triton as emulsifier) was added to make up a sprayable aqueous solution containing 1000 ppm of compound..The final instar larvae of Corcyra cephalonica (stainton) were taken as test insects. For each compound twenty larvae were sprayed with the prepared aqueous solution. The larvae in a petridish (9 cm) were sprayed along with some food. The larvae were allowed to crawl on the treated bottom of petridish for ten minutes. The larvae and food was taken out , air dried and kept for observation and parallelly checked with 20 larvae were sprayed with solution containing no test compounds. The observed mortality in treatment was corrected for natural mortality in check.

ABBOTTS FORMULA

Corrected Percent Mortality = T – C /100-C *100
Where T= Percent mortality in chemical treated plate
C= Percent mortality in check(without chemical)

Penultimate instar larvae were sprayed with 1000 ppm aqueous solution of each synthesized compound and the mortalities were recorded upto five days. No mortality was observed 2 days after treatment(DAT) in four compounds.(no. 4f, 4l, 4m and 4n). in the remaining compounds the percent mortality was 10.52 to 33.33. as 5 DAT the mortality ranged between 29.41 to 58.82 percent. All 14 compounds were tested and maximum insecticidal activity was observed in compound no. 4j, showing percent
mortality of 33.33 to 58.82 after 2 and 5 days respectively.

EXPERIMENTAL

2-[(5-Chloro-benzothiazol-2-yl)-hydrazono]-3-oxo-butyric acid ethyl ester (3a)

2-amino-5-chloro benzothiazole (0.01mole) was dissolved in a mixture of concentrated HCl (8ml) and water (6ml) and cooled to 0^oC in an ice bath, cold aqueous solution of sodium nitrite (0.02 mole) was then added. The cold diazonium salt solution was filtered into a cooled solution of ethyl acetoacetate (0.01 mole) and sodium acetate (0.05 mole) in ethanol (25ml) and stirred for 2 hrs and the resulting solid was filtered, dried and crystallized from ethanol. Yield 68%, m.p. 190^oC ; IR (KBr cm^{-1} ν_{max}: 3375 (>NH), 1490 (>NHN=C), 1635 (>C=O), 3035 (Aromatic). ^{1}HNMR ($CDCl_3$, ppm) : 1.5 (t, 3H, CH_3), 2.6 (s, 3H, $COCH_3$), 4.2 (q, 2H, OCH_2), 7.4-7.8 (m, Ar-H) and 8.6 (s, H, >NHN=C) ppm ; MS(m/z): 325.5 (found C,47.85,H,3.64, N,12.01,S,9.75,$C_{13}H_{12}ClN_3O_3S$ requires C, 47.93, H,3.71, N,12.9, S,9.84 %.)

4-[(5-chloro-benzothiazol-2-yl)-hydrazono]-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-carbothioic acid amide(4a)

2-[(5-chloro-benzothiazol-2-yl)-hydrazono]-3- oxo-butyric acid ethyl ester (0.01 mol) dissolved in glacial acetic acid (5 ml) and a solution of thiosemicarbazide (0.01 mol) in

glacial acetic acid (5 ml) was added and the mixture was refluxed for 4-5 hours on a water bath. Melting solid was dried and crystallized from ethanol m.p. 150 ^{0}C yield 60% ; IR (KBr cm^{-1} ν_{max}: 3360 (>NH), 1510 (>NHN=C), 1645 (>C=O), 3040 (Aromatic)., 1040-1050 (C=C), 3480(NH_2); ^{1}HNMR ($CDCl_3$, ppm) : δ 9.2 (s, H, >NHN=C), 2.5 (s, 3H, $COCH_3$), 7.2-7.8 (m,Ar-H), 7.4-7.8 (m, Ar-H) and 5.2 (NH_2) ppm ; MS(m/z): 352.5 (found C,40.86,H,32.5., N,23.74, S,17.28 ,$C_{12}H_9ClN_6OS_2$ requires C, 40.85, H,2.55, N,23.82, S,18.18 %.)

TABLE 1: Physical and analytical data of compounds synthesized (4a-n)

Compds	R	R'	R"	Yield	M.P. ^{0}C	Mol. Formula	Elemental Analysis Found/ (Calcd), %				Mass
							C	H	N	S	
4a	5-Cl	CH_3	$-CSNH_2$	60	150	$C_{12}H_9ClN_6OS_2$	40.86 40.85	2.58 2.55	23.74 23.82	17.28 18.18	352.5
4b	5-Cl	CH_3	CH_2=CH- CH_2NH-CS	58	92	$C_{15}H_{13}ClN_6OS_2$	45.88 45.85	3.34 3.31	21.23 (21.39)	16.25 (16.32)	392.5
4c	4-Cl	CH_3	$CSNH_2$	196	61	$C_{12}H_9ClN_6OS_2$	40.86 40.85	2.56 2.55	23.72 (23.82)	17.84 (18.18)	352.5
4d	4-Cl	CH_3	CH_2=CH- CH_2NH-CS	88	60	$C_{15}H_{13}ClN_6OS_2$	45.82 45.85	3.35 3.31	21.20 (21.39)	16.21 (16.32)	392.5
4e	6-F	CH_3	$CSNH_2$	165	58	$C_{12}H_9FN_6OS_2$	42.87 42.85	2.70 2.67	24.82 (24.98)	18.90 (19.07)	336
4f	6-F	CH_3	CH_2=CH- CH_2NH-CS	120	60	$C_{15}H_{13}FN_6OS_2$	47.90 47.87	3.49 3.45	22.14 (22.33)	16.89 (17.04)	376
4g	4-F	CH_3	$CSNH_2$	160	60	$C_{12}H_9FN_6OS_2$	42.88 42.85	2.71 2.67	24.84 (24.98)	18.93 (19.07)	336
4h	4–F	CH_3	CH_2=CH- CH_2NH-CS	112	59	$C_{15}H_{13}FN_6OS_2$	47.91 47.87	3.48 3.45	22.19 (22.33)	16.81 (17.04)	376
4i	6-F	OC_2H_5	C_6H_5	80	58	$C_{18}H_{14}FN_5O_2S$	56.41 56.39	3.69 3.65	18.01 (18.27)	8.12 (8.36)	383
4j	6–F	–OEt	2, 4-diNO_2 C_6H_3	138	60	$C_{18}H_{12}FN_7O_6S$	45.69 45.66	2.57 2.53	20.61 (20.71)	6.61 (6.77)	473
4k	6–F	–OEt		122	55	$C_{13}H_{11}FN_6O_2S_2$	42.65 42.62	3.04 3.00	22.80 (22.94)	17.39 (17.50)	366
4l	4–Cl	–OEt	$-C_6H_5$	128	60	$C_{18}H_{14}ClN_5O_2S$	54.09 54.06	3.54 3.50	17.41 (17.51)	7.86 (8.02)	399.5
4m	4–Cl	–OEt	2, 4-diNO_2- C_6H_3	130	62	$C_{18}H_{12}ClN_7O_6S$	44.16 44.12	2.47 2.45	19.79 (20.02)	6.48 (6.55)	489.5

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Received on February 3, 2012.