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Synthesis and fungitoxicity of 4-methyl-6-phenyl -2-phenylimino-1,3-oxathiolo [4,5-d]-pyrazole

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Abstract

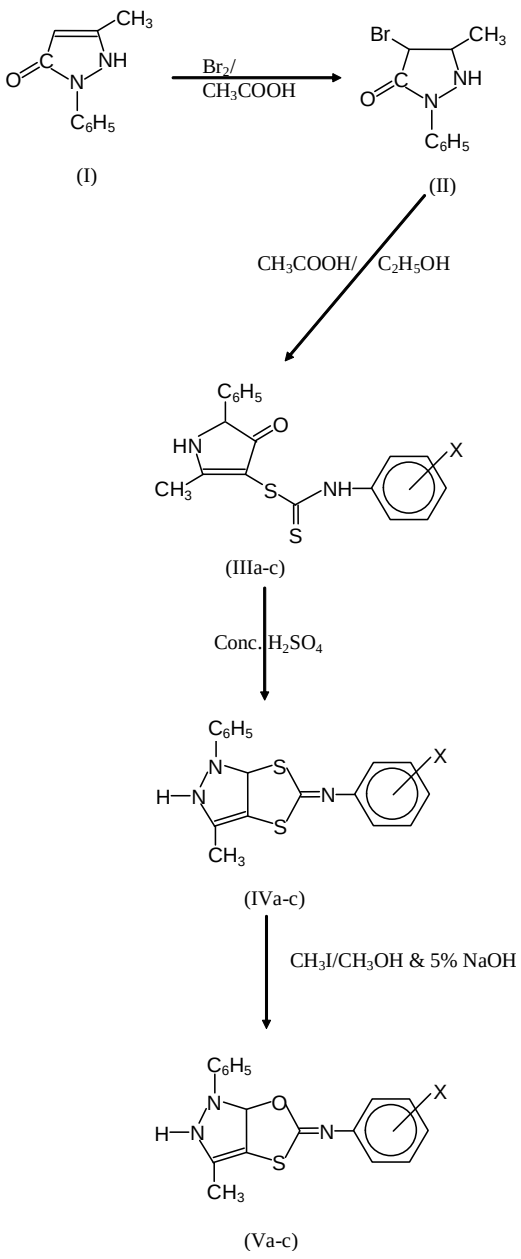
3-Methyl-1-phenylpyrazol-5-one (I) were prepared by mixing ethyl acetoacetate and phenyl hydrazine. These methyl phenyl pyrazolone was treated with bromine in glacial acetic acid to get 4-bromo-3-methyl-1-phenyl pyrazole-5-one (II). These were treated with ammonium N-(phenyldithiocarbamate) and sodium acetate in absolute ethanol to give 3-Methyl-1-phenylpyrazole-5-one-4-yl-N-(phenyl)-dithiocarbamates (III*a-c*). These carbamates when treated with concentrate H_2SO_4 give 4-methyl-6-phenyl-2-phenylimino-1,3,-dithiolo-[4,5-a]-pyrazole (IV*a-c*) and on treatment with methyl iodide in methanol gave 4-methyl-6-phenyl-2-phenylimino-1,3-oxathialo [4,5-d] pyrazole (V*a-c*). Fungitoxicity of the prepared compounds have been compared with Dithane M-45 a commercial fungicide for their fungitoxic action against *Puccinia recondita* and *Ustilago nuda maydis* and the screening results have been correlated with the structural features of the prepared compounds.

Introduction

Pyrazoles derivatives and pyrazoline derivatives are associated with broad spectrum of pesticidal activity like antifungal[1-2] antibacterial, anti-inflammatory[3-6], antitubercular[7], analgestic[8], insecticidal[9], antiparasitic[10] and antiviral[11] activity. Some of these compounds have also shown anticonvulasant[12] and anticancer[13] properties. Pyrazole and its several substituted derivatives are inhibitor and deactivator of liver and alcohol dehydrogenase[14].

In our title compounds (V*a-c*) the pyrazole ring is associated with 1,3-dithiolo and 1,3-oxathiolo ring with the hope that association of the biolabile triazole ring 1,3-dithiolo ring and 1,3-oxathiolo nuclei might result to the pesticides of enhanced potency. The reaction sequence leading to the formation of title compounds is given in the Scheme-I.

3-Methyl-phenyl pyrazol-5-one were prepared following the method[15], which were converted to 4-bromo-4-methyl-1-phenyl pyrazole-5-one (II). The pyrazolone was mixed



IIIa, IVa, Va, X = –H; IIIb, IVb, Vb, X = 4–F; IIIc, IVc, Vc, X = 4–Cl;

Scheme-I

with ammonium N-(phenyl dithiocarbamate) and anhydrous sodium acetate in ethanol gave 3-methyl-1-phenylpyrazole-5-one-4-yl-N-(phenyl)-dithiocarbamates (III*a-c*). These dithiocarbamates was treated with conc. H_2SO_4 to give 4-methyl-6-phenyl-2-phenyl imino-1,3-dithiolo[4,5-d]-pyrazole (IV*a-c*). Similarly dithiocarbamates on treatment with methyl iodide in methanol gave 4-methyl-6-phenyl-2-phenylimino-1,3-oxathiolo [4,5-d] pyrazole (V*a-c*).

Antifungal activity :

The antifungal activity of the compounds (IV*a-c*) and (V*a-c*) were evaluated against *Puccinia recondita* and *Ustilago nuda. maydis* by the agar plate technique at 1000, 100 and 10 ppm conc. Dithane M-45 a standard commercial fungicide, was also tested under similar conditions for comparing the results.

Most of the compound (III*a-c*) (IV*a-c*) (V*a-c*) significantly inhibited the mycelial growth of both the test fungi at 1000 ppm concentration but their activity decreased considerably at lower concentration (100 and 10 ppm). The compounds III*b*, III*c* & V*c* have similar activity to mancozeb at 1000 ppm and showed 43-43% growth inhibition of both the test fungi event at 10 ppm concentrations. Change in the relative position of the substituents on the compound causes significant alternation in the antifungal activity *e.g.* III*b*, III*c* & IV*c* are more active than compounds III*a*, IV*a* & V*c*. Similarly introduction of chloro group and fluoro group was far more effective than that of hydrogen-Cl compound shows more antifungal activity than fluoro compounds.

Experimental

Melting points were determined in open capillaries and are uncorrected, IR spectra in KBr were recorded either on Perkin-Elmer 157 or Hitachi-295 IR spectrometer. ^{1}HNMR spectra were recorded on a EM-360L (60 MHz) NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal reference. Chemical shifts are expressed in δ ppm.

Synthesis of 4-bromo-3-methyl-1-phenyl pyrazole-5-one :

3-Methyl-1-phenylopyrazole-5-one (0.03 mol) was treated with bromine (1.8 ml) in glacial acetic acid at 40-50^{0}C. After keeping the reaction mixture overnight it is poured into water when 4-bromo-3-methyl-1-phenyl pyrazole-5-one (II) was filtered and washed with aqueous Na_2CO_3 solution and recrystallized from EtOH, m.p. 115^{0}C, yield 64%.

Synthesis of 3-methyl-1-phenylpyrazole-5-one-4-yl-N-(phenyl)-dithiocarbamates (IIIa-c) :

A mixture of 4-bromo-3-methyl-1-phenyl pyrazole-5-one (0.05 mol), ammonium N-(phenyldithiocarbamate) (0.06 mol) and anhydrous sodium acetate was refluxed for 2 hours in absolute ethanol. On cooling and pouring into water we get 3-methyl-1-phenyl pyrazole-5-one-4-yl-N-(phenyl)-dithiocarbamates which were recrystallized from ethanol.

Following dithiocarbmates were prepared.

III*a*. 3-Methyl-1-phenylpyrazole-5-one-4-yl-N-(phenyl)-dithiocarbamates m.p. 203^{0}C, yield 76%.

III*b*. 3-Methyl-1-phenylpyrazole-5-one-4-yl-N-(4-fluorophenyl) dithiocarbamates),m.p., 208^{0}C, yield 71%.

III*c*. 3-Methyl-1-phenylpyrazole-5-one-4-yl-N-(4-chlorophenyl) dithiocarbamates), m.p., 204^{0}C, yield 72%.

Synthesis of 4-methyl-6-phenyl-2-phenylimino-1,3-dithiolo-[4,5-d]-pyrazole (IVa-c):

3-Methyl-1-phenyl pyrazol-5-one-4-yl-N-(phenyl)-dithiocarbamates (0.01 mol) was treated with conc. H_2SO_4 (5 ml). The mixture was cooled and poured into ice water after 30 min. On neutralization with ammonia the desired product was precipitated and recrystallized from ethanol.

IV*a*. 4-Methyl-6-phenyl-2-phenylimino-1,3-dithiolo-[4,5-d]-pyrazole
M.P. 210^{0}C, Yield 80%.
Found : C, 69.62; H, 4.78; N, 14.33;
Molecular Formula $C_{17}H_{15}N_3S_2$
Requires : C, 69.52; H, 4.74; N, 14.30%
IR (KBr) : 1670 (exocyclic C=N) 1376 (C–S–C) cm^{-1}
^{1}HNMR ($CDCl_3$) δ : 7.02-8.20 (11H, m, Ar–H), 2.3 (3H, s, $–CH_3$)

IV*b*. 4-Methyl-6-phenyl-2-[p-fluorophenylamino]-1,3-dithiolo-[4,5-d], pyrazoles, m.p., 215^{0}C, yield 81%.

IV*c*. 3-Methyl-6-phenyl-2-[p-chlorophenylamino]-1,3-dithiolo-[4,5-d], pyrazoles, m.p., 209^{0}C, yield 80%.

Synthesis of 4-methyl-6-phenyl-2-phenylimino-1,3-oxathialo [4,5-d] pyrazole (Va-c) :

An equimolar mixture of 3-methyl-1-phenyl pyrazol-5-ones-4-yl-N-(phenyl)-dithiocarbamates and methyl iodide was refluxed for 6 hours in methanol and excess of solvent was distilled off. Residue was treated with 5% NaOH and the product thus obtained was washed with water and cyrstallized from ethanol.

V*a*. 4-Methyl-6-phenyl-2-phenylimino-1,3-oxathialo [4,5-d] pyrazole
M.P. 216^0C, Yield 72%
Found : C, 66.02; H, 48.54; N, 13.59;
Molecular Formula $C_{17}H_{15}N_3SO$
Requires : C, 66.04; H, 48.23; N, 13.56%
IR (KBr) : 1680 (exocyclic C=N) 1145 (C–O–C) cm^{-1}
^{1}HNMR ($CDCl_3$) δ : 7.00-8.22 (H, m, Ar–H), 2.3 (3H, s, $–CH_3$), 6.5 (s, 1H, –NH)

V*b*. 4-Methyl-6-phenyl-2-[p-fluorophenylimino]-1,3-oxathiolo-[4,5-d]-pyrazoles, m.p., 222^0C, yield 75%.

V*c*. 4-Methyl-6-phenyl-2-[p-chlorophenylamino]-1,3-oxathiolo-[4,5-d], pyrazoles, m.p., 219^0C, yield 82%.

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