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SYNYHESIS AND ANTIFUNGAL ACTIVITY OF SOME NEWLY SYNTHESIZED SUBSTITUTED 1,2,4-TRIAZOLO- 1,3,4 THIADIAZOLES

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Abstract

A novel series of substituted 1,2,4 Triazolo-1,3,4 Thiadiazoles were synthesized by the cyclo dehydration of substituted 1,3,4 thiadiazole-2 thioles with suitable semicarbazide and potassium salt of substituted 1- Hydrazine carbodithionic acid in presence of Conc. H_2SO_4 .The newly synthesized compound were characterized by IR and ^{1}HNMR spectra and were screened for their promising antifungal activity against A. Solani and A. Tenius. Some of newly synthesized compounds show their promising antifungal activity

Introduction

Chronic diseases of advanced age have become a greater problem. The ever increasing stress and strain of modern life have raised a number of Psychosomatic and mental dis-orders to expected levels. Therefore every kind of drug needs improvement and replacement by more specific agents with minimum side effects. Several five-membered aromatic systems having three heteroatoms at symmetrical positions such as thiadiazoles have been studied extensively owing to their interesting pharmacological activities. There is a broad variety of heterocyclic compounds which are having medicinal importance, and recently, much attention has been focused on thiadiazole derivatives in view of their broad spectrum activities. Thiadiazole is one such heterocyclic nucleus. There are several isomers of thiadiazole, that is 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole [1], 1,3,4-Thiadiazole is the main iso- mer of thiadiazole series having versatile pharmacological activities.

Thiadiazole is a heterocyclic organic compound that has a five-member ring having one sulphur and two nitrogen atoms [2]. 1,3,4-Thiadiazoles represent one of the most biologi- cally active classes of compounds, possessing a wide spec- trum of activities. Thiadiazoles have become very important.

A recent literature survey revealed that the 1,3,4-thiadiazole moiety has been widely used by the medicinal chemist in the past to explore its biological activities. The development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazines and hydrazine in the late nineteenth century. The first 1,3,4-thiadiazole was described by Fischer in 1882, but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh.

Thiadiazole is a five-member heterocyclic compound having one sulphur and two nitrogen atoms. There are several isomers of thiadiazole, that is, 1,2,3-thiadiazole [3], 1,2,5- thiadiazole [4], 1,2,4-thiadiazole [5], and 1,3,4-thiadiazole [1].

1,3,4-Thiadiazoles

1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Bush and his coworkers, but true nature of the ring system was demonstrated first in 1956 by Goerdler et al. [6]. The advent of sulphur drugs and the later discovery of mesoionic compound greatly accelerated.the rate of progress in the field of thiadiazole. Thiadiazole carrying mercapto, hydroxyl, and amino

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substituents can exist in many tautomeric forms. The 1, 3, 4-thiadiazoles are conveniently divided into three subclasses:

1. Aromatic systems which include the neutral thiadia- zoles and constitute a major part of this paper;
2. Mesoionic systems which are defined as five-membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring;
3. Nonaromatic systems such as the 1,3,4-thiadiazoles and the tetrahydro 1,3,4-thiadiazoles.

A number of 1, 2, 4 triazole derivatives have been found of exhibit herbicidal[7,8] bactericidal [7-9], fungicidal [10-12], protozoacidal [8] and nemotocidal [14] properties.1,3,4. Thiadiazole Nucleus is associated with a broad spectrum of Pesticidal activity [15-20].
Taking into consideration these observation, 1,2,4 Triazole and 1,3,4 Thiadiazole nuclei have been fused with the hope of better fingicidal protency.

Experimental

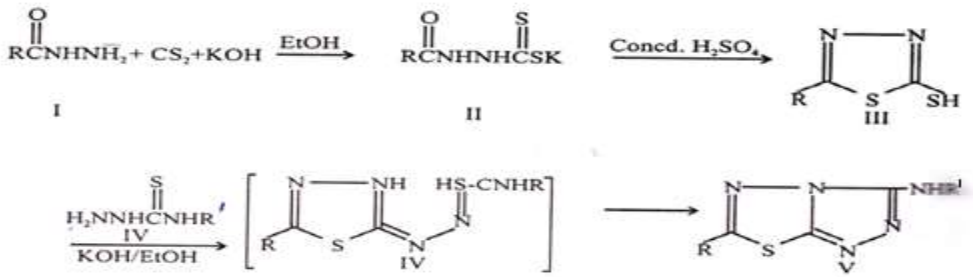
Material:

All the substituted phenylamine, α-haloacyl benzene and reference compound were purchased from Aldrich Chemical. Ethanol, Glacial acetic acid and all other reagents were purchased from S.D. Fine Chem. Analytical TLC was performed on precoated plastic sheet of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany)

General:

The melting point of the newly synthesised compounds were determined by using melting point apparatus (MP-DSTID 2000V scientific) and were uncorrected. The IR spectra of the synthesised compounds were recorded on IR spectrophotometer (perkin Elmer 1605 series) using KBr pellets. ^{1}HNMR spectra were recorded at 300 MHz on Bruker Ft. NMR spectrometer using $CDCl_3$ and the chemical shift (δ) reported are in ppm, using TMS as internal reference.

Scheme of work



Synthesis of various substituted 1,2,4, Triazolo-1,3,4 Thiadiazoles

It was prepared by following the method proposed by Baxter et al. 1 Aryl/aroyloxy methyl Hydrazides (0.1.mol) was shaken for 60 minutes in Aq EtOH. Solid Potassium Salt of 2-aroyl/ aroyl oximethyl -1 Hydrazine carbodithioicacid was obtained. This solid was filtered, dried and Hydrated with Conc H_2SO_4 to give Thiadiazole-2 thiolsIII were prepared during the tenure of the work.The synthesis of compounds selected for study have been outlined as follows.The I.R. spectra and elemental analysis of compounds were also studied.

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Compound No	R	% Yield	M.P^{O}C	M.F R^1=H	% C (calculated)	%H (calculated)
1	C_6H_5	78	166	$C_9H_7N_5S$	49.77	3.23
2	OCl C_6H_4	80	94	$C_9H_6ClN_5S$	42.94	3.39
3	$2,4Cl_2C_6H_3OCH_2$	82	137	$C_{10}H_7C_{l2}N_5OS$	37.97	2.22
4	$2,4Me_2C_6H_3OCH_2$	67	125	$C_{12}H_{13}N_5OS$	52.36	4.73
5	$OMeC_6H_4$	72	100	$C_{10}H_9N_5S$	51.95	3.90

I.R. Spectra of Trizolothiadiazoles shows characterstic bands for –NH,C = N and -C = C- groups at 3300-3425cm-1, 1650-1700cm-1 and 1450-1620cm-1 respectively.

Results and Discussion

All the triazolo-thiadiazoles were found to be more active against both the fungal species viz. Alternaria solani causing early blight of potato and alternaria. Tenius causing black point disease of wheat grains as compared to thosemicarbazides. The compounds 2 and 5 (Table 2) exhibited fungal toxicity comparable to that of captain.

Fungicidal Screening

Compound R=R^1=H	Organism A-Solani			Organism A-Tenius		
	Concentration used			Concentration used		
	1000 ppm	100 ppm	10ppm	1000 ppm	100ppm	10ppm
1	66.2	50.0	19.5	69.2	51.5	20.0
2	87.5	59.5	31.4	86.8	61.5	32.4
3	87.9	58.7	31.2	89.2	61.6	33.8
4	64.7	45.0	19.6	65.7	47.0	20.0
5	65.5	44.5	19.6	68.0	43.2	20.4
captain	97.0	84.5	70.00	100	87.6	72.5

The test organisms were Alternaria Solari causing early blight of potato and Alternaria Tenius which causes Black Point diseasein wheat grains. The antifungal activity was evaluated by agar plate Technique 17 at different concentrations viz.1000ppm,100ppm and 10ppm.In each case the number of replication was three. A commercial fungicide captan (N-Tri chloromethy1 mercapto 4-cyclohexene 1,2 di carboximide) was tested under similar conditions for comparison of results. The percentage inhibitions by various compounds are recorded in Table 2.It is evident from antifungal screening data ggiven in the Table 2 the most of the compounds have significant fingiyoxicity at 1000ppm concentration against both the test fungi viz. A Solani and A. Tenius although compound 7 and 8 shows fungicidal action of the order of captan at 1000ppm concentration and inhibited > 50% growth of both the test organisms even at 10ppm concentration. Thio semicarbazide (IV) in general and less toxic than Triazole (V) derivatives. Compact size and Planarity of the molecule is probably responsible for lower toxicity.

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