SYNTHESIS OF 1,3,4-THIADIAZOLES AND ITS ISOMERIZATION BY NEOTERIC ROUTE AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

Some derivatives of thidiazoles are known to possess insecticidal fungicidal and bacterial activity Similarly substituted trizoles are reported to have herbicidal, antihypertensive an useful as defoliants also shows antidiabetic agent.Several 2-ary1/akkylimino-3H-5-(pyrid-4yl)-1,3,4-thiadiazoles (III) have been synthesized by the interaction of I- isonicotinoyl-4-aryl/alkyl thiosemicarbazides (II) with molecular iodine in alkaline ethanolic medium. These compoundes (III) were benzoylated with benzoyl chloride and excess 10% sodium hydroxide to transform them into their corresponding benzoyl derivatives (IV). On the other hand, the compounds (III) on refluxing with 5% sodium hydroxide in ethanol for 1 hryielded l H-3-(pyrid-4yl)-4aryl/alkyl-5-thio-1,2,4- triazole(V).

The structures of newly synthesized compounds were elucidated on the basis of their elemental IR ^{1}H-NMR and mass

The title compounds were assayed for both antifungal and antibacterial activity against gram positive and gram negative micro-organisms.

Keywords;- *Synthesis, 1,3,4 -thiadiazole, antibacterial activity, isomerization into 1,2,4- triazole.*

Introduction

1,3,4- Thiadiazoles were first described in 1882 by fisher and further developed by Busch and his coworkers. Heterocyclic are used in analytical chemistry[1] and have pharmaceutical properties[2]. A large number of 1,3,4-thiadiaoles have been patented in the agricultural fields as herbicides and bactericides[3-4] Also represent one of the most biologically active [5-6] classes of compounds, possessing a wide spectrum of activities. Several five membered aromatic system having three heteroatoms at symmetrical positions such as thiadiazoles have been studied extensively owing to their interesting pharmacological activities[7]. As thiadiazole is with heterocyclic nucleus and have different isomers i.e. 1,2,3,-thiadiazole, 1,2,4-thiadiazole1,2,5,- thiadiazole and 1,3,4-thiadiazole. Results and study of thiadiazoles encourages us to synthesize more compounds including thiadiazole nuclei. Thus we prepared a new series of thiadiazole derivatives and tested their antimicrobial activity.

Result and discussion

Initially the compound. 1. Isonicothinoy-4 aryl/alkyl thiosemicarbazide(IIa-c) were prepared by reflexing Isoniazide and aryl \ alky thiocyanate in (1:1) ratio in chloroform medium for 1 hr. on completion of reaction and distillation off chloroform. The solid product were separated out. They were crystallizes from ethanol and identified as 1-isonicotinoyl -4-ary\alkyl thiosemicasbazides the oxidatire cyclization of 1-isonicothinoyl-4 aryl\alky\ thiosemicarbazides(II_a-II_c) was carried out by drop wise addition of ethanolic molecular iodine to the alkaline ethanolic suspension of I-isonicothinoyl 4- aryl\alkyl\thiosemicarbazides (III_{a-c}) till blue colour persisted. the reaction mixture was left for overnight at room temperature when a soild 2-phenylimino- 3H-5 (pyrid-4yl)-1,3,4.Thiadiazole (III_a) was obtained. It crystallised from ethanol m.p. 146^0 c. the other 2-ary/alky/imino-3H-5-(pyrid-4yl)-1,3,4-thiadiazole(III_{b-c}) have been prepared By extending this reaction to other I-isonicothinoyl 4-ary/alkyl thisosemicarbozide(II-c). IR spectrum of IIIa showed the presence of v(C=N), (1633cm-^{I}) v(N-H) (3428cm^{-I}), v(Ar C=C) (1587 cm^{-I}, V(C-N), (1307 cm^{-I}), v(C-S) (755cm^{-I}). H-NMR Spectrum of the compound showed the peaks due to Ar-H(6.93-7.79, m5H) and peaks at (6.93 to 7.79, m5H) and peaks at (8.67 to 7.81ppm 4H) Due to pyridyl protons. Any peak at (9.57 ppm, 1H) due to N-H proton on the basis of above facts the compound III_a have been assigned structure 2-phenylimino-H-5 (pur) 2,3,4- thiadiazole. 1H-3 (pyrid-4yl)-4-aryl/akyI-5-thio-1,2,4- triazole (Iv_{a-c})(isomerization)were obtained by boilinhg-2 phenylimino 3H-5 (pyrid-4yl)-1,3,4-thiadiazole (IIIa) with 5% aqueous ethanotic

(1:1) Soduium hydroxide sol^{n}(20.0) on water bath the reaction mixture was cooled and kept at room temp. After evaporation solid was obtained and crystallized from ethanol m.p. 154^{0}C.IR Spectrum odf IV a showed the presence of D(N-H)(3275cm), y(C=N)(1530 cm-1) y(C-N)(1307),v(Arc=C)(1496), (C=S) (1242), v(N-N) (1182 CM-1),H=NMR Spectrum of the compound showed the peaks due to Ar-H(8.67 -6.81m.54) and peaks at (9.60, S, 1H) due to NH and peaks due to (7.58 and 8.67, 4 H, 5) due to pyridyl-protons. On the basis of above facts the compound have been assigned structure of 1H-3(pyrid-4yl)-4-phenyl-5-thio-1,2,4 Thiazine. V_a

Antimicrobial Activity

The title compound (Iv_{a-c}) were screened for their antimicrobial activity against gram positive and gram negative organisms like E-Coil, S. alreus, A. aero genes, B. sublihs and P. vulgaris i.e. Antibacterial agents. Same compounds (Iv_{a-c}) were Screened for their antifungal Activity against C. albicans , A. niger, A. fluvus .using Cop –plate method 9-10 the concentration was $1*10^{5}$ CIU/ml and each well (cup) was of diameter 10 mm. The zones of inhibition were recorded after incubation for 24 hrs. Using verger, caliper. Compunds IV_b shows moderate activity against S. Cureus, B. Sceblilis highly activity against E. coil, The compound IV_a shows highly activity against A. aerogenes, and moderate activity against S. curecws. IV_c shows moderate activity against E.Coil and A. aerogenes. Same compound shows antifungal activity i.e. compound IV_a highly active against C. albicans, A. fluvus. Compounds IV_c highly active against C.albicans and A. fluvus. While compound IV_b shows its moderate activity against A. niger and it is resistant against C. albicans and A. fluvus. All these antifungal and antibacterial activity summarised in the table I and table II.

Table I Antibacterial activity of 2 aryl/alkyl substituted amino 3H-5(pyrid-4yl) -1,2,3 Thadiazole IV_a .

Entry	Comp	E.coil	S.cureus	B. Sublilis	A. areogenes
1	IV_{4a}	-	++	-	+++
2	IV_{4b}	+++	++	++	-
3	IV_{4c}	++	-	-	++

P. vulgaris

(Diameter inhibition zone in mm) (conc100 ug/ml)

(-) resistant <10.0 mm

(+) lightly active>10.0 to 15.0 mm

Table II Antifungal activity of 2 aryl/alkyl substituted amino 3H-5(pyrid-4yl) -1,2,3 Thadiazole IV_a.

Entry	comp	C. albicans	A. niger	A. fluvus
1	IV_{4a}	+++	-	+++
2	IV_{4b}	-	++	-
3	IV_{4c}	++	+++	++

(++) Moderately active > 15.0 to 2.0 mm.

(+++) Highly Active > 25.0 mm.

Experimental

The meetings points of all compounds were recorded using hot paraffin bath and are uncorrected. PMR spectra were recorded with TMS as internal. Standard using $CDCI_3$ and DMSO-d_6 as solvent.IR-spectra were recorded or Perkin-Elmer spectra photometer in the range 4000-400 cm-1 in Nujol mail and as KBr pellets. Purity of compounds were checked on silica gel-G plated by TLC.

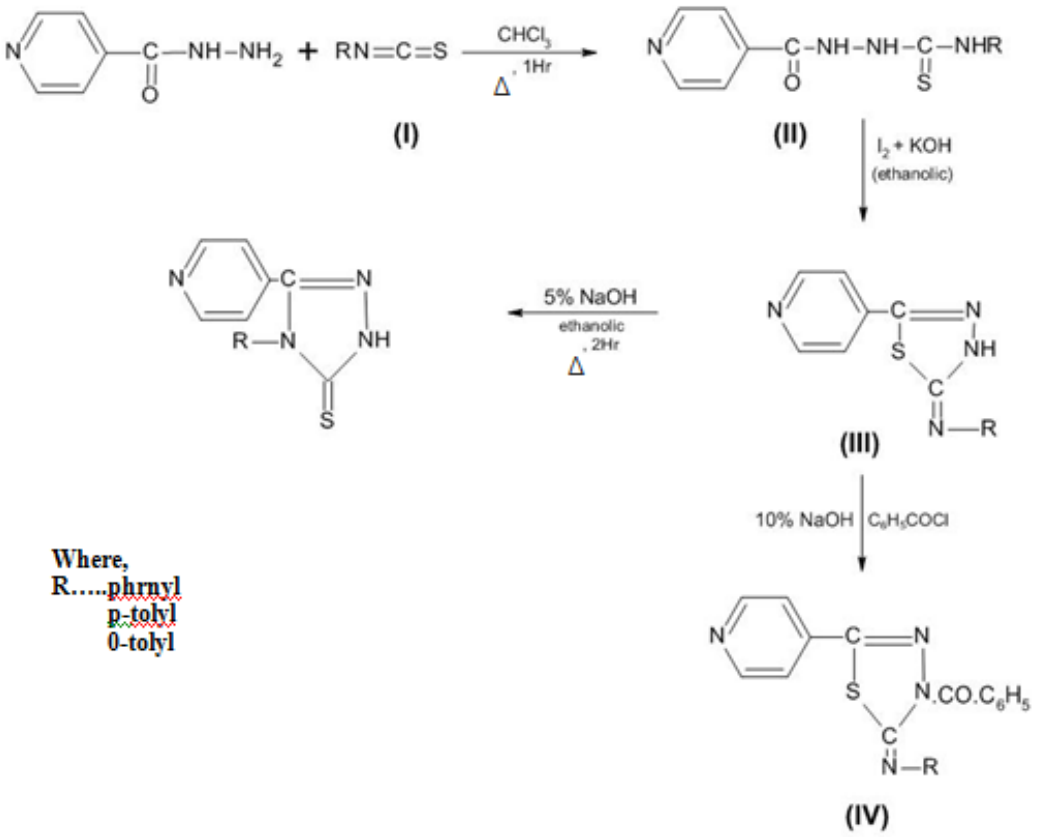
Synthesis of 1-isonicothinoyl-4-phenyl-thiosemicarbazide. III_a

The suspension of I-I sonicotinoyl-4-phenyl this osemicarbazide II^a was obtained by refluxing Isoniazid and phenyl Isoniazid and phenyl isothioGyanate in 1:1 ratio in chloroform medium for 1 hr. On completion of reaction and distillation off chloroform, the solid product were separated out. Ther were crystallized from ethanol and identified as 1-isonicotinoyl-4-phenyl thiosemicarbazides IIa M.P.194^0C

Synthesis of 2- phenyllmino-34-5 (pyraid-4yl)-1,3,4- Thiadiazole IV_a.

The suspension of I-isonicotonoyl-4-phenyl thiosemicarbazide II_a was made in 5% potassium hydroxide in ethanol. To this suspension the initially the colour of iodine disappeared. The addition of iodine was made in slightly excess till the violet colour of iodine persisted. The reaction mixture was left for overnight at room temperature. When a granular solid(III_a) was obtained. It was crystallised from ethanol m.p-146^0 Element analysis %:(Found C, 61.05,H ,4.12;N, 22.97;S,12.65 ;cal-cd for $C_{12}H_{10}N_4S_1$C,61.41;H, 3.93;N,22.04;S, 12.59).

Systhesis of 1H-3(pyrid-4yl)-4-phenyl-5-thio-1,2,4-triazole(v_a).



2- phenylimino-3H-5(pyrid-4yl) -1,3,4-thiazole(IIIa) (0.01 mole) was boiled for 1hr with 5% aqueous ethanolic(1:1) sodium hydroxide solution (2.0ml) on water bath. The reaction mixture was cooled and kept at room temp. After evaporation of ethanol,m.p 154^0 C. Elemental analysis % :(C, 61.03;4;4.02,N,22.74;S,12.97; calcd for $C_{12}H_{10}N_4S$,C,61.41;H,3.93;N,22.04;S,12.59)

Synthesis of 2- aryl/alkylimino-3 H- 5-(pyrid-4yl)-1, 3, 4 Thiadiazoles IV

Reactants: - 1-Isonicotony1-4-ary1/alkyl thiosemicarbazide and alkaline molecular iodine in ethanol.

2-Aryl/alkylimino-3H-5-(pyrid-4yl)-1,3,4-thiadiazoles(IV)		Yield (%)	M.P. (^{o}C)	Elemental analysis; Found (Calcd.) (%)			
				C	H	N	S
2-Phenylimino-3H-5-(pyrid-4yl)-1,3,4-thiadiazole	(IVa)	83	146	61.05 (61.41)	4.12 (3.93)	22.97 (22.04)	12.65 (12.59)
2-p-tolylimino-	(IVb)	79	134	62.52 (62.68)	4.88 (4.47)	21.10 (20.89)	12.14 (11.94)
2-o-tolylimino-	(IVc)	75	172	62.49 (62.68)	4.50 (4.47)	20.80 (20.89)	11.91 (11.94)
1H-3-(pyrid-4yl)-4-phenyl-5-thia-1,2,4-triazole	(Va)	80	154	61.03 (61.41)	4.02 (3.93)	22.74 (22.04)	12.97 (12.59)
4-p-tolyl-	(Vb)	77	173	62.62 (62.68)	3.98 (4.47)	21.02 (20.89)	12.11 (11.94)
4-0-toyl-	(Vd)	71	144	62.42 (62.68)	4.42 (4.47)	20.79 (20.89)	11.91 (11.94)

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