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Synthesis and Antimicrobial Activity of 2-Alkyl/aryl-5-(pyrid-4-yl)-1,3,4-oxadiazole

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Some new 2-substituted-5-(pyrid-4-yl)-1,3,4-oxadiazoles (**IIIa-f**) have been synthesized by oxidative cyclization of N-substituted isoniazids (**IIa-f**) with molecular iodine in presence of alkali in ethanolic medium. The latter have been synthesized by condensing isoniazid with different acid chlorides (**Ia-f**). All these compounds were screened for their antimicrobial activity against gram positive and gram negative microorganisms.

Key Words: 2-Alkyl/aryl-5-(pyrid-4-yl)1,3,4-oxadiazole, Synthesis, Antimicrobial activity.

INTRODUCTION

2-Alkyl/aryl-5-(pyrid-4-yl)-1,3,4-oxadiazole nucleus is reported to show antibacterial[1], antiiinflammatory[2], CNS-stimulant[3], antihypertensive[4] activity. 1,3,4-Oxadiazoles are known to have been prepared by heating tetrazoles with acylating agents *via* rearrangement of a first formed 2-acyl derivative[5]. They are also obtained by cyclohydration of N-N′-diarylhydrazines or their equivalent[6]. In this communication, a simple one step synthesis of 1,3,4-oxadiazoles by oxidative cyclization of N-substituted isoniazids with molecular iodine has been reported.

EXPERIMENTAL

The melting points of all compounds were recorded using hot paraffin bath and are uncorrected. PMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvent. IR-spectra were recorded or Perkin-Elmer spectrophotometer in the range 4000-400 cm^{-1} in Nujol mull and as KBr pellets. Purity of compounds were checked on Silica gel-G plates by TLC.

Synthesis of N-benzoyl isoniazid (IIa): A mixture of isoniazid (0.01 mol) and benzoyl chloride (0.01 mol) was refluxed in presence of ethanol for 1 h. The solvent was then vacuum distilled when a solid residue was obtained. It was crystallized from ethanol, m.p. 120ºC. Elemental analysis %: (Found C, 64.65; H, 4.49; N, 17.38; Calcd. for $C_{13}H_{11}N_3O_2$, C, 64.73, H, 4.56, N, 17.42).

This reaction was extended to synthesize other compounds (**IIb-f**) using other alkyl/aryl acids chlorides (**Ib-f**).

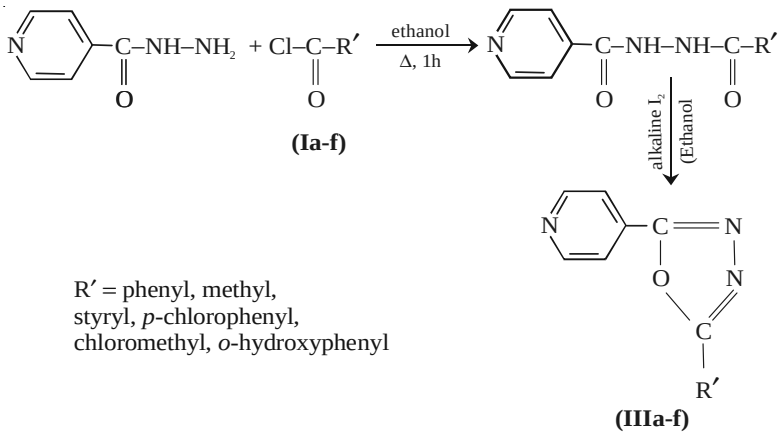
Synthesis of 2-phenyl-5-(pyrid-4-yl)-1,3,4-oxadiazole (IIIa): The suspension of N-benzoyl isoniazid was made in alkaline ethanol. To this, the dropwise addition of ethanolic molecular iodine was made with constant stirring till the blue colour of iodine persisted. The reaction mixture was then left overnight at room temperature. The solid residue was obtained in 82%. It was crystallized from ethanol, m.p. 194ºC. Elemental analysis %: (Found C, 69.75; H, 3.26; N, 18.72; Calcd. for $C_{13}H_9N_3O$, C, 69.95, H, 4.03, N, 18.83).

On extending the above reaction to other N-substituted isoniazids (**IIb-f**), the related 1,3,4-oxadiazoles (**IIIb-f**) have been isolated in good yields. (Table-1).

TABLE-1
PHYSICAL DATA AND ELEMENTAL ANALYSIS OF **II** AND **III**

Compd.	R	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis (%) Found (Calcd.)	
					C	N
IIa	Phenyl	$C_{13}H_{11}N_3O_2$	120	80	64.65 (64.73)	17.38 (17.42)
IIb	Methyl	$C_8H_9N_3O_2$	105	65	53.47 (53.63)	23.37 (23.46)
IIc	Styryl	$C_{15}H_{13}N_3O_2$	93	70	67.28 (67.41)	15.57 (15.73)
IId	*p*-Cl-phenyl	$C_{13}H_{10}N_3O_2Cl$	95	80	64.95 (65.00)	17.35 (17.50)
IIe	Chloromethyl	$C_8H_8N_3O_3Cl$	110	63	53.85 (53.93)	23.43 (23.59)
IIf	*o*-Hydroxy phenyl	$C_{13}H_{11}N_3O_3$	85	68	60.58 (60.70)	16.20 (16.34)
IIIa	Phenyl	$C_{13}H_9N_3O$	194	82	69.75 (69.95)	18.72 (18.83)
IIIb	Methyl	$C_8H_7N_3O$	112	75	59.40 (59.62)	25.91 (26.08)
IIIc	Styryl	$C_{15}H_{11}N_3O$	120	79	72.97 (72.28)	16.65 (16.86)
IIId	*p*-Cl-phenyl	$C_{13}H_8N_3OCl$	135	83	70.04 (70.27)	18.85 (18.91)
IIIe	Chloromethyl	$C_{13}H_8N_3O_3Cl$	198	72	59.95 (60.00)	26.18 (26.25)
IIIf	*o*-Hydroxy phenyl	$C_{13}H_9N_3O_2$	182	70	55.63 (55.91)	14.94 (15.05)

The title compounds (**IIIa-f**) were screened for their antimicrobial activity against microorganisms *E. coli, S. aureus, A. aeruginosa* and *P. vugaris*.



(Ia-f)

(IIIa-f)

RESULTS AND DISCUSSION

Initially, the mixture of isoniazide and benzoyl chloride (**Ia**) was refluxed for 1 h in ethanol as solvent. On vacuum distilling off the solvent a solid residue of N-benzoyl isoniazid (**IIa**) obtained, it was crystallized from ethanol, m.p. 120ºC. Similarly, other N-alkyl/aroyl isoniazids (**IIb-f**) have been obtained by refluxing the isoniazid with different acid chlorides (**Ia-f**).

Oxidative cyclization of N-benzoyl isoniazid (**IIa**) was carried out by dropwise addition of ethanolic molecular iodine to the alkaline ethanolic suspension of N-benzoyl isoniazid till blue colour persisted. The reaction mixture was left for overnight at room temperature, when a solid 2-phenyl-5-(pyrid-4-yl)-1,3,4-oxadiazole (**IIIa**) was obtained. It was crystallized from ethanol, m.p. 194ºC. The other 2-alkyl/aryl-5-(pryd-4-yl)-1,3,4-oxadiazoles (**IIIb-f**) have been prepared by extending this reaction to other N-alkoyl/aroyl isoniazids (**IIb-f**).

IR spectrum of **IIIa** showed the presence of *v*(C=N) (1636 cm^{-1}), *v*(C–N) (1293 cm^{-1}), ν(C–O) (1156 cm^{-1}). ^{1}H NMR spectrum of the compound showed the peaks due to Ar–H (δ 7.5 to 7.9 ppm, m, 5H) and peaks at (δ 8.5 to 8.88 ppm, m, 4H) due to pyridyl-protons. On the basis of above facts the compound **IIIa** have been assigned structure 2-phenyl-5-(pyrid-4-yl)-1,3,4-oxadiazole.

Antimicrobial activity: The title compounds **IIIa-f** were screened for their antimicrobial activity against gram positive and gram negative microorganisms like *E. coli, S. aureus, A. aerogenes* and *P. vulgaris* using cup-plate method[7,8]. The concentrations was of $1x10^5$ CIU/mL and each

well (cup) was of diameter 10 mm. The zones of inhibition were recorded after incubation for 24 h using vernier caliper.

Compounds **IIIa** and **IIIe** showed enhanced activity against *E. coli*, while other compounds showed moderate activity. Compounds **IIIb**, **IIIc** and **IIId** showed moderate activity against *A. aerogenes* and *P. vulgaris*. All other compounds showed very low activity against *S. aureus*.

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