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Synthesis and Antimicrobial Activity of 3-Amino-5-aryl/alkylimino-1,2,4-thiadiazolines

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The 3-amino-5-aryl/alkyl imino-1,2,4-thiadiazolines (**IV**) have been synthesized by the oxidative cyclization of 1-amidino-3-aryl/alkyl thiocarbamides (**II**) with iodine followed by basification. The thiocarbamides (**II**) were prepared by refluxing the mixture of guanidine nitrate and aryl/alkyl isothiocyanates (**I**) in ethanolic sodium hydroxide solution. the title compounds on acetylation with acetic anhydride (1:1) in glacial acetic acid afforded monoacetyl derivatives (**V**). The structures of all these compounds were confirmed on the basis of elemental analysis and spectral data and assayed for their antimicrobial activity against gram-positive as well as gram-negative micro-organisms.

Key Words: Synthesis, Antimicrobial activity, 1,2,4-thiadiazolines.

INTRODUCTION

The synthesis of 1,2,4-thiadiazolines have been achieved by using the reagent N-aryl/alkyl-S-chloro isothiocarbamoyl chloride[1,2]. The synthesis of 1,2,4-thiadiazolines have also been achieved by oxidative cyclization[3] with the help of iodine. In present communication we are extending the application of iodine in the synthesis of 3-amino-5-aryl/alkyl imino-1,2,4-thiadiazolines.

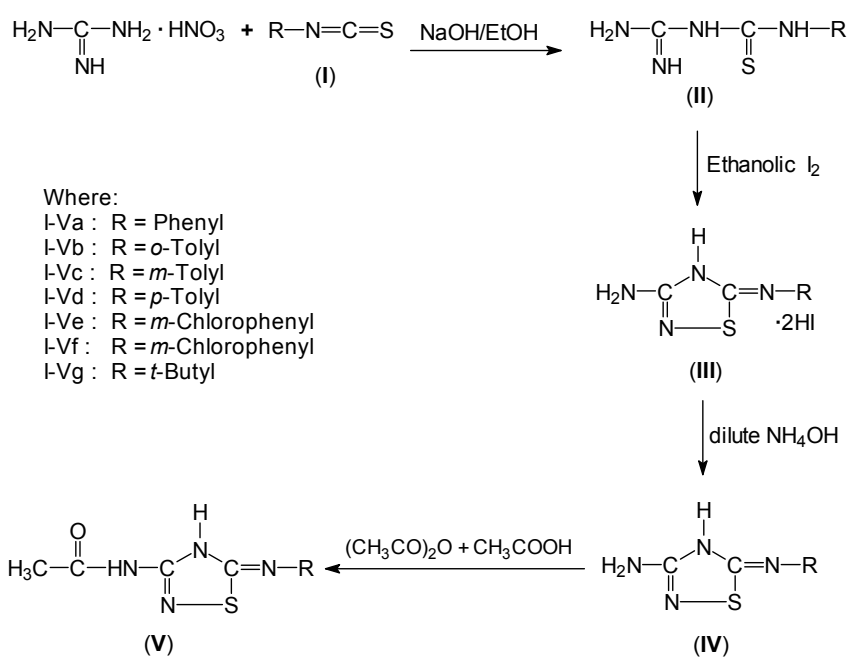
EXPERIMENTAL

The melting points were recorded using hot paraffin bath and uncorrected. Chemicals used were AR grade. IR spectra were recorded on Perkin-Elmer spectrometer in the range 4000-400 cm^{-1} in Nujol mull and as KBr pellets. PMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. Purity of the compounds was chekced on silica gel-G plates by TLC.

Synthesis of 1-amidino-3-phenyl thiocarbamide (IIa): 1-Amidino-3-phenyl thiocarbamide (**IIa**) was prepared by refluxing the mixture of guanidine nitrate (0.01 mol) phenyl isothiocyanate (0.01 mol) and sodium hydroxide (0.1 mol) in ethanolic medium (20 mL) for 2 h. The reaction mixture was cooled and poured on a little crushed ice, when a solid was separated. It was crystallized from ethanol, yield 83 %, m.p. 148 ºC, Found:

C, 49.39; H, 5.03; N, 28.74; S, 16.42; Calculated for $C_8H_{10}N_4S$: C, 49.48; H, 5.15; N, 28.86; S, 16.49 %.

Synthesis of 3-amino-5-phenylimino-1,2,4-thiadiazoline (IVa): A paste of 1-amidino-3-phenyl thiocarbamide (**IIa**) (2 g) was prepared in ethanol. To this ethanolic iodine solution was added drop by drop with constant stirring. The colour of iodine was initially disappeared. The addition was continued till violet colour of the iodine persisted. The reaction mixture was left overnight at room temperature and the separated solid was crystallized from ethanol. It was acidic to litmus and on determination of equivalent weight found to be dihydroiodide (**IIIa**). Yield 82 %, m.p. 155ºC. It on basification with dilute ammonium hydroxide solution afforded a free base, 3-amino-5-phenylimino-1,2,4-thiadizoline (**IVa**). It was recrystallized from aqueous ethanol, m.p. 141ºC, Found: C, 49.92; H, 4.01; N, 29.04; S, 16.49; Calculated for $C_8H_8N_4S$: C, 50.00; H, 4.16; N, 29.16; S, 16.66 %.



Scheme-I

Synthesis of 3-acetyl amino-5-phenylimino-1,2,4-thiadiazoline (IVa): A mixture of 3-amino-5-phenylimino-1,2,4-thiadiazoline (**IVa**) (0.01 mol) and acetic anhydride (0.01 mol) in glacial acetic acid (10 mL) was refluxed for 1.5 h. The reaction mixture was cooled and poured on a little

crushed ice, when a cream coloured solid was precipitated (**Va**). It was recrystallized from ethanol, yield 73 %, m.p. 92ºC, Found: C, 51.11; H, 4.21; N, 23.85; S, 13.56; Calculated for $C_{10}H_{10}N_4OS$: C, 51.28; H, 4.27; N, 23.93; S, 13.67 %.

The formation of product **II, III, IV** and **V** and be shown as given in reaction **Scheme-I**.

RESULTS AND DISCUSSION

Initially, the parent compound guanidine nitrate was reacted with phenyl isothiocyanate (**Ia**) and sodium hydroxide in ethanolic medium for 2 h. The reaction mixture was cooled and poured on a little crushed ice. The solid of 1-amidino-3-phenyl thiocarbamide[4] was separated. It was recrystallized from ethanol, m.p. 180ºC. The compound was found to be desulphurizable when boiled with alkaline lead acetate solution indicating presence of >C=S group. The above reaction was extended to other aryl/alkyl isothiocyanates (**Ib-g**) to synthesize other thiocarbamides (**IIb-g**).

A paste of 1-amidino-3-phenyl thiocarbamide (**IIa**) was prepared in ethanol. To this ethanolic iodine solution was added drop by drop with constant stirring. The colour of iodine was initally disappeared. The addition was continued till violet colour of iodine persisted. The reaction mixture was left overnight at room temperature. The separated solid was crystallized from ethanol. It was acidic and on determination of equivalent weight found to be dihydroiodide of 3-amino-5-phenylimino-1,2,4-thiadiazoline (**IIIa**) ($C_8H_8N_4S{\cdot}2HI$) which on basification with aqueous ammonium hydroxide solution afforded a free base (**IVa**). It was recrystallized from aqueous ethanol, m.p. 141ºC. It was found to be non-desulphurizable with alkaline lead acetate solution indicating absence of >C=S group.

The IR[5] spectral bands (cm^{-1}) of (**IVa**) showed the presence of bands due to ν(N–H) 3423, 3370, ν(C=N) 1548, ν(C–N) 1332 and ν(C–S) 743.

The ^1H NMR spectrum showed the peaks at δ 6.8-7.3(5H, aromatic, δ 7.4 (2H, $-NH_2$), δ 7.6 (1H, NH).

Therefore, the product has been assigned structurally as 3-amino-5-phenylimino-1,2,4-thiadiazoline (**IVa**).

The other compounds (**IVb-g**) were prepared by extending the above reaction to other thiocarbamides (**IIb-g**) and the related products were isolated in good yield (Table-1).

The compound (**IVa**) was acetylated using acetic anhydride and glacial acetic acid in (1:1) ratio to give 3-acetyl amino-5-phenylimino-1,2,4-thiadiazoline (**Va**), m.p. 92ºC.

The IR spectral bands (cm^{-1}) of (**Va**) showed the presence of bands due to ν(N–H) 3217, ν(C–O) 1636, ν(C=N) 1557, ν(C–N) 1307, ν(C–S) 744.

TABLE-1
PHYSICAL DATA AND ELEMENTAL ANALYSIS OF COMPOUNDS (**IV**) AND (**V**)

Compd.	R	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis Found (Calcd.) %	
					N	S
IVa	Phenyl	$C_8H_8N_4S$	141	82	29.04 (29.16)	16.49 (16.66)
IVb	*o*-Tolyl	$C_9H_{10}N_4S$	134	70	27.00 (27.18)	15.40 (15.53)
IVc	*m*-Tolyl	$C_9H_{10}N_4S$	137	74	27.12 (27.18)	15.48 (15.53)
IVd	*p*-Tolyl	$C_9H_{10}N_4S$	126	87	27.01 (27.18)	15.45 (15.53)
IVe	*m*-Chlorophenyl	$C_8H_7N_4SCl$	139	72	24.68 (24.72)	14.02 (14.12)
IVf	*p*-Chlorophenyl	$C_8H_7N_4SCl$	130	83	24.60 (24.72)	13.99 (14.12)
IVg	*t*-Butyl	$C_6H_{12}N_4S$	121	64	32.47 (32.55)	18.53 (18.60)
Va	Phenyl	$C_{10}H_{10}N_4OS$	92	73	23.85 (23.93)	13.56 (13.67)
Vb	*o*-Tolyl	$C_{11}H_{12}N_4OS$	89	69	22.43 (22.58)	12.74 (12.90)
Vc	*m*-Tolyl	$C_{11}H_{12}N_4OS$	95	75	22.50 (22.58)	12.86 (12.90)
Vd	*p*-Tolyl	$C_{11}H_{12}N_4OS$	78	84	22.45 (22.58)	12.71 (12.90)
Ve	*m*-Chlorophenyl	$C_{10}H_9N_4OSCl$	80	79	20.72 (20.85)	11.79 (11.91)
Vf	*p*-Chlorophenyl	$C_{10}H_9N_4OSCl$	84	82	20.79 (20.85)	11.82 (11.91)
Vg	*t*-Butyl	$C_8H_{14}N_4OS$	81	64	28.17 (28.28)	16.01 (16.16)

^{1}H NMR spectrum showed the peals at δ 2.3 (3H, -CO-CH_3), δ 7.0-7.2 (5H-aromatic), δ 7.3 (1H, NH), δ 7.6 (1H, NH).

Therefore, the product has been assigned structurally as 3-acetyl amino-5-phenylimino-1,2,4-thiadiazoline (**Va**).

The other compounds (**Vb-g**) were prepared by extending the reaction of acetylation to other 1,2,4-thiadizolines (**IV-b-g**). The related products were isolated in good yield (Table-1).

Antimicrobial activity: The title compounds (**IVa-g**) were screened for their antibacterial activity using cup plate method[6,7]. The bacterial organisms used in the present investigation were isolated from human

being with characteristic infections and diseases. The isolates were pathogenic. The pathogens used included both gram-positive and gram-negative strains like *E. coli, B. subtilis, S. aureus, P. vulgaris* and *Shigella*. Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU/mL and each well (diameter 10 mm) was loaded with 0.1 mL of test compound solution (1000 µg/mL) in DMF, so that the concentration of each test compound was 100 µg/mL. The zones of inhibition were recorded after incubation for 24 h.

Inhibition zones for different compounds against different microorganism indicated that **IVa** against *E. coli*, **IVb** and **IVe** against *B. subitilis* **IVe** against *S. aureus* **IVg** and **IVg** against *P. vulgaris* are highly active. Most of the compounds are active against these microorganisms except **IVb** against *S. aureus* **IVd** against *P. vulgaris* and **IVc** against *Shigella* (Table-2).

TABLE-2
MICROBIAL ACTIVITIES OF 3-AMINO-5-ARYL/ALKYL IMINO-1,2,4-THIADIAZOLINES (**IVa-g**)

Organism	**IVa**	**IVb**	**IVc**	**IVd**	**IVe**	**IVf**	**IVg**
E. coli	30	28	16	24	18	20	19
B. subtilis	24	36	19	27	32	17	21
S. aureus	15	>12	20	28	34	18	25
P. vulgaris	28	20	18	>12	24	35	30
Shigella	22	24	>12	14	28	18	20

(Diameter of inhibition zone in mm) (concentration 100 µg/mL)
30 and above = Highly active; 20-30 mm = Moderately active;
12-20 mm = Active; >12 mm = Inactive

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