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Chloramine-T mediated synthesis of 1,3,4-Oxadiazole as antibacterial agents

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ABSTRACT

The novel 2,5-diphenyl-1,3,4-oxadiazole were prepared by reacting isoniazide with various aromatic aldehydes at 65^{0}C to get N'-benzylidenebenzohydrazide. Then title compound can be synthesized by cyclization with Chloramine-T . The structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR and Mass spectral technique. The final compounds were screened for their antibacterial activities. The novel compounds showed significant antibacterial activity when compared to the standard drug ampicillin.

Key words: isoniazide, schiff's base and antibacterial activity.

INTRODUCTION

Oxadiazole types of heterocyclic compounds contain oxygen and two nitrogen atoms. These derivatives are synthesized by both conventional as well as microwave assisted. Oxadiazole nucleus is continuously drawing interest for development of newer drug moiety. Widely substituted oxadiazole and their derivatives embedded with variety of biological agents and a significant amount of research activity has been directed towards this class. A systematic investigation of this class of heterocyclic compound revealed that the common synthetic approaches to oxadiazoles involve cyclization of diacylhydrazines. A variety of reaction conditions influence the cyclization reaction. Typically, the reaction is promoted by heat and anhydrous oxidizing reagents. Oxadiazole derivatives have a long history of application in medicinal chemistry. The literature is flooded with reports of a variety of biological activities of substituted-1,3,4-oxadiazoles. These include anticancer[1], antibacterial[2], antimalarial[3], anticonvulsant[3], anti-inflammatory[4] etc. a steady research is going on in oxadiazole nucleus. The present work deals with the reaction of Isoniazide with different aromatic aldehydes to form schiff's bases (1a-d) and the cyclization of the *N*'-benzylidenebenzohydrazide with chloramine-T a strong oxidizing agent to form the final compounds 2,5-diphenyl-1,3,4-oxadiazole derivatives(2a-d). Finally, the structures of all the various synthesized compounds were assigned

on the basis of IR and ^{1}H NMR spectral data and these compounds were screened for their antibacterialactivity.

MATERIALS AND METHODS

Melting points were determined with open capillary and are uncorrected. I.R spectra were recorded on a Shimadzu FTIR model 8010 spectrophotometer, 1H NMR spectra were recorded in CDCl3 on a Bruker supercon FT-NMR instrument using TMS as internal standard. Mass spectra were recorded on GCMS in dimethyl sulphoxide (University Science Instrument Center, Dharwad, India).

Synthesis of Schiff'base 1a-d

Equimolar amount of the Isoniazide compound (0.01mol**)** and various aromatic aldehydes (0.01mol) in ethanol (40 ml) were refluxed for 4-8 h. The resulting Schiffs bases **1a-d** were cooled and poured into crushed ice. The precipitate thus obtained was filtered, washed with cold water and recrystallized from ethanol. The physicochemical of the compounds **3a-j** is described in table **1**.

***N*'-benzylidenebenzohydrazide (1a)**

IR (KBr) cm^{-1} 3431 (NH), 3102(Ar-H), 1640 (C=O), 1580 (N=CH), ^{1}H NMR (DMSO D_6, 400 MHz) δ ppm 10.50 (s, 1H, CONH), 8.95 (s, 1H, N=CH), 7.56- 6.54 (m, 10H, Ar).

N'-(4-chlorobenzylidene)benzohydrazide(1b)

IR (KBr) cm^{-1} 3423 (NH), 3011(Ar-H), 1654 (C=O), 1535 (N=CH), ^{1}H NMR (DMSO D_6, 400 MHz) δ ppm 10.70 (s, 1H, CONH), 8.89 (s, 1H, N=CH), 7.72-6.60 (m, 9H, Ar).

***N*'-(4-bromobenzylidene)benzohydrazide (1c)**

IR (KBr) cm^{-1} 3340(NH), 3100(Ar-H), 1635 (C=O), 1572 (N=CH).^{1}H NMR (DMSO D_6, 400 MHz) δ ppm 10.82 (s, 1H, CONH), 8.70 (s, 1H, N=CH), 7.42-6.30 (m, 9H, Ar).

***N*'-(4-nitrobenzylidene)benzohydrazide (1d)**

IR (KBr) cm^{-1} 3438 (NH), 3120(Ar-H), 1658(C=O), 1552 (N=CH). ^{1}H NMR (DMSO D_6, 400 MHz) δ ppm 10.35 (s, 1H, CONH), 8.90 (s, 1H, N=CH), 7. 67- 6. 45 (m, 9H, Ar).

Synthesis of 1,3,4-oxadiazole (2a-d)

To a equimolar mixture of compound **1a-d** and chloramine-T was added in 50ml of ethanol and the reaction mixture was refluxed on a water bath for 5 hr. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid thus obtained was filtered, washed with water and recrystallized from ethanol. The physicochemical of the compounds **2a-d** is described in table **2**.

2,5-diphenyl-1,3,4-oxadiazole (2a)

IR (KBr) cm^{-1} 3112(Ar-H), 1569 (N=CH),1474 (C=C), 925, 817, 771, ^{1}H NMR (DMSO D_6, 400 MHz) δ ppm 8.82-6.23 (m, 11H, Ar). MS: m/z (%) 221 (60%) [M^{+1}].

2-(4-chlorophenyl)-5-phenyl-1,3,4-oxadiazole (2b)
IR (KBr) cm^{-1} 3118(Ar-H), 1560(N=CH), 1478 (C=C), 927, 820, 776. ^1H NMR (DMSO D_6, 400 MHz) δ ppm 8.33-6.42 (m, 10H, Ar). MS: m/z (%) 257 (56%) $[M^{+1}]$.

2-(4-bromophenyl)-5-phenyl-1,3,4-oxadiazole (2c)
IR (KBr) cm^{-1} 3120(Ar-H), 1556(N=CH), 1485(C=C), 930, 824, 776 ^1H NMR (DMSO D_6, 400 MHz) δ ppm 8.52-6.35 (m, 10H, Ar). MS: m/z (%) 301 (63%) $[M^+]$.

2-(4-nitrophenyl)-5-phenyl-1,3,4-oxadiazole (2d)
IR (KBr) cm^{-1} 3210(Ar-H), 1566(N=CH), 1478(C=C), 933, 811, 778. ^1H NMR (DMSO D_6, 400 MHz) δ ppm 8.70- 6.54 (m, 11H, Ar) . MS: m/z (%) 267 (58%) $[M^+]$.

Antibacterial Activity[5]:
The synthesized 23 compounds were screened for antibacterial activity studies at a concentration of 50µg/ml and 100µg/ml using DMSO as a control against *Staphylococcus aureus, Bacillus pumilus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa* by disk-diffusion method on nutrient agar media. Ampicillin was used as standard drugs for the comparison at the concentration 50 µg/ml and 100 µg/ml against Gram positive and Gram-negative bacteria used for the study.

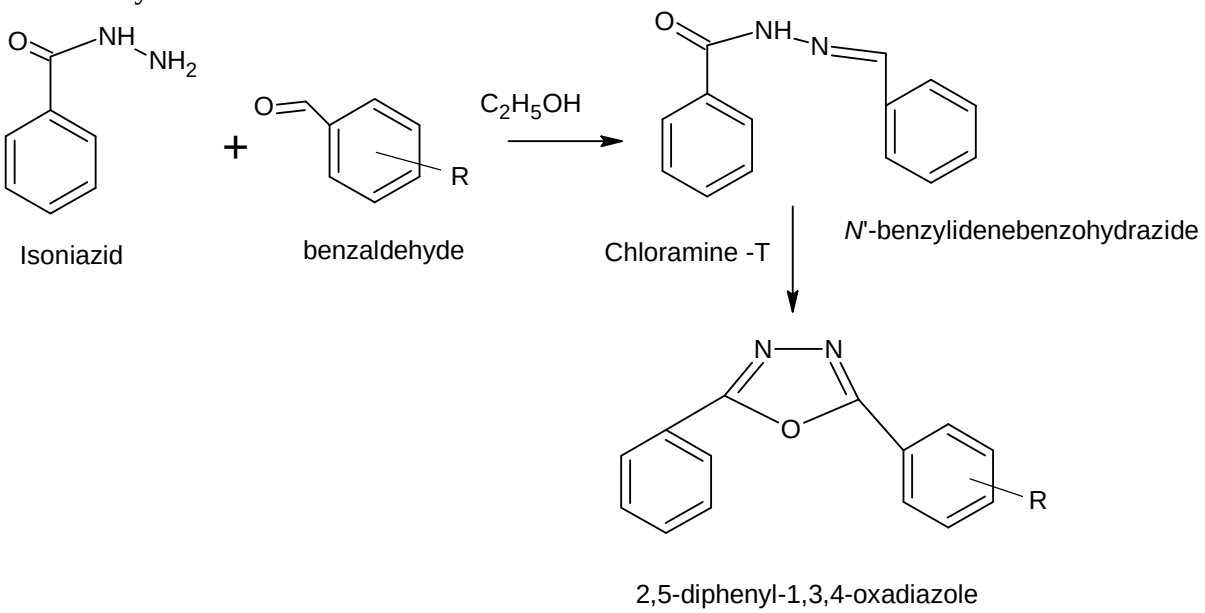

Table-1: Physical characterization of newly synthesized compounds 1a-d

Compound	Physical state	Yield	m.p.
1a	Yellow resinous	74	112^0 c
1b	white crystals	85	158^0 c
1c	light brown crystals	68	164^0 c
1d	Light yellow crystals	72	84^0 C

Table-2: Physical characterization of newly synthesized compounds 2a-d

Compound	Physical state	Yield	m.p.	Rf value
2a	white resinous	64	131^0 c	0.65
2b	cream crystals	43	140^0 c	0.56
2c	brown crystals	81	128^0 c	0.75
2d	Dark brown crystals	69	98^0 C	0.72

Table 3: Antibacterial activity of newly synthesized compounds

Sample Code	*Inhibition zone diameter in mm							
	B. subtilis		*B. pumilis*		*E. coli*		*P. aureginosa*	
	50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
1a	13	18	16	27	21	30	18	26
1b	20	25	17	28	12	21	14	26
1c	13	25	11	29	09	30	17	29
1d	15	27	10	28	12	23	12	24
2a	11	21	17	28	09	20	14	21
2b	20	30	13	30	19	29	12	22
2c	17	32	23	29	18	30	15	33
2d	14	31	17	33	13	31	19	33
Ampicillin	21	26	21	26	22	30	22	34
DMSO	-	-	-	-	-	-	-	-

**Average of triplicate ± Standard deviation*
Note: '-'denotes no activity, 10-15mm moderate activity, 16-35 mm potent activity.

CONCLUSION

The presence of free hydrazine hydrate present in isoniazid easily undergoes condensation reaction to give schiff's base. This intermediate will serve to synthesize wide variety of heterocyclic compounds. When schiff's base reacts with chloramines-T a strong oxidizing agent to form the final compounds 2,5-diphenyl-1,3,4-oxadiazole derivatives(2a-d).

The final chemical structures were confirmed by IR, ^{1}H NMR and Mass spectral analysis. In the intermediate product i.e. Schiff' base confirmed by presence of 3431 (NH), 3102(Ar-H), 1640 (C=O)in IR spectra and 10.50 (s, 1H, CONH). Then final oxadiazoles were confirmed by absence of NH and C=O peak by IR and –CONH in ^{1}H NMR, and presence of 1569 (N=CH),1474 (C=C) in IR and 8.82-6.23 (m, 11H, Ar) in ^{1}H NMR.

Then all the novel compounds are tested for antibacterial activity active. When we compared the activity of intermediate and final compounds, however the activities of tested compounds are much significant than those of standard antibacterial agents used. The compounds 2c and 2d showed potent antibacterial activity against *B.subtilis, P.aureginosa* than the intermediate i.e. 1c and 1d. Hence the cylic ring is essential for significant activity.

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