SSRG International Journal of Applied Chemistry
ISSN: 2393 – 9133 /doi:10.14445/23939133/IJAC-V8I1P102

Volume 8 Issue 1, 6-9, Jan-April 2021

Synthesis, Spectral and Antimicrobial Studies of Some Furohydroxamic Acids

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Abstract: *Some furohydroxamic acids have been synthesized and screened for their possible antimicrobial activity biological profile like antibacterial activity against four different strain viz. Lactobacillus (gram-positive bacteria), Rhizobium, E.coli, Pseudomonas (gram-negative bacteria), and antifungal activity against three different fungal strains viz. Alternaria, curvularia, and Rhizoctonia by paper disc plate method have been studied.*

Keywords: *FHA, MFHA, PFHA, p-TFHA, p-CIPFHA, antimicrobial, antibacterial activity.*

INTRODUCTION

Furohydroxamic acids constitute an important class of heterocyclic hydroxamic acids. Various substituted hydroxamic acids are reported to elicit a wide range of biological activities [1-5]. Recent progress in hydroxamic acid chemistry has been stimulated by isolation of naturally occurring compounds, found mainly in fungi, which are active as antibiotics, antibacterial [6-7], antifungal [8-9], anticancer agents [10-11], anti-inflammatory [12-13], specific enzyme inhibitors [14-15] and siderophores [16]. Heterocyclic compounds are found to exhibit different types of pharmacological properties, and hence in our search for the synthesis of some biologically active heterocycles, we report here in some furohydroxamic acids possessing antibacterial and antifungal activity.

EXPERIMENTAL

Synthesis of unsubstituted and N-substituted furohydroxamic acids are described below:

(i) 2- Furohydroxamic acid (FHA)

A mixture of 0.1 mole of finely powdered hydroxylamine hydrochloride in 50ml of diethyl ether and a 0.1 mole of sodium carbonate in 5ml of water was added to a 0.1 mole of furoyl chloride in 50ml diethyl ether for about an hour with constant stirring. The temperature of the reaction mixture was maintained at 0°C by external cooling. Almost 80% of the product was precipitated during the reaction. Some of the product, which was dissolved in the ether layer during the coupling reaction process, was recovered from the ethereal layer by distillation under reduced pressure.

The total product was triturated with sodium hydrogen carbonate and then repeatedly washed with cold water to remove the acidic impurities.

The crude 2-furohydroxamic acid was thus obtained was dissolved in ethyl acetate, and the recrystallized furohydroxamic acid was obtained by keeping the filtrate at room temperature. It gave white crystals, and the product was dried over P_2O_5 in vacuum desiccation, melting point = 115°C.

(ii) N- Methyl -2- furohydroxamic acid [MFHA]

MFHA was prepared in following two steps A and B:

Step A: - Preparation of N-methyl hydroxylamine prepared according to recommended procedures [19].

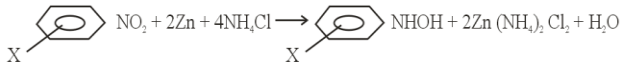
15.53g (0.2375 moles) of zinc dust was added gradually to a mechanically stirred mixture of nitromethane 5.65g (0.0925 moles), ammonium chloride 3.4g (0.0633 moles), and distilled water 800ml in a 2 litre conical flask. It was cooled in an ice bath. The reaction mixture's temperature was kept between 0° and 15°C, and the addition of zinc dust was extended over a period of 2-3 hours. When the reaction was complete, the precipitates of unreacted zinc dust and zinc oxide were removed from the reaction mixture by filtration. The filtrate containing N-methyl hydroxylamine was used as such for the synthesis of corresponding furohydroxamic acid.

Step B: - A freshly prepared aqueous solution of N-methyl hydroxylamine and 50ml of diethyl ether were taken in a 500ml conical flask containing a saturated aqueous solution of sodium hydrogen carbonate. Then an ethereal solution of furoyl chloride was added over a period of about one hour so that all the hydroxylamine was completely reacted with furoyl chloride and Tollen's reagent tested this. Care must be taken in testing the absence of free hydroxylamine in the reaction mixture.

The ethereal layer was removed by vacuum distillation. The volume of the aqueous layer was reduced under reduced pressure to get the light brown solid product. The sodium salt of N-methyl substituted hydroxamic acid was extracted with hot methanol. N-methyl furohydroxamic acid was obtained from their sodium salt by hydrolysis with 6N acetic acid. The product was purified by crystallization in methanol. The light brown crystals were obtained after keeping the solution in the deep freeze overnight, melting point =161°C.

(iii) N – Aryl-2- furohydroxamic acids [PFHA, p-TFHA, and p-CIPFHA]

These compounds were also synthesized in two steps A and B.Step A:- N-phenyl-, N-p-tolyl, N-p-chlorophenyl- were prepared by the reduction of corresponding nitro-compounds with zinc dust in an aqueous or aqueous ethanolic solution buffered with ammonium chloride at 60 – 75°C (Scheme I)



$Zn(NH_4)_2Cl_2 + H_2O \longrightarrow ZnO + {}_2NH_4Cl$

(Where X = H, p – CH_3, p – Cl)

Scheme-I

The N-aryl hydroxylamines were prepared on the basis of the optimum experimental conditions so as to obtain maximum yields. The different preparative conditions are shown in Table 1.

Table 1: Experimental Condition for the Preparation of N – Arylhydroxylamines

S.N	Reactants								
		–NO_2	Zn	NH_4Cl					
	X	Gram (mole)	Gram (mole)	Gram (mole)	Medium	Temp °C	Yield %	Melting Point (reported)	Ref.
1	H	50.0 (0.41)	100.0 (1.53)	26.0 (0.49)	aqueous	65-75	70	82 (82)	20 21(a)
2	p–CH_3	25.0 (0.18)	30.0 (0.46)	12.5 (0.23)	aqueous	65-75	65	93 (93)	21(b) 22
3	p–Cl	24.0 (0.15)	30.0 (0.46)	2.5 (0.05)	aqueous alcoholic	60-65	60	86 (86) (86.5) (88)	21(c) 23-26

Step B: - 0.1 moles of freshly crystallized N – aryl hydroxylamine was taken in a conical flask (500ml) and dissolved in about 50ml of diethyl ether. A saturated aqueous solution of 0.15 to 0.2 mole of sodium hydrogen carbonate was also placed in the flask. The flask contents were stirred mechanically with external cooling to bring the temperature to 0°C or even less. Now the solution of 0.1 moles of furoyl chloride in 50ml of diethyl ether was chloride in 50ml of diethyl ether was added dropwise for one hour. A granular white precipitate was obtained, which was separated from the ethereal layer.

More quantity of the product was also obtained after distillation of the ethereal layer under reduced pressure. The quantities of the product were mixed and triturated with sodium hydrogen carbonate for 15 minutes in a glass mortar and repeatedly washed with cold water to remove the acidic impurities. N-aryl substituted furohydroxamic acids were dissolved in hot benzene and filtered through fluted filter paper using a stem-less funnel.

The filtrate was diluted with petroleum ether (boiling range 60 – 80°C) and kept overnight in the deep freeze. Crystals were obtained, and these were separated by filtration and washed with 50% benzene- petroleum ether mixture. The product was dried over P_2O_5 under vacuum. PFHA; melting point = 135°C, p-TFHA; melting point = 141°C and p – ClPFHA; melting point =161°C.

Table – 2: Characterization Data

				Found (required) %		
Compound	Mol. Formula	Melting Point °C	Yield %	C	H	N
FHA	$C_5H_5NO_3$	115	52	47.99 (47.24)	4.11 (3.93)	11.59 (11.02)
MFHA	$C_6H_7NO_3$	161	62	50.02 (51.06)	4.05 (4.96)	8.55 (9.93)
PFHA	$C_{11}H_9NO_3$	135	82	65.02 (65.02)	4.40 (4.43)	7.24 (6.89)
p-TFHA	$C_{12}H_{11}NO_3$	141	74	65.12 (66.36)	4.76 (5.06)	6.02 (6.45)
p-ClPFHA	$C_{11}H_8NO_3Cl$	162	69	56.50 (55.58)	3.63 (3.37)	6.08 (5.89)

Table: 3 Spectral Data

Compound	IR (cm^{-1})	^1H NMR (S, ppm)
FHA	3307 (N-H), 3163 (O–H), 1648 (–C=0), 1482 (C–N), 1236 (C–O–C, furan ring)	1.90 (s, IH, H–N–) 6.59 (m, Ar–H, furan) 7.04 (d, Ar–H, furan) 7.58 (s, Ar–H, furan) 8.82 (s, 1H, furan)
MFHA	3148 (O–H), 1619 (C=O), 1482 (C–N), 1244 (C–O–C, furan ring)	3.30 (s, 3H, CH_3 – N) 6.54 (m, Ar–H, furan) 7.16 (d, Ar–H, furan) 7.62 (s, Ar–H, furan) 8.30 (s, 1H, –OH)
PFHA	3177 (O–H), 1612 (C=O), 1474 (C–N), 1244 (C–O–C, furan ring)	6.56 (m, Ar–H, furan) 7.16 (d, Ar–H, furan) 7.26 – 7.59 (t, 5H, phenyl) 7.66 (s, Ar–H, furan) 8.60 (s, 1H, –OH)
p–TFHA	3141 (O–H), 1604 (C=O), 1474 (C–N), 1244 (C–O–C), furan ring)	2.38 (s, 3H, CH_3^-) 6.56 (m, Ar–H, furan) 7.09 (d, Ar–H, furan) 7.20 (d, 2H, ortho position phenyl grp) 7.43 (d, 2H, meta position phenyl grp) 7.65 (s, Ar–H, furan)
p–ClPFHA	3127 (O–H), 1612 (C=O), 1496 (C–N), 1244 (C–O–C, furan ring)	8.60 (s, 1H, –OH) 6.59 (m, Ar–H, furan) 7.25 (d, Ar–H, furan) 7.41 (m, 2H, ortho position, phenyl grp) 7.63 (m, 2H, meta position, phenyl grp) 7.70 (s, Ar–H, furan) 8.60 (s, 1H, –OH)

RESULTS AND DISCUSSION

The title compounds were synthesized from our laboratory as per standard method[17]. These compounds are characterized by elemental analyses, IR, and ^1H NMR Spectra (Table I and II). Minimum inhibitory concentration (MIC) for all the synthesized compounds have been tested against the same bacterial and fungal strains by paper-disc plate method[18] using DMSO as solvent at 1000 µg/ml concentration in comparison with standard drug Norfloxacin and Penicillin. The results are summarized in Table:4

The synthesized furohydroxamic acids reflected significant antibacterial activity against the bacterial strains studied. p-CIPFHA and MFHA showed significant antibacterial activity against the bacteria studied. Other compounds p-TFHA, PFHA, and FHA exhibited moderate to least actions against the bacteria.

The reference standard antibiotic Norfloxacin exhibited better antibacterial activity than the synthesized compounds against the bacterial strains.

No significant antifungal activity was reflected by prepared compounds. In general, the compounds were found to possess better bactericidal and not fungicidal properties.

Table -4: Antimicrobial Activity of Synthesized Compounds

Compound	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)		
	Gram-positive		Gram-negative		Fungi		
	Lactobacillus	Rhizobium	E.coli	Pseudomonas	Alternaria	Curvularia	Rhizoctonia
FHA	8	14	9	11	2	-	4
MFHA	12	19	14	18	5	6	6
PFHA	6	10	11	8	-	3	5

p-TFHA	11	13	15	12	3	4	-
p-ClPFHA	17	16	18	15	8	7	9
Penicillin	-	-	-	-	-	-	-
Norfloxacin	19	23	21	20	17	15	19

ACKNOWLEDGEMENT

The authors are thankful to Principal Dr. B.N. Sharma, Dr. H.S. Kar, Head, Department of Chemistry, Govt. College of Science, Raipur (C.G.) for providing laboratory facilities.

The authors also gratefully acknowledge Head, SAIF, IIT-Mumbai for elemental analysis and spectral data.

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