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Efficient Ultrasound Synthesis and Antimicrobial Studies of Novel Schiff Bases of Isoniazid

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A B S T R A C T

Hydrazones possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. In the present protocol we have synthesized six INH hydrazide-hydrazones by reacting isoniazid with various aldehydes by conventional as well as ultrasound irradiation method. The synthesized compounds were evaluated for antimicrobial activities. Utilization of ultrasound irradiation, simple reaction condition, isolation and purification makes this manipulation very interesting from an economic and environmental perspective.

Keywords: Ultrasound irradiation, Conventional method, INH hydrazide-hydrazones, Antimicrobial activities

A R T I C L E I N F O

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1. Introduction

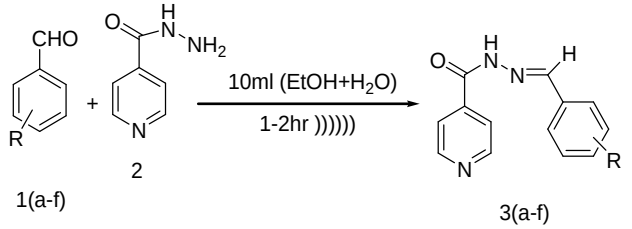
The development of the field of bioinorganic chemistry has increased the interest in Schiff base complexes as they easily form stable complexes with most transition metal ions and many of these complexes may serve as model for

biologically important species [1-3]. The Schiff bases are also used as versatile components in nucleophilic addition with organometallic reagents [4] and in cycloaddition reactions [5, 6]. Hydrazones have been demonstrated to possess antimicrobial, antituberculosis, anti-inflammatory and antitumoral activities [7-9]. Isoniazid (isonicotinic acid hydrazide; INH) is a drug of proven therapeutical importance, used against wide spectrum bacterial ailments, *viz.*, and tuberculosis. Hydrazones derived from the condensation of isonicotinic acid hydrazide (isoniazid, INH) with aldehydes represent an important class of chelating ligands and their metal complexes are of great interest due to their importance in biological, pharmacological and clinical applications [10]. Owing to biological importance of hydrazones, we became interested to synthesis a series of novel hydrazide-hydrazones by reacting isoniazid with various aldehydes under ultrasound irradiation for the first time. The synthesized compounds were evaluated for antibacterial and antifungal screening. The use of ultrasound in organic transformation is now well known to enhance reaction rates and yields/selectivity of reactions and in several cases facilitates organic transformation at ambient conditions [11]. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication. Therefore organic reaction carried out by using ultrasound irradiation is an efficient and eco-friendly synthetic strategy.

2. Materials and Methods

All used chemicals were purchased from Merk or S.D. Fine chemicals. Melting points were determined on an electrochemical digital melting point apparatus. The formation of the product was determined by thin layer chromatography. Products were characterized by comparison of spectroscopic data (UV-Visible, FT-IR, ^{1}HNMR spectra) and melting points with authentic samples. The wavelength of absorbance was determined by UV-Visible spectrophotometer [JASCO 503] using a quartz quvette and ethanol as reference. The IR spectra were recorded on FT-IR spectrophotometer [JASCO, FT-IR/4100] Japan using dry KBr as standard reference. ^{1}H NMR spectra were recorded on an Broker Avance II 400 MHz FT-NMR spectrometer in DMSO as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Elemental analyses were done using Perkin Elmer 2400CHN analyzer.

General procedure for the synthesis of Schiff base derivatives: Six Schiff base were synthesis, depending on the chemical reaction given in scheme1.



Scheme 1: Synthesis of Schiff bases using ultra sound irradiation

INH (10.0mmol) was dissolved in 10 ml of ethanol+H_2O (6:4) stir for some time to give a clear solution to this aromatic aldehydes (10.0mmol) was added drop wise over 5 min. The resulting reaction mixture was irradiated for an appropriate time as indicated in Table 2 under Ultrasound. After completion of the reaction it was allowed to cool slowly and stand overnight. Obtained crystalline solid was filtered off. Finally washed with hot water, dried and recrystallize to afford pure crystals.

Spectral data of representative compounds:

(3a):- IR (KBr disk, ν_{max}): 3431.4 (CO-NH-), 2946.0 (C-H, aromatic), 1727.5 (C=O), 1688.4 (C=N), 1599.2-1619.6 (C=C), 1227.2 (C-O) cm^{-1}; ^{1}H-NMR(DMSO-400MHz) δ=11.81 (s,2H,CO-NH-), 8.71 (s,2H,CH=N), 7.55-7.83 (m,8H,Ar), 3.49 (s, 5H), 2.95-2.91 (s, 2-CH_3); ^{13}C NMR (DMSO-400MHz) δ= 163.09, 151.65, 150.20, 149.90, 140.78, 128.66, 128.51, 123.20, 121.13, 111.71, 56.05, 40.03, 39.82, 38.99; UV/Vis(DMSO)nm: 410, 370nm, Anal Calcd for $C_{15}H_{16}N_4O$: C, 67.16. H, 5.97. N, 20.89%. Found: C, 67.21. H, 5.89. N, 20.81%.

(3d):- IR (KBr disk, ν_{max}): 3435.2(CO-NH-), 3209.5 (-NH), 3035.9 & 2950.1 (C-H, aromatic), 1673.6 (C=O), 1602.8 (C=N), 1550.7 (C=C),1295.0 (C-O) cm^{-1}; ^{1}H-NMR(DMSO-400MHz) δ=12.32 (s,2H,CO-NH-), 8.81 (s,2H,CH=N), 7.16-8.04 (m,8H,Ar), 3.41 (s, 5H); ^{13}C NMR (DMSO-400MHz) δ= 161.71, 150.30, 147.71, 140.31, 139.85, 132.98, 128.90, 128.87, 121.50, 40.02, 39.01, 39.60, 39.39; UV/Vis(DMSO)nm: 362nm, Anal Calcd for $C_{13}H_9N_3O_2$: C, 61.39. H, 4.18. N, 19.53%. Found: C, 61.43. H, 4.16. N, 19.49%

(3e):- IR (KBr disk, ν_{max}): 3421.3 (CO-NH-), 3250.4 (-NH), 3009.8 & 2953.5 (C-H, aromatic), 1680.2 (C=O), 1624.3 (C=N), 1546.2 (C=C), 1274.4 (C-O)cm^{-1}; ^{1}H-NMR(DMSO-400MHz) δ=12.321 (s,2H,CO-NH-), 8.813 (s,2H,CH=N), 7.165-8.043 (m,8H,Ar), 5.121 (s, aromatic C-OH); ^{13}C NMR (DMSO-400MHz) δ= 163.21, 140.23, 149.52, 149.23, 122.33, 123.50, 115.98, 150.21, 143.13, 131.20, 122.5, 161.56, UV/Vis(DMSO)nm: 374nm, Anal Calcd for $C_{13}H_{11}N_3O_2$: C, 64.73. H, 4.56. N, 17.42%. Found: C, 64.52. H, 4.59. N, 17.39%

(3f):- IR (KBr disk, ν_{max}): 3446.7 (CO-NH-), 3207.76 (-NH), 3039.8 & 2993.5 (C-H, aromatic), 1689.5 (C=O), 1649.4 (C=N), 1599.2 (C=C), 1227.2 (C-O)cm^{-1}; ^{1}H-NMR(DMSO-400MHz) δ=12.321 (s,2H,CO-NH-), 8.813 (s,2H,CH=N), 7.165-8.043 (m,8H,Ar); ^{13}C NMR (DMSO-400MHz) δ= 163.23, 160.32, 149.72, 149.84, 143.51, 141.11, 132.23, 130.26, 122.89, 122.87, 121.72, 116.13, 114.58, 55.92; UV/Vis(DMSO)nm: 368nm, Anal Calcd for $C_{14}H_{13}N_3O_2$: C, 65.88. H, 5.09. N, 16.47%. Found: C, 65.83. H, 5.12. N, 16.44%.

3. Results and Discussion

The INH hydrazide-hydrazones 3(a-f) were prepared by reacting isoniazid with various aldehydes 1(a-f) using ethanol and water in 6:4 ratio as solvent (scheme1). ^{1}H NMR spectroscopy still remains as valuable tool for establishing the structural characterization. ^{1}H NMR spectra of prepared hydrazones have been recorded in DMSO. Each

type of signal has a characteristic chemical shift rang that can be used as initial assignment. The broad single of the –NH- group of hydrazone in the range of 12.26 to 11.87 (δ in ppm) confirm the formation of imine linkage. The two set of protons of 4-substituted pyridine ring shows two triplets at 8.75 and 7.74 (δ in ppm), the proton of –N=C–H at *δ* 8.79–8.21 ppm, the characteristic protons of benzylidene at *δ* 7.77–6.78 ppm and the 2 protons of Ar–CH_2–N at *δ* 3.69–3.49 ppm, the ^{13}C-NMR spectra of most compounds had characteristic signals of C=O at around *δ* 163.91–161.18 ppm, of pyridine at *δ* 149.88–122.15 ppm, of the –N=C–H group at *δ* 143.48–143.19 ppm, of benzylidene at *δ* 157.58–115.75 ppm and Ar–CH_2–N at *δ* 55.89–45.59 ppm. Generally, all amides show two absorption bands, (i) the carbonyl absorption band near 1640 cm^{-1} known as amide-I band and (ii) strong band in the 1500–1600 cm^{-1} region, known as amide-II band. The origin of these bands in hydrazones, that is, the carbonyl absorption responsible for the amide-I band, is likely to be lowered [12] infrequently by the NH group as in normal amides. The amide-I band in INH-derivative, however appears at 1700 and 1655 cm^{-1} [13,14]. The NH stretching absorption in free Ligands occurs at $\bar{V}$ 3300 and 3220 cm^{-1} [15] another important band occurs at $\bar{V}$ 1585 cm^{-1}attributed to *ν*(C=N) (azomethine) mode [16–18]. In general, the IR spectra of all compounds 3a–f showed absorption band in the 3279–3255, 2978–2946, 2862–2835, 1677–1663, 1659–1641, 1581–1552, 1174–1125 and 1079–1038 cm^{-1} regions, conforming the presence of NH, CH, CH_2, C=N, C=O, C=C and C–N, respectively. UV/Vis spectrum in DMSO generally showed intense peak in the region 360-412 nm due to aromatic imine in conjugation to isoniazide skeleton [19] confirms the formation of Schiff bases of isoniazide. The yield of products depends on the nature of aldehyde. The aldehydes with electron withdrawing groups are more reactive and give good yield of product. Comparative study results obtained by ultrasonication synthesis, versus conventional refluxing method was that reaction which required 480min by conventional method, was completed within 120 min by ultrasonication technique and yields have been improved from 75-85%. The comparison study data of ultrasonication and conventional method with physical data of the compounds were represented in Table I. The reaction yield was improved with short time under sonication compared to that of conventional method.

Antimicrobial screening

All the synthesized derivatives were then assayed for their *in-vitro* antibacterial activity against a panel of pathogenic as well as standard bacterial strains such as *Bacillus Subtilis, Staphylococcus aureus, Escherichia colis, Salmonella Typhi* and antifungal screening has been tested against *Aspergillus niger* using dimethyl sulphoxide as solvent. Gentamicin was recovered from their commercial preparation as a reference standard. The antibacterial activities were carried out by standard procedure of agar well diffusion method. A uniform suspension of test organism of 24 hours old culture was prepared in test tube containing sterile saline solution. A sterile nutrient agar was then added in each of the Petri dishes. The dishes were related to ensure the uniform mixing of the micro organism in the agar medium which was then allowed to solidify. The DMSO was used a control of the solvent incubated at 37°C for 24 hours. The compounds to be tested were dissolved in respective solvent. The concentration of the test compound in DMSO was 100μg ml^{-1}. Gentamicin was used as a standard compound for comparison. The discs were placed into the plates and incubated at 37 °C for 24h. The diameter of zone of inhibition around each disc was measured by scale and results were recorded in terms of mm (Table II). The screening results indicate the Compounds 3(a-f) showed moderate to excellent antimicrobial activities against the selected pathogens.

Table I: Synthesis of Schiff's bases using variously substituted aromatic aldehydes.

			With ultrasound[a]		Without ultrasound[b]	
Entry	**R**	**M.P.(°C)**	**Time (min)**	**Yield (%)**	**Time (min)**	**Yield (%)**
3a	3-$N(CH_3)_2C_6H_4$	218-220	150	80	485	72
3b	4-ClC_6H_4	215-217	120	90	520	79
3c	3-$NO_2C_6H_4$	190-192	135	87	490	73
3d	2-furfural	225-227	155	83	525	77
3e	2-OHC_6H_4	196-198	140	82	530	76
3f	4-$OCH_3C_6H_4$	138-140	145	85	510	71

[a]Reaction of aldehydes with INH under ultrasonic waves; [b]Reaction under reflux condition; [c]isolated yield

Table II: *In-vitro* antibacterial screening of synthesized compounds

	Antibacterial zone of inhibition (in mm)				
	Gram positive		**Gram negative**		**Fungi**
	B. subtilis	***S. aureus***	***S. typhi***	***P. aeroginosa***	***A. niger***
Conc.(μg/ml)	**100**	**100**	**100**	**100**	**100**
Comp. No.					
3a	9	9	6	6	7
3b	9	9	5	5	6
3c	9	9	8	8	8

3d	10	10	9	9	11
3e	10	10	8	8	7
3f	11	11	6	6	7
Gentamicin	12	16	15	17	8

4. Conclusion

In the present work various INH hydrazide-hydrazones were synthesized by conventional as well as ultrasound irradiation and their structures confirmed on the basis of spectral analysis. The synthesized compounds are active against all bacterias and fungies and found to be promising candidate as new antimicrobial agents. In summary, this work demonstrated a rapid, efficient and environmentally friendly method for the synthesis of INH hydrazide-hydrazones under ultrasound irradiation and results obtained confirmed the superiority of ultrasound irradiation method over the conventional method.

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