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Synthesis of 2-Pyridin-3-yl-1,3-benzoxazole and 2-Pyridin-3-yl-1,3-benzimidazole under Microwave Irradiation and Their Antimicrobial Evaluation

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A one pot synthesis for 2-pyridine-benzoxazole and 2-pyridine-benzimidazole under microwave irradiation is described. The synthesized compounds were subjected to spectral analysis and their results were reported. The title compounds were evaluated for their antimicrobial activity and found to exhibit a variable degree of activity.

Key Words: Synthesis, Microwave irradiation, Antimicrobial activity, Benzoxazole, Benzimidazole.

INTRODUCTION

There has been much interest in the development of microwave assisted technique in the synthesis of organic compounds especially heterocyclic compounds[1]. In view of utility of irradiation[2] in the synthesis of heterocyclic compounds and the biologically importance[3] of 2-pyridin-3-yl-1,3-benzoxazole and benzimidazole, it was thought worth while to develop a new selective method for the synthesis of the title compounds.

Benzoxazoles and benzimidazoles are well known for diverse activities and play a vital role as antiinflammatory[4], antihistaminic[5], antimicrobial[6], antitumour[7], antiasthmatic[8] and anthelmintics[9]. Benzoxazoles and benzimidazoles are useful structural elements in medicinal chemistry. The general protocol for the synthesis of both 2-pyridin-3-yl-1,3-benzoxazole and 2-pyridin-3-yl-1,3-benzimidazole involves condensation of nicotinic acid with *o*-aminophenol and *o*-phenylenediamine in ethanol, respectively. However the combination of solvents and long reaction time makes the method environmentally hazardous. Thus the utility of microwave irradiation in the synthesis of the title compounds will be definitely an environmentally benign approach for the synthesis of 2-pyridin-3-yl-1,3-benzoxazole and 2-pyridin-3-yl-1,3-benzimidazole. Further attractions of this method are that it allows reaction in open vessel (thus avoiding risk of high pressure development) and synthesis on preparative scales[10].

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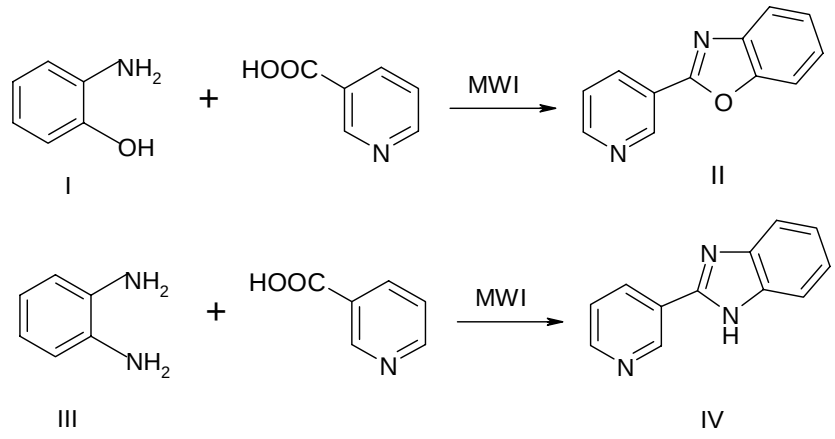
EXPERIMENTAL

All the chemicals used for the synthesis were of laboratory grade and the glassware used were thoroughly cleaned and dried. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrometer using KBr discs. ^{1}H NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer. Mass spectra were recorded on Jeol-D 300 EIMS spectrometer. Elemental analyses were done at CDRI, Lucknow, India. The purity of the compounds was confirmed by TLC on silica gel G. Reactions were carried out in a Samsung 2300 ET domestic microwave oven.

Synthesis of 2-pyridin-3-yl-1,3-benzoxazole (II): A mixture of **I** (0.01 mol) and nicotinic acid (0.01 mol) in DMF (15 mL) was dissolved in a borosil beaker (250 mL) and placed in a microwave oven and irradiated for 2 min. The reaction mixture was allowed to attain room temperature and treated with cold water and made alkaline with 10 % $NaHCO_3$ solution. The product was filtered and recrystallized from ethanol to afford compound **II**.

Synthesis of 2-pyridin-3-yl-1,3-benzimidazole (IV): A mixture of **III** (0.01 mol) and nicotinic acid (0.01 mol) in DMF (15 mL) was dissolved in a borosil beaker (250 mL) and placed in a microwave oven and irradiated for 2 min. The reaction mixture was allowed to attain room temperature and treated with cold water and made alkaline with 10 % $NaHCO_3$ solution. The product was filtered and recrystallized from ethanol to afford compound **IV**.



Reaction of *o*-aminophenol and *o*-phenylenediamine with nicotinic acid to afford the title compounds 2-pyridin-3-yl-1,3-benzoxazole and 2-pyridin-3-yl-1,3-benzimidazole, respectively. Compound **I** = *o*-amino phenol, Compound **II** = 2-pyridin-3-yl-1,3-benzoxazole, Compound **III** = *o*-phenylenediamine, Compound **IV** = 2-pyridin-3-yl-1,3-benzimidazole, MWI = Microwave irradiation.

Scheme-I: Synthesis of the title compounds

Antimicrobial activity: The synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus, Proteus vulgaris, Pseudomonas aureginosa, Escherichia coli* and antifungal activity against *Candida albicans* using cup diffusion method using DMF as solvent. The compounds were tested at 50 µg level. The results were compared with ciprofloxacin (30 µg/disk) for antibacterial activity and clotrimazole (10 µg/disk) for antifungal activity.

RESULTS AND DISCUSSION

The reaction mixture was irradiated in a microwave oven to yield the title compounds **II** and **IV**. This was evidenced by the disappearance of the IR absorption band in the region 3420-3250 and 3250-3050 due to the -NH_2 and -OH groups, respectively. The compound **II** exhibited ^{1}H NMR signals only at aromatic region for aromatic protons and not for amino or hydroxyl protons. The compound **IV** exhibited ^{1}H NMR signals besides aromatic protons at 6.9-7.85 a broad singlet at 12.4 for the -NH of benzimidazole (Table-1). Both the compound (**II**) and (**IV**) exhibited molecular ion peaks at 196 and 195, respectively which indicate the formation of the title compounds (Table-1).

TABLE-1
ANALYTICAL AND SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

Compounds	m.p. (ºC)	Period (min)	Yield (%)	M^+	^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ ppm
2-Pyridin-3-yl-1,3-benzoxazole (II)	168	2.0	82	196	6.9-7.85 (complex, m, 8H, 4H, Ar-H, 4H, Pyridyl-H)
2-Pyridin-3-yl-1,3-benzimidazole (IV)	194	2.0	86	195	6.9-7.85 (complex, m, 8H, 4H, Ar-H, 4H, Pyridyl-H) 12.4 (s, 1H, NH of benzimidazole)

Elemental analyses of the compounds were in good agreement with calculated values.

TABLE-2
DATA OF ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS BY ZONE OF INHIBITION METHOD

Strains of microorganism	Diameter of zone of inhibition (mm)			
	Compounds (50 µg)		Control	
	II	**IV**	Ciprofloxacin (30 µg)	Clotrimazole (10 µg)
Staphylococcus aureus	20	19	24	–
Proteus vulgaris	12	10	22	–
Pseudomonas aureginosa	21	20	20	–
Escherichia coli	20	20	24	–
Candida albicans	18	13	–	13

(–) Indicates no inhibition zone (no activity)
Compound **II** = 2-Pyridin-3-yl-1,3-benzoxazole.
Compound **IV** = 2-Pyridin-3-yl-1,3-benzimidazole.

The synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus, Proteus vulgaris, Pseudomonas aureginosa, Escherichia coli* and antifungal activity against *Candida albicans* using cup diffusion method using DMF as solvent. Both the compounds exhibited significant activity against all the bacterial strains used except *Proteus vulgaris*. Compound **I** showed appreciable activity against *Candida albicans* whereas compound **IV** showed reasonable activity against the fungal strain used (Table-2).

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