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Synthesis of heterocyclic derivatives of pyrrole under Solvent-free Conditions

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Abstract— The biological significance of the pyrrole derivatives has led us to the synthesis of substituted pyrrole using microwave oven method. The structures of compounds have been established by means of IR, ^{1}H-NMR, and 13C-NMR. All the compounds were evaluated for antibacterial activity. Among them, compound 3c shows the highest antibacterial activity.

Keywords—pyrrole derivatives; pyrimidine; solvent-free

I. INTRODUCTION

At the present time the use of microwave energy for heating chemical reactions has shown tremendous benefits in organic synthesis. This technique as an alternative to conventional energy sources for introduction of energy into reactions has become a very well-known and practical method in various fields of chemistry. Microwave-assisted organic synthesis is known for the spectacular accelerations produced in many reactions as a consequence of the heating rate, a phenomenon that cannot be easily reproduced by classical heating methods. Its specific heating method attracts extensive interest because of rapid volumetric heating, suppressed side reactions, energy saving, direct heating, decreased environmental pollutions, and safe operations. Another area of interest which has been under focus recently is to avoid the use of organic solvent, which leads to wastage and is detrimental to the environment. Microwave heating for carrying out reactions in solid state has also attracted considerable attention in recent years [1].

Pyrrole and its derivatives play an important role in pharmaceutical and natural chemistry. Commonly they are widely used as an intermediate in the synthesis of pharmaceuticals, medicines, agrochemicals, dyes, photographic chemicals, perfumes and other organic compounds. For example, chlorophyll, heme are derivatives which are made by four pyrrole ring formation of porphyrin ring system. In addition they are used as catalysts for polymerization process, corrosion inhibitors, preservatives, solvents for resins and terpenes, standard in a chromatographic analysis and they are also used in organic synthesis in the pharmaceutical industry. It is an important constituent in the structure of a number of pharmaceutical products and new active agents with variety of pharmacological effects like: atorvastatine - antihyperlipidemic, aloracetam for treatment of Alczheimer' disease, elopiprazole - antipsychotic, lorpiprazole - anxiolytic, tolmetin - anti-inflammatory activity [6].

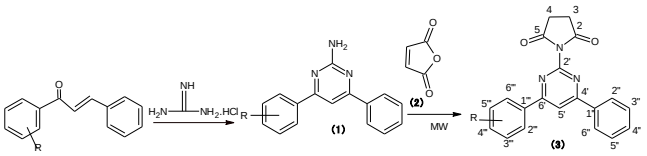
In the present research, we report the synthesis of some pyrrole derivatives using microwave oven and the evaluation of their biological activitiy.

II. EXPERIMETAL

General experimental procedures

Melting point was measured by using Thiele's apparatus in capillary and uncorrected. The FTIR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in form of mixing with KBr and using reflex-measure method. 1H-NMR (500 MHz), 13C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, German) at 500.13 MHz, using DMSO-d6 as solvent and TMS as an internal reference, δ in ppm. Bioassays were carried out in Hospital 19-8, Hanoi, Vietnam.

Maleic anhydride (0,01 mol) and 2-amino-4,6-diarylpyrimidine (0,01 mol) were dissolved separately in DMF (50 mL) to yield solutions A and B, respectively. Solution B was added dropwise into solution A to give solution C. Solution C was stirred for 2 hours at 20°C in a water bath. P_2O_5 (12 g) was dissolved in H_2SO_4 (10 mL). This mixture was added dropwise into solution C and was stirred for five minutes [5]. which was then evaporated and placed in a procelain and subjected to microwave irradiation above 3-5 minutes [1]. The mixture was kept chilled in the ice bath and poured into cold water. A precipitate formed that was filtered, washed with distilled water and finally recrystallized from 2-propanol and dried in a vacuum oven at 65 °C for 24 hours [4].



R : p-Cl (3a), p-Br (3b), p-OH (3c), m-NO3(3d), p-OCH_3(3e)

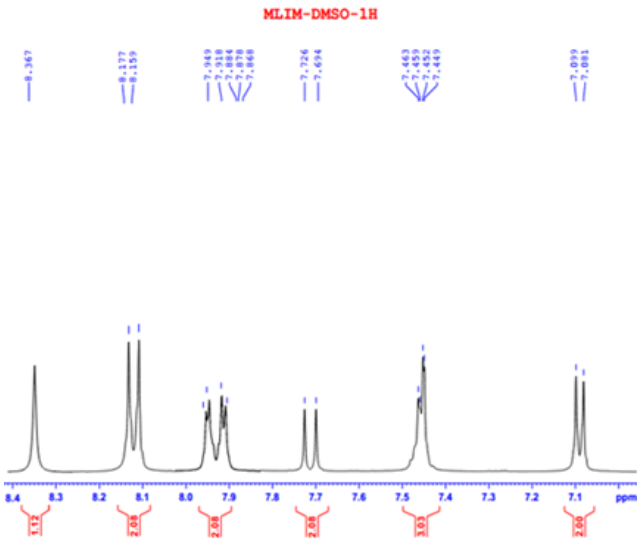
Scheme 1. Synthetic reaction of heterocyclic derivatives of pyrrole 3a-e.

II. RESULTS AND DISCUSSION

The derivatives of pyrrole could be easily synthesized by nucleophilic addition of corresponding 2-amino-4,6-diarrylpyrimidine compounds to maleic anhydride. We performed this reaction using microwave irradiation. We have found that the solvent-free conditions under microwave irradiation offers several advantages because solvents are not only often expensive, toxic, but also difficult to remove in case of aprotic dipolar solvents with high boiling point, and they are environmentally polluting agents. Moreover, liquid-liquid extraction is avoided in the isolation of reaction products. The absence of solvent prevents the risk of hazardous explosions when the reaction takes place in a microwave oven [2,3] . The reactions were usually completed within 3 – 5 minutes and gave pyrroles 3a-e in good to excellent yields (60 – 80%) over conventional methods in the shorter time. The IR spectra of compounds (3a-e), contained absorption at 1649 – 1762 cm-1 (C=O), 1523 – 1665 cm-1 (C=N), and 1025 – 1285 cm-1 (C-O-C, aryl ether). The 1H-NMR spectra of compounds 3a-e showed singlet signals at δ = 8.36 – 8.75 ppm (H-5'). The 13C-NMR spectra showed signals of the carbonyl C=O shifted downfield at δ 161-163 ppm. In addition, there were resonance peaks in lowest region at δ = 169.7-169.9 ppm that indicated the presence of C=N of hetero-aromatic due to the influence of adjacent electronegative nitrogen atoms and δ = 114.9 – 140.3 ppm belonged to C=C. Only the signals of carbon belongs to methoxy group have appeared in the up field region at δ =55.9 ppm.

Table 1. 1H-NMR spectral data of some pyrroles (3a-e)

Compound	δH (ppm)
3a	8.65 (s, 1 H, H5'); 8.25 (d, 2H, J = 7.26 Hz, H2"'& H6"'), 8.02 (d, 2H, J = 7.25 Hz, H2"& H6"), 7.90 (d, 2 H, J = 5,20 Hz, H3& H4),7.85 (d, 2 H, J = 7,26 Hz, H3"'& H5"'), 7.55 (d, 2 H, J = 7,26 Hz, H3"& H5")
3b	8.50 (s, 1 H, H5'); 8.55 (d, 2H, J = 7,25 Hz, H2"'& H6"'), 7.94 (d, 2H, J = 7.25 Hz, H2"& H6"), 7.86 (d, 2 H, J = 5.20 Hz, H3& H4),7.55 (d, 2 H, J = 7.25 Hz, H3"'& H5"'), 7.49(d, 2 H, J = 7.26 Hz, H3"& H5")
3c	8.78 (s, 1 H,OH) 8.98 (s, 1 H, H5'); 7.95 (d, 2H, J = 7.25 Hz, H2"& H6"), 7.89 (d, 2 H, J = 5,20 Hz, H3& H4, 7.25 (d, 2H, J = 7,26 Hz), H2"'& H6"')) 7.55 (d, 2 H, J = 7.26 Hz, H3"& H5"). 7.35 (d. 2 H. J = 7.26 Hz. H3"'& H5"')
3d	8.55 (s, 1 H, H5'), 8.25(d, 2 H, J = 7.25 Hz, H3"'& H5"'), 8.01 (d, 2H, J = 7,26 Hz, H2"'& H6"'), 7.96 (d, 2H, J = 7.25 Hz, H2"& H6"), 7,80 (d, 2 H, J = 5,20 Hz, H3& H4), 7.55 (d, 2 H, J = 7.26 Hz, H3"& H5")
3e	8.36 (s, 1 H, H5'), 8.13 (d, 2H, J = 7.25 Hz, H2"& H6"), 7.87 (d, 2 H, J = 5.20 Hz, H3& H4), 7.85 (d, 2H, J = 7,26 Hz, H2"'& H6"'), 7.94 (d, 2 H, J = 7,26 Hz, H3"& H5") 7.05 (d, 2 H, J = 7,26 Hz, H3"'& H5"'), 3.85 (s, 3H, OCH3)



Scheme 2. ^{1}H-NMR spectrum of 1-[4-(4-methoxyphenyl)-6-phenylpyrimidin-2-yl]pyrrolidine-2,5-dione(3e)

Table 2. 13C-NMR spectral data of some pyrole derivaties (3a-e)

Carbon	Compounds				
	3a	3b	3c	3d	3e
C-2	163.5	162.5	162.3	161.9	161.9
C-3	134.5	134.9	135.9	135.9	135.9
C-4	134.5	134.8	135.9	135.9	135.9
C-5	163.5	162.5	162.3	161.9	161.9
C-2'	169.7	169.7	169.9	169.8	169.7
C-4'	163.2	163.0	162.1	163.2	162.5
C-5'	103.0	102.3	102.3	102.5	102.3
C-6'	165.9	165.7	165.4	165.6	165.3
C-1"	140.3	135.9	135.9	135.9	135.9
C-2"	134.3	127.6	127.6	127.5	127.5
C-3"	135.5	129.5	129.3	129.5	129.2
C-4"	135.2	128.3	128.9	128.7	128.7
C-5"	135.5	129.5	129.3	129.5	129.2
C-6"	134.3	127.6	127.6	127.5	127.5
C-1"'	133.5	134.5	129.3	144.9	128.2
C-2"'	129.5	129.5	129.9	126.5	128.5
C-3"'	130.5	135.1	115.5	125.5	114.9
C-4"'	135.3	123.1	159.5	147.9	161.8
C-5"'	130.5	135.1	115.5	125.5	114.9

C-6'''	129.5	129.5	129.9	126.5	128.5
C-others					55.9(OCH3 Ar)

The synthesized compounds were exposed to antimicrobial activity. Antimicrobial activities were observed for all compounds using strains of gram positive such Staphylococcus aurous gram negative (Salmonella typhi, Escherichia coli). The antimicrobial activities of the synthesized compounds were studied by disc diffusion method. Bacterial inoculums were spread on Nutrient agar. After the inoculums dried, 6 mm diameter wells were made in the agar plate with a sterile cork borer. The synthesized compounds were dissolved in DMSO at concentrations of 10 µg, 20 µg, per ml. ampicillin 50 µg/ml was used as standard for the antibacterial activity. The Petri plates were incubated at 37ºC for 24 hours. The zone of inhibition was measured in mm to estimate the potency of the test compounds Results are shown in Table-2. The synthesized compounds were screened for antimicrobial activity against strains of gram positive and gram negative. All compounds showed good to moderate antibacterial activity.

Table 2: Response of various micro-organisms to substituted pyrroles 3a-e

Entry	Diameter of zone inhibition (mm)					
	E.coli		*S. aureus*		*Salmonella*	
	10 µg/ml	20 µg/ml	10 µg/ml	20 µg/ml	10 µg/ml	20 µg/ml
3a	15	18	15	17	27	29
3b	22	29	18	20	15	18
3c	25	28	15	15	11	15
3d	10	16	21	21	17	15
3e	13	12	19	19	11	18
Std	46	50	44	47	36	45

A series of pyrroles were prepared by condensation of 2-amino-4,6-diarylpyrimidine with maleic anhydride using microwave-assisted method.Their structures were identified by the combination of IR, ^{1}H- and 13C-NMR spectral data. This method affords the pyrrole derivatives in good to excellent yields. The tested results showed that they possess remarkable antimicrobial activities.

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