MICROWAVE-ASSISTED SYNTHESIS OF MALEIMIDE DERIVATIVES

NGHIÊN CỨU TỔNG HỢP MỘT SỐ DẪN XUẤT MALEIMIDE BẰNG PHƯƠNG PHÁP SỬ DỤNG LÒ VI SÓNG

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ABSTRACT

Some new derivatives of maleimide were synthesized using microwave oven method. The structures of compounds were established by means of IR, ^{1}H-NMR, and ^{13}C-NMR. All the compounds were evaluated for antibacteria activity. At concentrations 10µg/ml, 20µg/ml all tested compounds exhibited anti bacterial activity with inhibition diameter of 10-29 mm.

Keywords: *Maleimide; solvent-free; microwave-assisted method.*

TÓM TẮT

Một số dẫn xuất maleimide mới đã được tổng hợp bằng phương pháp sử dụng lò vi sóng. Cấu trúc của các hợp chất này đã được chứng minh bằng phương pháp phổ cộng hưởng từ hạt nhân ^{1}H và ^{13}C. Ở nồng độ 10µg/ml, 20µg/ml các hợp chất tổng hợp được đều có hoạt tính kháng vi sinh vật kiểm định *E.coli, S. aureus, Salmonella typhi* với đường kính vùng ức chế 10-29 mm.

Từ khóa: *Maleimide, không dung môi, phương pháp sử dụng lò vi sóng.*

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1. INTRODUTION

Now a days Microwave–induced Organic Reaction Enhancement chemistry has found as an important utility value for carrying out chemical reactions in organic synthesis of compounds. 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.

Maleimides are an important class of substrates for biological, pharmacological and chemical applications. In biological applications, they are used as chemical probes of protein structure, as immunoconjugates for cancer therapy, as solid-supported enzymes for synthetic applications, for the productions of antibodies. In pharmacological applications, they are used as analogues of the cyclic entrapeptide chlamydocin, photoactivatable fluorescein derivatives, naltrexone [6,7].

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

2. EXPREMENTAL

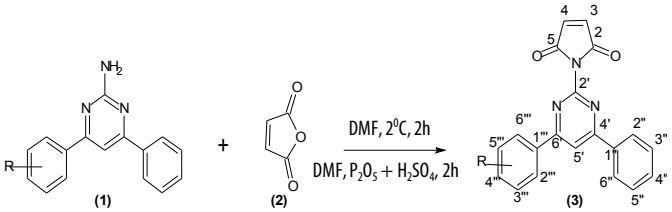
Chemistry

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. ^{1}H-NMR (500 MHz), ^{13}C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, German) at 500.13 MHz, using DMSO-d_6 as solvent and TMS as an internal reference, δ in ppm. Bioassays were carried out in 19-8 Hospital, Hanoi, Vietnam.

General procedure for synthesis of maleimide (3a-e).

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) and DMF (70 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*-NO_3(3d), *p*-OCH_3(3e)

Scheme 1. Synthetic reaction of maleimides **3a-e**.

3. RESULTS AND DISCUSSION

The derivatives of maleimide 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 maleimides **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). The ^{1}H-NMR spectra of compounds **3a-e** showed singlet signals at δ = 8.36 - 8.75 ppm (H-5'). The ^{13}C-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 carbon signals of methoxy group appeared in the up field region at δ = 55.9 ppm.

Table 1. ^{1}H-NMR spectral data of some maleimides (3a-e)

Compd.	δ_H (ppm)
3a	8.65 (s, 1H, H5'); 8.25 (d, 2H, *J* = 7.26 Hz, H2"'& H6"'); 8.02 (d, 2H, *J* = 7.25 Hz, H2"& H6"); 7.90 (d, 2H, *J* = 5,20 Hz, H3& H4); 7.85 (d, 2H, *J* = 7,26 Hz, H3"'& H5"'); 7.55 (d, 2H, *J* = 7,26 Hz, H3"& H5").
3b	8.50 (s, 1H, H5'); 8.55 (d, 2H, *J* = 7,25 Hz, H2"'& H6"'); 7.94 (d, 2H, *J* = 7.25 Hz, H2"& H6"); 7.86 (d, 2H, *J* = 5.20 Hz, H3& H4); 7.55 (d, 2H, *J* = 7.25 Hz, H3"'& H5"'); 7.49(d, 2H, *J* = 7.26 Hz, H3"& H5").
3c	8.78 (s, 1 H,OH) 8.98 (s, 1H, H5'); 7.95 (d, 2H, *J* = 7.25 Hz, H2"& H6"); 7.89 (d, 2H, *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, 1H, 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, 1H, H5'); 8.13 (d, 2H, *J* = 7.25 Hz, H2"& H6"); 7.87 (d, 2H, *J* = 5.20 Hz, H3& H4); 7.85 (d, 2H, *J* = 7,26 Hz, H2"'& H6"'); 7.94 (d, 2H, *J* = 7,26 Hz, H3"& H5"); 7.05 (d, 2 H, *J* = 7,26 Hz, H3"'& H5"'); 3.85 (s, 3H, OCH_3).

Table 2. ^{13}C-NMR spectral data of some maleimides (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 (OCH_3)

The synthesized compounds were exposed to antimicrobial activity. Antimicrobial activities were observed for all compounds using strains of gram positive such *Staphylococcus aureus* 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 37°C for 24 hours. The zone of inhibition was measured in mm to estimate the potency of the test compounds Results are shown in Table3. All compounds

showed good to moderate antibacterial activity against *S. aureus*, *Salmonella typhi*, *Escherichia coli.*

Table 3. Response of various micro-organisms to maleimides 3a-e

Compounds	Diameter of zone inhibition (mm)					
	E.coli		*S. aureus*		*Salmonella typhi*	
	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	13	21	17	15
3e	13	12	18	19	11	18
Std	46	50	44	47	36	45

Ampicillin (50µg/ml) was used as a positive control

4. CONCLUSIONS

A series of maleimides 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 ^{13}C-NMR spectral data. This method affords the maleimide derivatives in good to excellent yields. The tested results showed that they possess remarkable antimicrobial activities.

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