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SYNTHESIS OF SOME 2-AMINO-4,6-DIARYLPYRIMIDINE DERIVATIVES USING MICROWAVE-ASSISTED METHOD

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ABSTRACT

Some new compounds of 2-amino-4,6-diarylpyrimidines have been synthesized from corresponding substituted chalcones and guanidine hydrochloride using two different synthetic methods in microwave oven. The products formed were equally available and confirmed by IR, ^{1}H-NMR and mass spectral data.

I - INTRODUCTION

The microwave-assisted organic synthesis method is becoming an increasingly popular method of heating which replaces the classical ones because it proves to be a clean, cheap, and convenient method. This method often affords higher yields in short reaction times and has been extended to almost all areas of chemistry. Numerous organic reactions assisted by microwave heating have been performed and reviewed in articles or books [1]. These reactions involved different ones, such as the acylation and alkylation reaction, aromatic nucleophilic substitution, condensation, cycloaddictions, heterocyclization, rearrangements, reaction of organometallic compounds, oxidation and reduction. On another hand, pyrimidine derivatives occupy unique positions as leiodynamic agents, both as essential components of nucleic acids and also as therapeutic agents [2, 3].

In the previous paper, we reported on synthesis of several 2-amino-4,6-diarylpyrimidines from guanidine hydrochloride and substituted chalcones using classical heating method [4, 5]. In the present study, these amines have been synthesized using

microwave-assisted method.

II - EXPERIMENT

Melting point of the synthesized compound 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. The ^{1}H-NMR was 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. The high-resolution mass (HR-MS) spectra were recorded on mass spectrometer AutoSpec Premier (WATERS, USA).

Synthesis of 2-amino-4,6-diarylpyrimidine

General Procedure A (Refluxing Method in MW oven)

A mixture of substituted chalcones **3** (0.01 mole), guanidine hydrochloride (0.015 mol) and sodium hydroxide (0.045 mole) in 2ml of water and 5 ml 96% ethanol was refluxed for 10 minutes in home MW oven at 750 Watts, concentrated and cooled. The separated product was filtered and recrystallized from an appropriate solvent to give 2-amino-4,6-diarylpyrimidines **4a-j**.

General Procedure B (under solvent-free condition)

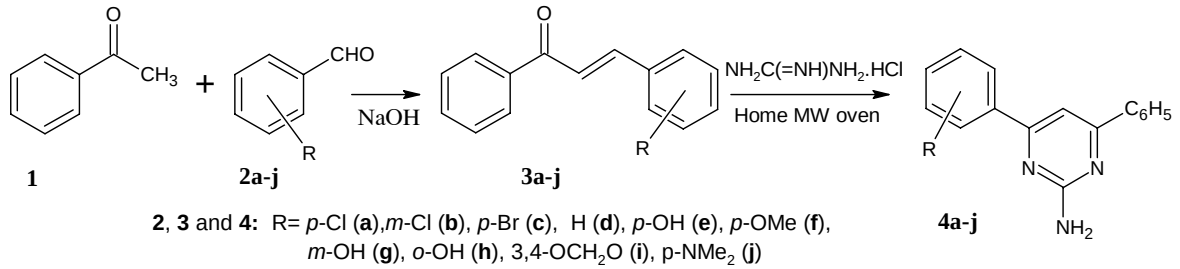
Substituted chalcone **3** (0.01 mole), guanidine hydrochloride (0.015 mole) and sodium hydroxide (0.045 mole) were mixed carefully with a little water. Obtained mixture was irradiated about 2-3 minutes in home MW oven at 750 Watts. The mixture had become dark-yellow. Cooled it to room temperature, recrystallized from solvent system of ethanol and toluene (1:1 in volume) to give ivory-white crystals of 2-amino-4,6-diarylpyrimidines **4a-j**. Results of these above syntheses were represented in Table 1.

III - RESULTS AND DISCUSSION

Some substituted benzylidenacetophenones (chalcones), which are used in this paper, were easily synthesized by the addition reaction of corresponding substituted benzaldehydes on acetophenone. This reaction was rapidly performed in base medium at the temperature of 15 - 20°C in only several minutes [6]. By that way, we successfully synthesized 10 substituted

benzylideneacetophennone derivatives, which are required for synthesis of 2-amino-4,6-diarylpyrimidines. The structures of these chalcones were confirmed by IR spectroscopic data analyzed and in comparing their melting point with those one in literatures. In the IR-spectra of the above synthesized compounds, it's shown that stretching band of C=O bond in α,β-unsaturated ketones appeared in the region of 1662 - 1649 cm^{-1}, moved to short waves when compared with absorption of C=O bond in acetophenone. Absorption band of corresponding substituents also appeared in IR spectra of each derivatives, for examples, the characteristic absorption bands of nitro substituted were shown at 1527 cm^{-1} and 1350 cm^{-1} or in case of hydroxyl derivative at 3231cm^{-1}.

The derivatives of 2-amino-4,6-diarylpyrimidines could be easily synthesized by the cycloaddition of corresponding guanidine hydrochloride on corresponding substituted chalcones derivatives. We performed this reaction using two different microwave-assisted methods: by refluxing in ethanol about 10 minutes and by executing under solvent-free condition in several minutes. The synthetic processes could be represented in schema 1.



Scheme 1: Synthetic reactions of 2-amino-4,6-diarylpyrimidines **4a-j**

We have found that the addition of guanidine hydrochloride to substituted chalcones has taken place fairly easily. Reaction yields were high in both the methods (or with reflux either in solvent-free condition using MW oven) and given 69-80% and 64-76%, respectively. All these synthesized 2-amino-4,6-diarylpyrimidines could dissolve in common organic solvents (such as ethanol, methanol, toluene, benzene, DMF,□) and couldn't dissolve in water. Their structure had been confirmed by spectroscopic data (such as IR, NMR and mass spectra).

In the IR-spectra of these compounds, the appearance of strong, shade absorption in the region of 3504 - 3281 cm^{-1}, characterized for stretching vibrations of N-H bonds in amine linkage (*see table 1*). Furthermore, the absent of C=O absorption band at 1662 - 1649 cm^{-1} in comparison with corresponding α,β-unsaturated ketones indicated that the reaction was finished and products of 2-amino-4,6-diarylpyrimidines were formed. The specific structures of amines were then further investigated using ^{1}H-NMR spectroscopic method. In the ^{1}H-NMR spectra of these amines there are the resonance signals which are specified for protons in amine group in the region of δ = 6.50 - 6.80 ppm. The movement of chemical shifts depends on Hammett's σ constant of corresponding substituents. It will move to upfield if has strong

donating group and to downfield when has withdrawing substituent group. The aromatic protons signals showed clearly with three separated regions. One singlet signal around δ 7.64 - 7.78 ppm could be assigned for proton H-5 in pyrimidine ring. The signals in the most upfield region around δ 7.50 ppm and 8.20 ppm belong to unsubstituted phenyl moiety. Remaining aromatic protons signals with *para, meta* or ABX system characterized for another *para, ortho* and *meta*-substituted or 3,4-substituted phenyl rings (*see table 2*).

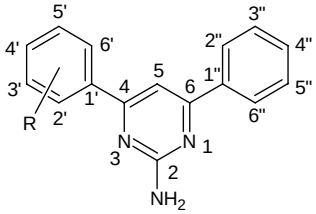
Table 1: Some derivatives of 2-amino-4,6-diarylpyrimidines **(4a-j)**

No	R	Melting Point (□C)		Yield (%)		IR spectra (cm^{-1})		$M^{+\bullet}$	$M_{cal.}$ (Da)	Irradiation time (min.)
		A	B	A	B	ν_{NH2}	δ_{NH2}			
4a	*p*-Cl	160-161	160-161	80	76	3493; 3314	1634	281.0496/ 283.0560	281.07198/ 283.06902	2
4b	*m*-Cl	118-119	118-119	75	63	3491; 3315	1634	281.0824; 283.0860	281.07198/ 283.06902	2
4c	*p*-Br	171-172	171-172	80	71	3493, 3294, 3159	1632	325.3736/ 327.4207	325.0215/ 327.0194	2
4d	H	118-119	118-119	72	69	3469; 3320	1601	247.0929	247.1109	1
4e	*p*-OH	239-240	239-240	73	71	3505, 3397	1601	263.1096	263.1059	1
4f	*p*-OMe	151-152	151-152	80	73	3363, 3327, 3191	1642	277.0977	277.1215	1
4g	*m*-OH	231-232	231-232	66	64	3484, 3333, 3197	1637	263.0910	263.1059	1
4h	*o*-OH	181-182	181-182	70	68	3519, 3362, 3204	1629	263.0977	263.1059	1
4i	3,4-OCH_2O	190-192	190-192	77	75	-	-	291.0646	291.1008	1
4j	*p*-NMe_2	140-142	140-142	69	66	3480, 3281, 3165	1621	290.1313	290.1531	1

(A): by refluxing; (B): under solvent-free in microwave oven.

The mass spectra of amines containing aromatic rings had some features that are characterized with high intensity of molecular ion peak. There are not many fragment ions on the spectra indicated the stability of molecular. We also found that the fragmentation of those amines can be divided by two main tendencies. First was characterized by the cleavage of substituted phenyl group at the position of ion peaks such as $[M\text{-}ArX]^+$, $[M\text{-}ArX\text{-}NH_3\text{-}H]$. These fragments was observed on the mass spectra at position of m/z of 172, 156. A remain tendency can be observed by the cleavage of pyrimidine ring to form stable azetidene ring. This tendency showed clearly with the loss of HN=C=NH radical. All of these features are very important clues for structure affirmation of type of these amines.

Table 2: ^{1}H-NMR spectral data of 2-amino-4,6-diarylpyrimidines **4b-j**



No	R	^{1}H-NMR spectra, δ (ppm)
4b	*m*-Cl	8.304 (s, 1H, H-2'); 8.251-8.233 (m, 2H, H-3" & H-5"); 8.204 (d, 1H, *J* = 7.5 Hz, H-4'); 7.779 (s, 1H, H-5); 7.591-7.754 (m, 2H, *J* = 7.5 Hz & 3.0Hz, H-5' & H6'); 7.532 - 7.520 (m, 3H, H-2", H-4" & H-6"); 6.801 (s, 2H, NH_2)
4c	*p*-Br	8.221 - 8.205 (m, 2H, H-3" & H-5"); 8.178 (d, 2H, *J* = 8.5 Hz, H-3' & H5'); 7.723 (s, 1H, H-5); 7.721 (d, 2H, *J* = 8.5 Hz, H-2' & H6'); 7.527 - 7.507 (m, 3H, *J* = 3.5 Hz, H-2", H-4" & H-6"); 6.756 (s, 2H, NH_2)
4d	H	8.222-8.203 (m, 4H, H-3' & H5' and H-3"& H-5"); 7.698 (s, 1H, H-5); 7.528-7.516 (m, 6H, H-2', H-4' & H-6' and H-2", H-4" & H-6")
4e	*p*-OH	9.900 (s, 1H, OH); 8.191-8.172 (m, 2H, H-3" & H-5"); 8.084 (d, 2H, *J*=9.0Hz, H-3' & H5'); 7.586 (s, 1H, H-5); 7.512-7.498 (m, 3H, H-2", H-4" & H-6"); 6.869 (d, 2H, *J*=8.5Hz, H-2' & H6'); 6.596 (s, 2H, NH_2)
4f	*p*-OMe	8.202 - 8.184 (m, 2H, H-3" & H-5"); 8.193 (d, 2H, *J* = 9.0 Hz, H-3' & H5'); 7.637 (s, 1H, H-5); 7.518 - 7.504 (m, 3H, H-2", H-4" & H-6"); 7.061 (d, 2H, *J* = 9.0 Hz, H-2' & H6'); 6.614 (s, 2H, NH_2); 3.839 (s, 3H, OCH_3)
4g	*m*-OH	9.585 (s, 1H, OH); 8.199-8.179 (m, 2H, H-3" & H-5"); 7.610 (s, 1H, *J* = 1.0 Hz, H-2'); 7.598 (m, 1H, *J* = 7.5 Hz & 4.5Hz, H-4'); 7.593 (s, 1H, H-5); 7.520 - 7.507 (m, 3H, H-2", H-4" & H-6"); 7.304 (t, 1H, *J* = 2.75 Hz, H-6'); 6.911 (ddd, 1H, *J* = 8.0Hz, 2.5Hz & 1.0Hz, H-5'); 6.675 (s, 2H, NH_2)
4h	*o*-OH	8.253 - 8.214 (m, 3H, H-3", H-5" & H-3'); 7.864 (s, 1H, H-5); 7.540 - 7.527 (m, 3H, H-2", H-4" & H-6"); 7.371-7.337 (td, 1H, *J* = 8.5Hz & 1.25 Hz, H-6'); 7.180 (br., OH & NH_2); 6.903 (t, 1H, *J* = 7.0 Hz, H-5'); 6.904 (dd, 1H, *J* = 8.5 Hz & 1.25 Hz, H-4')
4i	3,4-OCH_2O	8.219 - 8.200 (m, 2H, H-3" & H-5"); 7.838 (dd, 1H, *J* = 8.5 Hz & 1.25Hz, H-6'); 7.800 (d, 1H, *J* = 1.5, H-2'); 7.648 (s, 1H, H-5); 7.516 - 7.503 (m, 3H, H-2", H-4" & H-6"); 7.045 (d, 1H, *J* = 8.0 Hz, H-5'); 6.640 (s, 2H, OCH_2O); 6.114 (s, 2H, NH_2)
4j	*p*-NMe_2	8.186 - 8.168 (m, 2H, H-3" & H-5"); 8.096 (d, 2H, *J* = 9.0 Hz, H-3' & H5'); 7.599 (s, 1H, H-5); 7.504-7.494 (m, 3H, H-2", H-4" & H-6"); 6.789 (d, 2H, *J* = 8.5 Hz, H-2' & H6'); 6.496 (s, 2H, NH_2); 3.000 (s, 6H, $N(CH_3)_2$)

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