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ORIGINAL ARTICLE

A Comparative Study of Microwave-Assisted and Conventional Heating Approaches for the Multicomponent Synthesis of 4,6-Diarylpyrimidines

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Abstract

A series of 2-amino-4,6-diarylpyrimidines were synthesized using a Biginelli-type three-component strategy optimized in conventional-heated reflux, in contrast to a non-conventional approach using a mono-mode microwave reactor. Conventional heating protocols involved organic solvents and general base catalysis, whereas a microwave-assisted method followed experimental protocols framed within the principles of green chemistry by using $CaCl_2$ as a catalyst in solvent-free conditions. This study revealed that although conventional heating led to the main product in higher yields at longer reaction times, the microwave strategy suceeded in substantially shorter reaction times, with yields ranging from acceptable to good and efficiencies comparable to conventional heating methodology.

Keywords: 4,6-diarylaminopyrimidines; microwave-irradiated synthesis; monomode reactor; Biginelli-type reaction.

1. Introduction

Pyrimidine derivatives have played a key role in the development of heterocyclic chemistry and organic and medical chemistry, due to their unique properties and pervasive occurrence in biological structures, for instance in the nitrogenous bases constituting nucleosides and nucleotides in DNA and RNA molecules [1]. Moreover the well-studied role of this heterocyclic core as antiviral [1, 2, 3], anthelmintic [4], analgesic [5], and anti-depressor (e.g., barbituric acid) [6, 7, 8], among others [9, 10, 11] has led to its classification as a central scaffold in therapeutic research [12]. Additionally, pyrimidine derivatives possess broad optoelectronic properties, such as high electron conjugation (especially in aryl-substituted examples), low band gaps, and good electron transmission capacity, which can lead to future developments in the field of materials chemistry [13].

The obtention of these heterocyclic rings can be rationalized by retrosynthetic strategies involving either the condensation of 1,3-dinucleophiles such as urea, thiourea, amidines or guanidine, with 1,3-dielectrophile compounds (such as α,β-unsaturated carbonyl derivatives and their synthetic equivalents) (Figure 1A) or via the classic Biginelli-type three-component reaction (Figure 1B) [14, 15, 16]. The latter strategy usually increases the conversion of the starting materials, often sacrificing selectivity towards the desired product. For this reason and in order to achieve a substantially fast, simple, and efficient synthesis of the named heterocycles, several reaction parameter assessments have been performed through time.

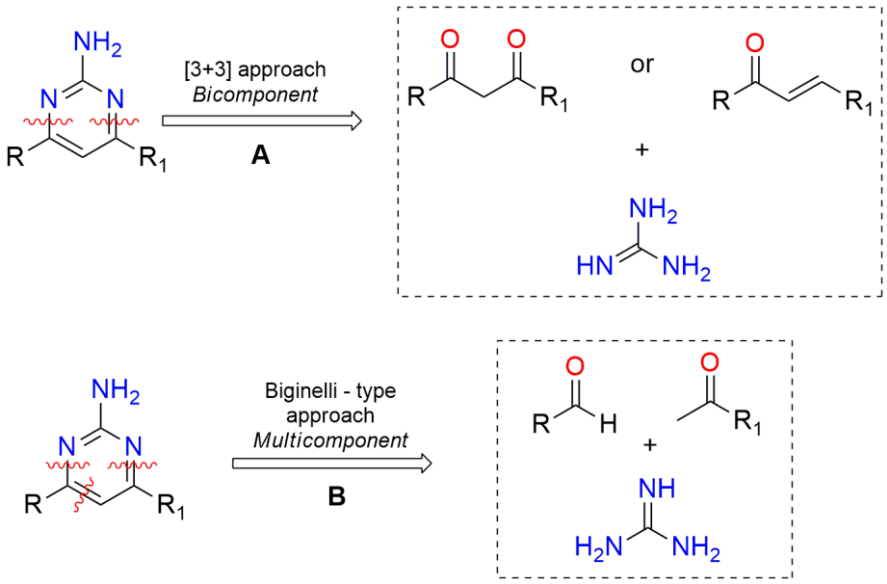


Figure 1. Classic disconnections to obtain 2-aminopyrimidines as target molecules: **A.** [3+3] disconnection leading to 1,3-dielectrophile and guanidine as 1,3-dinucleophile. **B.** Biginelli-type disconnection leading to guanidine, enolizable carbonyl compounds and non-enolizable carbonyl compounds in a three-component methodology.

A multicomponent reaction (MCR) in organic synthesis is viewed as a chemical process in which three or more components are combined in a one-pot transformation to produce a single final product, without further additions or manipulations (excepting the isolation of the final product). A particular feature of MCRs is that most of the atoms of the components (reactants) become part of the target molecule or final product [17, 18, 19].

Consequently, when many reactions occur in the same reactor without isolation or purification of intermediates, such as in the case of MCRs, the amount of solvents, waste, time, labor, and cost can be considerably reduced [20]. This particular set of advantages has been taken even further by using non-conventional heating methods, such as microwave irradiation currently considered as a strategic part of green chemistry and atomic economy [21, 22]. This is especially important in MCRs, where the aforementioned common advantages can converge with those of MW techniques, thus giving even better results than expected using both approaches independently. This remarkable discovery has led to revising many of these classic reactions, such as the Biginelli-type MCR, in order to significantly contribute to their enhancement [23, 24, 25].

Taking this into account, herein we report a comparative synthetic study under conventional heating reflux, using organic solvents and base catalysis, in contrast to a methodology involving solvent-free microwave induction and $CaCl_2$ as catalyst, in a three-component process framed in most of the green chemistry postulates such as atomic economy, low waste generation, cleanness and effective purification protocols; as an improvement to the classic Biginelli approach [26, 27, 28, 29, 30, 31].

2. Experimental conditions

Reactions were performed in conventional heating with magnetic stirring under nitrogen atmosphere or by using a Monomode CEM-Discover microwave reactor in sealed microwave tubes. The outcomes were assessed with thin layer chromatography (TLC) in Macherey-Nagel pre coated silica gel sheets Alugram® Xtra-SIL G/UV254 as stationary phase and a hexane-ethyl acetate

(15:8) mixture as mobile phase. Melting points were measured using the open capillary method without correction. All reagents and solvents were used without further purification. FT-IR spectra were recorded on a Nicolet is-10 infrared spectrophotometer and the absorptions were reported as wavenumber (cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a FT-NMR Bruker Avance (400 MHz) spectrometer with chemical shifts expressed as ppm; coupling constants (J) are given in Hertz (Hz). CHNS elemental analyses of title compounds were carried out using a Thermo Scientific Flash 2000 Elemental Analyzer.

2.1. Conventional heat-driven synthesis of 2-amino-4,6-diarylpyrimidines 4 a-g.

One mmol of the corresponding benzaldehyde, 1 mmol of acetophenone (or *p*-methyl acetophenone), 1.6 mmol of guanidine hydrochloride and, 2.0 mmol of NaOH were mixed and dissolved in 10 mL of EtOH, refluxing in an oil-bath for 16 to 24 h under nitrogen (or argon) atmosphere. The reaction was left to stand, and then, 15 mL of diluted hydrochloric acid (3.0 mol/L) were added to the reaction crude and the emulsion formed was destroyed by extraction with DCM (3 portions × 15 mL). The organic layers were combined, dried with magnesium sulphate, and evaporated under reduced pressure. The obtained product was dried in oven at 343 K overnight, and the resinous product was treated with hexane giving rise to the seven 2-amino-4,6-diarylpyrimidine 4a-g products) (Figure 2), as a solid of acceptable purity without further purification.

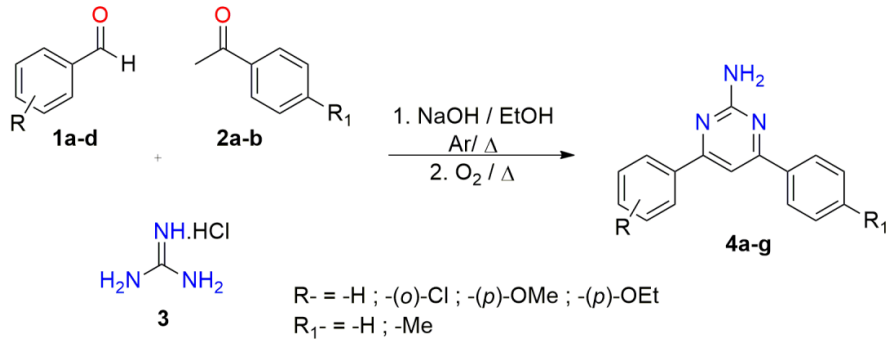


Figure 2. Synthesis of 2-aminopyrimidines 4a-g by conventional heating.

3. Microwave assisted synthesis of 2-amino-4,6-diarylpyrimidines 4a-g.

In a high-pressure microwave tube, 0.4 mmol of calcium chloride, 4.0 mmol of guanidine hydrochloride, and two drops of distilled water were mixed and homogenized by magnetic stirring for 5 min; then, 1.0 mmol of the benzaldehyde and 1.2 mmol of acetophenone (or *p*-methyl acetophenone) were added, and the tube was sealed and irradiated in a CEM-microwave reactor, at 523 K and 150 W for 10 min with vigorous magnetic stirring. The reaction mixture was cooled to room temperature, followed by adding 5 mL of hydrochloric acid (3.0 mol/L). Subsequently, the tube was manually shaken, and the formed emulsion treated with DCM (3 portions × 10 mL). The organic layers were combined and dried with anhydrous magnesium sulfate, and the DCM evaporated under reduced pressure. The obtained crude was heated at 343 K overnight. The resinous product was treated with hexane, giving rise to the desired 2-amino-4,6-diarylpyrimidines (**4a-g**) as an amorphous solid (Figure 3), with acceptable purity without further purification.

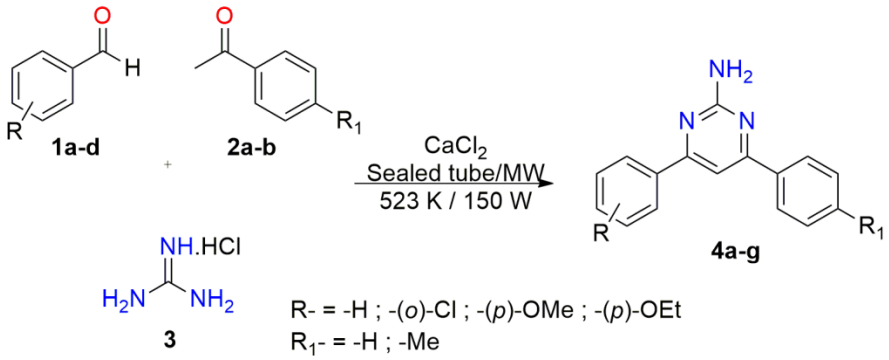


Figure 3. Microwave-assisted synthesis of 2-aminopyrimidines **4a-g**.

2-Amino-4,6-diphenylpyrimidine (4a): Yellow solid; (Conv. Heating yield: 94 %) (MWI yield: 86%); Melting point: 408 – 409 K (rep 408 – 410 K)[20], FT-IR (KBr, cm^{-1}): 3325 (N-H), 3196 (N-H), 3050 (=C-H), 1644 (C=N), 990 (C=C-R), 820 (C=C-R). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 5.42 (s, 2H, -NH_2), 7.48 (s, 1H, =C-H), 7.51 – 7.53 (m, 6H, =C-H), 8.08 (dd, 4H, J = 6.7 Hz, 3.0 Hz, =C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 104.3, 127.2, 128.8, 130.5, 137.8, 163.7, 166.3. Anal. calcd. for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.67; H, 5.41; N, 17.04.

2-Amino-4-(4-methoxyphenyl)-6-phenylpyrimidine (4b): Yellow solid; (Conv. Heating yield: 90 %) (MWI yield: 78 %); Melting point: 408 – 409 K (rep 408 – 410 K)[21], FT-IR (KBr, cm^{-1}): 3324 (N-H), 3316 (N-H), 3050 (=C-H), 2929 (-C-H), 1644 (C=N), 1029 (-C-O), 990 (C=C-R), 820 (C=C-R). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 3.88 (s, 3H, -OCH_3), 5.21 (s, 2H -NH_2), 7.00 (dd, 2H, J = 8.9 Hz, 5.7 Hz -C-H), 7.41 (s, 1H, -C-H), 7.51 – 7.53 (m, 3H, -C-H), 8.05 – 8.09 (m, 4H, -C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 55.4, 103.6 114.1, 127.1, 128.6, 128.8, 130.1, 130.3, 137.9, 161.7, 163.6, 165.7, 166.0. Anal. calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.57; H, 5.51; N, 15.09.

2-Amino-4-(4-ethoxyphenyl)-6-phenylpyrimidine (4c): Yellow solid; (Conv. Heating yield: 92 %) (MWI yield: 67 %); Melting point: 364 – 365 K, FT-IR (KBr, cm^{-1}): 3324 (N-H), 3196 (N-H), 3030 (=C-H), 2929 (-C-H), 2836 (-C-H), 1644 (C=N), 1029 (-C-O), 820 (C=C-R), 769 (C=C-R). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 1.48 (t, 3H, J = 6.8 Hz, -CH_3), 4.13 (q, 2H, J = 6.8 Hz, -CH_2), 5.25 (s, 2H, -NH_2), 7.02 (d, 2H, J = 8.0 Hz -C-H), 7.44 (s, 1H, -C-H), 7.50 – 7.53 (m, 3H, -C-H), 8.05 – 8.08 (m, 4H, -C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 14.8, 55.5, 103.7 114.2, 127.2, 128.8, 128.9, 130.3, 130.5, 138.1, 161.8, 163.7, 165.8, 166.1. Anal. calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.13; H, 5.76; N, 14.30.

2-Amino-4-(2-chlorophenyl)-6-phenylpyrimidine (4d): Orange solid; (Conv. Heating yield: 80 %) (MWI yield: 72 %); Melting point: 335 – 336 K, FT-IR (KBr, cm^{-1}): 3201 (N-H), 3194 (N-H), 3031 (=C-H), 1675 (C=N), 820 (C=C-R), 769 (C=C-R), 695 (C-Cl). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 5.66 (s, 2H, -NH_2), 7.46 (s, 1H, -C-H), 7.53 – 7.54 (m, 4H, -C-H), 8.06 – 8.08 (m, 3H, -C-H), 8.15 – 8.17 (m, 2H, -C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 108.4, 127.1, 127.3, 129.3, 129.6, 130.4, 130.5, 131.0, 132.3, 134.8, 138.0, 141.0, 163.6, 165.6. Anal. calcd. for $C_{16}H_{12}ClN_3$: C, 68.21; H, 4.29; N, 14.91. Found: C, 68.13; H, 4.37; N, 14.85.

2-Amino-4-(4-methoxyphenyl)-6-(4-methylphenyl)pyrimidine (4e): Yellow solid; (Conv. Heating yield: 93 %) (MWI yield: 83 %); Melting point: 392 – 394 K (rep 398 – 399 K)[22], FT-IR (KBr, cm^{-1}): 3466 (N-H), 3327 (N-H), 3028 (=C-H), 2928 (-C-H), 2833 (-C-H), 1647 (C=N), 1030 (-C-O), 809 (C=C-R), 568 (C=C-R). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 2.47 (s, 3H, -CH_3),

3.92 (s, 3H, -OCH_3), 5.88 (s, 2H -NH_2), 7.06 (d, 2H, J = 7.8 Hz, -C-H), 7.26 (s, 1H, -C-H), 7.36 (d, 2H, J = 7.2 Hz, -C-H), 8.04 (d, 2H, J = 7.5 Hz, -C-H), 8.16 (d, 2H, J = 7.8 Hz, -C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 21.5, 55.4, 103.5, 114.2, 127.3, 128.9, 129.3, 129.6, 134.2, 141.2, 162.0, 165.5, 165.8, 176.1. Anal. calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.28; H, 5.93; N, 14.50.

2-Amino-4-(4-ethoxyphenyl)-6-(4-methylphenyl)pyrimidine (4f): Yellow solid; (Conv. Heating yield: 90 %) (MWI yield: 75 %); Melting point: 383 – 385 K, FT-IR (KBr, cm^{-1}): 3466 (N-H), 3327 (N-H), 2928 (-C-H), 2833 (-C-H), 1647 (C=N), 1030 (-C-O), 809 (C=C-R), 568 (C=C-R). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 1.47 (t, 3H, J = 6.8 Hz, -CH_3), 2.44 (s, 3H, -CH_3), 4.12 (q, 2H, J = 6.8 Hz, -OCH_2), 5.25 (s, 2H, -NH_2), 7.01 (d, 2H, J = 8.4 Hz -C-H), 7.32 (d, 2H, J = 7.7 Hz -C-H), 7.42 (s, 1H, -C-H), 7.98 (d, 2H, J = 7.7 Hz, -C-H), 8.05 (d, 2H, J = 8.4 Hz, -C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 14.8, 21.4, 63.5, 103.2, 114.6, 127.0, 128.6, 129.5, 130.0, 135.1, 140.6, 161.0, 163.6, 165.6, 165.9. Anal. calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.68; H, 6.33; N, 13.80.

2-Amino-4-(2-chlorophenyl)-6-(4-methylphenyl)pyrimidine (4g): Orange solid; (Conv. Heating yield: 90 %) (MWI yield: 72 %); Melting point: 372 – 374 K, FT-IR (KBr, cm^{-1}): 3201 (N-H), 3190 (N-H), 3001 (=C-H), 2832 (-C-H) 1675 (C=N), 830 (C=C-R), 756 (C=C-R), 695 (C-Cl). ^{1}H-NMR: (400 MHz, $CDCl_3$): δ: 2.44 (s, 3H, -CH_3), 5.49 (s, 2H, -NH_2), 7.30 (d, 2H, J = 8.0 Hz, -C-H), 7.38 – 7.40 (m, 2H, -C-H), 7.49 – 7.53 (m, 1H, -C-H), 7.61 – 7.65 (m, 1H, -C-H), 7.96 (d, 2H, J = 8.0 Hz, -C-H). ^{13}C-NMR: (100 MHz, $CDCl_3$): δ: 21.4, 108.3, 127.0, 127.1, 129.5, 130.2, 130.3, 130.9, 132.1, 134.7, 137.9, 140.9, 163.5, 165.5, 165.8. Anal. calcd. for $C_{17}H_{14}ClN_3$: C, 69.03; H, 4.77; N, 14.21. Found: C, 69.10; H, 4.68; N, 14.35.

4. Results and discussion

4.1. Synthesis of 2-aminopyrimidines 4a-g by conventional heating

The seven 2-amino pyrimidines 4a-g, were synthesized with conventional heating, following Biginelli's three-component strategy, for gram-scale obtention [16] (Figure 1B). Reaction optimizations proceeded by adjusting solvent, catalyst, and temperature as leading factors for scoping. To this end, benzaldehyde (**1**), acetophenone (**2**), and guanidine**-**HCl (**3**) were used as control substrates.

Initial experiments were conducted unsuccessfully at low temperatures (298 – 323 K), using ultrasound or vigorous magnetic stirring to promote the reaction. Considering this, we carried out the synthesis under reflux in diverse solvents (protic and aprotic) and using sodium hydroxide as a base (1.1 equiv.), as described in Figure 4. The yields obtained in this scoping ranged from 5 % to 58 % with the most favorable conditions involving the use of ethanol as solvent under reflux (Table 1).

Table 1. Temperature and solvent scoping in conventional heating conditions for product **4a**[*].

Entry	Solvent	Temperature (K)	Yield (%)[**]
1	H_2O	343	5
2	H_2O	353	6
3	H_2O	Reflux	7
4	EtOH (96 %)	323	22
5	EtOH (96 %)	343	25
6	**EtOH (96 %)**	**Reflux**	**58**
7	*i*-PrOH	323	20
8	*i*-PrOH	Reflux	45
9	THF	Reflux	24
10	1,4-dioxane	Reflux	50
11	DMF	353	54
12	DMF	Reflux	5
13	MeCN	Reflux	15

[*]All experiments were carried out during 24 h and temperatures were measured in oil-bath.
[**]Yields determined by isolation of pure product **4a** as model reaction.

Following the determination of the optimal temperature and solvent for the desired reaction, the next step consisted of exploring the possibility of using other bases to improve the overall yield of the process. Nevertheless, there was no improvement in reaction efficiency when alternative bases replaced sodium hydroxide (Table 2).

Table 2. Base scoping in conventional heating conditions for product **4a** in the main reaction[*].

Entry	Base	Equiv.	Yield (%)[**]
1	KOH	0.1	10
2	KOH	0.5	12
3	KOH	1.0	25
4	KOH	1.5	88
5	KOH	2.0	92
6	NaOH	1.0	45
7	NaOH	1.5	88
8	**NaOH**	**2.0**	**94**
9	NaOH	2.5	94
10	$Ca(OH)_2$	1.0	33
11	$Ca(OH)_2$	2.0	52
12	$Ca(OH)_2$	2.5	55
13	$Ca(OH)_2$	3.5	57
14	EtONa	2.0	90
15	EtONa	3.0	94
16	*i*-PrONa	3.0	91

[*]All experiments were carried out during 20 h and temperatures were measured in oil-bath.
[**]Yields determined by isolation of pure product (**4a**) as model reaction.

With optimal operational conditions established, the compounds 2-amino-4,6-diarylpyrimidines **4a-g** were synthesized by the conventional heating methodology. This approach resulted in good yields of the expected compounds, using aldehydes **1a-d** and acetophenones **2a** y **2b** as main precursors, as detailed in Table 3.

Table 3. Yields of 2-aminopyrimidines **4a-g** obtained with the optimized conditions.

Entry	R	R_1	Yield (%)	Time (h)
4a	H	H	94	16.0
4b	*p*-OMe	H	90	17.0
4c	*p*-OEt	H	92	17.5
4d	*o*-Cl	H	80	15.0
4e	*p*-OMe	Me	93	18.0
4f	*p*-OEt	Me	90	20.0
4g	*o*-Cl	Me	90	16.5

In this study, we identified a plausible mechanism to explain the formation of multiple 2-amino pyrimidines in the established conditions. Such a mechanistic pathway involves the initial acid-base reaction between guanidine**-**HCl and sodium hydroxide to generate guanidine as a free base, which then reacts with aldehyde to produce the corresponding Schiff's base **II**, available to react, in the subsequent step, with the enolate of acetophenone **III** produced by deprotonation. The resulting intermediate **IV** performs an intramolecular 6-exo-*trig* cyclization with further dehydration, yielding a dihydro-2-aminopyrimidine **V**, which in turn undergoes oxidation in the presence of atmospheric oxygen, giving rise to the aromatic aminopyrimidine **4** (Figure 4).

In agreement with the results shown in Table 3, we highlight that the series of synthesized compounds (**4a-g**) were obtained with yields exceeding 80 %; nevertheless, it is also evident that reaction times are higher than 15 h. This aspect increases the total costs of the chemical process due to the continuous and exhaustive heating. Seeking to reduce reaction times while aiming at more sustainable conditions, we next explored the reaction by dielectric heating using microwave irradiation, as will be discussed in the following section.

4.2. Microwave induced synthesis of 2-aminopyrimidines 4a-g.

The synthesis of target 2-aminopirimidines using microwave induction in monomode reactor, began using control substrates **1a**, **2a** and guanidine**-**HCl (**3**), seeking to obtain product **4a** in a sealed tube, testing operational parameters such as solvent, catalyst (Table 4), irradiation power and temperature (Table 5).

Table 4. Solvent and catalyst scoping in microwave reaction for product **4a** (Temperature = 373 K, 10 min of irradiation).

Entry	Solvent**	Catalyst (Equiv)	Yield (%)***
1	H_2O	None	1
2	H_2O	NaOH (1.0)	6
3	H_2O	KOH (1.0)	7
4	H_2O	$CaCl_2$ (0.4)	10
5	EtOH (96 %)	None	NR

Table 4. Solvent and catalyst scoping in microwave reaction for product **4a** (Temperature = 373 K, 10 min of irradiation).

6	EtOH (96 %)	NaOH (0.5)	NR
7	EtOH (96 %)	KOH (0.5)	5
8	EtOH (96 %)	$CaCl_2$ (0.5)	6
9	EtOH (96 %)	EtONa (1.0)	8
10	EtOH (96 %)	NaOH (2.0)	8
11	None*	None	NR
12	None*	NaOH (2.0)	28
13	None*	NaOH (1.0)	24
14	None*	NaOH (0.5)	5
15	None*	NaOH (0.2)	4
16	None*	KOH (0.5)	6
17	None*	$CaCl_2$ (0.5)	54
18	None*	$CaCl_2$ (0.3)	50
19	**None***	**$CaCl_2$ (0.4)**	**56**
20	None*	EtONa (0.5)	29

NR: No reaction was observed.
*Two drops of water were added to moisturize the reaction mixture.
**1 mL of solvent was used.
***Yields determined by isolation of pure product (**4a**).

The experiments shown in Table 4 were conducted by keeping an isothermal parameter (373 K) and constant irradiation power (100 W). Noteworthy, the experiments exhibiting higher yields involved catalytic amounts of calcium chloride (0.4 equivalents) as reaction promoters without a solvent (Table 4, Entry 19). Under the conditions studied, $CaCl_2$ could be hydrolyzed to calcium hydroxide or converted to calcium oxide; these are basic catalysts potentially formed *in situ* in the reaction medium in the presence of small amounts of water and oxygen. Additionally, salts like $CaCl_2$ enhance MW irradiation and accelerate reactions, such as hydrolysis and condensation [32, 33, 34]. We thoroughly explored this solvent-free reaction through assays with varying temperatures and irradiation power, whereby the overall reaction yield increased, reaching 86 % at 523 K and 150 W (Table 5, entry 9).

Experiments evaluating non-thermal effects associated with microwave irradiation in the multicomponent synthesis were carried out with the same operational parameters, but using a conventional heating approach in a sealed reactor (Anton Parr's Monowave50®). This assay yielded comparable results to the microwave-assisted method (Yield (**4a**) = 85 %), confirming the absence of non-thermal effects associated with microwave irradiation and leading to the conclusion that the key advantage of the MWI approach is a faster heating of the reaction mixture, which is essential in shortening the length of the process. On the other hand, temperatures above guanidine**-**HCl's melting point (451 – 458 K) [35, 36] tend to promote the generation of a liquid phase that allows better component convection, thus giving rise to a faster and more efficient reaction, leading to desired 2-amino pyrimidines (**4a-g**) (Table 6).

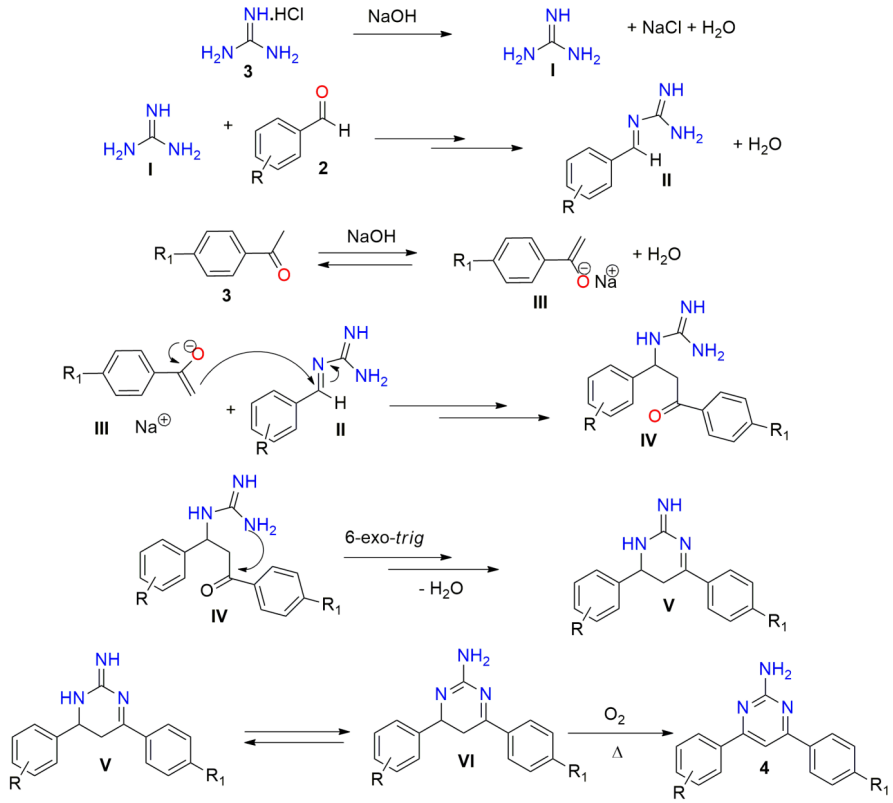


Figure 4. Proposed mechanism of conventional heating Biginelli-type reaction.

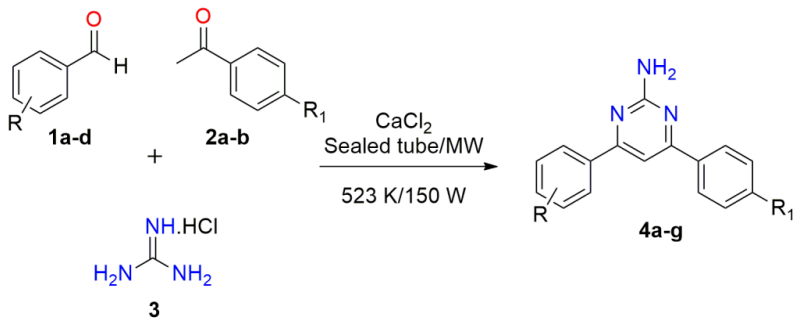
Table 5. Scoping of temperature and irradiation power in microwave-assisted synthesis.

Entry	Temperature (K)	Power (W)	Time (min)	Yield (%)*
1	343	50	40	NR
2	353	60	40	NR
3	373	110	40	10
4	423	110	40	12
5	463	150	20	25
6	473	150	18	32
7	483	150	10	54
8	493	150	10	60
9	**523**	**150**	**10**	**86**
10	543	150	8	78
11	553	150	5	70
12	573	200	3	Deg.

NR: No reaction was observed. Deg: Degradation of precursors.
*Yields determined by isolation of pure product (**4a**).

Based on the aforementioned results, the obtained 2-amino-4,6-diarylpyrimidines were synthesized looking to evaluate the versatility of the new synthetic method (Table 6).

Table 6. Yields of 2-amino pyrimidines **4a-g** obtained by the optimized MW-heating method.



Entry	R	R_1	Yield (%)
4a	H	H	86
4b	*p*-OMe	H	78
4c*	*p*-OEt	H	67
4d*	*o*-Cl	H	72
4e	*p*-OMe	Me	83
4f*	*p*-OEt	Me	75
4g*	*o*-Cl	Me	72

*Compounds reported for the first time in this work.

5. Conclusions

Through a multicomponent process, a series of 4,6-diaryl-2-aminopyrimidines were successfully synthesized using conventional heating methods and microwave irradiation. The former approach studied and optimized under reflux in ethanol (conventional heating), led to title compounds in reaction times of 15-24 h and yields ranging from 80-94 %. In turn, the microwave-assisted method proceeded under solvent-free conditions, using $CaCl_2$ as catalyst and at remarkably shorter reaction times (10-20 min), giving rise to target molecules efficiently in 67-86 % yields, but with the additional advantage associated with conditions more in line with a sustainable organic synthesis. It is important to state that both strategies imply easy purification methods and high selectivity to desired products, under simple and reproducible protocols.

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7. Conflict of interest

This paper has not been published previously and is not under consideration elsewhere. Authors are responsible for the reported research and have participated in the concept and design, analysis, and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted. We wish to confirm that there are no known conflicts of interest associated with this publication.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Estudio Comparativo entre Enfoques de Calentamiento Asistido por Microondas y Calentamiento Convencional para la Síntesis Multicomponente de 4,6-Diarielpirimidinas

Resumen: Resumen. Se sintetizaron una serie de 2-amino-4,6-diarielpirimidinas utilizando una estrategia tricomponente de tipo Biginelli optimizada en reflujo con calentamiento convencional. Esta estrategia se comparó con un enfoque no convencional que utilizaba un reactor de microondas de modo único. Los protocolos de calentamiento convencionales involucraban disolventes orgánicos y catálisis de base general, mientras que el método asistido por microondas seguía protocolos experimentales enmarcados dentro de los principios de la química verde al utilizar $CaCl_2$ como catalizador en condiciones libres de solventes. Este estudio reveló que, aunque el calentamiento convencional llevó a un mayor rendimiento del producto principal, esto se logró con tiempos de reacción más largos. Mientas que la estrategia de microondas tuvo éxito con tiempos de reacción sustancialmente más cortos y condujo a rendimientos que variaban entre aceptables y buenos con eficiencias comparables a las de la metodología de calentamiento convencional.

Palabras Clave: 4,6-diarielaminopirimidinas; síntesis irradiada por microondas; reactor de modo único; reacción de tipo Biginelli.

Estudo Comparativo entre Abordagens de Aquecimento Assistido por Micro-ondas e Aquecimento Convencional para a Síntese Multicomponente de 4,6-Diarielpirimidinas

Resumo: Uma série de 2-amino-4,6-diarielpirimidinas foi sintetizada utilizando uma estratégia tricomponente do tipo Biginelli otimizada em refluxo com aquecimento convencional. Essa estratégia foi comparada com uma abordagem não convencional que utilizava um reator de micro-ondas de modo único. Os protocolos de aquecimento convencionais envolviam solventes orgânicos e catálise de base geral, enquanto o método assistido por micro-ondas seguia protocolos experimentais enquadrados nos princípios da química verde, utilizando $CaCl_2$ como catalisador em condições livres de solventes. Este estudo revelou que, embora o aquecimento convencional tenha levado a um rendimento superior do produto principal, isso foi alcançado com tempos de reação mais longos. Enquanto a estratégia de micro-ondas obteve sucesso com tempos de reação substancialmente mais curtos e levou a rendimentos entre aceitáveis e bons, com eficiências comparáveis às da metodologia de aquecimento convencional.

Palavras-chave: 4,6-diarielaminopirimidinas; síntese irradiada por micro-ondas; reator de modo único; reação do tipo Biginelli.

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