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Antinociceptive pyrimidine derivatives: aqueous multicomponent microwave assisted synthesis

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ABSTRACT

Pyrimidines and their oxo-derivatives are well researched due to their anti-inflammatory, analgesic, antimicrobial, antiviral, and interferon inducing activities. New pyrimidine derivatives are therefore frequently synthesized to build up small molecule libraries for the discovery of drug candidates. Synthesis of 2,6-diaryl-4-(3*H*)-pyrimidinones and 2,6-diaryl-4-aminopyrimidines is traditionally a 2-day laboratory effort carried out in two steps, always using ethanol as solvent, and triethylamine as base. In this Letter, we advance a one-step alternative synthetic method with a 40 min reaction time using a microwave reactor in an aqueous media with potassium carbonate as base. The average yields were also somewhat improved. This new method thus emerges as more eco-friendly, not only because it does not employ triethylamine as base, but also due to a much reduced usage of organic solvents, leading to less harmful residues. Using this method, we synthesized twenty pyrimidine derivatives with antinociceptive activities in satisfactory chemical yields.

Introduction

Pyrimidines and their oxo derivatives are six-membered heterocycles of importance to medicinal chemistry due to their biological activities. They are closely related to nucleic acids, since they are very much alike in structure to the pyrimidine bases.[1] Perhaps, because of this structural similarity, compounds with such heterocycles in their molecular structure were reported as antitumor,[2,3] interferon inducer,[4] antiviral,[5] anti-hipertensive,[6] hypoglycemic,[7] anticonvulsant,[8] antinociceptive,[9,10] and anti-inflammatory[11] agents.

Risperidone (**I**), bropirimine (**II**), and 5-fluorouracil (**III**) are three successful examples of therapeutical tools that contain the pyrimidinone nucleus in their structures (Fig. 1). Risperidone is an atypical second-generation antipsychotic drug used in the treatment of schizophrenia, and bipolar and behavior disorders.[12] Other examples are bropirimine and 5-fluorouracil, which are both anticancer agents.[13,14]

Pyrimidine or pyrimidinone scaffolds can be prepared in different ways.[1] Usually, a Michael adduct and an uronium-containing molecule (guanidine,[15] amidines,[16] urea,[17] thiourea, and their derivatives[18,19]) are condensed in the presence of an organic base to prepare the heterocyclic nucleus. In general, this process may take about two days of laboratory work for the preparation of one sole product.[1,2,9–11,16] Faster synthetic routes are thus desirable to prepare such bio-active heterocycles.

Microwave radiation has been used since the 1980's as an alternative manner to accelerate endothermic organic reactions.[20] Microwave radiation can be focused in the reaction medium and efficiently transfer energy directly to the reacting species, superheating them in a much faster manner, when compared to regular convection heating,[20] thereby facilitating the desired chemical transformations. As a result, many organic reactions have been performed using microwave energy, like cycloadditions,[21] additions to carbonyl group,[22] electrophylic substitutions,[23] and heterocycle synthesis.[24]

Multicomponent reactions (MCRs) are one-pot reactions that begin with three or more reagents that are mixed together, but react in sequence. In general, these reactions are driven by an irreversible step that precedes equilibrium in favor of the final product.[25] The use of microwave energy could accelerate this type of reaction since the conductive heating could improve the rate determining step for the overall process. Having this in mind, Matloobi and Kappe, for example, used microwave irradiation to perform the synthesis of several 2-amino-4-arylpyrimidine derivatives through a Biginelli multicomponent approach.[26]

Our research group has been involved in synthesizing and testing the biological activities of pyrimidines and their oxo derivatives.[10,11,16] Some of the products we designed and prepared presented relevant antinociceptive activities.[10] However, the methodology employed for the synthesis of such products is quite laborious and requires two or more steps to finish the whole

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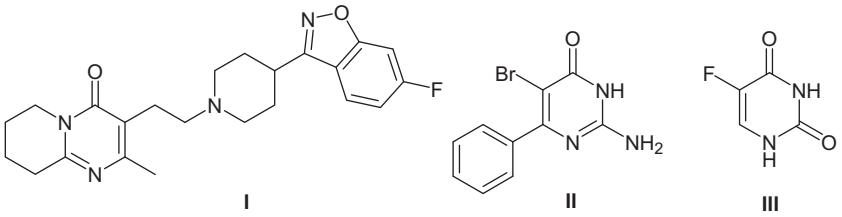
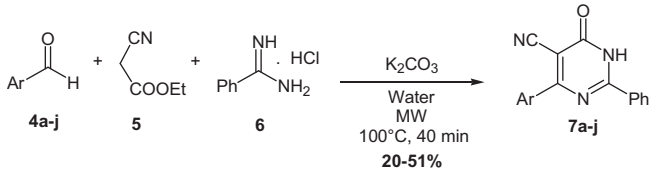


Figure 1. Some examples of drugs containing the pyrimidine scaffold.



Scheme 1. Three-component reaction of aromatic aldehydes, ethyl cyanoacetate, and benzamidine.

Table 1
Microwave assisted multicomponent reaction for the synthesis of 6-oxo-2,4-diaryl-1,6-dihydro-pyrimidine-5-carbonitriles (**7a–j**)

Compound	Ar	Yield (%)
7a	Ph	42
7b	*m*-Tolyl	47
7c	*p*-Tolyl	33
7d	*p*-ClPh	49
7e	*p*-BrPh	46
7f	*p*-FPh	45
7g	*p*-OCH_3Ph	41
7h	*m*-NO_2Ph	20
7i	*p*-NO_2Ph	43
7j	3,4-diClPh	51

synthetic process.[16] Indeed, synthesis of 2,6-diaryl-4-(3*H*)-pyrimidinones and 2,6-diaryl-4-aminopyrimidines is traditionally a two-day effort carried out in two steps always using ethanol as solvent and triethylamine as base: in the first, one obtains the alicyclic derivative from aromatic aldehydes and a methylene-active compound, and, in the second, a condensation of this alicyclic derivative with an uronium donor is performed, followed by an intramolecular cyclization.

Thus, the development of multicomponent methods for the production of these bioactive heterocycles will speed up the synthetic part of the discovery process for new pyrimidinic drugs.[27]

Accordingly, in this Letter we report our development of a new, multicomponent, and eco-friendly methodology route for the synthesis of 4-amino-2,6-diaryl-pyrimidine-5-carbonitrile and 6-oxo-2,4-diaryl-1,6-dihydro-pyrimidine-5-carbonitrile derivatives. Some of these derivatives have shown significant analgesic activity in mice.[10]

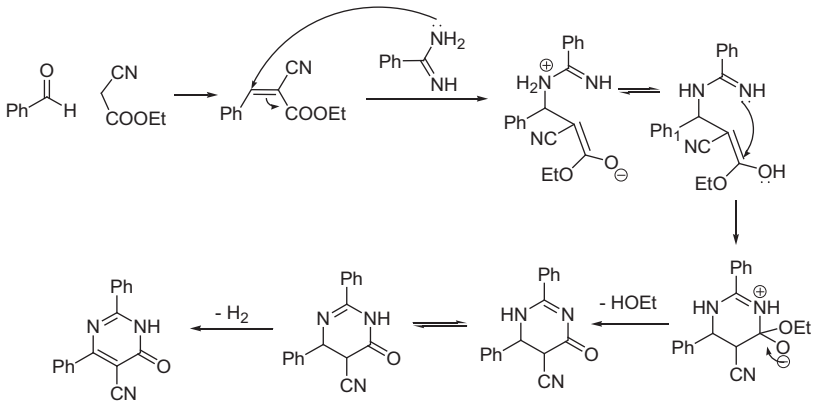
Results and discussion

In our synthetic approach, aromatic aldehydes (**4a–j**) were allowed to react with ethyl cyanoacetate (**5**) and benzamidine hydrochloride (**6**), in the presence of potassium carbonate as base. The reaction was performed in water, under microwave irradiation and led to the pyrimidinones **7a–j** in moderate yields (Scheme 1, Table 1).[28,29]

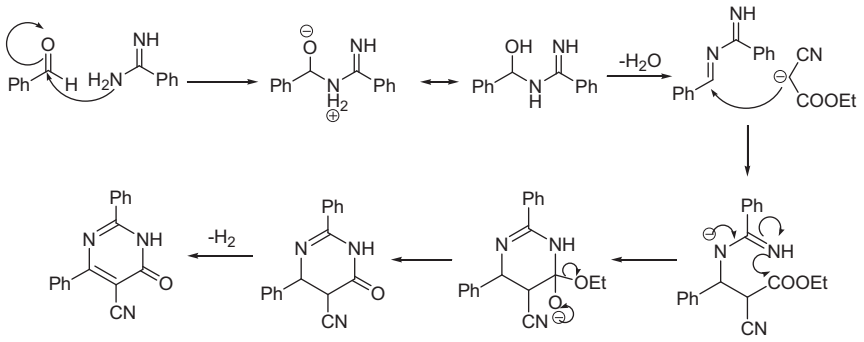
The reaction conditions using microwave irradiation were optimized with benzaldehyde. Under microwave irradiation, the reaction took place in about 40 min.

In order to be able to compare the methods, we also performed the same reaction without microwave irradiation, using the same solvent (water) and the same quantities for the reagents and benzaldehyde, in reflux. For 6-oxo-2,4-diphenyl-1,6-dihydro-pyrimidine-5-carbonitrile (**7a**), the yield was only 18%, 8 h after the beginning of the reaction.

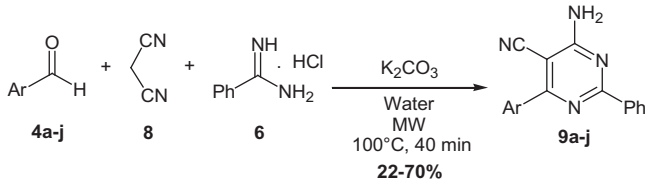
In both cases, there are, possibly, two subsequent reactions occurring in order to arrive at the heterocycle scaffold: the first one is the Knoevenagel reaction,[30] where an aromatic aldehyde reacts with ethyl cyanoacetate, a so called 'methylene active' compound because of its easily deprotonable central methylene group, to form Michael's intermediate. Once formed, the Knoevenagel adduct can react with benzamidine. Michael's adduct can then be attacked by the lone electron pair of a nitrogen atom in the uronium portion. There is then a sequence of additions with a subsequent ring closure to form the corresponding heterocycle. However, the last step in this mechanistic explanation for the pyrimidinone scaffold formation is quite intriguing. According to Mendonça et al.,[16]



Scheme 2. Mechanism of formation of pyrimidinone derivatives.



Scheme 3. Another mechanistic explanation for the formation of 2,6-diaryl-4-(3*H*)-pyrimidinones.



Scheme 4. Synthesis of 2,6-diaryl-4-aminopyrimidines via multicomponent reaction.

atmospheric oxygen is responsible for this oxidation and loss of a H_2 molecule, leading to the heterocycle (Scheme 2).

Another mechanism which can also explain the formation of the title compounds is the formation of an imine derivative which takes place as a first step. This intermediate can be produced by the reaction between the aldehyde and the amidine. Then, a subsequent reaction of this imine derivative with ethyl cyanoacetate forms the desired heterocycle. Once again, in a process analogous to the pyrimidinone ring formation, oxygen can perform the oxidation of the dihydro derivative to a pyrimidine nucleus in the last step (Scheme 3).

In order to expand this reaction profile to similar scaffolds, we tested the protocol changing the "methylene active" compound and thus, building the pyrimidine nucleus (**9a–j**). To achieve this goal, the aromatic aldehydes reacted with malononitrile (**8**) and benzamidine under the same reaction conditions (Scheme 4, Table 2).[28,29]

Some of the pyrimidinone derivatives described herein (**7a**, **7d**, and **7g**) had their antinociceptive activity evaluated in mice through acetic acid induced stimuli.[10] It was reported that, at the dose of 50 mg/kg, pyrimidinone **7a** showed 85% of analgesia, thus more potent than indomethacin (76% of activity, in comparison to non-treated animals), the reference drug. It is suggested that some compounds that contain the pyrimidinone scaffold may interfere with the acute inflammatory response induced by acetic acid, inhibiting or modulating the migration or production of chemical mediators in the inflammatory site.[11,31,32]

Table 2
Microwave assisted multicomponent reaction for the synthesis of 4-amino-2,6-diaryl-pyrimidine-5-carbonitriles (**9a–j**)

Compound	Ar	Yield (%)
9a	Ph	56
9b	*m*-Tolyl	36
9c	*p*-Tolyl	47
9d	*p*-ClPh	70
9e	*p*-BrPh	48
9f	*p*-FPh	27
9g	*p*-OCH_3Ph	48
9h	*m*-NO_2Ph	40
9i	*p*-NO_2Ph	67
9j	3,4-diClPh	22

Conclusions

In short, we advanced in this article a multicomponent approach employing microwave energy and water as solvent to synthesize pyrimidines and their oxo-derivatives. This environmentally friendlier protocol furnishes products with higher chemical yields, employs potassium carbonate as base instead of triethylamine, and is performed in 40 min, showing to be much faster than the usual 2 day route. We exemplified this synthetic methodology by preparing 20 different 2,6-diaryl-4-(3*H*)-pyrimidinones and 2,6-diaryl-4-aminopyrimidines with antinociceptive activities, in satisfactory chemical yields.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.099.

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28. *General procedure for the multicomponent synthesis of 6-oxo-2,4-diaryl-1,6-dihydro-pyrimidine-5-carbonitriles (**7a–j**) and 4-amino-2,6-diaryl-pyrimidine-5-carbonitriles (**9a–j**)*: To a sealed vessel appropriated for reactions in microwave reactors (capacity: 35 mL), were added 1.13 mmol (176 mg, 1.2 equiv) of benzamidine hydrochloride and 1.88 mmol (249 mg, 2.0 equiv) of potassium carbonate dissolved in 10 mL of distilled water. This mixture was stirred at room temperature until the neutralization of the benzamidine salt. To the clear basic solution, 0.94 mmol of the corresponding aromatic aldehyde (1.0 equiv) and 1.88 mmol (2.0 equiv) of ethyl cyanoacetate (for the synthesis of **7a–j**) or malononitrile (for the synthesis of **9a–j**) were added. The mixture was placed in a microwave reactor under the following conditions: temperature 100 °C and 300 W of initial power for 40 min. After this time, the consumption of the starting aldehyde was verified by TLC (hexane/ethyl acetate, 7:3 v/v). The reaction was allowed to cool to room temperature and poured onto ice. The formed precipitate was then vacuum filtered, washed with distilled water (50 mL), and recrystallized from ethanol to provide the pure pyrimidinones or pyrimidines.
29. *Characterization data for representative compounds. 6-Oxo-2,4-diphenyl-1,6-dihydro-pyrimidine-5-carbonitrile (**7a**)*: Colorless solid, yield: 42%; R_f: 0,43 (AcOEt); mp: above 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.59–7.68 (m, 6H, H_{arom}); 8.04 (2H, d, *J* 8.0 Hz, H_{arom}); 8.25 (2H, d, *J* 8.0 Hz); 13.73 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 95.6; 115.8;128.6; 128.7; 128.8; 131.3; 131.7; 133.1; 135.5; 159.0; 161.8; 168.6. I.R (KBr pellets) ν_{max}/cm^{-1}: 2923 (ν_{C-H}); 2201 ($\nu_{C\equiv N}$); 1552 ($\nu_{C=O}$); 1488 ($\nu_{C=N}$). ESI-HRMS *m*/*z*: 274.0975 (calcd for $C_{17}H_{12}N_3O$ [M+H$^+$]: 274.0975). *4-Amino-2,6-diphenyl-pyrimidine-5-carbonitrile (**9a**)*: Colorless solid, yield: 56%; R_f: 0.60 (hexanes/AcOEt, 1:1 v/v); mp: 210–211 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.51–7.60 (m, 6H, H_{arom}); 7.97–7.99 (m, 4H, H_{arom}, NH_2); 8.41 (2H, dd, *J* 8.0 Hz, *J* 1.8 Hz, H_{arom}). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 84.4; 116.4; 128.4; 128.5; 128.6; 130.9; 131.5; 136.5; 136.6; 164.0; 164.6; 168.1. I.R (KBr pellets) ν_{max}/cm^{-1}: 3480 (ν_{N-H}); 3345 (ν_{N-H}); 2217 ($\nu_{C\equiv N}$); 1635 ($\nu_{C=N}$); 1541 ($\nu_{C=N}$). ESI-HRMS *m*/*z*: 273.1134 (calcd for $C_{17}H_{13}N_4$ [M+H$^+$]: 273.1140).
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