

A Simple and Efficient Microwave Assisted Synthesis of Pyrazolo [3,4-*D*] [1,2,4] Triazolo [1,5-*A*] Pyrimidines

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ABSTRACT

With the aim to extend the synthetic pathways to new planar heterocyclic ring systems, synthesis of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine, a new ring system, was achieved by using a one-pot, microwave-assisted, catalyst-free, Biginelli like cyclocondensation reaction. All the newly synthesized were characterized by various spectrometric techniques like FT-IR, mass spectra, ¹H NMR, ¹³C NMR and elemental analysis.

Keywords: Pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines; planar heterocyclic ring systems; catalyst-free; one-pot: Biginelli like cyclocondensation

I. INTRODUCTION

Pyrazole and fused heterocyclic pyrazole derivatives offer a great synthetic versatility and effective pharmacological importance.¹⁻³ Several heterocyclic compounds bearing pyrazolo[3,4-*d*]pyrimidine exhibited excellent antitumor and antileukemia activity.⁴⁻⁷ Some classes of pyrazolopyrimidine derivatives have been found to be glycogen synthase kinase-3 inhibitors which has been represented as emerging target for diseases such as Alzheimer's disease, type-2 diabetes mellitus, some kind of cancer, neurological disorders and inflammations.⁸ Recently, tetrahydropyrazolopyrimidine derivatives bearing adamantly group have been found to be potent class of potent calcium-sensing receptor antagonists.⁹ Moreover, 1,2,4-triazolo[1,5-*a*]pyrimidines have aroused increasing attention from the chemical and biological view points, due to their diverse pharmacological activities, such as antitumor potency,¹⁰⁻¹¹ inhibition of KDR kinase,¹² antifungal effect,¹³ and macrophage activation.¹⁴ They have proved to be promising anticancer agents with dual mechanisms of tubulin polymerization promotion¹⁰⁻¹¹

as well as cyclin dependent kinases 2 inhibition.¹⁵ In addition, several triazolopyrimidines have exhibited excellent antimalarial activity, inhibited *P. falciparum* dihydroorotate dehydrogenase (*PDHODH*) up to significant extent. Such derivatives also have been found to be associated with good *PDHODH* inhibition and lower parasite toxicity.¹⁶

The intriguing pharmacological activities of both the heterocycles, pyrazolopyrimidine and triazolopyrimidine, and our interest in synthesis of planner heterocycles with potential biological activities, prompted us to approach the synthesis pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines.

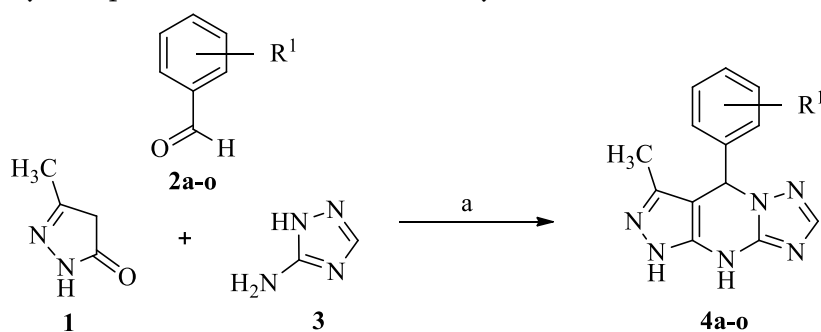
Pyrazolotriazolopyrimidines have been found to be highly potent and selective human A3,¹⁷⁻¹⁹ A2A²⁰ and A2B¹⁹ adenosine receptor antagonists. On the other hand, synthesis and chemistry of these compounds were not explored much in literature.²¹⁻²⁶ Among the various pyrazolotriazolopyrimidine ring systems, pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines have never been explored, and there are no reports on the

synthesis and chemical properties of these class of compounds.

The application of microwave-assisted organic synthesis for conducting chemical reactions at highly accelerated rates is an emerging technique which is practiced widely due to their ability to curtail reaction time, the number of steps, energy consumption, waste production, and to maximize synthetic effectiveness and environmental benignity.²⁷ Considering versatile biological activities of pyrazolotriazolopyrimidine, we focused on introducing novel ring system which was found to be absent in literature, pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine. As part of developing planner heterocycles of biological interests,²⁸⁻³² we approached simple, efficient, catalyst free, and Biginelli like cyclocondensation for the synthesis of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines.

The synthetic route for the preparation of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines **4a-o** is outlined in Scheme1. Synthesis of 3-methyl-1*H*-pyrazol-5(4*H*)-one was achieved using previously published methods.³³ All the pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines **4a-o** were synthesized by one-pot, microwave-assisted, catalyst-

free, Biginelli like cyclocondensation. A mixture of the aminoazole (0.01 mol), 3-methyl-1*H*-pyrazol-5(4*H*)-one (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in ethanol (5 mL) was irradiated under microwave conditions at 120 °C for 15-20 min. After irradiation in the microwave reactor, the reaction mixtures were allowed to stand at room temperature overnight, and the precipitated crystalline solids were subsequently filtered, washed with ethanol, and air-dried. The yields of the products **4a-o** were obtained in the range of 56–75%. All pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines **4a-o** were obtained in high purity and without further purification and were fully characterized by ¹H NMR, ¹³C NMR and MS data, in addition to elemental analysis. The ¹H NMR spectra of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines **4a-o** have the typical singlet of methine group lying in the region 5.35–6.87 ppm, and multiplet of aromatic part of molecules occurring in region between 6.16 and 7.51 ppm. The ¹³C NMR signal of methine group can be observed at 44.7–55.1 ppm. IR spectra of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines **4a-o** were also in agreement with the structures. The spectroscopic analysis confirmed the formation of desired products.



Scheme 1. Synthesized pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine derivatives **4a-o**. Reagents and conditions: (a) EtOH, MW, 120 °C, 10-12 min

Table 1. Synthesized pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine derivatives **7a-o**

Entry	R ¹	Product	Yield%
1	4-OCH ₃	7a	69
2	4-F	7b	68
3	4-NO ₂	7c	75
4	4-Cl	7d	74

5	4-CH ₃	7e	56
6	4-OH	7f	72
7	3-NO ₂	7g	58
8	3-Cl	7h	68
9	3-OH	7i	75
10	3-Br	7j	72
11	3,4-OCH ₃	7k	68
12	2-NO ₂	7l	72
13	2-Cl	7m	69
14	2-OH	7n	70
15	H	7o	59

To determine optimal reaction conditions, one-pot, microwave assisted condensation of aminoazole (0.01 mol), 3-methyl-1*H*-pyrazol-5(4*H*)-one (0.01 mol) and 4-methoxy aldehyde (0.01 mol) in different solvents via same reaction conditions, were examined (Table 2). The result showed that yields were better with ethanol than any other solvents. Moreover, the products from other solvents required further purification. Thus, ethanol was chosen as an optimal solvent for the one-pot, microwave assisted cyclocondensation. In order to confirm the best method for the synthesis of pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines, the reaction was also carried out using ultrasonic waves as an assisted technique.

The reaction mechanism of this three-component condensation is probably similar to the described³⁴ mechanism for the “classical” Biginelli reaction (**Pathway 1**). The first step is a nucleophilic addition of N₍₂₎ of the aminoazole to a carbonyl carbon of aldehyde, followed by subsequent cyclization with 3-methyl-1*H*-pyrazol-5(4*H*)-one to form the dihydropyrimidine ring. An alternate sequence is also possible, and cannot be excluded³⁵ (**Pathway 2**), that is the initial formation of an enamine by reaction of aminoazole with the 3-methyl-1*H*-pyrazol-5(4*H*)-one followed by cyclocondensation. The third alternative involving the formation of 3-methyl-4-benzylidene-1*H*-pyrazol-5(4*H*)-one derivatives as intermediates

requires the presence of a strong base,³⁶ and is most likely not possible for the cases described herein.

In conclusion, we have developed a simple and efficient procedure to generate pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines in excellent yields via a one-pot, microwave-assisted, catalyst-free Biginelli like cyclocondensation. The synthetic protocol utilizes mild reaction conditions and does not require work-up or column purification. Reaction times were considerably reduced and product yields increased under microwave irradiation. This simple and efficient synthetic protocol should be amenable to construct new substituted pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine scaffolds with potential biological applications.

II. REFERENCES

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