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Seyyed Hojjat Sadeghi
Imam Ali University
Alireza Khajeh-Amiri
a.khajehamiri@ajaums.ac.ir

Imam Ali University

Research Article

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Posted Date: June 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9858156/v1

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Additional Declarations: No competing interests reported.

Synthesis Pyrido [2,3-d:5,6-d′]dipyrimidines using citric acid as a novel nanocatalyst in a practical and environmentally friendly manner

Seyyed Hojjat Sadeghi[a], Alireza Khajeh-Amiri[b,c]*

Corresponding author:Alireza Khajeh-Amir

[a]*Department of Chemistry, Faculty of Basic Sciences, Imam Ali University, Imam Khomeini Street, P.O. Box 1317893471, Tehran 1317893471, Iran*

[b] *Toxicology Research Center, AJA University of Medical Sciences, Tehran, Iran*

[c] *Biomaterials and Medicinal Chemistry Research Centre, AJA University of Medical Sciences, Tehran, Iran*

Corresponding Email: a.khajehamiri@ajaums.ac.ir

Seyyed Hojjat Sadeghi Email: SeyyedHojjatSadeghi@gmail.com

Abstract

Heterocycle molecules are among the most important substances in organic chemistry. N-containing heterocyclic materials are highly significant among various heterocyclic compounds because of their many features that may be used in a variety of sectors.The use of pyrido[2,3-d:5,6- d']dipyrimidine derivatives in the synthesis of powerful medications and crucial biological substances makes them noteworthy substances. Accordingly, we introduced a novel approach for the solvent-free synthesis of pyrido[2,3-d:5,6-d']dipyrimidine utilizing tricarboxylic acid (Citric acid)as a natural and water-soluble catalyst. This method's benefits include a high product yield, a quick reaction time, easy workup, and a cheap catalyst. FT-IR and ^{1}HNMR techniques were used to describe each product, which was produced in good to excellent yields.

Keywords: *N*-containing heterocycle; Citric acid, Pyridopyrimidine; Tricarboxylic acid; Biological

1. Introduction

The structure of numerous biological and pharmacological substances makes heterocyclic compounds (HCs) one of the most significant chemicals in organic chemistry. Cyclic compounds with heteroatoms in their structure, including oxygen, sulfur, nitrogen, etc., are called HCs. Nitrogen-containing heterocycles are particularly significant among the many heterocycle chemicals that are known to exist. To put it another way, N-containing heterocyclic compounds offer a wide range of uses in medicine, such as antibacterial, enzyme inhibitor, antioxidant, and diabetic characteristics[1–5]. The presence of heterocyclic compounds in the structure of natural products and their diverse biological and medicinal functions make them a significant class of

organic chemicals [6,7]. Pyrido[2,3-d:5,6-d']dipyrimidines (Pydip)[8,9], include a pyrimidine ring in their structure, making them a particular kind of heterocyclic compounds. Derivatives of pyridodipyrimidines exhibit a variety of biological properties, including anticancer, anti-inflammatory, anti HIV, calcium channel antagonists, antifolate, tuberculostatic, analgesic, and anticonvulsants [10]. N-containing heterocycle compounds come in a variety of forms, including derivatives of tetrazoles, triazoles, thiadiazoles, pyrimidines, imidazoles, etc [11–13]. The antibacterial and anticancer characteristics of pyrimidine derivatives give them a unique position. The pyridopyrimidine and pyrimidine have many derivatives. This class of annulated uracil, known as pyridopyrimidine, has a wide range of uses in pharmacological, biological, and medical application areas. This N-containing heterocycle molecule has thus recently attracted significant attention [14–17]. (Pydip) is a specific class of N-containing HCs with a pyrimidine ring in their structure [18–20]. Multi-component reactions (MCR) are appropriate for the synthesis of complex molecules because they shorten reaction times and conserve energy and resources [21–25]. Pydip can be synthesized in a variety of methods, using either homogeneous or heterogeneous catalysts in multi-component processes. Several catalysts were utilized in this process, including magnetic-based catalysts[26], 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) [27] and different acid based supports [28]. There is a lot of interest in using solvent-free techniques to improve the cleanliness, non-toxicity, and ease of completion of classical processes. Solvent-free organic transformations and synthesis are thought to be primarily environmentally friendly and industrially useful. Scientists' concern about new environmentally friendly synthetic methods has led them to focus on reducing or eliminating, which are a primary source of pollution [16,29,30]. Heterogeneous and homogeneous catalysts are the two categories of catalysts that were discussed in the preceding paragraph. Because of their existence, catalysts are effective and beneficial in a variety of processes by speeding up the process. Heterogeneous catalysts are often found on a solid support and do not dissolve in the process [31–33]. Although they have the advantage of being easily separated from the reaction mixture, their inability to dissolve in the reaction means that not all of the catalyst's active sites are present, which might reduce their effectiveness. This is the opposite of homogeneous catalysts. due to the reaction mixture's dissolution of the homogenous catalysts. Because of this, the reaction may use all of the catalytic sites, which makes them extremely effective. However, the manufacture of homogeneous catalysts is inexpensive, but heterogeneous catalysts require solid support, which might be costly and unavailable at times [34,35]. Numerous homogeneous

catalysts, including various vitamins and inorganic and organic acids, are found in nature [36,37]. Green chemistry concepts state that using ecologically friendly chemicals and solvents is crucial. Natural, non-toxic, and biodegradable catalysts adhere to the best practices of green chemistry. The natural substance tricarboxylic acid, (generally known as citric acid), is particularly significant among those that are also employed as catalysts. This acid is mostly found in citrus fruits and contains acidic groups. Because citric acid has an acidic nature, it may be used as a powerful and acidic homogeneous catalyst for a variety of processes. Citric acid's chemical structure, primary source, and a few of its characteristics are shown in Figure 1 [38,39].

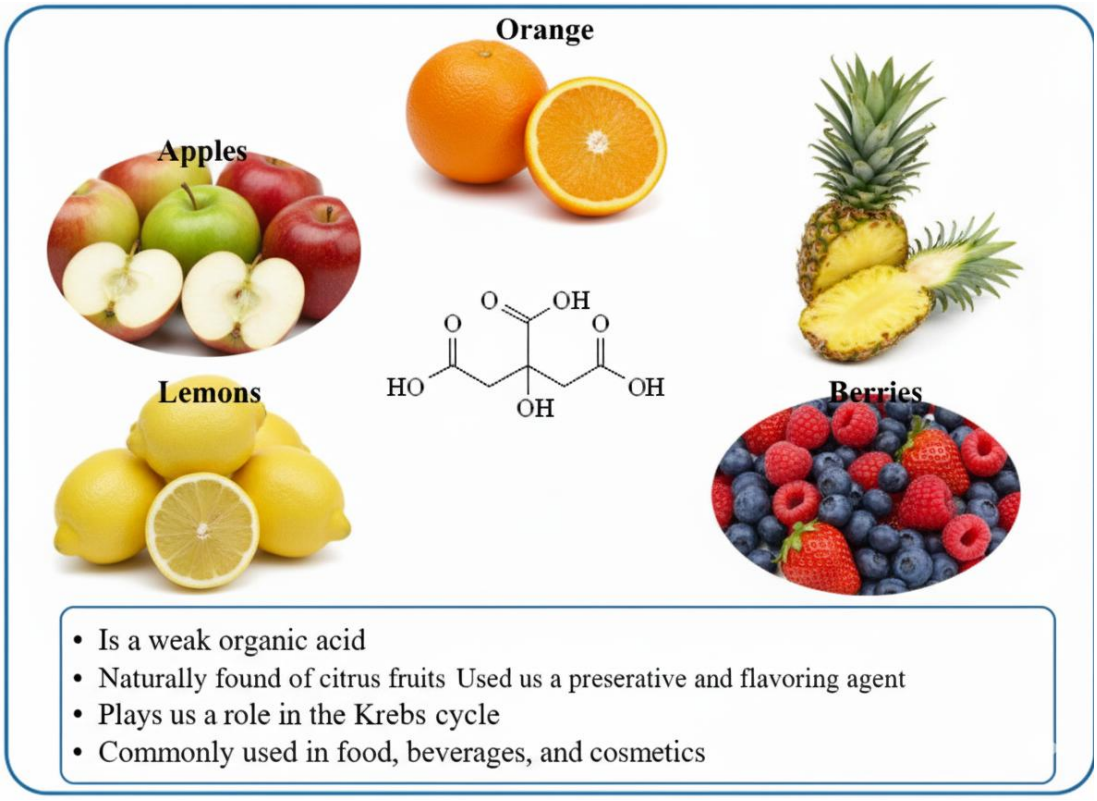
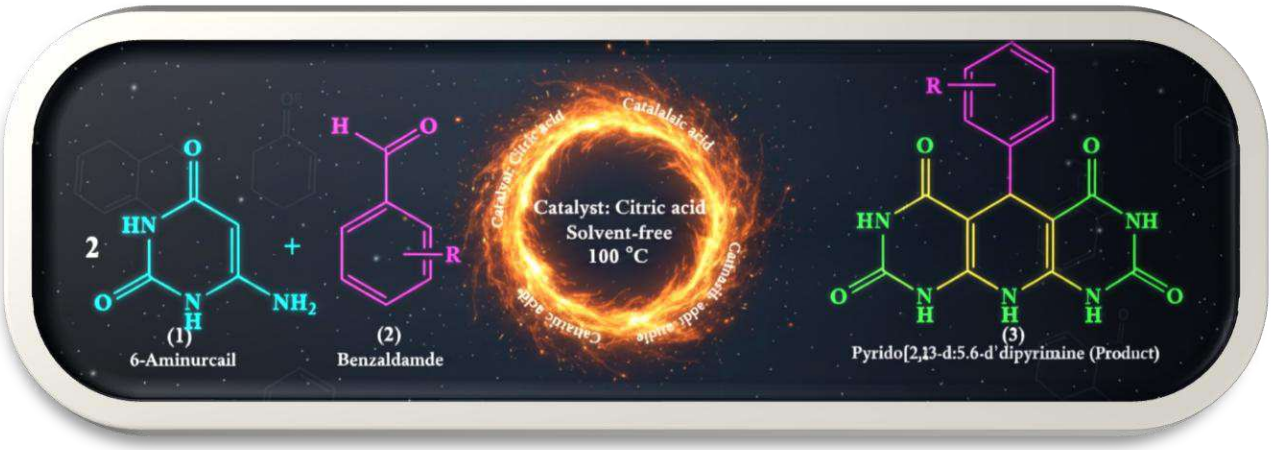


Figure 1. Schematic chemical structure, source, and some properties of citric acid

Citric acid was employed in this study as a homogeneous, green, and effective acidic-based catalyst. Using citric acid as a catalyst, we created Pydip in solvent-free (SF) conditions (Scheme 1). The aforementioned process is highly significant and effective as it follows the green chemistry protocol.



Scheme 1. Schematic synthesis procedure of the pyrido[2,3-d:5,6- d']dipyrimidine derivatives.

2. Experimental and device

The ingredients and chemicals used in this process were purchased from Sigma-Aldrich Co. and Merck, and they were used without any additional purification. Furthermore, Merck Co. supplied us with thin-layer chromatography (TLC) (silica gel 60 F254). For product characterisation, we employed ^{1}H nuclear magnetic resonance (NMR) and Fourier transform infrared (FT-IR) spectroscopies. The Perkin-Elmer 781 and Bruker DRX-400 spectrometers were used to record the FT-IR and NMR, respectively. For NMR spectra, we employed DMSO-d_6 and TMS as internal standards and solvents, respectively.

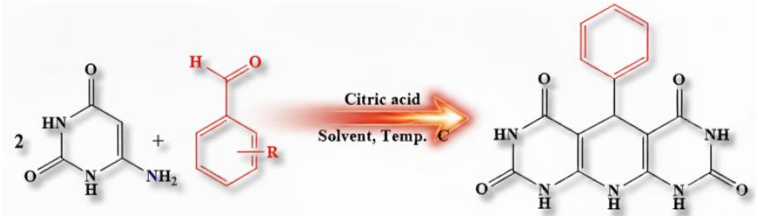
2.1 Generation of Pydip derivatives catalyzed by citric acid

This was accomplished by mixing 0.5 mmol of benzaldehydes, 1 mmol of 6-aminouracil, and 0.02 g of citric acid in a flask and stirring the mixture at 110°C under SF conditions. TLC is used to monitor the reaction's development (Ethyl acetate / n-Hexane4/2). After the reaction was finished, citric acid was washed with water to separate it from the products because it is a water-soluble catalyst. Following the solvent evaporation at a lower pressure, the resulting residue crystallized from the ethanol. The melting point, FT-IR, and 1H NMR spectroscopies and data used to describe the products are presented in the Supplementary Information.

3. Results and discussion

We produced Pydip derivatives using citric acid as a green catalyst at 110°C under SF conditions. For this purpose, we used the benzaldehyde (0.5 mmol) and 6-aminouracil (1 mmol) reaction model and adjusted several reaction variables such temperature, as solvent type, and catalyst quantity. Table 1 shows the whole set of results. We tuned the quantity of citric acid catalyst (entry 1-4) under SF conditions at 110°C. According to the findings, increasing the quantity of catalyst from 0.008 g to 0.02 g shortened the reaction time and boosted the yield. The reaction yield and time do not vary for values greater than 0.02 g; thus, we picked 0.02 g as the best value. Following that, we optimized the reaction temperature. That is, we used the SF conditions and 0.02 g of catalyst to run the reaction at various temperatures (entry 5-9). Decreased reaction temperatures (below 100°C) lead to longer reaction times and decreased yield. At temperatures over 110°C (120°C), there is no significant change in reaction time, making 110°C the optimal reaction temperature. Finally, we determine the solvent's optimal conditions. We performed the reaction using a 0.02 g catalyst, the proper temperature, and several solvents, including (CH_3CN), (EtOH), and (H_2O) in order to achieve this goal (entry 10–13). The results showed that the response time and yield both dropped and increased when SF conditions were applied.

Table 1. Synthesis of different pyrido[2,3-d:5,6- d']dipyrimidine derivatives.

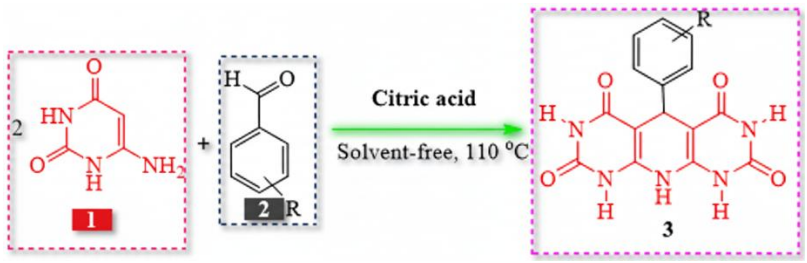


Entry	Solvent	Catalyst (g)	Temperature (ºC)	Time (min)	Yield (%)
1	solvent-free	0.01	100	28	50
2	solvent-free	0.015	110	18	58
3	solvent-free	**0.02**	**110**	**16**	**93**
4	solvent-free	0.025	110	16	93
5	solvent-free	0.02	50	91	58
6	solvent-free	0.02	60	43	63
7	solvent-free	0.02	80	33	75

8	solvent-free	0.02	100	27	83
9	solvent-free	0.02	120	15	88
10	CH_3CN	0.02	Reflux	110	47
11	EtOH	0.02	Reflux	85	73
12	H_2O	0.02	Reflux	160	38
13	$EtOH/H_2O$	0.02	Reflux	160	76

Additionally, we used a variety of benzaldehyde derivatives to synthesize the Pydip compounds (Table 2). The benzaldehyde derivatives included both electron-donating and electron-withdrawing groups. According to the suggested mechanism, the presence of electron-withdrawing groups in the benzaldehyde increased the reaction's yield (entry 2–7). However, using electron-donating groups resulted in a decrease in the reaction's yield (entry 8–12).

Table 2. Synthesizing of pyrido[2,3-d:5,6- d']dipyrimidine derivatives.

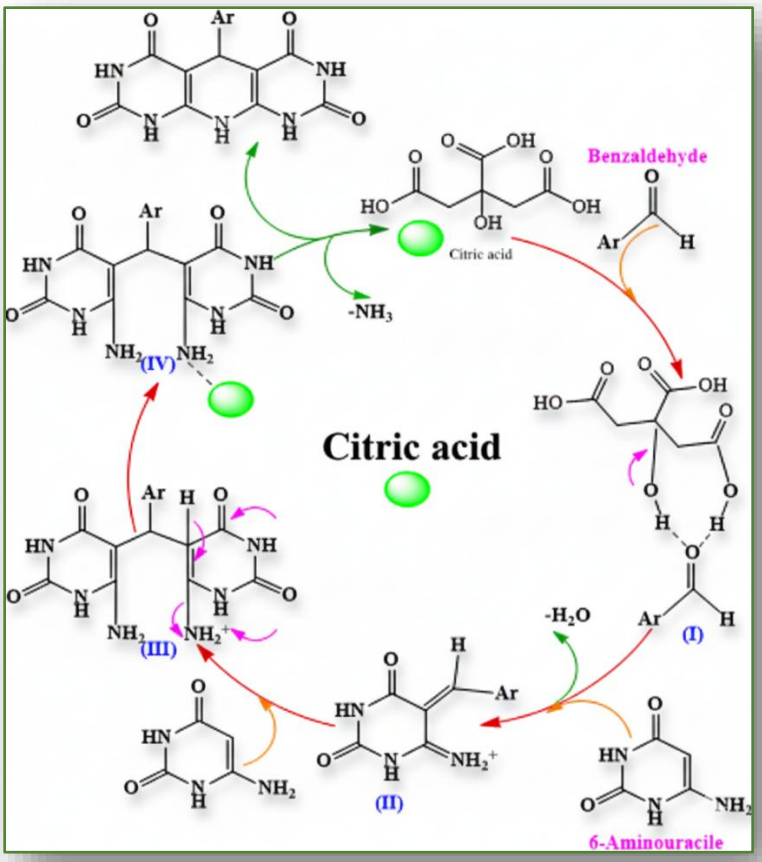


Entry	R	compound	Time (min)	Yield	M.P.(Ref.)
1	H	**3a**	16	93	295-298[10]
2	4-NO_2	**3b**	13	94	230-236[10]
3	$N(Me)_2$	**3c**	41	78	>300[10]
4	4-Cl	**3d**	17	91	>300[10]
5	3-NO_2	**3e**	13	93	296-299[10]
6	4-Br	**3f**	17	91	>300[10]
7	2,4-Cl	**3g**	22	88	>300[10]
8	4-F	**3h**	19	89	292-295[10]
9	4-Me	**3i**	50	87	295-298[10]
10	4-OH	**3j**	60	78	>300[10]
11	3-OH	**3k**	45	82	283-288[10]

12	4-OMe	**3l**	58	78	225-230[10]

3.2 Suggested mecha

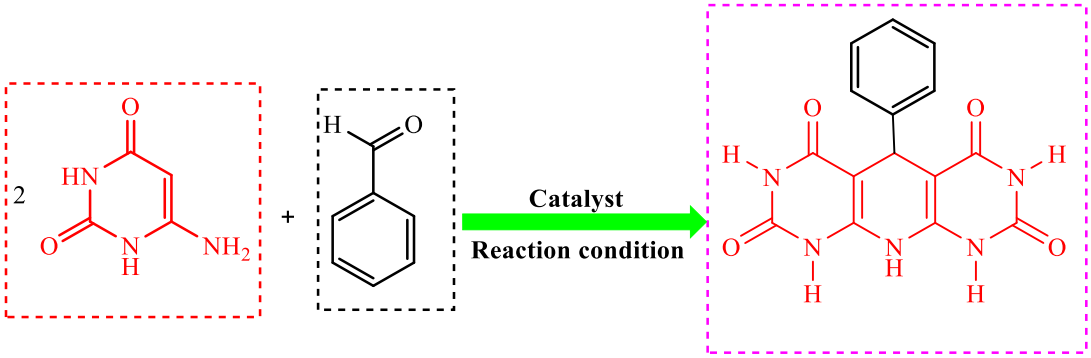
Scheme 2 presents our study's and earlier research's suggested methodology for the production of the Pydip derivatives [10]. First, citric acid activated the aldehyde's carbonyl group via hydrogen bonding to generate the intermediate (I). At this point, the presence of electron-donating groups on benzaldehyde prevents the carbonyl group from having the requisite activity, which is why, according to Table 2, the yields of these derivatives are low. However, the presence of electron-withdrawing groups activates the carbonyl group, resulting in higher and more significant yields. The second phase involved a reaction between intermediate (I) and 6-aminouracile, which resulted in intermediate (II). After then, the intermediate (II) and the second 6-aminouracile molecule interacted to create the intermediate (III). After the ring is closed and the Pydip derivatives are produced, the intermediate (III) can be tautomerized to intermediate (IV) (Scheme 2).



Scheme 2. The proposed mechanism for synthesis of the pyrido[2,3-d:5,6- d']dipyrimidine derivatives.

We created Table 3 to compare the catalytic performance of the citric acid and reaction conditions. As the reaction model, we selected the reaction between benzaldehyde and 6-aminouracil and contrasted it with previous research. Table 3 shows that since we don't utilize any solvents, the ideal reaction conditions are for our task. We thus operate in green circumstances. Furthermore, the catalyst we employed is eco-friendly. Our task has a very excellent time and yield.

Table 3. The comparison of our work with other studies for synthesizing of pyrido[2,3-d:5,6- d']dipyrimidine derivatives.



Entry	Catalyst	Condition	Time	Yield (%)	Ref.
1	$CoFe_2O_4$@SiO_2-3-aminopropyltrimethoxysilane-cyanuric chloride-guanidine-SO_3H	H_2O, r.t., 0.06 g catalyst	20 min	95	[40]
2	*p*-Toluenesulfonic acid	1-butyl-3-methylimid-azolium bromide solvent, 100 ºC	4 h	54	[41]
4	Vitamin C	solvent-free, 100 ºC	20 min	90	[42]
5	Citric acid	solvent-free, 110 ºC	16 min	93	Our work

4. Conclusion

HCs are among the most significant substances in organic chemistry. N-containing HCs are particularly significant among the several types of HCs that are available because of their numerous uses in pharmacology and medicine. In this work, we described the synthesis of Pydip derivatives, one of the most significant classes of N-containing heterocycle molecules. We employed citric acid, an effective, environmentally benign, and green homogenous catalyst, to achieve this goal. Due to its great performance and bio-based nature, citric acid is a very significant catalyst. Using a citric acid catalyst, we produced several Pydip derivatives at 110°C under SF conditions. Our work is innovative in that it uses a catalyst with a natural base that is environmentally benign, and it also uses SF reaction conditions, which prevent the release of hazardous and poisonous solvents into the environment. This makes the reaction circumstances entirely green.

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