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Vitamin C as an efficient and green homogeneous catalyst for the synthesis of pyride[2,3-d:5,6-d'] dipyrimidine derivatives

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Original Research

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Abstract:

In organic chemistry, one of the most important materials are heterocycle compounds. Among different heterocyclic compounds, the N-containing heterocyclic materials are very important owing to their numerous properties, which can be applied in different fields. In this work, we synthesized pyrido[2,3-d:5,6-d'] dipyrimidine derivatives over an efficient and green method. For this aim, we used vitamin C as a bio-based, green, and environmentally friendly catalyst for the synthesis of synthesis pyrido[2,3-d:5,6-d'] dipyrimidine derivatives through solvent-free conditions. The key advantages of our procedure are operational easiness, mild reaction conditions, high yields, and short reaction time, as well as green and eco-friendly catalysts.

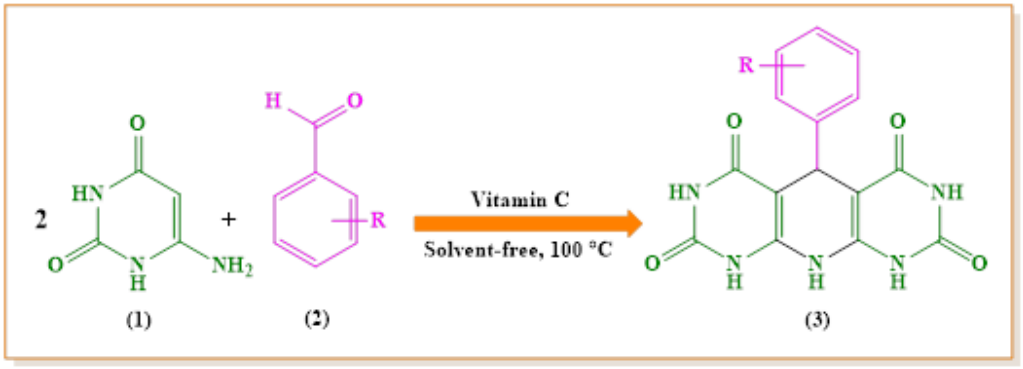
Keywords: Ascorbic acid; Homogenous catalyst; N-containing heterocycle; Pyridopyrimidine; Vitamin C

1. Introduction

Heterocyclic compounds (HCs) are one of the most important compounds in organic chemistry because they are the framework of many pharmaceutical and biological substances. HCs are cyclic compounds that have heteroatoms, such as nitrogen, sulfur, oxygen, etc., in their structure. Among the various heterocycle compounds that exist, heterocycles that have a nitrogen atom in their structure are of particular importance. In other words, *N*-containing heterocycle compounds have many applications in medical fields, including antibacterial, antioxidant, enzyme inhibitors, antidiabetic, and antioxidant properties [1–5].

There are different types of *N*-containing heterocycle compounds like triazole, tetrazoles, thiadiazoles, imidazole, pyrimidine, etc. derivatives [6–9]. Among them, pyrimidine derivatives have a special place owing to their antimicrobial and anticancer properties. There are various derivatives of the pyrimidine and the pyridopyrimidine. Pyridopyrimidine is a group of annulated uracil with a varied diversity of applications in various fields, such as medicinal, pharmacological, and biological applications. As a result, today, this *N*-containing heterocycle compound has recently gained noteworthy consideration [10, 11]. Pyrido[2,3-d:5,6-d'] dipyrimidines (Pydip) are a particular group of *N*-containing HCs that comprise a ring of pyrimidine in their structure [12, 13]. Multi-component reactions (MCR) reduce the reaction time and save energy and materials, so these reactions are suitable for the synthesis of complex compounds[14–18]. There are different ways for the synthesis of Pydip, which uses heterogeneous or homogeneous catalysts over multi-component reactions. This procedure used different catalysts such as 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) [19], magnetic-based catalysts [20, 21], and different acid-based supports [22, 23].

Solvent-free methods are of great attention in order to im-



Scheme 1. Schematic synthesis procedure of the Pydip derivatives.

prove classical processes, making them more clean, non-toxic, and easy to complete. It is believed that solvent-free organic synthesis and transformations are industrially useful and largely green. Scientist's apprehension for emerging environment-friendly synthetic techniques has made them turn their interest to diminishing or avoiding the use of solvents that are a major reason for pollution [24].

As mentioned in the previous paragraph, there are two types of catalysts, including heterogeneous and homogeneous catalysts. Catalysts increase the speed of the reaction; as a result of their existence, they are effective and useful in all kinds of reactions. Heterogeneous catalysts are catalysts that do not dissolve in the reaction and are usually located on a solid support [25–27]. They may have an important feature, which is easy separation from the reaction mixture, but because they do not dissolve in the reaction, all the active sites of the catalyst are not in the reaction and may not be very effective. They are in contrast to homogeneous catalysts. Because the homogeneous catalysts are dissolved in the reaction mixture. As a result, all the catalytic sites are available for the reaction and are, therefore, very effective. On the other hand, homogeneous catalysts have an inexpensive preparation process, while solid support must be used to make heterogeneous catalysts, which are sometimes very expensive and unavailable [28–33]. Many homogeneous catalysts exist naturally in nature, such as different types of vitamins, organic and inorganic acids, etc. [34, 35].

According to the principles of green chemistry, it is essential to use environmentally friendly solvents and compounds. Catalysts based on natural, non-toxic, and biodegradable compounds comply with the principles of green chemistry. Among the natural compounds that are also used as catalysts, ascorbic acid or vitamin C (also named ascorbate) is of particular importance. This vitamin has acidic groups, and its main source is citrus fruits. Owing to the acidic nature of vitamin C, it can be applied as an efficient and acidic homogenous catalyst for different reactions. The chemical structure, most important source, and some properties of the ascorbic acid are displayed in Figure 1 [36–42].

In this work, we used vitamin C as an efficient, green, and homogenous acidic-based catalyst. We synthesized Pydip using vitamin C as a catalyst under solvent-free (SF) conditions (Scheme 1). The mentioned protocol is according to the green chemistry protocol so is very important and efficient.

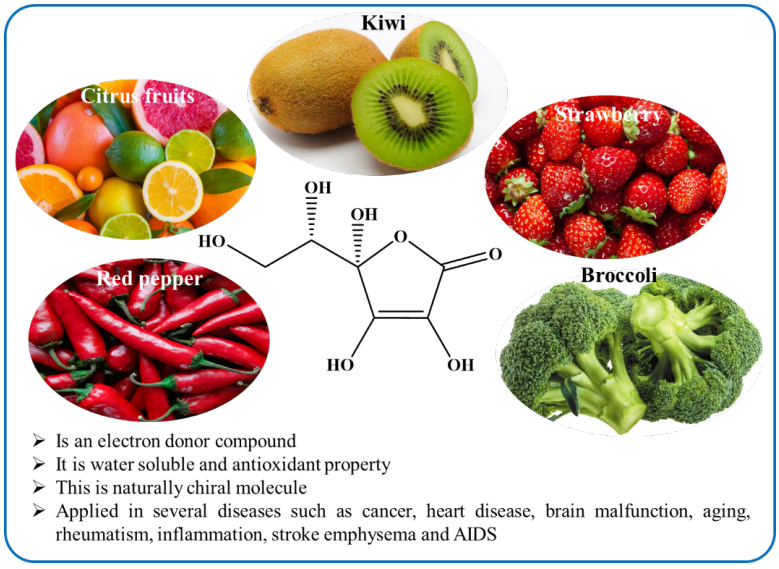


Figure 1. Schematic chemical structure, source, and some properties of ascorbic acid.

2. Experimental and device

The chemicals and materials applied in this method were bought from Merck and Sigma-Aldrich Co. and applied with no further purification. In addition, we purchased thin-layer chromatography (TLC) (silica gel 60 F254) from Merck Co. We used Fourier transform infrared (FT-IR), ^{1}H nuclear magnetic resonance (NMR) spectroscopies for characterization of the products. The FT-IR and NMR were recorded at Perkin-Elmer 781 and Bruker DRX-400 spectrometers, respectively. We used TMS and DMSO-d_6 as internal standards and solvents for NMR spectra, respectively.

2.1 Vitamin C catalyzed synthesis of Pydip derivatives

For this aim, in a flask, we mixed 1 mmol of benzaldehydes, 2 mmol of 6-aminouracil, and 0.04 g (22 mol%) or (0.22 mmol) of vitamin C, and the mixture was stirred at 100 °C under SF conditions. We follow the reaction progress using TLC (Ethyl acetate / n-Hexane 2/1). When the reaction was completed, as vitamin C is a water-soluble catalyst, it was separated from the products via washing with water. Then, the solvent was evaporated under reduced pressure, and the obtained residue crystallized from ethanol. The products characterized using melting point, FT-IR, and ^{1}H NMR spectroscopies and data are summarized in Supplementary information.

2.2 The gram scale experiment for the synthesis of 5-phenyl-5,10-dihydropyrido[2,3-d:6,5-*d′*]dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (3a)

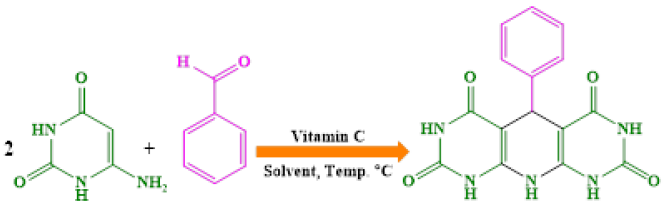
In this research for evaluating the performance of vitamin C as a catalyst in a large-scale process, we conducted the model study between benzaldehyde (0.05 mol, 5.3 g) and 6-aminouracil (0.1 mol, 12.7 g) in the presence of vitamin C (2 g) under solvent-free conditions at 100 °C. The progress of the reaction as well as purification steps was the same as those described in the previous section (Section 2.1). In this kind of experiment, we could obtain the corresponding pyrido[2,3-d:5,6-*d′*]dipyrimidine (3a) in 84% yield within 45 minutes which showed that the reaction can be performed in satisfactory conditions in a gram scale procedure.

3. Results and discussion

3.1 Synthesis of the Pydip derivatives

We synthesized Pydip derivatives using vitamin C as an efficient and green catalyst at 100 °C under SF conditions. For this aim, we chose the reaction of benzaldehyde (1 mmol) and 6-aminouracil (2 mmol) as the reaction model, and we optimized different reaction conditions, such as the amount of catalyst, different types of solvent, and temperature. All of the results are displayed in Table 1. First, we chose SF conditions at 100 °C, and then the amount of the catalyst (vitamin C) was optimized (entries 1-4). According to the results, when the amount of the catalyst was increased from 0.01 g to 0.04 g, the reaction time was reduced, and the yield was increased. In values higher than 0.04 g, the reaction time and yield do not change, so we chose the value of

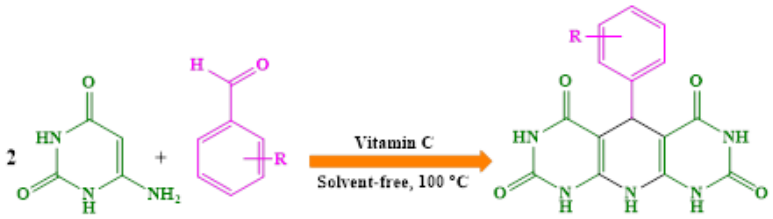
Table 1. Optimization reaction conditions for the synthesis of Pydip derivatives.

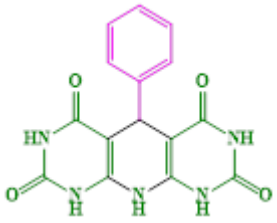
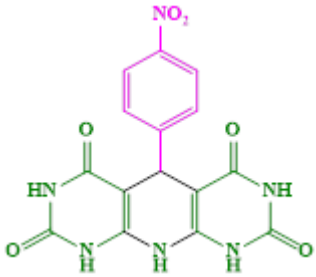
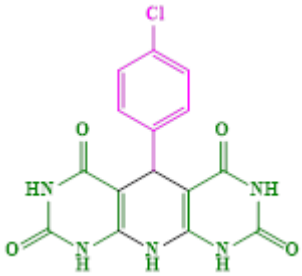
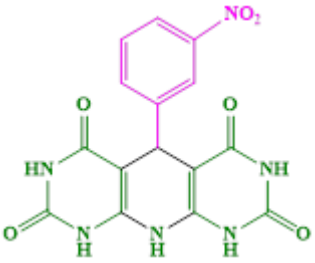
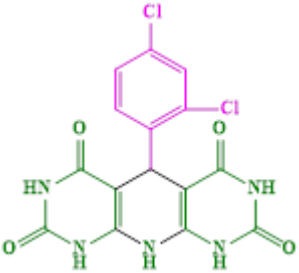


Entry	Solvent	Catalyst (g)	Mol (%)	Temperature (°C)	Time (min)	Yield (%)
1	SF	0.01	5.6	100	35	40
2	SF	0.02	11.3	100	25	50
3	SF	0.04	22.7	100	18	90
4	SF	0.05	28.3	100	18	90
5	SF	0.04	22.7	25	115	40
6	SF	0.04	22.7	60	65	45
7	SF	0.04	22.7	80	40	60
8	SF	0.04	22.7	90	30	80
9	SF	0.04	22.7	120	13	90
10	CH_3CN	0.04	22.7	Reflux	110	40
11	EtOH	0.04	22.7	Reflux	90	60
12	H_2O	0.04	22.7	Reflux	160	30
13	EtOH/H_2O	0.04	22.7	Reflux	130	50

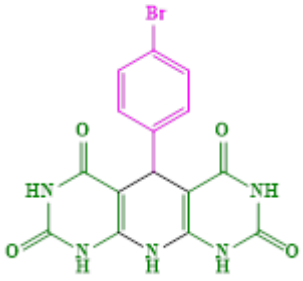
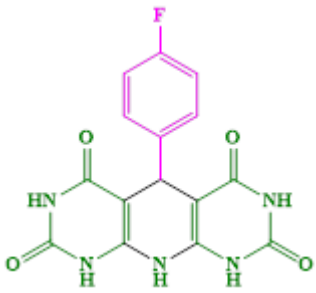
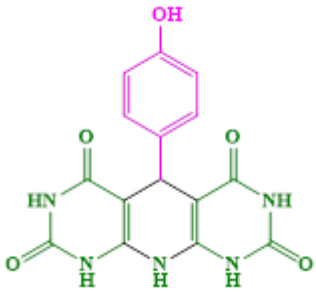
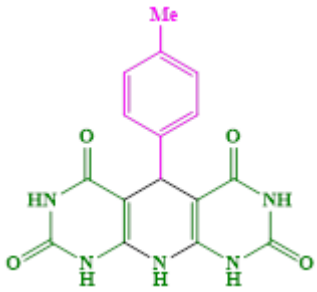
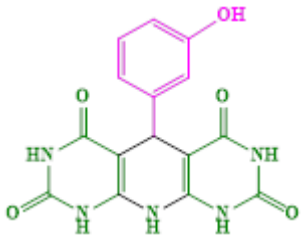
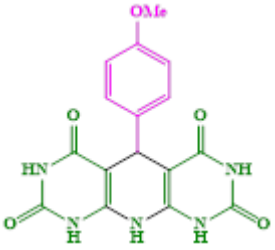
Reaction conditions: benzaldehyde (1 mmol), 6-aminouracil (2 mmol) under various reaction conditions.

Table 2. Synthesis of different Pydip derivatives.

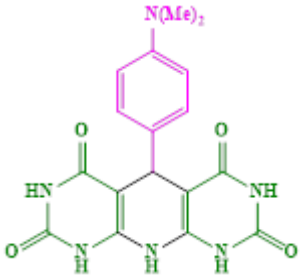
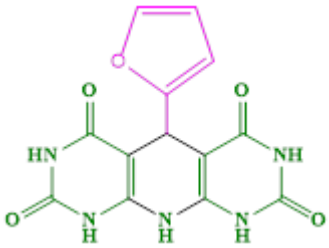
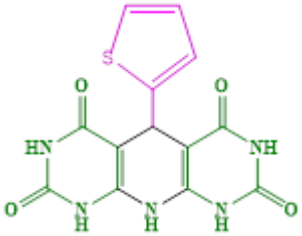


Entry	Aldehyde(R)	Product	Time (min)	Yield (%)	M.P./[ref.]
1	H		18	90	292-991[27]
2	4-NO_2		10	93	229-231[27]
3	4-Cl		15	90	296-297[27]
4	3-NO_2		11	92	298-300[27]
5	2,4-Cl		10	93	>300[27]

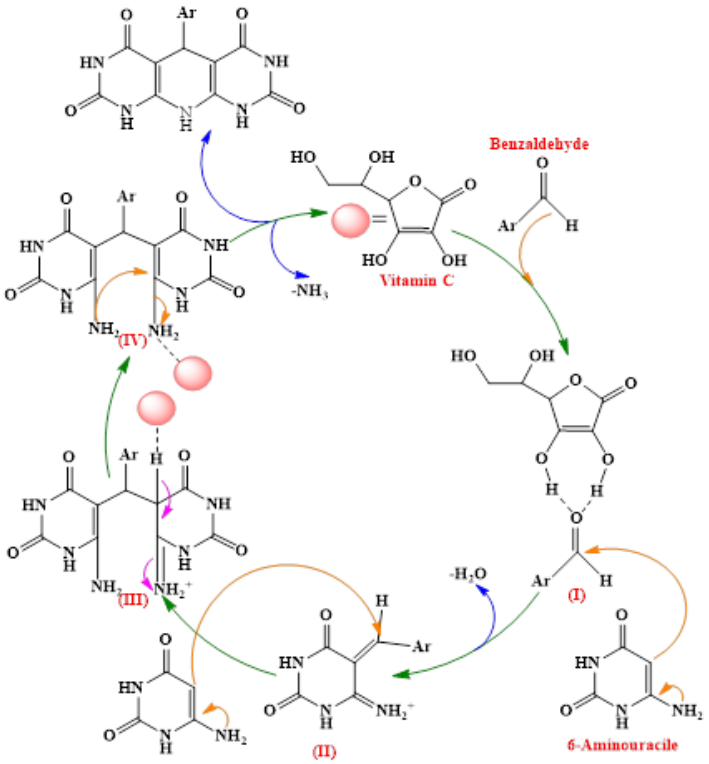
Continue of Table 2.

6	4-Br		15	93	>300[27]
7	4-F		18	90	293-295[27]
8	4-OH		30	80	>300[27]
9	4-Me		25	88	295-300[27]
10	3-OH		25	85	280-283[27]
11	4-OMe		27	85	223-230[27]

Continue of Table 2.

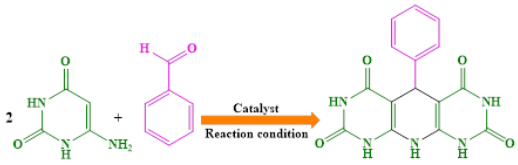
12	4-N(Me)$_2$		20	83	>300[27]
13	furan-2-carbaldehyde		50	Trace	-
14	thiophene-2-carbaldehyde		50	Trace	-

Reaction conditions: Aryl aldehyde derivatives (1 mmol), 6-aminouracil (2 mmol), catalyst (0.04 g) under solvent-free conditions at 100 °C.



Scheme 2. The proposed mechanism for synthesis of the Pydip derivatives.

Table 3. The comparison of our work with another study for the synthesis of Pydip derivatives.



Entry	Catalyst	Condition	Time	Yield (%)	TOF (min)	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	1985.5	[43]
2	*p*-Toluenesulfonic acid	1-butyl-3-methylimid-azolium bromide solvent, 100°C	4 h	54	153.8	[44]
3	SBA-15-SO_3H	SF, 120°C	10 min	96	24632.2	[23]
4	Vitamin C	SF, 100°C	18 min	90	22727.2	Our work

0.04 g as the optimum value. After that, we optimized the reaction temperature. That is, we considered the conditions SF and the amount of catalyst as 0.04 g and performed the reaction at different temperatures (entries 5-9). The results show that when the reaction temperature is lower than 100 °C, the reaction time increases and its yield decreases. At a temperature above 100 °C, i.e., 120 °C, there is no considerable difference in the reaction time, so the optimum reaction temperature is 100 °C. Finally, we choose suitable conditions for the solvent. For this aim, we carried out the reaction using a 0.04 g catalyst and appropriate temperature and used different solvents such as acetonitrile (CH_3CN), ethanol (EtOH), and water (H_2O) (entries 10-13). According to the results, when we used SF conditions, the reaction time and yield decreased and increased, respectively.

In addition, we used different derivatives of the benzaldehydes for the synthesis of the Pydip derivatives (Table 2). The benzaldehydes derivatives had electron-withdrawing and electron-donating groups. According to the suggested mechanism, when the electron-withdrawing groups were present in the benzaldehyde, the yield of the reaction was increased (entries 2-7). In contrast, when we used electron-donating groups, the yield of the reaction was decreased (entries 8-12).

3.2 Suggested mechanism

The proposed mechanism for the synthesis of the Pydip derivatives based on our study and previous literature is presented in Scheme 2 [23]. First, the carbonyl group in the structure of the aldehyde was activated by vitamin C via hydrogen bonding to form the intermediate (I). At this stage, the presence of electron-donating groups on benzaldehyde causes the carbonyl group to not have the necessary activity, and that is why, according to Table 2, the yields of these derivatives are lower. However the presence of electron-withdrawing groups makes the carbonyl group more active, and the yields of these derivatives are better and more significant. In the second step, the reaction between the intermediate (I) and 6-aminouracile was performed, and intermediate (II) was created. Then, the second molecule of the 6-aminouracile reacted with intermediate (II) to perform the intermediate (III). The intermediate (III) can be tautomerized to intermediate (IV) following when the ring is closed and the Pydip derivatives were created (Scheme 2). For a comparison of the catalytic performance of the vitamin C and reaction conditions, we designed Table 3. We chose the reaction of benzaldehyde and 6-aminouracil as the reaction model and compared it to other studies. According to Table 3, the best reaction conditions are for our work because we don't use any solvent. As a result, we work in green conditions. In addition, the catalyst that we used is green and environmentally friendly. The time and yield of our work are very good.

4. Conclusion

One of the most important compounds in organic chemistry is HCs. Among the various HCs that exist, N-containing HCs are of particular importance due to their many applications in medicine and pharmaceuticals. In this study, we reported the synthesis of one of the most important types of N-containing heterocycle compounds named Pydip derivatives. For this aim, we used an efficient, green, and eco-friendly homogeneous catalyst like vitamin C. Vitamin C is a very important catalyst because it has high performance as well as it is a bio-based material. We synthesized different derivatives of the Pydip using a vitamin C catalyst under SF conditions at 100°C. The innovation of our work is that the reaction conditions are completely green because a catalyst is used that has a natural base and is environmentally friendlyand also the reaction conditions are SF, and as a result, toxic and harmful solvents do not enter the environment.

Authors Contributions
Authors have equal contribution role in preparing the paper.

Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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