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2,2'-Bipyridine: An efficient organo-catalyst for the synthesis of pyrano[2,3-d]pyrimidine and pyrido[2,3-d]pyrimidine derivatives

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Original Research

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Abstract:

In this work, a highly efficient technique has been documented for the one-pot synthesis of pyrano[2,3-d]pyrimidine and pyrido[2,3-d]pyrimidine derivatives. This method employs 2,2'-bipyridine as a cost-effective and proficient organo-catalyst. All reactions take place within reasonable reaction periods, yielding favorable to excellent results. The reusability of the catalyst is also investigated during the reactions. Moreover, a rational mechanism was suggested via GC-Mass analysis of the trapped intermediates.

Keywords: One-pot synthesis; Pyrano[2,3-d]pyrimidines; Pyrido[2,3-d]pyrimidines; 2,2'-bipyridine; Organo-catalyst

1. Introduction

In the realm of organo-catalysis, a field that has captured the attention of numerous organic chemists, the pursuit of recyclable heterogeneous and homogeneous catalysts stands as a central objective. Employing organo-catalysts offers a multitude of benefits owing to their distinctive properties and attributes [1, 2]. In recent years, commercially available basic organo-catalysts have been used in some of the organic transformations. Some of these compounds are 1,4-diazabicyclo[2.2.2]octan (DABCO) [3], 4-dimethylaminopyridine (DMAP) [4] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [5]. In this line, 2,2'-bipyridine with the formula of C10H8N2 in the free and complex form with a variety of transition metals has attracted the attention of many organic chemists. For instance, in 2015, Lixin You and co-workers used Pd/Ln coordination polymers based on 2,2-bipyridine-4,4-dicarboxylic acid as a heteroleptic ligand for the Heck and Suzuki-Miyaura reactions [6]. After that, Hong Zhao and co-workers immobilized the bipyridine copper (I) complex on MCM-41 and used it for the oxidation of alcohols [7]. However, one of the significant aspects of small-molecule catalysts is the absence of transition metals in their structures. Metal-free organo-catalysts offer a more sustainable approach to catalysis compared to traditional metal-based catalysts and eliminate the risk of metal contamination in the end products, which is why using them has been widely spread in the food and drug industries.

Multi-component reactions (MCRs) play a crucial role in medical and synthetic organic chemistry due to the substantial benefits they provide compared to traditional linear syntheses. These strategies open up extensive opportunities for enhancing molecular diversity. By enabling multi-step syntheses within a single operation, MCRs yield a range of invaluable products. The advantages of MCRs encompass efficient atom utilization, convergence, operational ease, and diverse and intricate product structures. Notably, these

reactions frequently align with the principles of green chemistry [8–17].

Pyrano[2,3-d]pyrimidine and pyrido[2,3-d]-pyrimidine derivatives exhibit noteworthy pharmaceutical and biological effects. These include antimicrobial [18], antihypertensive [19], antifungal [20], antimalarial [21], anti-inflammatory [22], antitumor [23], antibacterial [24], and antiallergic [25]. Additionally, certain derivatives demonstrate photochemical properties [26]. Based on these reasons, different methods have been reported for the synthesis of these types of compounds. Among the known procedures, multi-component condensation of aromatic aldehydes, malononitrile, and barbituric acid or 6-amino-1,3-dimethyluracil are un-sophisticated methods for the synthesis of these compounds. For the promotion of these reactions, a variety of catalysts have been used which of them DABCO [3], $CaHPO_4$ [27], $[BMIm]BF_4$ [28], $H_{14}[NaP_5W_{30}O_{110}]$ [29], $Zn[(L)proline]_2$ [30], SBA-Pr-SO_3H [31], $KA1(SO_4)_2.12H_2O$ [32], $[H_2$-DABCO$][H_2PO_4]_2$ [33], L-proline [34], nano-MgO [35], Mn_3O_4 [36], $[(NH_4)_2HPO_4]$ (DAHP) [37] and $Fe_3O_4@SiO_2@(CH_2)_3S–\ SO_3H$ [38] are examples. Although these protocols are known for their own benefits and advantages, some of them are accompanied by disadvantages such as long reaction times, harsh reaction conditions, low yields, excessive use of catalysts, Inability to recover the catalyst, use of expensive reagents and distribution of environmental pollution through the use of extremely toxic solvents.

For instance, the use of DABCO [3], $CaHPO_4$ [27], $[BMIm]BF_4$ [28], $H_{14}[NaP_5W_{30}O_{110}]$ [29], $Zn[(L)proline]_2$ [30] and $KA1(SO_4)_2.12H_2O$ [32] for the synthesis of Pyrano[2,3-d]pyrimidine yields acceptable results, but the reaction times are significantly higher compared to this work. In addition, Although SBA-Pr-SO_3H [31] can serve as an efficient catalyst, their preparation is time-consuming and cost-intensive. Similarly, $Fe_3O_4@SiO_2@(CH_2)_3S–\ SO_3H$ [38] has been demonstrated as effective catalysts for the production of pyrido[2,3-d]pyrimidine derivatives, but this catalyst must be produced and cannot be purchased commercially. It is transparent that the catalyst preparation process would be demanding and cost-effective. Therefore, the introduction of simple, efficient, and mild procedures using reusable organo-catalysts to overcome these problems is still in demand.

2. Experimental section

2.1 Material and instrumentation

Chemicals were purchased from Merck, and Aldrich Chemical Companies. All yields refer to isolated products. Products were characterized by the comparison of their physical constants, infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy with authentic samples and those reported in the literature. Purity determination of the substrate and reaction monitoring were accompanied by TLC on silica gel polygram SILG/UV 254 plates.

2.2 General procedure for the preparation of pyrano[2,3-d]pyrimidine derivatives

A mixture of aldehyde 1 (1 mmol), malononitrile 2 (1.1 mmol), barbituric acid 3 (1 mmol), and 2,2'-bipyridine (10 mg, 6.4 mol%) in EtOH: H_2O (1:1) (6 mL) was heated at 70 °C. The progress of the reaction was monitored by TLC (EtOA: n-hexane, 1:5). After completion of the reaction, water was added to the mixture, and the product was filtered off. Ultimately, the pure product was obtained after recrystallization from ethanol (4a-o).

2.3 General procedure for the preparation of pyrido[2,3-d]pyrimidine derivatives

A mixture of aldehyde (1 mmol), malononitrile (1.1 mmol), 6-amino-1,3-dimethyluracil (1 mmol) and 2,2'-bipyridine (15 mg, 9.6 mol%) in EtOH (6 mL) was stirred magnetically at 70 °C. The progress of the reaction was indicated by TLC when EtOA: n-hexane (1:5) was utilized as a TLC solvent. After completion of the reaction, water was added to the reaction media, and the mixture was filtered off. Finally, the pure product was obtained after recrystallization from ethanol (6a-j).

3. Results and discussion

Due to the significant benefits offered by organo-catalysts, we continue to dedicate a portion of our ongoing research efforts to expanding the potential of these compounds in facilitating organic transformations. Their ability to promote a diverse range of reactions under mild conditions holds great promise for the development of more sustainable and efficient synthetic methodologies. By harnessing the power of organo-catalysts, we aim to address current challenges in organic synthesis and contribute to the advancement of greener chemical processes [39–42]. For this reason, we were interested to study the ability of 2,2'-bipyridine, as a heterocyclic organo-catalyst, in the synthesis of pyrano[2,3-d]pyrimidine and pyrido[2,3-d]pyrimidine derivatives.

At first and for the determination of the best and efficient reaction conditions for the synthesis of pyrano[2,3-d]pyrimidine derivatives, the reaction of 4-chlorobenzaldehyde (1 mmol), malononitrile (1.1 mmol) and barbituric acid (1mmol) was studied as a model under the influence of various conditions , including different amounts of the catalyst and temperatures under solvent-free conditions or in different types of solvents (Table 1). In the experimental procedure, the progress of the reaction was monitored using TLC. Reactions achieving 100% conversion were treated by separating their products and subsequently calculating their efficiency. However, reactions with less than 100% conversion, accompanied by multiple spots on the TLC, were reported as a mixture of products. It is hypothesized that the side products generated in these reactions could be a combination of malononitrile and aldehyde or a product resulting from the aldehyde-barbituric acid reaction. These approaches have led to an incomplete and inaccurate execution of the reaction. As a result, the products were not isolated, and their efficiency remained uncalculated. On the basis of

Table 1. The effect of different conditions in the synthesis of pyrano[2,3-d]pyrimidine derivatives in the presence of 2,2'-bipyridine.[a]

entry	catalyst (mol%)	solvent	temperature (°C)	time (min.)	yield (%)[b]
1	-	no solvent	r.t.	60	trace
2	-	no solvent	100	60	trace
3	12.8	CH_3CN	r.t.	60	trace
4	12.8	CH_3CN	reflux	60	mixture of products
5	12.8	CH_2Cl_2	r.t.	60	trace
6	12.8	CH_2Cl_2	Reflux	60	mixture of products
7	12.8	H_2O	r.t.	60	mixture of products
8	12.8	H_2O	reflux	60	mixture of products
9	12.8	EtOH	r.t.	60	mixture of products
10	12.8	EtOH	75	10	85
11	12.8	H_2O: EtOH (1:1)	r.t.	90	mixture of products
12	12.8	H_2O: EtOH (1:1)	reflux	10	97
13	12.8	H_2O: EtOH (1:1)	80	3	94
14	6.4	H_2O: EtOH (1:1)	70	3	94
15	6.4	H_2O: EtOH (1:1)	60	10	90

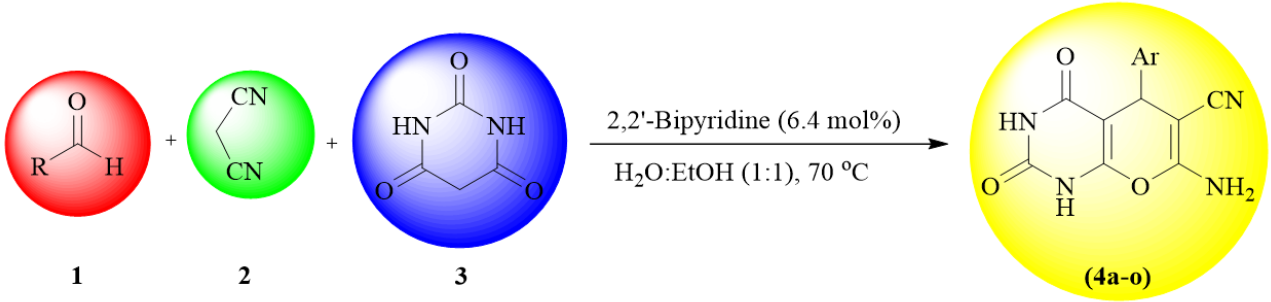
[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol), malononitrile (1.1mmol) and barbituric acid (1 mmol) in the presence of 2,2'-bipyridine as the catalyst.
[b] Isolated yields.

the obtained results, it was concluded that the reaction can be efficiently proceeded using 10 mg (6.4 mol%) 2,2'-bipyridine at 70 °C in a mixture of H_2O and EtOH (1:1) [(Table 1, entry 14) (Scheme 1)].

Following the fine-tuning of reaction parameters, a range of aromatic aldehydes featuring both electron-withdrawing and electron-donating groups were subjected to the reaction with malononitrile and barbitoric acid to generate pyrano[2,3-d]pyrimidine derivatives within concise reaction periods with elevated yields (Table 2, entries 1–14). Furthermore, when terephthalaldehyde was used as an aromatic dialdehyde in this procedure, the desired bis-product was also provided in short reaction times and high yields without any by-product (Table 2, entry 15). The effect of substituents on the aromatic ring was not observed on the progress of the reactions under the optimized conditions.

In the next step, 2,2'-bipyridine was used in the synthesis of pyrido[2,3-d]pyrimidine derivatives from the condensation of aldehydes, malononitrile, and 6-amino-1,3 dimethyluracil. Also, in this section of the study the optimized reaction conditions were determined by investigating the effect of different factors on the three-component condensation of 4-chlorobenzaldehyde (1 mmol), malononitrile (1.1 mmol), and 6-amino-1,3-dimethyluracil (1 mmol), and the results are tabulated in Table 3. The isolation process was specifically applied to reactions with a single spot on TLC. For these reactions, product separation and efficiency calculations were performed. However, reactions with multiple spots on TLC were reported as a Mixture of products. According to the compiled data in this table, it turned out that the best results can be obtained using 15 mg (9.6 mol%) 2,2'-bipyridine in ethanol at 70 °C [(Table 3, entry 11) (Scheme 2)].

Based on the data in Tables 1 and 3, the high yield and purity of the pyrano[2,3-d]pyrimidine and pyrido[2,3-d]pyrimidine derivatives synthesized under reflux conditions or at 60-80 °C in an H_2O:EtOH (1:1) mixture or in EtOH has been observed. These observations can be attributed to several factors. Firstly, the choice of solvent, ethanol or a mixture of ethanol and water, enhances the solvation of the reactants and intermediates, promoting efficient reaction kinetics and product formation. Additionally, the presence of 2,2'-bipyridine as a catalyst may



Scheme 1. Optimized conditions for the synthesis of pyrano[2,3-d]pyrimidines.

Table 2. Synthesis of pyrano[2,3-d]pyrimidines accelerated by 2,2'-bipyridine.

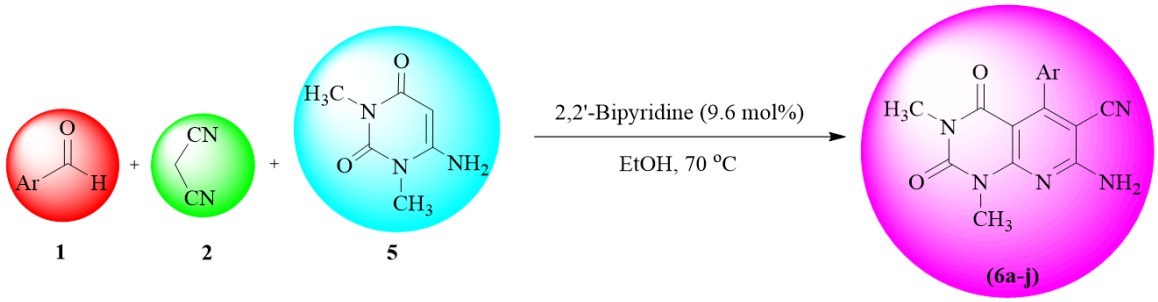
entry	Ar	product	time(min.)	yield (%)[a]	Mp (°C)	
					found	reported [Ref.]
1	C_6H_5	4a	5	88	212-213	208-210 [43]
2	2-Cl-C_6H_4	4b	10	90	219-221	213-215 [43]
3	3-Cl-C_6H_4	4c	4	92	241-242	240-241 [44]
4	4-Cl-C_6H_4	4d	3	94	230-232	228-230 [45]
5	4-Br-C_6H_4	4e	3	96	231-233	230-231 [45]
6	2-NO_2-C_6H_4	4f	3	95	252-254	257-258 [44]
7	3-NO_2-C_6H_4	4g	3	96	270-272	268-270 [44]
8	4-NO_2-C_6H_4	4h	3	95	236-238	237-238 [44]
9	2-OH-C_6H_4	4i	5	90	165-167	162-163 [44]
10	4-OH-C_6H_4	4j	3	93	>300	>300 [46]
11	4-OCH_3-C_6H_4	4k	15	85	277-279	280-281 [44]
12	4-$NMe_2C_6H_4$	4l	5	90	224-226	229-230 [44]
13	4-CH_3-C_6H_4	4m	5	87	220-223	226-227 [44]
14	4-CN-C_6H_4	4n	7	92	254-256	252-253 [45]
15	4-$CHOC_6H_4$	4o	5	94	>300	>300 [45]

[a] Isolated yields.

Table 3. Optimization of the reaction conditions for the synthesis of pyrido[2,3-d]pyrimidine derivatives catalyzed by 2,2'-bipyridine.[a].

entry	catalyst (mol%)	solvent	temperature (°C)	time (min.)	yield (%)b
1	-	no solvent	r.t.	120	trace
2	-	no solvent	100	120	trace
3	12.8	CH_3CN	r.t.	90	trace
4	12.8	CH_3CN	reflux	90	mixture of products
5	12.8	CH_2Cl_2	r.t.	90	trace
6	12.8	CH_2Cl_2	reflux	90	mixture of products
7	12.8	H_2O	r.t.	90	trace
8	12.8	H_2O	reflux	90	trace
9	12.8	EtOH	r.t.	90	mixture of products
10	12.8	EtOH	70	15	90
11	9.6	EtOH	70	16	91
12	6.4	EtOH	70	25	90
13	12.8	EtOH	60	25	92
14	9.6	H_2O: EtOH (1:1)	75	60	70
15	12.8	H_2O: EtOH (1:1)	75	60	75

[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol), malononitrile (1.1 mmol) and 6-amino-1,3-dimethyluracil (1 mmol) in the presence of 2,2'-bipyridine as the catalyst.
[b] Isolated yields.



Scheme 2. Optimized conditions for the Synthesis of pyrido[2,3-d]pyrimidines.

facilitate the formation of intermediates and cyclization reactions, given its solubility in ethanol and a mixture of water and ethanol. However, our study revealed that the catalytic activity of 2,2'-bipyridine is notably affected by solvent polarity. While organic solvents such as ethanol and a mixture of ethanol and water can enhance its catalytic performance, the presence of water solely might lead to decreased efficiency due to its limited solubility in water and reduced reactivity under such conditions. Moreover, certain solvents, particularly those with higher polarity, may increase the possibility of generating undesired by-products or side reactions, thereby affecting the overall yield and purity of the desired products. Consequently, the optimized temperature and solvent composition play crucial roles in maximizing the catalytic activity of 2,2'-bipyridine while minimizing the formation of by-products, ultimately leading to improved yields of the target compounds.

Continuing to establish the efficacy and viability of the chosen approach, we investigated the procedure using an array of uncomplicated and readily accessible substrates under the optimized conditions (Table 4). Notably, the established conditions facilitated the smooth conversion of a diverse set of aromatic aldehydes featuring electron-withdrawing or electron-donating groups at *ortho*, *meta*, and *para* positions on the benzene ring. This transformation led to the formation of the corresponding pyrido[2,3-d]pyrimidine derivatives in brief reaction periods, with yields ranging from good to outstanding.

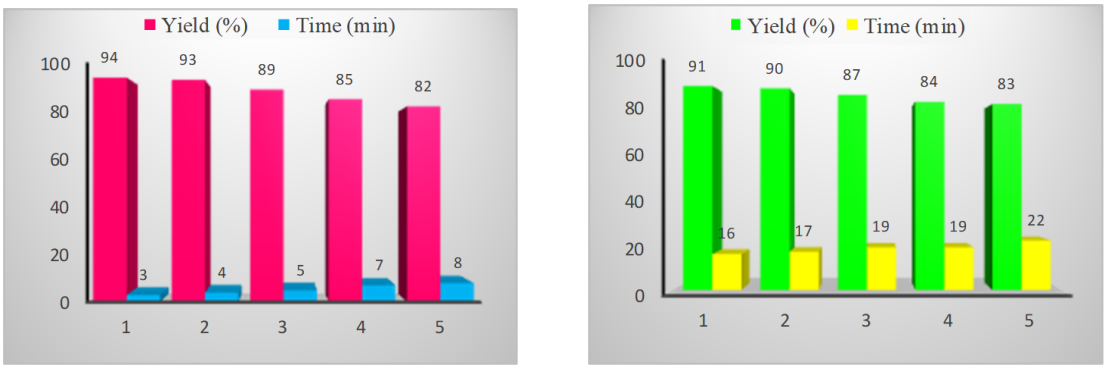
To evaluate the catalyst's ability to be reused, we systematically investigated the reaction involving 4-chlorobenzaldehyde, malononitrile, and either barbituric acid (Figure 1(a)) or 6-amino-1,3-dimethyluracil (Figure 1(b)) under carefully optimized conditions. The derivatives, namely pyrano[2,3-d]pyrimidine and pyrido[2,3-d]pyrimidine, synthesized in this study exhibited limited solubility in H_2O:EtOH (1:1) or EtOH, in contrast to the readily soluble 2,2'-bipyridine in the same solvent mixture. To assess the reusability of the catalyst, a filtration process was employed to collect the solid products upon completion of the reaction. Notably, for subsequent reaction cycles, we reintroduced the collected solid products directly into the reaction flasks without the addition of fresh catalyst or solvent. Impressively, even after five consecutive runs, the reactions consistently yielded the anticipated products without a substantial decline in catalytic activity, underscoring the catalyst's robust and excellent reusability (Figure 1).

To thoroughly characterize the catalyst, we performed FT-IR analyses both before and after recycling. In order to purify the catalyst, upon completion of the reaction, all

Table 4. Synthesis of pyrido[2,3-d]pyrimidine derivatives using 2,2'-bipyridine as the catalyst.

entry	Ar	product	time (min.)	yielde (%)[a]	Mp (°C)	
					found	reported [Ref]
1	C_6H_5	6a	16	92	>300	>300 [47]
2	2-Cl-C_6H_4	6b	16	94	>300	>300 [35]
3	3-Cl-C_6H_4	6c	15	94	295-297	>300 [35]
4	4-Cl-C_6H_4	6d	16	91	>300	>300 [35]
5	3-Br-C_6H_4	6e	14	92	>300	>300 [35]
6	4-F-C_6H_4	6f	18	91	>300	>300 [35]
7	4-CN-C_6H_4	6g	15	92	>300	>300 [48]
8	3-NO_2-C_6H_4	6h	11	92	>300	>300 [35]
9	4-NO_2-C_6H_4	6i	16	91	>300	>300 [35]
10	2-Naphtaldehyde	6j	20	93	294-296	>300 [48]

[a] Isolated yields.



(a) **(b)**

Figure 1. Reusability of catalyst in the synthesis of 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile **4d** (a) and 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile **6d** (b).

final products, were found to be insoluble in the water and ethanol. However, 2,2'-bipyridine exhibited solubility in the same mixtures. As a result, a two-step process was employed to separate 2,2'-bipyridine from the mixture. Initially, a filtration process was conducted to separate the solid products from the liquid phase. Given that the final products were insoluble, this filtration step aimed to collect and isolate the solid components. Following the filtration, the focus shifted to the selective separation of 2,2'-bipyridine from the remaining water and ethanol mixture or ethanol. To achieve this, a rotary evaporator was utilized. The rotary evaporator facilitated the removal of water and ethanol through controlled evaporation, creating precipitation of 2,2'-bipyridine. This method facilitated the isolation of 2,2'-bipyridine for subsequent characterization studies, such as FT-IR analyses conducted both before and after the recycling process (Figure 2).

In the FT-IR spectrum of 2,2'-bipyridine, the peaks that appeared at around 2900-3100 cm^{-1} are related to stretching vibrations of the sp^2 C-H bonds in the aromatic rings. Also, peaks at around 1600-1500 cm^{-1} can be attributed to the stretching vibrations of the C=C bonds in the aromatic rings. Furthermore, peaks observed in the region of 1600-1400 cm^{-1}, correspond to the stretching vibrations of the C-N bonds in the pyridine rings.

To highlight the noteworthy of our newly developed procedure we have compared two of our results obtained from the synthesis of 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4d**) and 7-amino-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**6h**) catalyzed by 2,2'-bipyridine with some of the other results reported in the literature for the same transformations. This comparison reveals that the current approach surpasses previously reported methods in terms of reagent quantities, reaction time, and operating temperature (Tables 5 and 6).

A plausible mechanism for the synthesis of pyrano[2,3-d]pyrimidine derivatives is depicted in Scheme 3. As illustrated, 2,2'-bipyridine acts as a potent catalyst, facilitating the formation of olefin (1) through Knoevenagel condensation. Following this, the olefin engages in a reaction with barbituric acid, resulting in the formation of the active intermediate (2). Subsequent intramolecular cyclization occurs, leading to the ultimate formation of the desired product through the rearrangement of hydrogen at positions 1 and 3 (Scheme 3).

The proposed mechanism for the synthesis of pyrido[2,3-d]pyrimidine derivatives in the presence of 2,2'-bipyridine as a catalyst is illustrated in Scheme 4. According to this mechanism, 2,2'-bipyridine serves as an effective catalyst for the formation of olefin (1), easily generated through Knoevenagel condensation between the desired aldehyde and the nucleophilic anion formed from malononitrile. This compound reacts with 6-amino-1,3-dimethyluracil, forming the active intermediate (2). Subsequently, intramolecular cyclization occurs, leading to the formation of a compound (3). Ultimately, through the rearrangement of hydrogen at positions 1 and 3 and the acquisition of aromaticity, the desired product is produced [49–52] (Scheme 4).

To more investigate the proposed mechanism, the synthesis of 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile **4d** (Table 2, entry 4) was selected as a model. The reaction process was checked by GC-Mass after 1 minute, and the obtained chromatogram is shown in Figure 3. Based on these spectra, molecular ion peak (M^+) appeared in m/e = 188 with a relative intensity of 100 and is correlated with the corresponding intermediate 4-$ClC_6H_4CH{=}C(CN)_2$. Besides, ion peak m/e = 153 (98) is related to (M^+- Cl), which can precisely support the proposed mechanism. On the other hand, in this spectrum, the ion peaks related to malononitrile and 4-chlorobenzaldehyde are not observed, whereas m/e = 126 (21) can be attributed to $C_4H_2N_2O_3$.

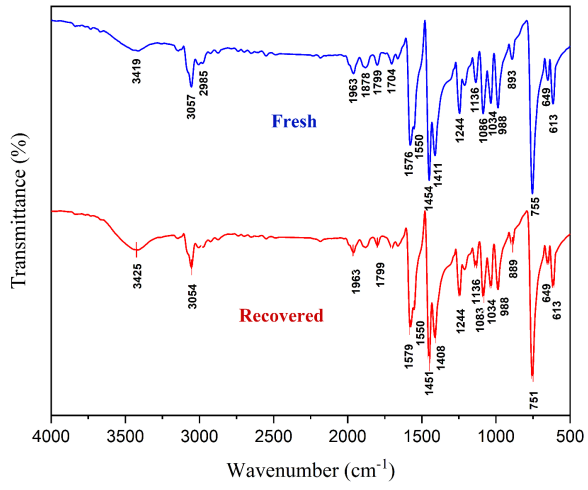


Figure 2. FT-IR Spectra of 2,2'-bipyridine before and after recycling.

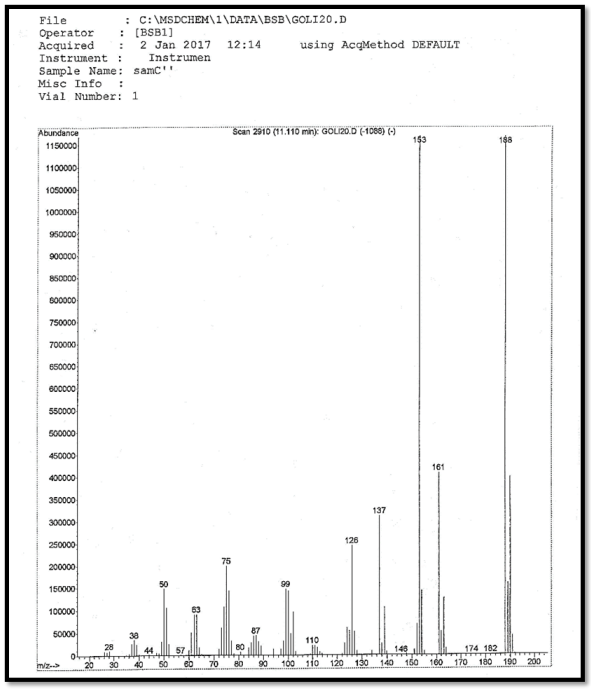
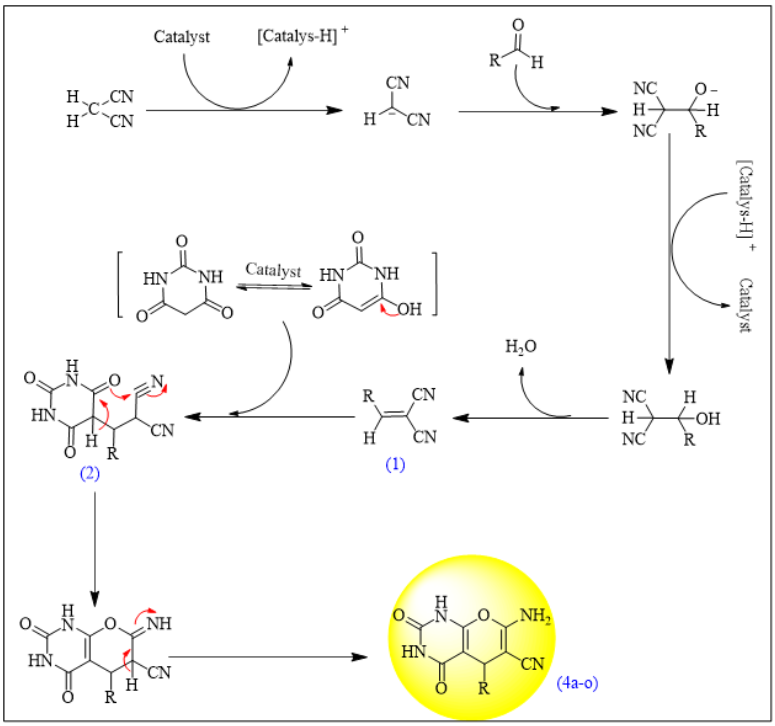
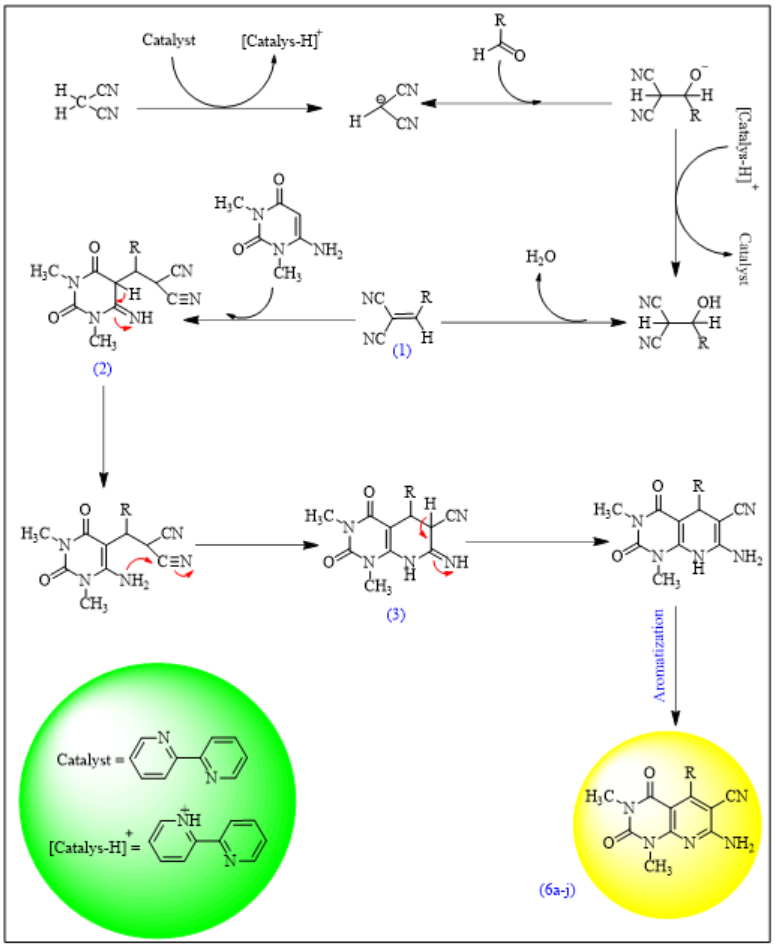


Figure 3. The GC-Mass data.



Scheme 3. Proposed mechanism for the synthesis of pyrano[2,3-d]pyrimidine derivatives using 2,2'-bipyridine.



Scheme 4. Proposed mechanism for the synthesis of pyrido[2,3-d]pyrimidine derivatives using 2,2'-bipyridine.

Table 5. Comparison of the obtained results from the synthesis of 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile **4d** (Table 2, entry 4) in the presence of 2,2'-bipyridine with some of other reported accelerators.

entry	Cat. loading (mol %)	conditions	time (min.)	yield (%)[a]	[Ref.]
1	DABCO (10)	r.t./H_2O:EtOH	40	86	[3]
2	$CaHPO_4$ (10)	90 °C/H_2O:EtOH	120	92	[27]
3	[BMIm]BF_4 (0.65)	90 °C/[BMIm]BF_4	120	92	[28]
4	$H_{14}[NaP_5W_{30}O_{110}]$ (1)	reflux/ EtOH	55	90	[29]
5	Zn[(L)proline]$_2$ (17)	reflux/ EtOH	50	90	[30]
6	SBA-Pr-SO_3H (0.02 g)	140 °C/ —	45	30	[31]
7	KA1$(SO_4)_2.12H_2O$ (10)	80 °C/ H_2O	40	93	[32]
8	L-proline (5)	EtOH	60	75	[34]
9	Mn_3O_4	reflux/ EtOH	90	60	[36]
10	2,2'-Bipyridine (6.4)	70 °C/H_2O:EtOH	3	94	[this work]

[a] Isolated yields.

Table 6. Comparison of the obtained results from the synthesis of 7-amino-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**6h**) (Table 4, entry 8) in the presence of 2,2'-bipyridine with some of other reported accelerators.

entry	Cat. loading (mol %)	conditions	time (min.)	yield (%)[a]	[Ref.]
1	nano-MgO (0.025)	80 °C/ H_2O	30	90	[35]
2	DAHP (10)	reflux/ H_2O	120	92	[37]
3	Fe_3O_4@SiO_2@$(CH_2)_3$S– SO_3H (0.5)	100 °C/—	16	89	[38]
4	2,2'-Bipyridine (9.6)	70 °C/ EtOH	11	92	[this work]

[a] Isolated yields.

This observation confirms that barbituric acid remains in the reaction media. Ultimately, all of the obtained out-comes prove the suggested mechanism as well.

4. Conclusion

In conclusion, 2,2'-bipyridine emerges as a proficient and potent homogeneous catalyst for crafting pyrano[2,3-d]pyrimidine and pyrido[2,3-d]pyrimidine derivatives. This approach offers numerous benefits, including a straightforward procedure, gentle reaction parameters, minimized catalyst loading, exceptional product yields devoid of side reactions, and swift reaction periods. Additionally, 2,2'-bipyridine exhibits reusability for up to five cycles, maintaining its catalytic activity to a significant degree. These attributes collectively highlight the viability and potential of this method for efficient and sustainable synthesis of diverse heterocyclic compounds. By harnessing the advantages of 2,2'-bipyridine catalysis, we open avenues for the development of greener and more streamlined synthetic protocols.

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Ethical Approval
This manuscript does not report on or involve the use of any animal or human data or tissue. So the ethical approval does not applicable.

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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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