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RESEARCH ARTICLE

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Simple and ecofriendly synthesis of dihydropyrimidinones (thiones), dihydropyridines, and pyridines using 3-formylchromones as substrates assisted by a recyclable Preyssler heteropolyacid

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Abstract

Several dihydropyrimidinones/thiones, 1,4-dihydropyridines, and pyridine derivatives were prepared in very good yields and purity values. The corresponding reactions were carried out by employing a bulk Preyssler heteropolyacid $H_{14}[NaP_5W_{29}MoO_{110}]$ as an efficient and recyclable catalyst. The preparation of pyridine derivatives was carried out not through a usual procedure, i.e., the opening of the γ-pyrone ring of 3-formylchromone. In general, reactions took place in solvent-free conditions at 80°C during short reaction times.

1. | INTRODUCTION

The chemist's attention is focused not only on achieving an efficient and specific product preparation but also on the process for compound preparation in order to minimize the environmental problems mainly associated with both the handling of potentially dangerous substances and the disposal of the generated waste. In this sense, one possible strategy consists in replacing the mineral acids traditionally used as catalysts in stoichiometric quantities by heteropolycompounds. Heteropolycompounds are effective, reusable, and stable solid catalysts that have intrinsic multifunctionality; they can be designed in order to enhance their redox or superacidic properties by varying the atoms present in their formula.[1–3] Among the heteropolycompounds is the Preyssler heteropolyanion, which consists of a cyclic assembly of five PW_6O_{22} units, each derived from the Keggin anion $[PW_{12}O_{40}]^{3-}$ by the removal of two sets of three corner-sharing WO_6 octahedra.[4] This material could be considered as a green catalyst with respect to safety, noncorrosive properties, quantity of waste separability, and stability.[5] It was used in several organic transformations, such as the synthesis of isoxazoles,[6] coumarins,[7] 2,4,6-triarylpyridines,[8] 2-amino-4*H*-chromenes,[9] and 1,5-benzodiazepine,[10] in the esterification of *n*-butanol with acetic acid,[11] in the alkylation of phenol with 1-octene,[12]

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and in oxidation reactions, such as alcohols,[13] primary aromatic amines,[14] and thiols using air as an oxidant,[15] and also in alkene epoxidation.[16]

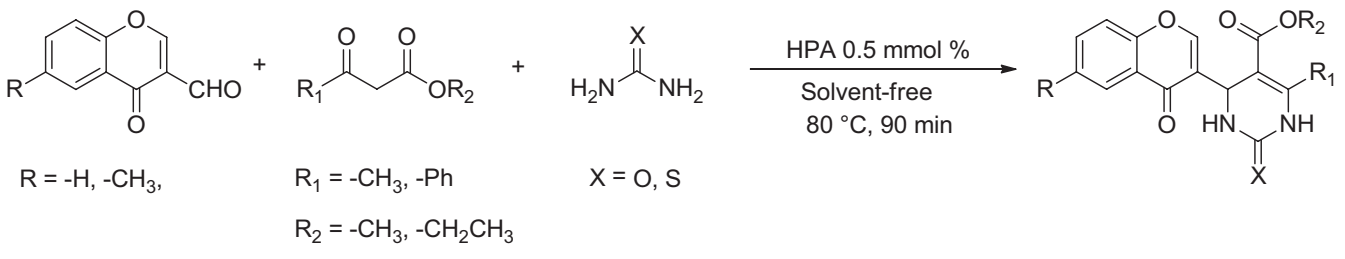
The synthesis of heterocyclic compounds is an area of interest in the search for new drugs because of their wide spectrum of significant biological activity. Among these compounds, it is possible to cite dihydropyrimidinones (DHPMs)/thiones, 1,4-dihydropyridines (1,4-DHPs), and pyridines. DHPMs are commonly known as Biginelli compounds, and they are medicinally important as antibacterial, antitumor, antiviral, and anti-inflammatory agents.[17–20] More recently, these compounds have emerged as potential calcium channel blockers, antihypertensives, α1a-adrenergic antagonists, and neuropeptide antagonists.[21] In addition, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature and in potent HIV gp-120-CD4 inhibitors.[22–24] However, 1,4-DHPs also have significant biological applications since they can function as neuroprotectants, antianginal,[25–27] analgesic,[28] antitubercular,[29] antithrombotic,[30,31] and anti-inflammatory agents,[32,33] among many other applications. Regarding pyridines, they are present in the important niacin and B6 vitamins, and also in highly toxic alkaloids, such as nicotine.[34] They are important as anti-inflammatory, antiasthmatic,[31] antidepressant,[34] antitubercular, and antibacterial agents.[30] There also are examples of pyridines that act as potent HIV protease inhibitors.[35]

Pyridine derivatives are mostly prepared through one of the following two procedures: by an oxidation reaction or through a condensation-type reaction. In the case of DHPMs/thiones and 1,4-DHPs, traditional methods for their preparation include the use of a multicomponent reaction that requires the use of an aldehyde, a 1,3-dicarbonyl compound, and urea/thiourea or ammonia, respectively, as starting materials.

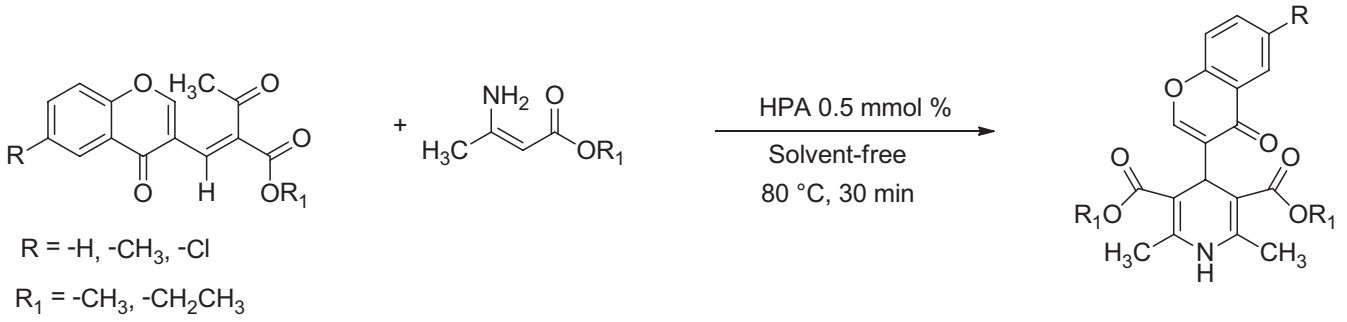
In previous work, we introduced the use of 3-formyl chromones as a starting aldehyde in the Hantzsch reaction, replacing the traditionally used benzaldehyde derivatives, in order to give a new perspective to this reaction.[36] 3-Formylchromones were selected due to several reasons: first, they represent a very reactive system owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C3 and, above all, a very reactive electrophilic center at C2;[37] second, they possess reactivity toward nucleophiles, such as hydrazine, phenylhydrazine, amidines, and aminopyrazoles;[38–41] and third, the derivatives of chromones are important natural products possessing a wide range of valuable physiological activities.[42] In addition, 3-formylchromones represent useful synthetic building blocks in organic and medicinal chemistry.[43] As a result, it was observed that 3-formylchromones showed an alternative direction of the Hantzsch condensation reaction. A functionalized pyridine in the 2-, 3-, and 5-positions was formed by opening the γ-pyrone ring after nucleophilic attack and subsequent cyclodehydration.[36] The tendency to opening of the pyrone ring is well known[44] and was also observed in 3-formylchromones and in substituted 3-formylchromones when amines or C-nucleophilic anilines were used as nucleophiles.[45–47] Ammonium and primary amines also act as nucleophiles on other closely related activated chromones. 2-Methylchromones[48] and 2-trifluoromethylchromones[49] afford aminoenones by attack at the C2 position.

In the above-mentioned previous work, the desired 1,4-DHP was finally prepared through a multistep procedure. Inspired on the mechanism for 1,4-DHPs formation suggested by Shen et al.,[50] we separately synthesized 2-acetyl-3-(3-chromonyl)acrylic acid ethyl ester as the α,β-unsaturated carbonyl compound and methyl 3-aminocrotonate as enamine. These two reactants were stirred at 80°C for 30 min in the presence of 1 mmol % of a Wells–Dawson heteropolyacid. The course of the reaction was monitored by TLC, yielding the corresponding 1,4-dihydropyridine 86%.[36]

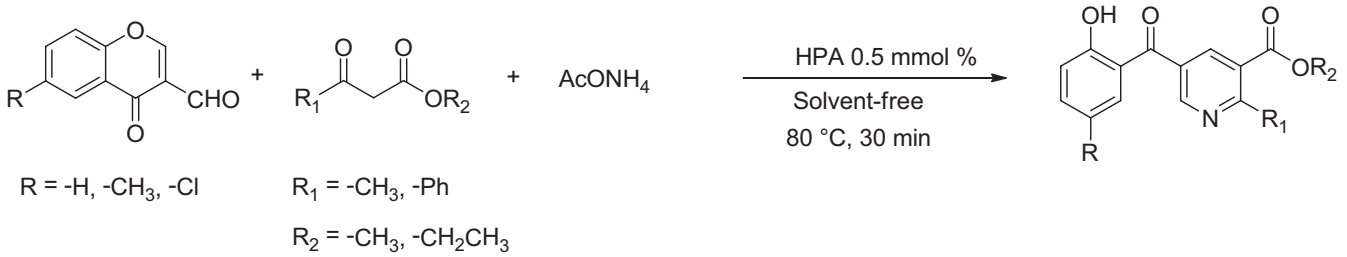
Herein, we report the preparation of DHPMs/thiones and 1,4-DHPs derivatives using a bulk Preyssler heteropolyacid (HPA) as catalyst through multicomponent solvent-free and multistep reactions, respectively. We also report a nontypical method for preparation of pyridines, i.e., through the opening of the γ-pyrone ring of 3-formylchromone working with the above-mentioned catalyst and under similar reaction conditions. The three above-mentioned synthetic procedures are shown in Schemes 1–3.



SCHEME 1 General outcome of solvent-free Biginelli-like condensation reaction with 3-formylchromone as starting aldehyde



SCHEME 2 General outcome of the final step in the multistep solvent-free 1,4-dihydropyridines synthesis



SCHEME 3 General outcome of solvent-free substituted pyridine synthesis using 3-formylchromone as a substrate

2. | RESULTS AND DISCUSSION

2.1. | Preparation of dihydropyrimidinones (thiones)

Several catalytic tests were conducted in order to determine the optimal reaction conditions. 3-Formylchromone, methyl acetoacetate, and urea were employed as starting materials. Temperature was varied between 60 and 100°C, while catalyst amounts, from 0 to 2 mmol %. After 120 min of working at 80°C without catalyst, a very low yield was obtained (Table 1, entry 1). When the catalyst amount was increased from 0.25 to 0.5 mmol %, the product yield also increased, but no significant change was observed by employing 2 mmol % of HPA (Table 1, entries 2–4). If the reaction temperature increases or decreases from 80°C, product yields are lower (Table 1, entries 5 and 6). Since the use of reaction times of 60 and 120 min did not give better results (Table 1, entries 7 and 8), the optimal reaction conditions were established as 80°C, 0.5 mmol % of HPA for 90 min (Table 1, entry 3). It was demonstrated that after three catalytic cycles the catalytic material maintained its activity (Table 1, entries 9 and 10).

TABLE 1 HPA-catalyzed multicomponent synthesis of dihydropyrimidinones by reaction between 3-formylchromone, methyl acetoacetate and urea

Entry	Temperature (°C)	Time (min)	Catalyst amount (%)	Yields (%)
1[a]	80	120	–	15
2	80	90	0.25	80
3	80	90	0.5	**88**
4	80	90	2	87
5	100	90	0.5	78
6	60	90	0.5	75
7	80	60	0.5	82
8	80	120	0.5	87
9[b]	80	90	0.5	87
10[c]	80	90	0.5	86

[a]Reaction without catalyst. [b]First and [c]second reuse, respectively.

The bold values correspond to the obtained yield under the optimal reaction conditions for each presented reaction.

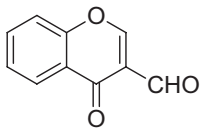
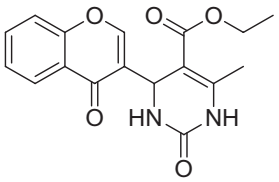
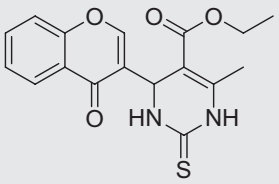
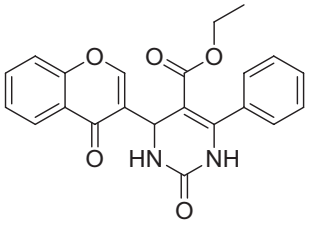
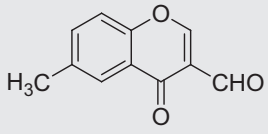
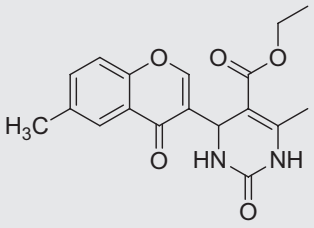
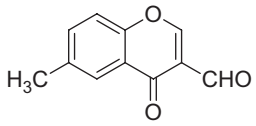
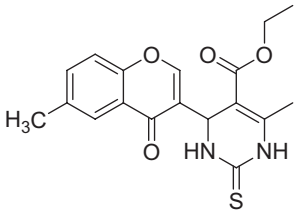
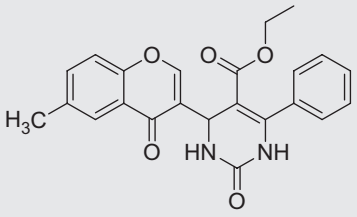
By employing the optimal reaction conditions and varying the starting materials, six different dihydropyrimidinones (thiones) were prepared (Table 2). In all cases, the desired product was obtained with high selectivity, achieving product yields greater than 80%.

In order to quantify the sustainability of the methodology, the atomic economy (AE), atomic efficiency factor (E), process mass intensity (PMI), and EcoScale were calculated for each reaction product, and the results are also presented in Table 2. The resulting parameters indicate an improvement in the synthetic method from a green chemistry point of view, with better yield, AE, environmental factor, PMI, and EcoScale factors than those obtained by traditional synthetic procedures.

2.2. | Preparation of 1,4-dihydropyridines

Optimum reaction conditions for this preparation were determined by carrying out a series of catalytic tests. With this

TABLE 2 HPA-catalyzed synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones containing 3-formylchromone moiety[a]

Comp.	3-formylchromone	Dihydropyrimidinones (thiones)	Yield (%)	AE (%)	E factor	PMI	Eco scale
1			88	100	13.69	16.45	91
2			82	100	14.06	16.94	88
3			80	100	12.67	15.45	7
4			89	100	12.99	15.65	1.5
5			85	100	13.02	15.73	89.5
6			81	100	12.09	14.76	87.5

[a]*Reaction conditions:* HPA (0.5 mmol %), 3-formylchromone (1 mmol), 1,3-dicarbonylcompounds (1 mmol), and urea or thiourea (1.5 mmol). The mixture was stirred at 80°C for 90 min.

purpose, 2-acetyl-3(-chromonyl)-acrylic acid methyl ester and 3-amino-2-butenoic acid methyl ester (previously prepared) were employed as reactants. After 30 min of reaction at 80°C without catalyst, a poor product yield was obtained (Table 3, entry 1). Then, the catalyst amount was varied from 0.25 to 2 mmol % of HPA: the results showed that yields increased when the catalytic material amount increased from 0.25 to 0.5 mmol %, but no difference was observed when 2 mmol % of HPA was employed (Table 3, entries 2–4). The effect of reaction temperature was also evaluated when the reaction temperature increased to 100°C or decreased to 60°C, the product yield was lower (Table 3, entries 5 and 6). As the use of shorter and longer reaction times did not give better results (Table 3, entries 7 and 8), the optimal reaction

TABLE 3 HPA-catalyzed synthesis of 1,4-dihydropyridines by reaction between 3-2-acetyl-3(-chromonyl)-acrylic acid methyl ester and 3-amino-2-butenoic acid methyl ester

Entry	Temperature (°C)	Time (min)	Catalyst amount (%)	Yields (%)
1[a]	80	30	–	35
2	80	30	0.25	83
3	80	30	0.5	**87**
4	80	30	2	87
5	100	30	0.5	59
6	60	30	0.5	50
7	80	15	0.5	82
8	80	60	0.5	85
9[b]	80	30	0.5	87
10[c]	80	30	0.5	87

[a]Reaction without catalyst. [b]First and [c]second reuse, respectively.

The bold values correspond to the obtained yield under the optimal reaction conditions for each presented reaction.

conditions were established as 30 min at 80°C with 0.5 mmol % of HPA (Table 3, entry 3). It was seen that the catalytic material did not lose its activity after three catalytic cycles (Table 3, entries 9 and 10).

Five different 1,4-DHP derivatives (Table 4) were efficiently prepared using the optimal reaction conditions. Product yields were equal to or greater than 80%. In order to quantify the sustainability grade of the proposed methodology, the AE, E, PMI, and EcoScale were calculated for each reaction product and the results are also presented in Table 4. The resulting parameters indicate an improvement in the synthetic procedure from a green chemistry point of view, with better yield, AE, environmental factor, PMI, and EcoScale factors than those obtained by traditional synthetic procedures.

1,4-Dihydropyridines must be prepared through this multistep reaction instead of using a multicomponent reaction if 3-formylchromones are employed as reactants, in order to minimize the formation of the corresponding pyridine derivative by γ-pyrone ring opening.[36] When the multicomponent reaction takes place, a competitive mechanism appears (Scheme 4).

First, 3-formylchromone **I** is activated by the HPA and reacts with the 1,3-dicarbonylic compound in a Knoevenagel condensation. After a dehydration step, a 2-acetyl-3(-chromonyl)-acrylic acid alkyl ester **II** is obtained (Scheme 4). Then, two different carbonyl groups of **II** could be activated by the HPA, giving two possible reaction pathways A and B.

Pathway A: The carbonyl group that comes from the 1,3-dicarbonylic compound is activated by the HPA to give the corresponding enamine by condensation reaction with ammonia. After its dehydration, structure IV is obtained.

Pathway B: The carbonyl group that comes from 3-formylchromone is activated by the HPA, and a nucleophilic attack to the 2-position of the γ-pyrone ring takes place, producing its opening to give **V**.

In the case of intermediate **IV**, it not only produces the 1,4-DHP but could also form the corresponding pyridine derivative. The difference is due to the taken pathway: A1 or A2. Then, **V** could only give the pyridine derivative after cyclization and dehydration reactions.

Pathway A1: The carbonyl group that comes from the 1,3-dicarbonylic compound is activated by the HPA to react with the intermediate of structure IV. The subsequent dehydration and cyclization produces the 1,4-DHP.

Pathway A2: Intermediate **IV** undergoes cyclization and dehydration to give the pyridine derivative functionalized in 2, 3, and 5 positions.

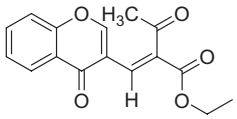
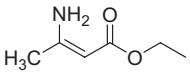
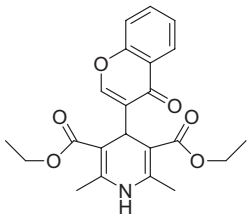
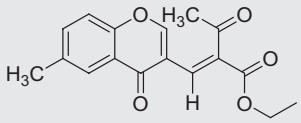
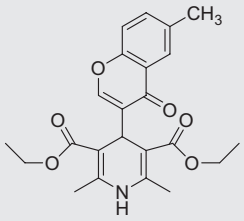
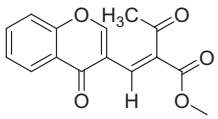
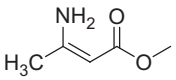
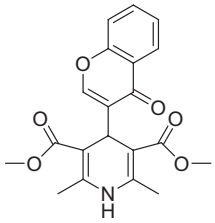
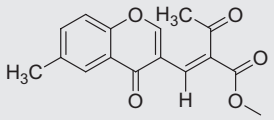
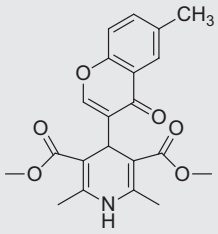
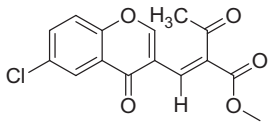
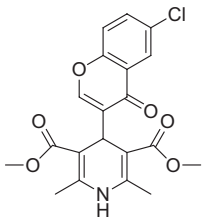
From this, it can be said that intermediates **IV** and **V** are key structures in the mechanisms competition. Structure V could be more stable due to a more intense conjugation effect and, furthermore, from **V** it could be possible to prepare the pyridine derivative by simple intramolecular cyclization (with high probability of occurrence) without the need of an additional condensation step, as occurs with 1,4-DHP formation from intermediate **IV**. As can be seen, pyridine formation is much more favored than 1,4-DHP formation if this preparation strategy is employed.

However, when a multistep reaction is applied to prepare 1,4-DHPs, the possible reaction mechanism changes (Scheme 5). In its last step, 2-acetyl-3(-chromonyl)-acrylic acid alkyl diester **II** reacts with 3-amino-2-butenoic acid alkyl ester through Michael condensation to give, after cyclization and dehydration, the corresponding 1,4-DHP derivative, avoiding the above-mentioned side reactions.

2.3. | Preparation of substituted pyridines

In order to find a convenient method for pyridine synthesis, several catalytic tests were carried out. 3-Formylchromone, methyl acetoacetate, and ammonium acetate were used as starting materials. Temperature varied from 60 to 100°C, while the catalyst amount was established between 0 and 2 mmol %. After 30 min of working at 80°C without catalyst, a 39% product yield was obtained (Table 5, entry 1). When the catalyst amount was increased from 0.25 to 0.5 mmol %, the product yield increased slightly, but no change was observed by employing 2 mmol % of HPA with respect to the system with 0.5 mmol % (Table 5, entries 2–4). If the reaction temperature increases or decreases from 80°C, product yield

TABLE 4 HPA-catalyzed synthesis of 1,4-dihydropyridine derivatives containing 3-formylchromone moiety[a]

Comp.	2-Acetyl-3(-chromonyl)-acrylic acid alkyl esters	3-Amino-2-butenoic acid alkyl esters	1,4-Dihydropyridine	Yield (%)	AE (%)	E factor	PMI	Eco scale
7				87	95.7	11.33	13.78	0.5
8				83	95.8	11.47	14.00	88.5
9				86	95.3	12.33	14.91	0
10				80	95.5	12.78	15.51	87
11				83	95.7	11.68	14.28	88.5

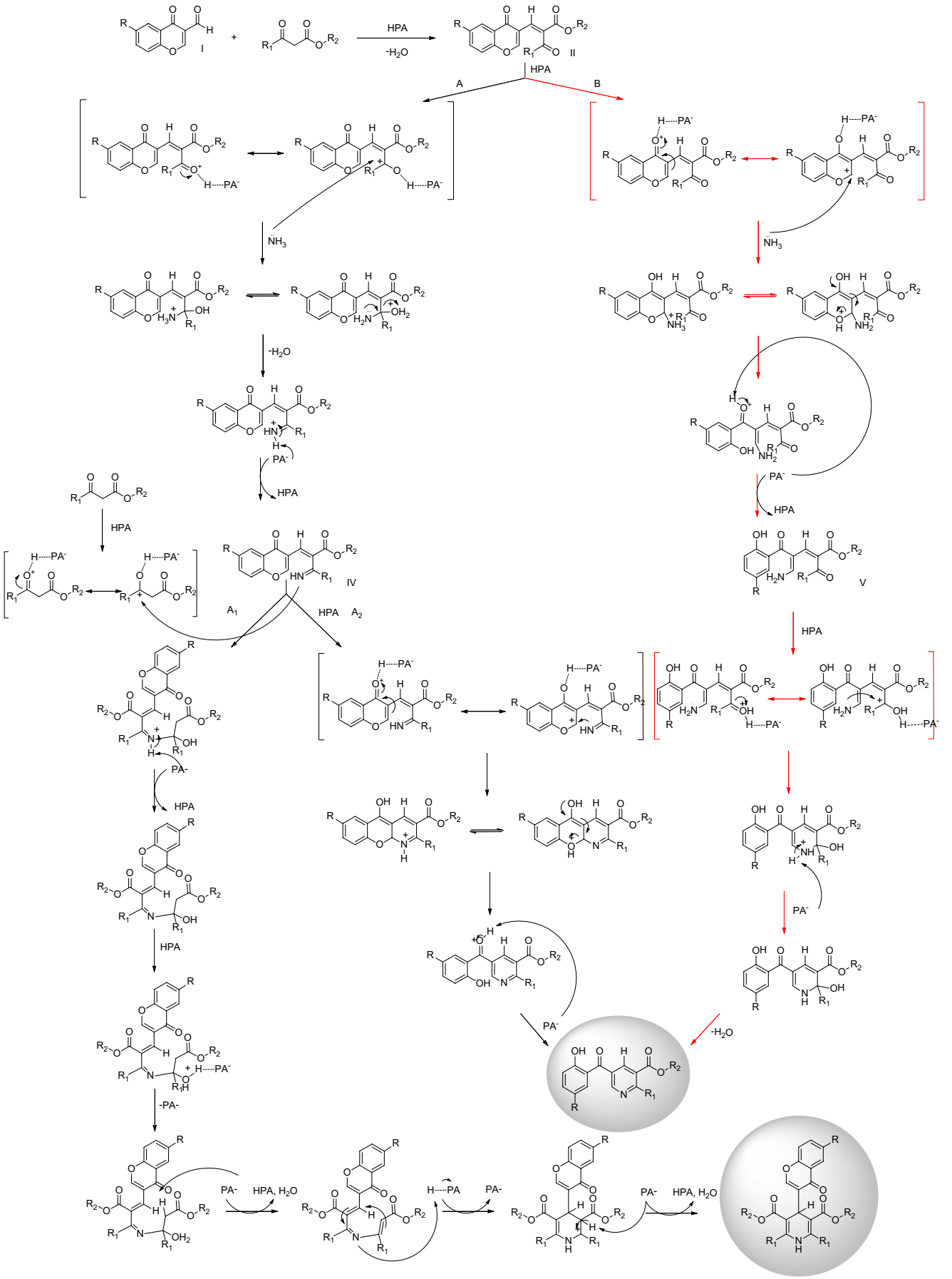
[a]Reaction conditions: HPA (0.5 mmol %), 2-acetyl-3(-chromonyl)-acrylic acid alkyl ester (1 mmol), and 3-amino-2-butenoic acid alkyl ester (1 mmol). The mixture was stirred at 80°C for 30 min.

values are lower (Table 1, entries 5 and 6). Therefore, the optimal reaction conditions were established as 80°C, 0.5 mmol % of HPA and 15 min (Table 1, entry 3). Finally, the results showed that after 3 catalytic cycles the catalytic material maintained its activity (Table 5, entries 8 and 9).

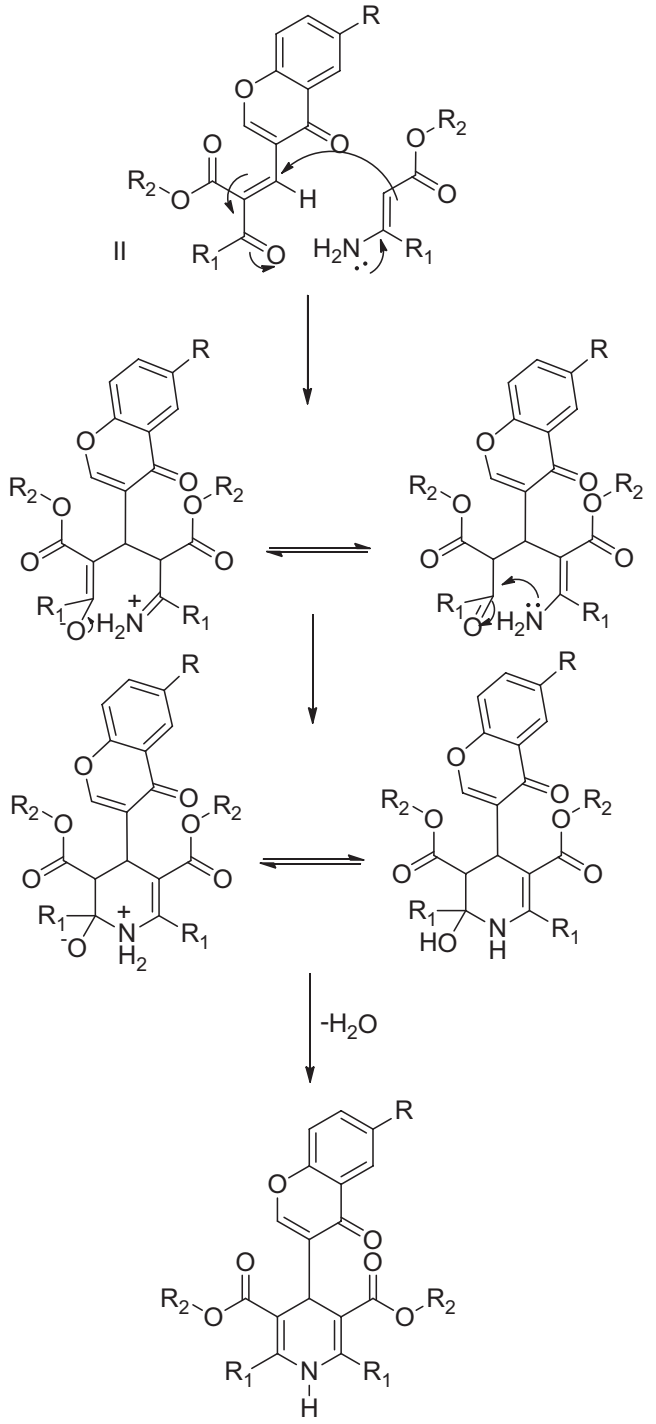
As is shown in Table 6, seven different pyridine derivatives were efficiently prepared by using the optimal reaction conditions, achieving, in almost all cases, product yields greater than 85%.

In order to quantify the sustainability grade of the proposed methodology, the AE, E, PMI, and EcoScale were calculated for each reaction product, and the results are also presented in Table 6. The resulting parameters indicate an improvement in the synthetic procedure from a green chemistry point of view, with better yield, AE, environmental factor, PMI, and EcoScale factors than those obtained by traditional synthetic procedures.

Based on present and previous results,[36] a possible reaction mechanism for pyridine preparation from



SCHEME 4 Possible reaction mechanisms competition in the multicomponent synthesis of 1,4-DHP



SCHEME 5 Possible reaction mechanism in the final step of the multistep synthesis of 1,4-DHP

3-formylchromones is proposed, and it was exhaustively described in the previous section (Scheme 4).

3. | CONCLUSIONS

The three desired heterocyclic families were efficiently prepared through clean and simple procedures in short reaction times under mild conditions. The employed catalytic material is a noncorrosive and it could be reused without significant loss of activity. A multistep synthetic strategy that allows obtaining more structurally complex 1,4-dihydropyridines from 3-formylchromones as main reaction product was presented. Furthermore, pyridine derivatives were prepared through a nontypical method, i.e., by opening the γ-pyrone ring of 3-formylchromone.

TABLE 5 HPA-catalyzed synthesis of substituted pyridines

Entry	Temperature (°C)	Time (min)	Catalyst amount (%)	Yield (%)
1[a]	80	30	–	39
2	80	15	0.25	83
3	80	15	0.5	**87**
4	80	30	2	87
5	100	30	0.5	59
6	60	30	0.5	50
7	80	60	0.5	85
8[b]	80	30	0.5	87
9[c]	80	30	0.5	87

[a]Reaction without catalyst. [b]First and [c]second reuse, respectively.

The bold values correspond to the obtained yield under the optimal reaction conditions for each presented reaction.

4. | EXPERIMENTAL

4.1 | General

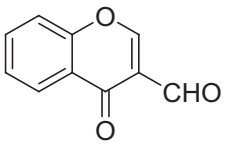
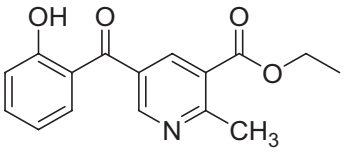
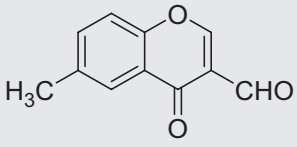
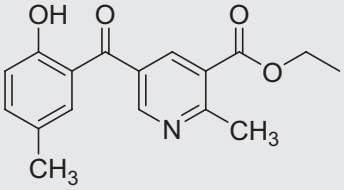
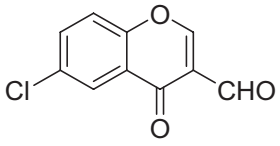
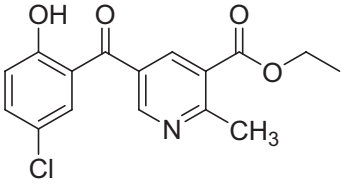
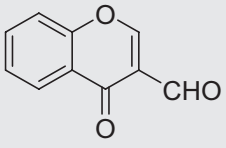
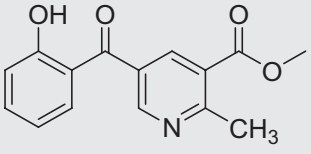
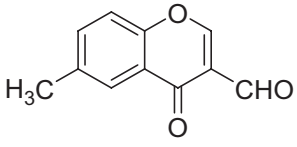
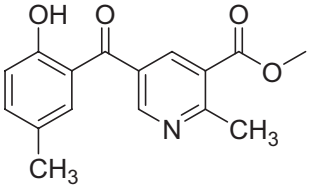
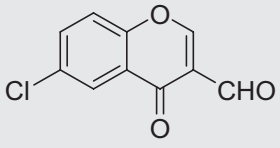
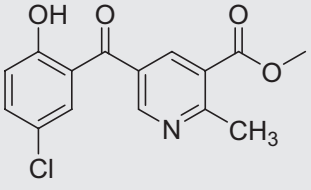
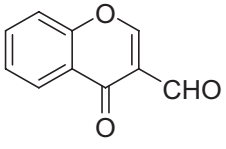
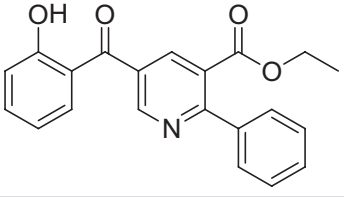
All chemicals were purchased commercially and used without further purification. The yields were calculated from crystallized products. All the products were identified by comparison of analytical data, melting point (mp), elemental microanalyses, thin layer chromatography (TLC), and nuclear magnetic resonance (NMR) data with those reported.

The starting materials are commercial products. 2-Acetyl-3(-chromonyl)-acrylic acid alkyl esters were prepared using a literature procedure[36] and 3-amino-2-butenoic acid alkyl esters by warming a 1:5 mixture of alkyl acetoacetate and ammonium acetate at 80°C for 120 min. Melting points of the compounds were determined in open capillary tubes and are uncorrected. ^{13}C NMR and ^{1}H NMR spectra were recorded at room temperature on a Bruker AC 400 using tetramethylsilane (TMS) as internal standard. Elemental microanalyses were performed in a F & M instrument.

4.2. | Catalyst preparation

The heteropolyacid used in the present paper was synthesized essentially following a procedure performed by us with slight modifications.[4] The Preyssler salt, $K_{12.5}Na_{1.5}[NaP_5W_{30}O_{110}].15H_2O$ (HPAK), was

TABLE 6 HPA-catalyzed synthesis of substituted pyridines[a]

Comp.	3-Formylchromones	Substituted pyridines	Yield (%)	AE (%)	E factor	PMI	Eco scale
12			90	74.8	15.25	18.43	92
13			88	75.7	14.88	18.03	91
14			87	76.9	14.07	17.12	90.5
15			90	73.8	16.03	19.31	92
16			91	74.8	15.10	18.25	92.5
17			92	76.1	13.92	16.90	93
18			68	77.6	17.31	21.24	81

[a]Reaction conditions: HPA (0.5 mmol %), 3-formylchromone (1 mmol), 1,3-dicarbonylic compound (1 mmol), and ammonium acetate (1 mmol). The mixture was stirred at 80°C for 15 min.

prepared from $Na_2WO_4.2H_2O$ according to a previously reported method and converted to the corresponding acid $H_{14}[NaP_5W_{29}MoO_{110}]$ (HPA), by passing it through a Dowex-50Wx8 ion-exchange column. In a typical experiment, 66.27 g (0.2 mol) $Na_2WO_4.2H_2O$ was dissolved in 100 mL water and mixed at 60°C for 30 min. The solution was cooled to room temperature, and 50 mL concentrated phosphoric acid was added. The solution was refluxed for 18 h. Then, it was brought to room temperature, diluted with 35 mL water, and then 23.5 g potassium chloride was added with stirring. The mixture was stirred for 30 min and then heated up to dryness, and a solid was obtained. This raw

product was dissolved in 85 mL warm water and upon cooling to room temperature crystals formed, which were collected and recrystallized from boiling water (yield, 18%).

The heteropolyanion was converted to its corresponding acid $H_{14}[NaP_5W_{30}MoO_{110}]$ (HPA) by passing an aqueous solution of HPAMoK through a Dowex-50Wx8 ion-exchange column. The catalyst was properly characterized.

4.3. | General procedure for the preparation of dihydropyrimidinones (thiones)

The solid catalyst (0.5 mmol %) was added to a mixture of 3-formylchromones (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and urea or thiourea (1.5 mmol). The mixture was stirred at 80°C for 90 min. The progress of the reaction was monitored by TLC. After completion of the reaction, hot toluene was added (2 × 2.5 mL) and the catalyst was filtered. The extracts were combined dried with anhydrous sodium sulfate, and the solvents concentrated in vacuum. All the solid crude products were recrystallized (Compounds 1–6).

4.4. | General procedure for the preparation of 1,4-dihydropyridines

The solid catalyst (0.5 mmol %) was added to a mixture of 2-acetyl-3(-chromonyl)-acrylic acid alkyl esters (1 mmol) and 3-amino-2-butenoic acid alkyl esters (1 mmol). The mixture was stirred at 80°C for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, hot toluene was added (2 × 2.5 mL) and the catalyst was filtered. The extracts were combined dried with anhydrous sodium sulfate, and the solvents were concentrated in vacuum. All the solid crude products were recrystallized (Compounds 7–11).

4.5. | General procedure for the preparation of substituted pyridines

The solid catalyst (0.5 mmol %) was added to a mixture of 3-formylchromones (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and ammonium acetate (1 mmol). The mixture was stirred at 80°C for 15 min. The progress of the reaction was monitored by TLC. After completion of the reaction, hot toluene was added (2 × 2.5 mL) and the catalyst was filtered. The extracts were combined, dried with anhydrous sodium sulfate, filtered, and the solvent was evaporated and then concentrated in vacuum. All the solid crude products were recrystallized (compounds 12–18).

4.6. | Catalyst reuse

Stability tests of the Preyssler catalysts were carried out by running three consecutive experiments, under the same reaction conditions for the three compound families. After each test, the catalyst was separated from the reaction mixture by filtration, washed with toluene (2 × 2 mL), dried under vacuum, and then reused.

4.7 | Green metrics

In order to quantify the sustainability for the methodology presented, various green metric parameters were calculated for each reaction performed. Thus, relevant quantitative factors such as atom economy (AE), atomic efficiency factor (E), process mass intensity (PMI), and semiquantitative EcoScale were determined.

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