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Nanostructured $Na_2CaP_2O_7$: A New and Efficient Catalyst for One-Pot Synthesis of 2-Amino-3-Cyanopyridine Derivatives and Evaluation of Their Antibacterial Activity

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Abstract: A facile and novel synthesis of thirteen 2-amino-3-cyanopyridine derivatives **5(a–m)** by a one-pot multicomponent reactions (MCRs) is described for the first time, starting from aromatic aldehydes, malononitrile, methyl ketones, or cyclohexanone and ammonium acetate in the presence of the nanostructured diphosphate $Na_2CaP_2O_7$ (DIPH) at 80 °C under solvent-free conditions. These compounds were brought into existence in a short period with good to outstanding yields (84–94%). The diphosphate $Na_2CaP_2O_7$ was synthesized and characterized by different techniques (FT-IR, XRD, SEM, and TEM) and used as an efficient, environmentally friendly, easy-to-handle, harmless, secure, and reusable catalyst. Our study was strengthened by combining five new pyrido[2,3-*d*]pyrimidine derivatives **6(b, c, g, h, j)** by intermolecular cyclization of 2-amino-3-cyanopyridines **5(b, c, g, h, j)** with formamide. The synthesized products were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR and by comparing measured melting points with known values reported in the literature. Gas chromatography/mass spectrometry was used to characterize the newly synthesized products and evaluate their purity. The operating conditions were optimized using a model reaction in which the catalyst amount, temperature, time, and solvent effect were evaluated. Antibacterial activity was tested against approved Gram-positive and Gram-negative strains for previously mentioned compounds.

Keywords: catalyst; antibacterial activity; solvent-free conditions; heterogeneous catalysis; synthesis; cyanopyridines; pyrimidines; nanostructured $Na_2CaP_2O_7$; catalyst recovery

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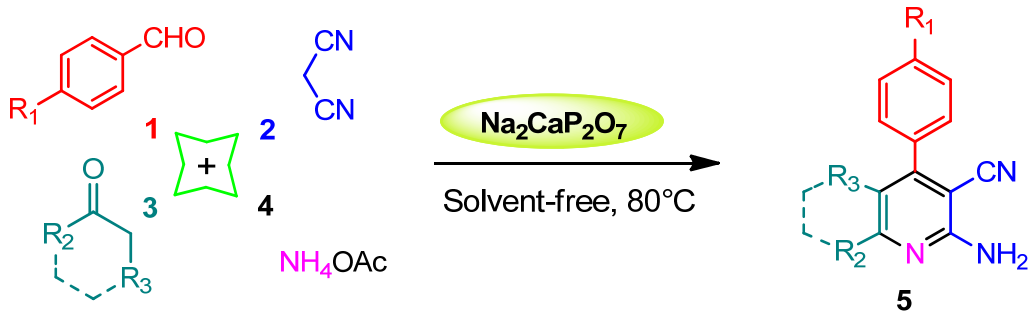
1. Introduction

Pyridine and its derivatives are known to be the essential chemical compounds in medicinal chemistry [1–3]. They are key scaffolds in biologically active and naturally occurring substances. Many pharmacological properties of pyridine and its derivatives have been reported, including antimicrobial [4], anticancer [5], anti-inflammatory [6], antiviral [7], antidiabetic [8], and antimalarial activities [2]. In addition, heterocyclic systems

involving the β-enaminonitrile moiety represent a class of intermediates considered to be extremely reactive and used as precursors for synthesis of brand-new heterocyclic compounds [9–11]. The literature mentions that several different pyridine derivatives, particularly 2-amino-2-cyanopyridines, have been prepared as target structures using sustainable catalyst materials [12] coupled with environmentally benign protocols. Moreover, it is interesting to note that multicomponent reactions (MCRs) have drawn the attention of many researchers in the last decade due to their productivity and simplicity. MCRs are used for the development of biologically active compounds from accessible commercial reagents with a single step [13]. Furthermore, in our case, the combination of this process with a solvent-free medium for the preparation of these heterocyclic derivatives makes the use of MCRs compliant with the principles of green chemistry.

Several studies have reported the usefulness and importance of these processes, in which they were exploited for the synthesis of 2-amino-3-cyanopyridine in the presence of various catalysts, such as ytterbium perfluorooctanoate [$Yb(PFO)_3$] [14], $Bu_4N^+Br^-$ [15], Cu@imineZCMNPs [16], cellulose-SO_3H [17], MgO [18], HBF_4 [19], Fe_3O_4@SiO_2@(CH_2)Im}$C(CN)_3$ [20], $FePO_4$ [21], and poly(ethylene glycol) (PEG-400) [22]. However, these procedures present several inconveniences, such as long reaction time, undesirable reaction conditions, the need for loads of reagents, the use of organic solvents and toxic reagents, and the non-recoverability of the catalyst. Thus, a new, efficient, and environmentally friendly protocol for the synthesis of 2-amino-3-cyanopyridines is required. The aim of this work is to investigate and examine $Na_2CaP_2O_7$ as an alternative catalyst, as it has received increased attention recently, mainly in the environmental field [23–25].

This work is a continuation of our investigation and according to our results obtained in a previous study based on adopting $Na_2CaP_2O_7$ as a catalyst in organic synthesis [26–28], particularly in the synthesis of heterocyclic compounds via multicomponent reactions in an ecofriendly medium [29,30]. Herein, we report here an efficient and rapid one-pot synthesis of thirteen 2-amino-3-cyanopyridine derivatives by condensation of aromatic aldehydes, malononitrile, methyl ketone, or cyclohexanone and ammonium acetate using a nanostructured diphosphate $Na_2CaP_2O_7$ as a heterogeneous catalyst under solvent-free reaction conditions at 80 °C (Scheme 1). Five prepared 2-amino-3-cyanopyridine were converted to pyrido[2,3-*d*]pyrimidines, and we examined the antibacterial activity of all prepared compounds.



Scheme 1. Synthesis of 2-amino-3-cyanopyridine derivatives catalyzed by $Na_2CaP_2O_7$.

2. Results and Discussion

2.1. Synthesis and Characterization of $Na_2CaP_2O_7$ Nanoparticles

$Na_2CaP_2O_7$ nanoparticles were synthesized according to procedures described in the literature [31]. Nanostructured pyrophosphate was synthesized using the dry method. Stoichiometric amounts of sodium carbonate (Na_2CO_3), calcium carbonate ($CaCO_3$), and ammonium dihydrogen phosphate ($NH_4H_2PO_4$) with a molar ratio of 1:1:2 were blended in an agate mortar. The mixture was transferred to a porcelain crucible and heated progressively from 100 to 600 °C (Figure 1). Then, the obtained powder was characterized by X-ray diffraction, Fourier transform infrared spectroscopy, scanning electron microscopy, and transmission electron microscopy.

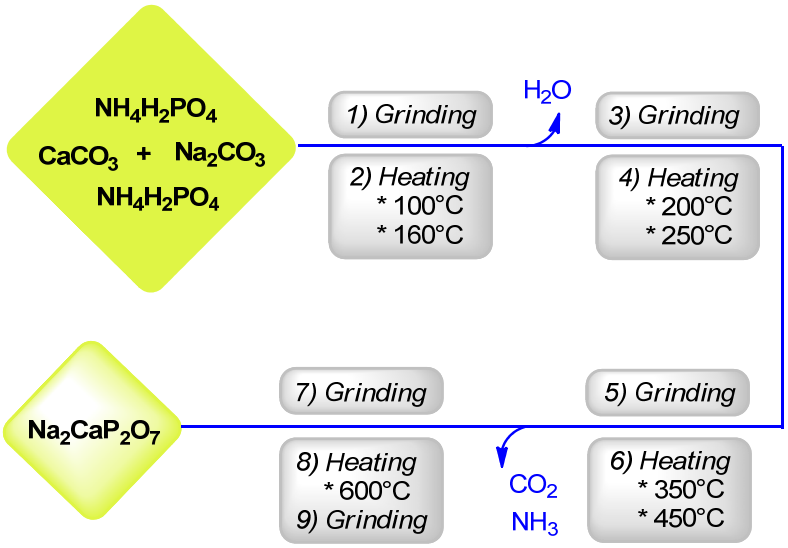


Figure 1. Schematic describing the preparation of $Na_2CaP_2O_7$ nanoparticles.

2.2. Characterization of Diphosphate $Na_2CaP_2O_7$

The X-ray diffraction pattern of diphosphate $Na_2CaP_2O_7$ is shown in Figure 2. All diffraction peaks are consistent with the standard data of the ICSD collection code: 89,468. Crystals of diphosphate $Na_2CaP_2O_7$ have a triclinic structure, space group P1bar and crystal parameters a = 5.361 Å, b = 7.029 Å and c = 8.743 Å, V = 308.31 $Å^3$, and Z = 2.

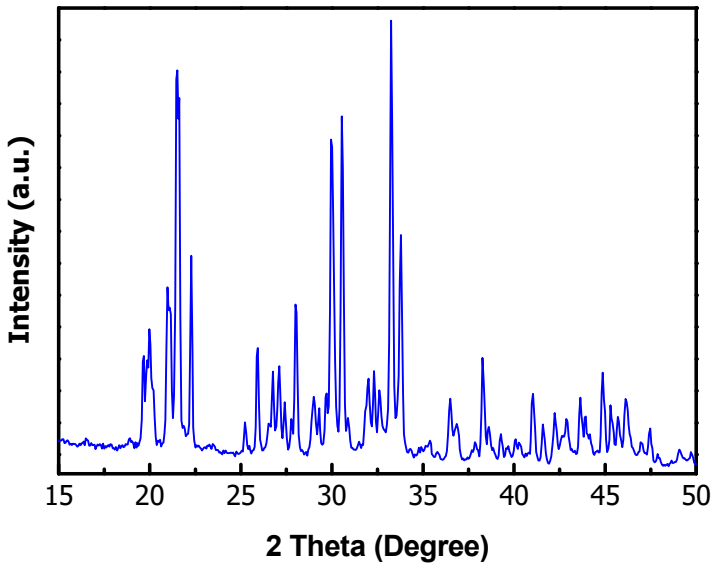


Figure 2. X-ray powder diffraction pattern of $Na_2CaP_2O_7$.

The FT-IR spectrum of $Na_2CaP_2O_7$ is displayed in Figure 3. The bands at 720 cm^{-1} and 888 cm^{-1} are defined as the symmetrical (sym) and antisymmetric (anti) vibration of P-O-P, respectively. These bands confirm the presence of pyrophosphate P_2O_7 groups. Two fields share the associated vibrations of the PO_4 groups: a symmetrical vibration field (997 cm^{-1}, 1031 cm^{-1}) and the other from 1112 cm^{-1} to 1278 cm^{-1}. The described bands confirm that $Na_2CaP_2O_7$ was prepared.

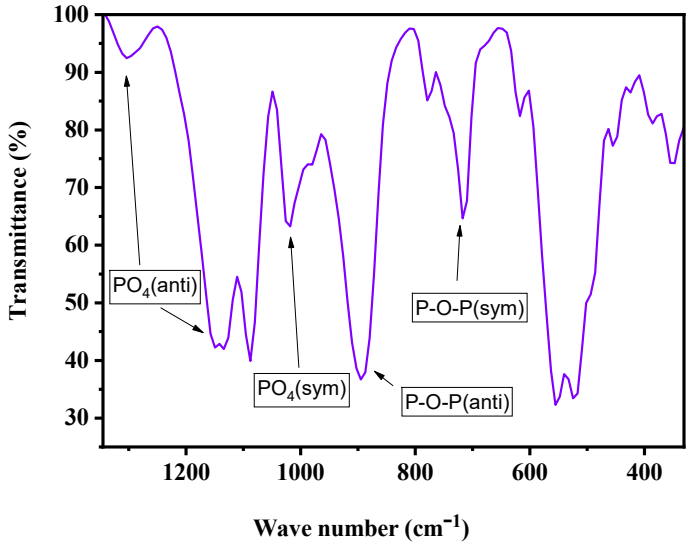


Figure 3. FT-IR spectrum of $Na_2CaP_2O_7$.

The morphology of the $Na_2CaP_2O_7$ surface was elucidated by scanning electron microscopy (SEM, Figure 4). $Na_2CaP_2O_7$ has a homogeneous microstructure that contains layers of various sizes and forms.

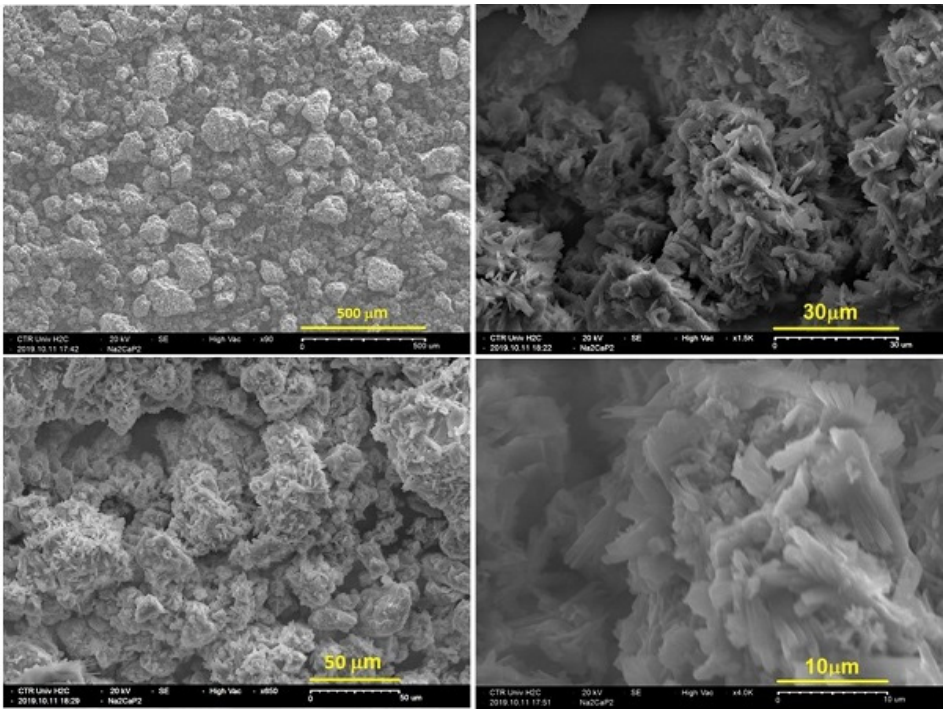


Figure 4. SEM images of $Na_2CaP_2O_7$ at different magnifications.

Transmission electron microscopy (TEM) was further used to study the morphology and microstructure of $Na_2CaP_2O_7$. Figure 5 shows rod-like nanoparticles that agglomerate to form superstructures with different grain crystal aspect ratios. The powder forms show irregular grains with a lateral size of 90–150 nm. The specific surface of the $Na_2CaP_2O_7$ areas were determined by the Brunauer–Emmett–Teller (BET) method from the adsorption–desorption isotherm of N_2 at 77 K and was identified to be 4 $m^2 \cdot g^{-1}$.

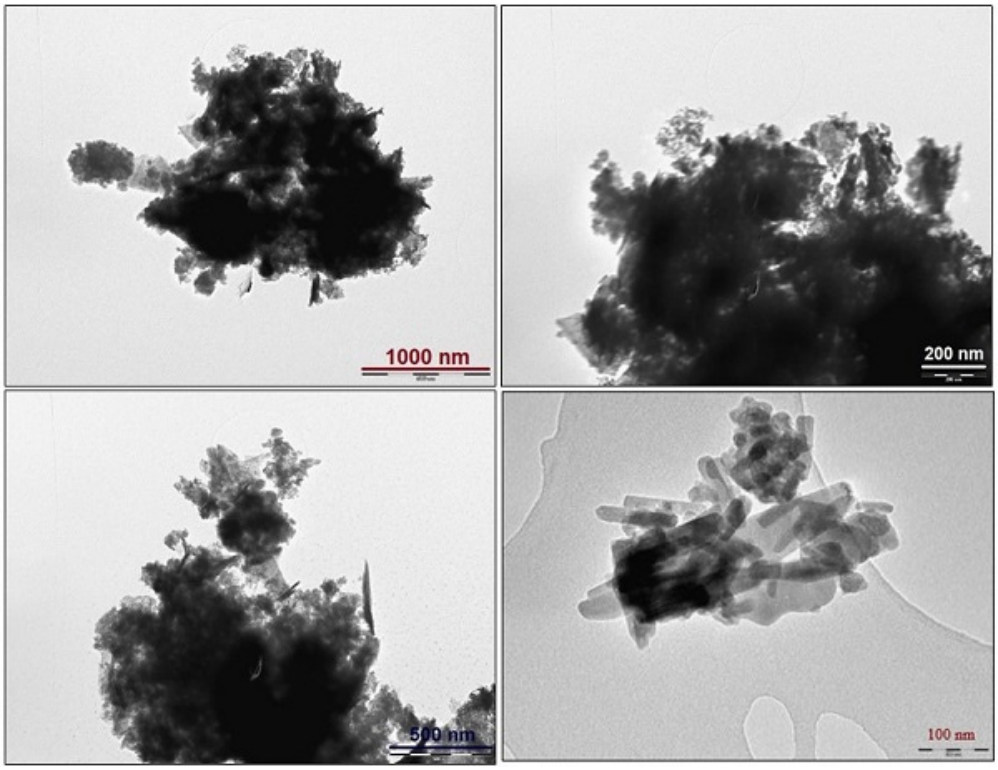
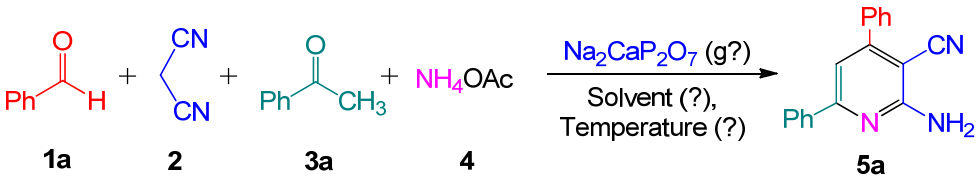


Figure 5. TEM micrographs of $Na_2CaP_2O_7$ nanopowder.

2.3. Optimization of Reaction Conditions

In order to establish the optimal synthesis condition for substituted 2-amino-3-cyanopyridines, a reaction of benzaldehyde **1a** (1 mmol), malononitrile **2** (1.1 mmol), acetophenone **3a** (1 mmol), and ammonium acetate **4** (1.5 mmol) was chosen as a model and carried out under various conditions; $Na_2CaP_2O_7$ was used as a catalyst (Scheme 2).



Scheme 2. Synthesis of 2-amino-3-cyanopyridine (**5a**).

2.4. Influence of the Amount of the Catalyst

To optimize the catalyst amount, the model reaction was performed with different quantities of the catalyst and according to obtained results (Table 1, entries 2–8). An amount of 0.05 g (20%) of the nanostructured diphosphate $Na_2CaP_2O_7$ was chosen as the optimal catalyst amount; with this amount, the reaction can be performed in 30 min, providing a 94% yield of **5a** (Figure 6). With an increased amount of $Na_2CaP_2O_7$, there was no improvement in the product yields (Table 1, entries 7 and 8). This may be due to the attainment of the maximum conversion efficiency of the catalyst. No target product was observed without the catalyst. This result suggests that our catalyst plays an important role in this transformation (Table 1, entry 1).

Table 1. Optimization of reaction conditions for the synthesis of 2-amino-3-cyanopyridine **5a**.

	Entry	Amount of Catalyst (g)	Temperature (°C)	Time (Min.)	Yield (%) [a],[b]
Absence of a catalyst	1	0	80	120	-
Influence of the amount of the catalyst	2	0.01	80	30	20
	3	0.02	80	30	40
	4	0.03	80	30	60
	5	0.04	80	30	84
	6	0.05	80	30	94
	7	0.06	80	30	94
	8	0.07	80	30	94
Influence of temperature and reaction time	9	0.05	80	20	65
	10	0.05	80	15	53
	11	0.05	80	40	95
	12	0.05	40	30	75
	13	0.05	60	30	85
	14	0.05	100	30	94

[a] Isolated yields; [b] reaction conditions: benzaldehyde (1 mmol), malononitrile (1.1 mmol), acetophenone (1 mmol), and ammonium acetate (1.5 mmol).

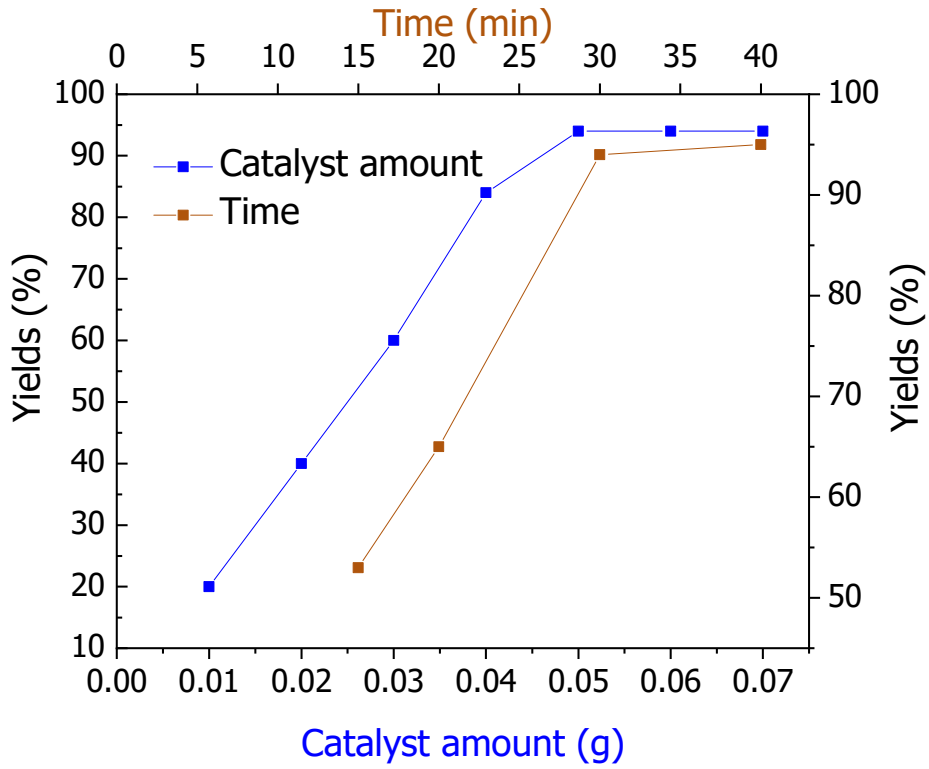


Figure 6. Influence of the amount of the $Na_2CaP_2O_7$ catalyst and reaction time on the synthesis of 2-amino-3-cyanopyridine **5a**.

2.5. Influence of Reaction Time

Temperature and time also play a significant role in reaction kinetics. In order to study the effect of these two parameters, a varied range of temperature (40–100 °C) was used to carry out the model reaction for different time periods (15–120 min) and by using 0.05 g of $Na_2CaP_2O_7$ (Table 1, entries 9–14). The first period, time ranges from 15 to 30 min, was characterized by significant changes in the yield of the product. During this period, the product yield increased by 12% after 5 min (from 15 to 20 min) and by 29% during the following 10 min (from 20 to 30 min). The highest yield (94%) was achieved at 80 °C after 30 min. The yield of **5a** remained unchanged even after extending the reaction time and increasing the temperature (Table 1, entries 11, 13, and 14).

2.6. Influence of the Solvent

The effect of the solvent on the reaction rate was also investigated by carrying out the model reaction in the presence of 0.05 g of $Na_2CaP_2O_7$ for 30 min with various solvents (1 mL), such as water, ethanol, dichloromethane (DCM), ethyl acetate (EtOAc), *n*-hexane, and acetonitrile (MeCN). Figure 2 summarizes the effects of various solvents on the percentage yield of 2-amino-3-cyanopyridine **5a**. We observed that when solvents were used, the yield decreased, indicating that the use of a solvent has a strong inhibitory effect on the reaction yield. This effect can be explained by the dilution of the reaction medium, which leads to a decrease in the interaction between the reactant and the catalyst ($Na_2CaP_2O_7$).

However, the highest yield of the desired product was achieved when the reaction was carried out under solvent-free conditions (Figure 7).

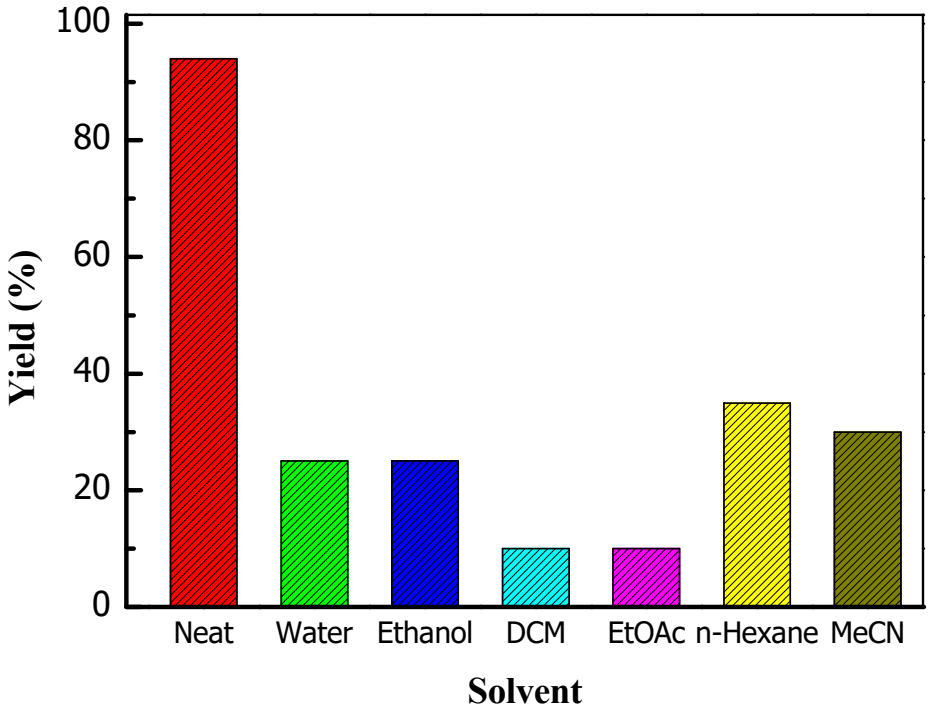
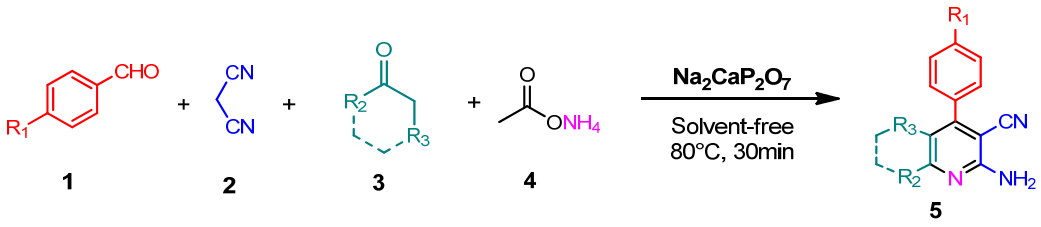


Figure 7. Influence of the solvent in the catalytic synthesis of 2-amino-3-cyanopyridine **5a**.

After determining the optimal conditions for the synthesis of 2-amino-3-cyanopyridine 5a, the reactions of different aromatic aldehydes containing substituents in the aromatic ring, such as Me, OMe, Cl, and NO_2, with malononitrile **2**, acetophenone derivatives, or cyclohexanone **3** and ammonium acetate **4** were carried out under identical reaction conditions. The thirteen desired 2-amino-3-cyanopyridine derivatives 5(a–m) were obtained with good to excellent yields (84–94%), as shown in Table 2. The nature of aromatic ring substituents had no noticeable effect on the yields of synthesized 2-amino-3-cyanopyridines 5. All reactions with aromatic aldehydes proceed without the formation of byproducts.

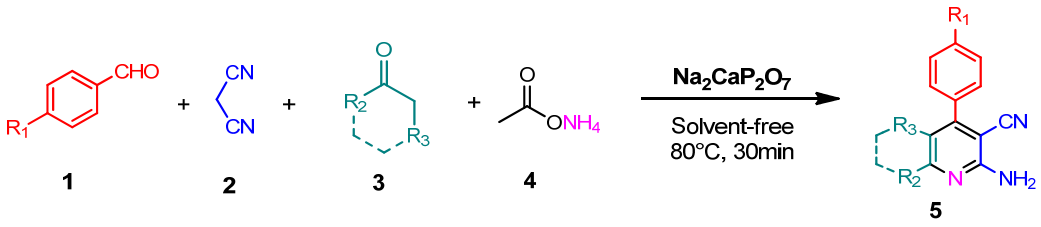
Table 2. Synthesis of 2-amino-3-cyanopyridine derivatives **5**.



1 2 3 4 5

Entry	R_1	R_2	R_3	Product [a]	Yield [b] (%)
1	H	Ph	H	**5a**	**94**
2	CH_3	Ph	H	**5b**	**85**
3	CH_3O	Ph	H	**5c**	**84**
4	Cl	Ph	H	**5d**	**95**
5	NO_2	Ph	H	**5e**	**86**
6	NO_2	Ph	H	**5f**	**93**

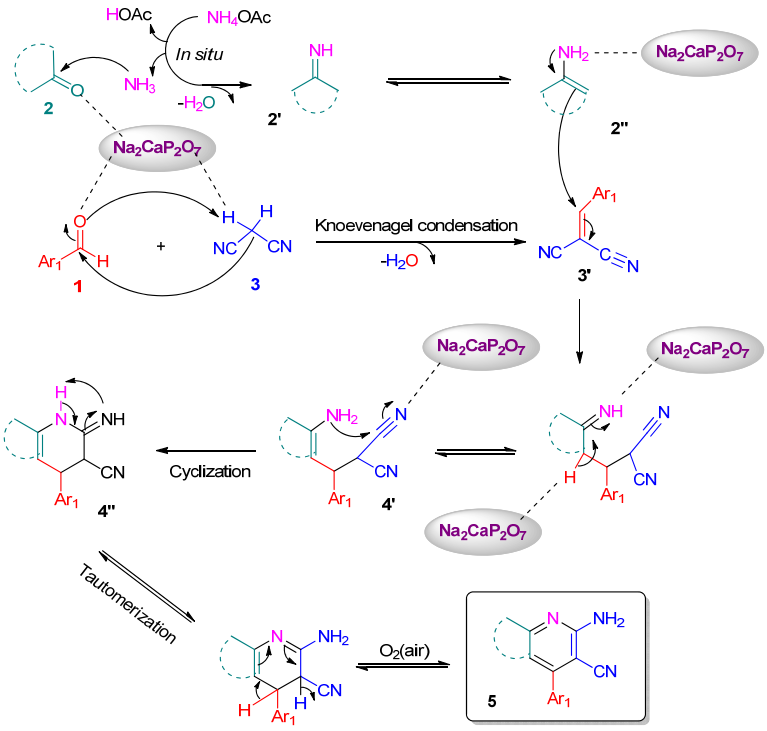
Table 2. *Cont.*



Entry	R_1	R_2	R_3	Product [a]	Yield [b] (%)
7	H	4-$CH_3C_6H_4$	H	**5g**	**92**
8	Cl	4-$CH_3C_6H_4$	H	**5h**	**90**
9	H	4-$CH_3OC_6H_4$	H	**5i**	**91**
10	Cl	4-$CH_3OC_6H_4$	H	**5j**	**89**
11	H	-$(CH_2)_4$-		**5k**	**94**
12	CH_3	-$(CH_2)_4$-		**5l**	**88**
13	Cl	-$(CH_2)_4$-		**5m**	**94**

[a] All products were characterized by ^1H, ^{13}C NMR, and IR spectral data (see Supplementary Data); [b] isolated yields.

In order to explain the formation of 2-amino-3-cyanopyridine 5, we propose a credible mechanism, which is shown in Scheme 3.



Scheme 3. Proposed mechanism for $Na_2CaP_2O_7$-catalyzed synthesis of 2-amino-3-cyanopyridine derivatives.

$Na_2CaP_2O_7$ catalyzes the synthesis of 2-amino-3-cyanopyridine derivatives **5** by activating the carbonyl group of aromatic aldehyde **1,** making it more susceptible to nucleophilic attack by malononitrile to form arylidenemalononitrile derivative **3′**, which reacted with imino derivative **2′**, which was formed by the reaction between ammonium acetate and ketone **2** via Michael addition to form adduct **4′**. Intermediate **4′** cyclized to dihydropyridine **4″**, followed by tautomerization aromatization to afford 2-amino-3-cyanopyridine derivative **5**. The proposed mechanism presented in Scheme 3 was confirmed by another mechanism reported in the literature [16,20].

2.7. Recyclability of $Na_2CaP_2O_7$ Catalyst

To investigate the recyclability and regeneration of the catalyst, $Na_2CaP_2O_7$ was regenerated by two procedures. In the first method, the catalyst was rinsed with acetone and dried for 1h at 100 °C after each experiment. The second method employed for regeneration involved calcination at 500 °C for 1 h after washing with acetone and drying at 100 °C. Figure 3 summarizes the reusability and regeneration research of $Na_2CaP_2O_7$. This result shows that calcination of the recovered catalyst at 500 °C has a positive effect on the catalytic activity of the diphosphate $Na_2CaP_2O_7$. The increase in catalytic activity upon calcination can be explained by the rearrangement of the active sites of the catalyst [32,33]. The recycled $Na_2CaP_2O_7$ revealed almost the same catalytic performance compared with the first run (Figure 8).

The importance of the prepared 2-amino-3-cyanopyridines is apparent through their reactions with formamide to form the corresponding pyrido[2,3-*d*]pyrimidines, which have received considerable attention in recent years due to their diverse biological and pharmacological activities, such as antibacterial [34], antiallergic [35], anti-inflammatory [36], anti-HIV [37], antihypertensive [38], and antitumor activity [39]. Pyrido[2,3-*d*] pyrimidine **6** was synthesized by reaction of 2-amino-3-cyanopyridines **5** with formamide (Scheme 4). Our study was focused on the synthesis of the pyrido[2,3-*d*]pyrimidine derivatives **6(b, c, g, h, j)** by the condensation of the 2-amino-3-cyanopyridines **5(b, c, g, h, j)** with formamide.

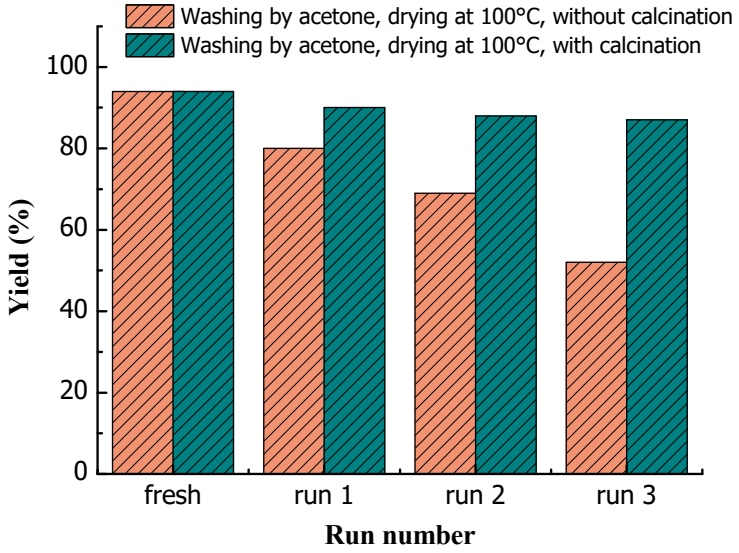
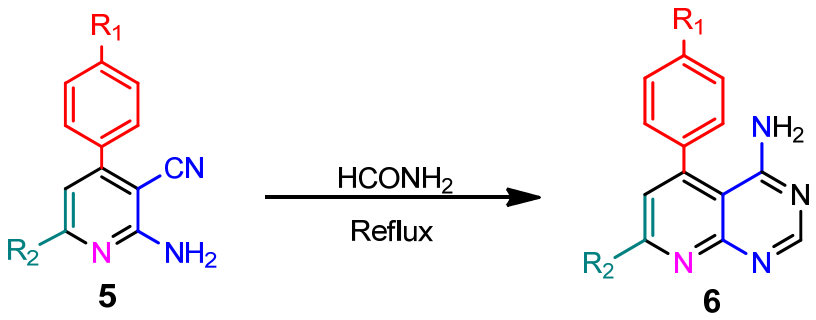


Figure 8. Recyclability and regeneration study of $Na_2CaP_2O_7$ in the synthesis of **5a**.



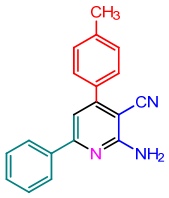
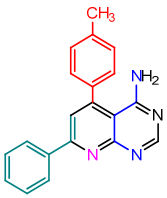
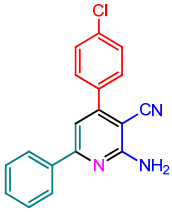
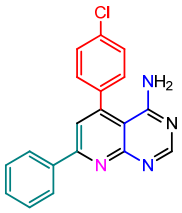
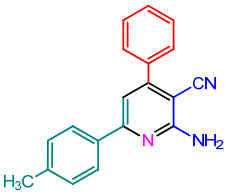
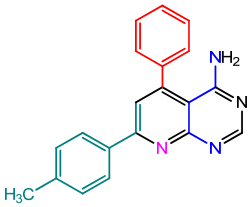
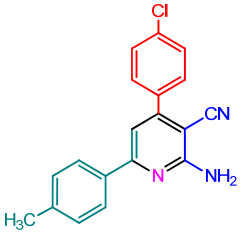
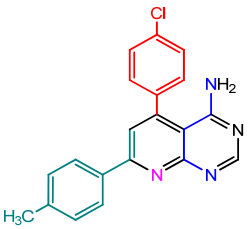
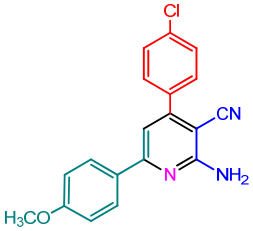
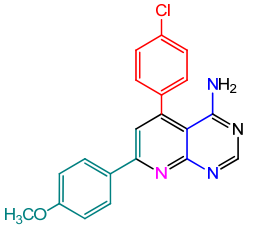
Scheme 4. Synthesis of pyrido[2,3-*d*]pyrimidine derivative **6**.

As mentioned below, the five pyrido[2,3-*d*]pyrimidine derivatives **6(b, c, g, h, j)** were obtained in moderate yields (71–81%), as shown in Table 3.

2.8. Antimicrobial Activity

Three derivatives, namely cyanopyridine (**5a** and **5b**) and pyrimidine (**6b**), revealed their effectiveness against Gram-positive and Gram-negative bacteria tested with minimum inhibitory concentrations (MIC) and minimum bactericidal concentration (MBC) values ranging from 64.5 to 250 µg/mL. Table 4 reports the inhibition zone diameter (IZD), MICs, and MBC values. In general, pyrimidine (**6b**) was the most active in comparison with the other components. It showed a strong effect against *S. aureus* and *B. subtillis*, with IZD values of 21–20.5 mm. Cyanopyridine (**5a** and **5b**) were less active against *S. aureus* and slightly less active against *B. subtillis*, with an IZD of 18.5 and 17 mm, respectively. Moreover, the MBC to MIC ratios calculated for the derivatives indicate that they are bactericidal rather than bacteriostatic molecules. Hence, the derivatives possessing a methyl group exhibited good antibacterial activity, as the methyl group is considered an electron-donating group, which increases the electron density, makes the compounds effective against micro-organisms, and enhances their antibacterial activity [40].

Table 3. Synthesis of pyrido[2,3-*d*]pyrimidine derivative **6**.

Entry	2-Amino-3-Cyanopyridine	Pyrido[2,3-*d*]pyrimidine [a]	Yield [b] (%)
1		**6b** 	**74**
2		**6c** 	**71**
3		**6g** 	**81**
4		**6h** 	**79**
5		**6j** 	**71**

[a] All products were characterized by ^{1}H, ^{13}C NMR, MS, and IR spectral data(see Supplementary Data); [b] isolated yields.

Table 4. Determination of the inhibition zone diameter of the synthesis of cyanopyridine derivatives (**5a**, **5b**) and pyrimidine (**6b**).

	Cyanopyridine 5a			Cyanopyridine 5b			Pyrimidine 6b		
	IZD (mm)	MIC (µL/mL)	MBC (µL/mL)	IZD (mm)	MIC (µL/mL)	MBC (µL/mL)	IZD (mm)	MIC (µL/mL)	MBC (µL/mL)
P. aeruginosa (−)	NS	-	-	NS	-	-	NS	-	-
S. aureus (+)	NS	-	-	NS	-	-	21	125	125
S. epidermidis (+)	NS	-	-	NS	-	-	NS	-	-
K. pneumonaie (−)	NS	-	-	NS	-	-	NS	-	-
B. subtillis (+)	18.5	64.5	64.5	17	64.5	125	20.5	64.5	64.5
E. coli (−)	13	125	125	12	125	250	12	125	125
E. feacalis (+)	NS	-	-	NS	-	-	NS	-	-
C. albicans	NS	-	-	NS	-	-	NS	-	-

NS: not susceptible; IZD: inhibition zone diameter; MIC: minimum inhibitory concentration; MBC: minimum bactericidal concentration.

3. Discussion

In this study, we synthesized thirteen cyanopyridines and five pyrimidines and screened for antibacterial activity in eight strains. We found that cyanopyridine derivatives (**5a** and **5b**) have an antibacterial effect against *E. coli* and *B. subtilis*. However, other synthesized molecules of the same family did not exhibit any antimicrobial effects against either bacteria or fungi at the tested concentrations **[41,42]**.

A single pyrimidine derivative (6b) showed antibacterial activity, probably due to the nature of the heterocycle. Our results are in agreement with other scientific findings [43] from studies on the antibacterial and antifungal effect of new pyrimidine derivatives based on benzothiazole by testing on bacterial strains (*S. aureus*, *E. coli*, *K. pneumonia*, and *P. aeruginosa*) and on the fungal agent *C. albicans*. These studies revealed that the derivatives exert an antibacterial and antifungal effect, which varies from one molecule to another, and some of the derivatives were found to have antibacterial effects on all the strains tested, as well as an antifungal effect against *C. albicans*. This effect can be influenced by aromatic substituents, in particular, those with electron-donating properties.

Several targets have been described for antibacterial agents, such as disruption of cell walls, membrane permeabilization, targeting of drug efflux pumps, targeting of R plasmids, and targeting quorum sensing, which plays an important role in regulating biofilms. Several studies showed that antibacterial agents tend to act more strongly on Gram-positive than on Gram-negative bacteria. This is probably due to the differences in cell wall composition and structure, as Gram-negative bacteria possess an outer membrane [44].

4. Conclusions

Based on the results obtained in the present study, we can conclude that $Na_2CaP_2O_7$ is a green and recoverable catalyst for the synthesis a series of 2-amino-3-cyanopyridine derivatives. In this paper, we reported the synthesis of five new pyrido[2,3-*d*]pyrimidine derivatives by intermolecular cyclization reaction of 2-amino-3-cyanopyridines with formamide. These synthesized products have a significant antibacterial effect. The absence of a solvent, simplicity of preparation, and the use of a green catalyst are some of the significant advantages of this ecofriendly procedure. Therefore, we suggest that $Na_2CaP_2O_7$ should receive increased attention in the future as an alternative catalyst for the one-pot synthesis of molecules known for their various biological and pharmacological activities.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app12115487/s1, The supporting information includes the experimental procedures, the materials used in this research work, and full characterization data for organic products. References [45–52] are cited in the supplementary materials.

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