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Synthesis of pyrazolopyranopyrimidines catalyzed by caffeine supported on boehmite nanoparticles and their evaluation for anti-bacterial activities

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ABSTRACT

The reaction of 3-chloropropyl boehmite nanoparticles with caffeine and sulfuric acid afforded BNPs-3-propyl-imidazolopyridinium hydrogen sulfate [BNPs-Caff]HSO_4 as a new BNPs-supported ionic liquid (IL) catalyst. [BNPs-Caff]HSO_4 proved to be an efficient heterogeneous catalyst for the synthesis of pyrazolopyranopyrimidines *via* a one-pot four-component reaction of hydrazine hydrate, ethyl acetoacetate, barbituric acid, and an aldehyde. The attractive features of this method are simple procedure, clean reaction, use of a reusable catalyst, easy workup, and performing a multi-component reaction (MCR) in water. A number of synthesized compounds were screened for their *in vitro* anti-bacterial activities against the Gram-positive and Gram-negative bacteria using a well-diffusion method.

***Keywords**: Boehmite nanoparticles, Reusable catalyst, Caffeine, Pyrazolopyranopyrimidine, Anti-bacterial activity.*

1. Introduction

Multicomponent reactions (MCRs) are powerful tools for the construction of novel and structurally complex molecules in a single-pot reaction with high atom-economy, high overall yields, short reaction times, minimum waste, and low cost of purification processes. Generally, these environmental friendly MCRs are used to produce a wide range of compounds with diverse functionalities [1-3]. Among these compounds, pyrano-pyrimidines and pyrano-pyrazoles have received considerable attention due to their pharmaceutical applications [4-9]. However, our extensive literature survey showed that there were only a few reports related to the preparation of pyrazolopyranopyrimidines [10-15]. Thus, we found it desirable to investigate the synthesis of these compounds. Recently, ionic liquids (ILs) have become powerful alternatives for the conventional organic solvents due to their particular dissolving abilities for different organic and inorganic substances [16]. In addition, ILs are readily recycled and are tunable to specific chemical tasks.

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Among different ILs, the Brønsted acidic ionic liquids [17-20] are environment friendly, efficient, and simple acid catalysts, which have been used in various organic transformations [21-23]. However, chemical industries still prefer to use heterogeneous catalysts owing to their easy separation and efficiency in comparison with the homogenous Ils [24,25].

Boehmite is aluminum oxide hydroxide (γ-AlOOH), which contains extra hydroxyl groups on its surface. Among different methods used for the preparation of boehmite nanoparticles (BNPs), the hydrothermal-assisted sol-gel technique has some advantages such as preparation in a one-pot process and processing at low temperatures. The most promising property of the hydrothermal-processed BNPs is the formation of a highly crystalline single-phase product with no organic residues [26,27]. Mirzaee et al. have recently reported the epoxidation of different olefins using oxosulfate vanadium(IV) and hexacarbonyl molybdenum complexes anchored onto the amine and/or Schiff base functionalized BNPs [28,29]. Recently, Ghorbani et al. have reported some heterocyclic synthetic reactions catalyzed by BNPs [30-33]. Our strategy for developing a versatile heterogeneous catalyst was based on the concept of immobilizing a Brønsted acidic ionic liquid onto the surface of BNPs. Caffeine

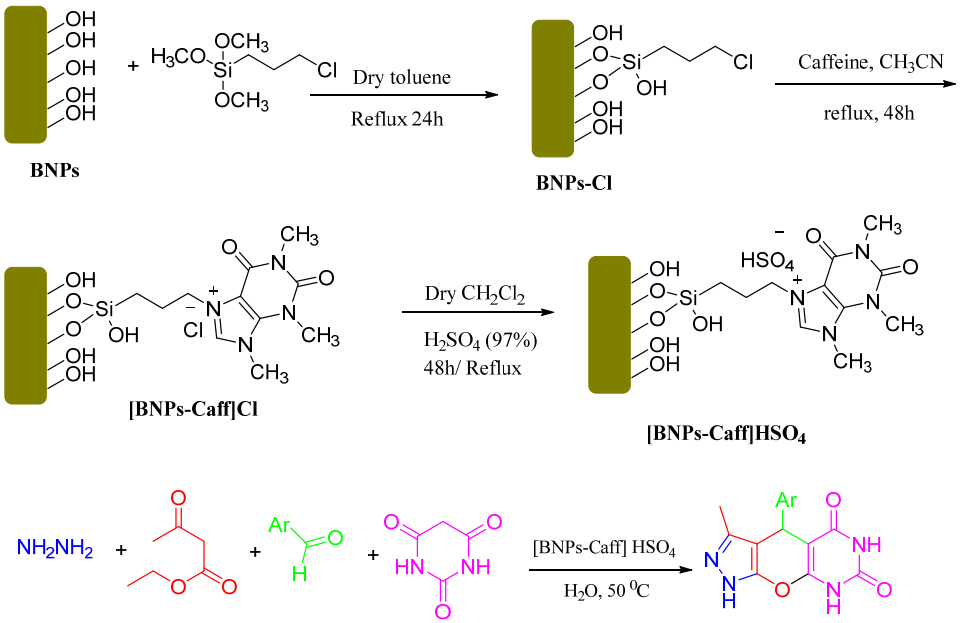
is a natural product, which can be found in more than 60 plant species whose biosynthesis results from the purine nucleotides [34]. It is a cheap source of N-methyl imidazole resulting from the decaffeination of coffee. The use of caffeine has been recently reported for the synthesis and structural characterization of N-heterocyclic carbenes [35-37] but, to the best of our knowledge, caffeine has not yet been used in the preparation of the reusable ILs. In this paper, we wish to report the supporting of caffeine acidic ILs onto the surface of BNPs, and their use for the synthesis of pyrazolo-pyrano-pyrimidines in water (Scheme 1).

2. Experimental

All the chemicals used were purchased from Merck or Fluka Chemical Companies. All the known compounds were identified by comparison of their melting points and ^{1}H NMR data with the corresponding data reported in the literature. NMR spectra were recorded on a Bruker Avance 300 MHz instrument. FT-IR spectra were obtained as potassium bromide pellets in the range of 400–4000 cm^{-1} on a Bomem MB series spectrometer. Powder X-ray diffraction (XRD) patterns were collected using a Philips PW-1800 or STOE diffractometer with Cu Kα radiation. Elemental analyses were performed using a Thermo Finnigan Flash EA microanalyzer. Electron microscopy was performed with a JEOL JSM-6360LV transmission electron microscope. Morphology of the products was determined using Hitachi Japan, model s4160 Scanning Electron Microscopy (SEM) at an accelerating voltage of 15 KV.

2.1. Preparation of BNPs-3-propyl-imidazolopyridinium hydrogen sulfate ([BNPs-Caff]HSO$_4$)

Aluminium 2-butoxide was prepared according to the general method reported for the synthesis of aluminium alkoxides. Then, it was used for the preparation of BNPs as reported earlier. [26] To 1.0 g of the prepared BNPs powder in a 100 mL round-bottom flask were added 50 mL of anhydrous toluene and 1.97 g (10 mmol) of (3-chloropropyl) trimethoxysilane. The solution was refluxed for 24 h under an inert atmosphere and the obtained powder was filtered off, washed with toluene (3 × 20 mL) and methanol (3 × 20 mL), and dried in vacuum at 100 °C for 10 h. The dry white solid obtained (1.0 g) was then refluxed with caffeine (1.36 g, 7.0 mmol) in 30 mL of CH_3CN at 80°C for 48 h. The resulting solid product was filtered off, washed with toluene (3 × 20 mL) and acetone (3 × 20 mL), and dried in vacuum at 100°C for 12 h to obtain [BNPs-Caff]Cl. The loading level of caffeine was determined by potentiometric titration of the chlorine content. For this purpose, 0.03 g of the sample was added to 5.0 mL of deionized water and titrated by Ag^+ standard solution. The results showed that the loading level of caffeine was 0.24 mmol g^{-1}. Also, the nitrogen content of this compound was found to be 1.4% by the elemental analysis.



Scheme 1. Preparation of [BNPs-Caff]HSO_4 and the synthesis of pyrazolopyranopyrimidines catalyzed by [BNPs-Caff]HSO_4.

Then, 1.0 g of [BNPs-Caff]Cl was dispersed in 30 mL of dichloromethane, and sulfuric acid (98.99%) (0.1 g, 1 mmol) was added to this suspension. After stirring the mixture reaction for 24 h at 60°C, the [BNPs-Caff]HSO_4 powder obtained was filtered off and washed with dichloromethane (3 × 20 mL), and acetone (3 × 20 mL) respectively, to remove the unreacted compounds, and then dried at 80°C overnight. Elemental analysis showed the sulfur content to be 0.23%. According to sulfur content, the number of H^+ sites of [BNPs-Caff]HSO_4 is 0.07 mmol/g. Furthermore, this result was confirmed by back-titration analysis of the catalyst.

2.2. General procedure for preparation of pyranopyrazolopyrimidine derivatives (5)

Hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), aldehyde (1.0 mmol), and barbituric acid (1.0 mmol) were added to a 25 mL round-bottom flask containing [BNPs-Caff]HSO_4 (0.1 g) and water (5.0 mL). The resulting mixture was stirred at 50°C. After completion of the reaction, the mixture was cooled to room temperature. The resulting precipitate was filtered off, dried and then dissolved in hot EtOH to separate the [BNPs-Caff]HSO_4 catalyst. The pure pyranopyrazolopyrimidine product was obtained after being washed with EtOH. In order to recover the catalyst, the separated catalyst was washed with acetone (5 mL) twice and reused after drying.

2.3. Biological method: Antibacterial assay

The anti-bacterial activity of the understudied pyranopyrazolopyrimidines was evaluated using a well-diffusion method. First, the nutrient agar and nutrient broth cultures were prepared according to the manufacturer's instructions, and were then incubated at 37°C. After incubation for an appropriate time period, a suspension of 30 µL of each bacterium was added to the nutrient agar plates. Cups (5 mm in diameter) were cut in the agar using a sterilized glass tube. Each received well 30 µL of the test compounds at a concentration of 1000 µg/mL in DMSO. Then, the plates were incubated at 37°C for 24 h, after which time the inhibition zone was measured; the values were expressed in mm. The anti-bacterial activities of the pyranopyrazolopyrimidines were compared with those of Penicillin G and tetracycline as the standards. DMSO was used as a negative control.

3. Results and Discussion

BNPs were prepared according to the reported procedure [26] and were then reacted with (3-chloropropyl) trimethoxysilane in refluxing toluene for 24 h. The BNP-bonded n-propylchloride was then reacted with caffeine in acetonitrile at 80°C for 48 h to afford [BNPs-Caff]Cl. Subsequently, sulfuric acid was added and resulting mixture was stirred for 24 h at 60°C. Finally, [BNPs-Caff]HSO_4 was filtered off and dried at 80°C overnight.

Fig. 1 shows the XRD patterns of BNPs and [BNPs-Caff] HSO_4 IL catalyst. Comparison of these patterns confirmed the retention of boehmite structure after preparation of the catalyst, and calculation of the particle size according to the Scherer equation showed 10-nm particles for the BNPs (Fig. 1) and the [BNPs-Caff]HSO_4. This was also confirmed by the transmission electron microscopy images of BNPs and the [BNPs-Caff]HSO_4 (Fig. 2). In these images, needle-shaped BNPs were seen with over 50 nm length and up to 10 nm width. The effective surface area of BNPs was 326 m^2 g^{-1} according to the BET experiments.

The FT-IR spectra for the BNP-bonded n-propylchloride (a) and BNPs-bonded n-propyl caffeine hydrogen sulfate [BNPs-Caff]HSO_4 (b) are shown in Fig. 3. A broad band was observed in the range of 3444-3336 cm^{-1} in both samples, which was assigned to the O-H stretching vibration. The C-H stretching vibration of BNP-bonded n-propyl chloride was also observed in 2954 cm^{-1}. In addition, the characteristic bands for BNPs were observed in 1068, 771, and 486 cm^{-1}, which were assigned to the stretching and bending vibrations of its Al–OH. Moreover, the band at 1631 cm^{-1} for the BNP-bonded n-propyl chloride was assigned to the bending vibration of the adsorbed water. Attachment of caffeine onto the BNP-bonded n-propyl chloride was confirmed by the appearance of new bands at 1704, 1650, and 1550 cm^{-1} due to the C=O, C=N, and C=C stretching vibrations, respectively.

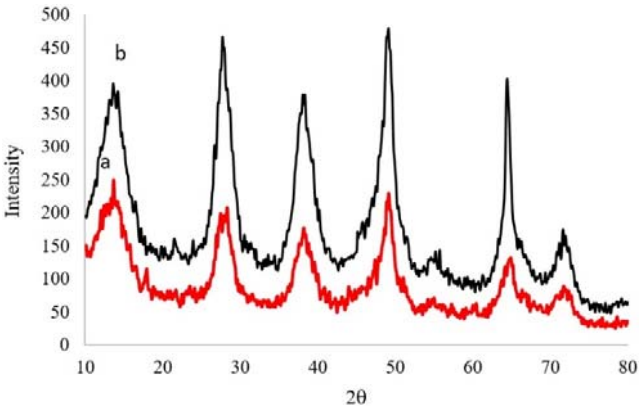


Fig. 1. XRD patterns of BNPs (a) and [BNPs-Caff]HSO_4 (b).

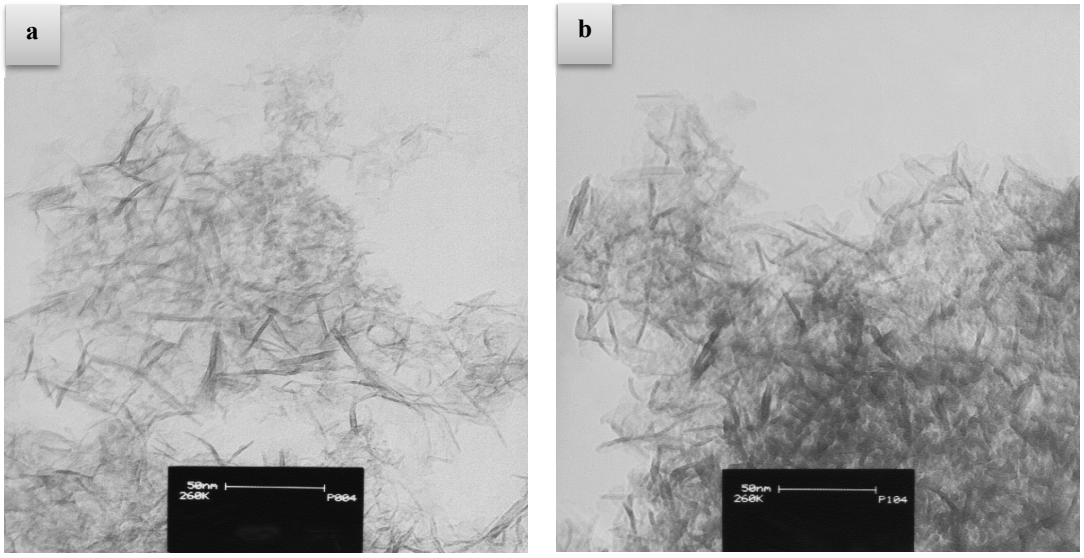


Fig. 2. Transmission electron microscope image of BPN (a) and [BNPs-Caff]HSO_4 catalyst (b).

The morphology of BNPs and the acidic IL catalyst were investigated by scanning electron microscopy (SEM) (Fig. 4). The comparison of their SEM images showed that the reaction procedure for the preparation of [BNPs-Caff]HSO_4 from BNPs did not change the size and morphology of the particles.

Moreover, Fig. 5 shows the TG/DTG thermogram of the [BNPs-Caff]HSO_4 catalyst. There were two important weight-loss regions in the TG curve. The first one was in the temperature range of 150-350ºC, which was accompanied by three endothermic peaks in the TGA curve that could be related to the decomposition of the organic residue onto the surface of BNPs. The other weight loss was observed in the temperature range of 550-750ºC, which was accompanied by another peak in the TGA curve, which was related to the dehydroxylation of boehmite and crystallization of γ-alumina.

To assess the efficacy and scope of our new catalyst, initially, the synthesis of the pyranopyrazolopyrimidine derivatives *via* the four-component reaction of hydrazine hydrate, ethyl acetoacetate, barbituric acid and an aldehyde was studied. To optimize the reaction conditions, condensation of hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol), and barbituric acid (1.0 mmol) was selected as a model reaction (Table 1).

The above four-component reaction was carried out at 50ºC in water in the absence of any catalyst to establish the real efficacy of the [BNPs-Caff]HSO_4 catalyst. As shown in Table 1, only a low product yield was obtained even after the reaction time was prolonged to 3 h (Table 1, entries 1-3). To compare the effects of catalyst loadings, temperature, and solvent on the reaction, various parametric investigations were carried out.

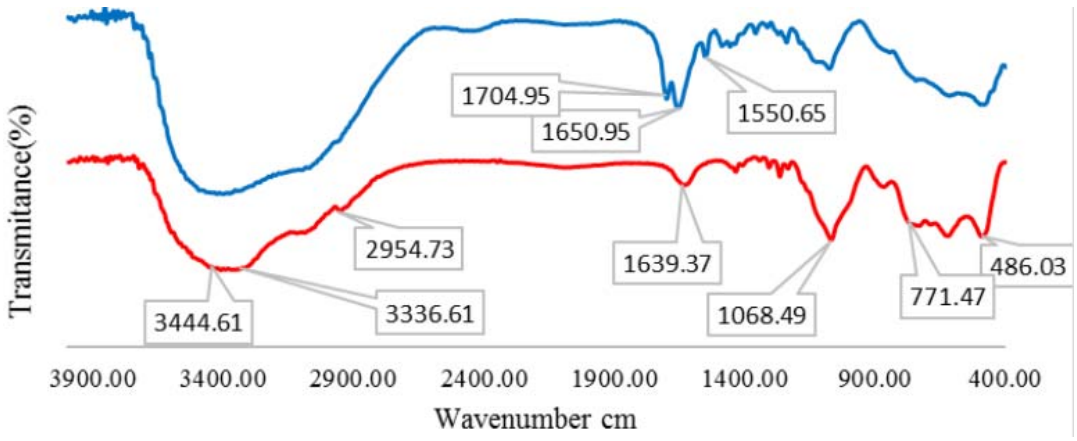


Fig. 3. FT-IR spectra of BNPs-bonded n-propylchloride (a) and [BNPs-Caff]HSO_4 (b).

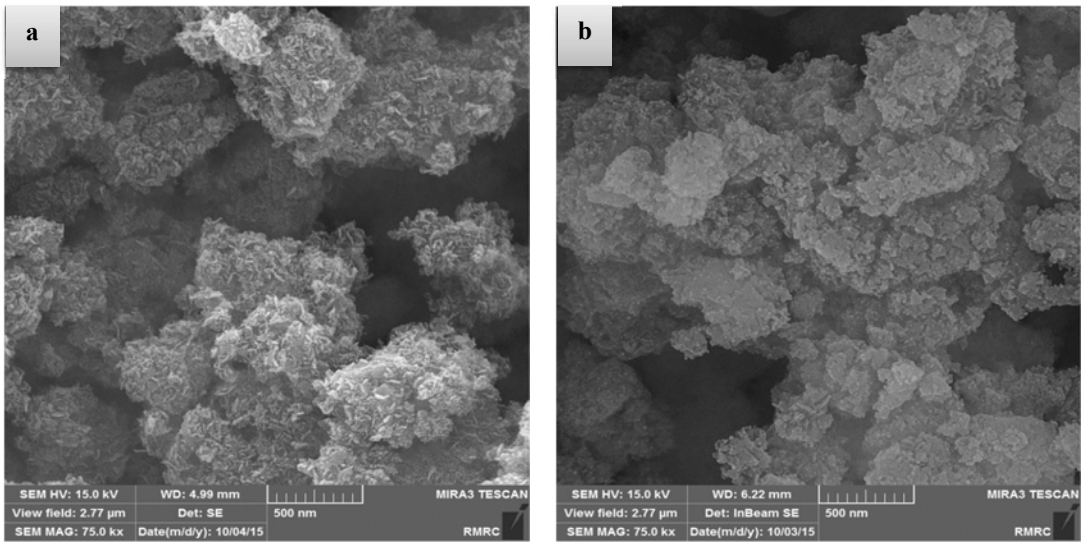


Fig. 4. Scanning electron micrograph of BNPs (a) and [BNPs-Caff]HSO_4 (b).

The model reaction was examined in the presence of different molar ratios of [BNPs-Caff]HSO_4 in water at 50ºC. As Table 1 indicates, a higher yield and a shorter reaction time was obtained when the reaction was carried out in the presence of 0.1 g of the catalyst in water; under these conditions, the corresponding pyranopyrazolopyrimidine **5a** was produced in 98% yield within 40 min (Table 1, entry 5). Increasing the amount of the catalyst to 0.3 g showed no substantial improvement in the reaction yield (Table 1, entry 6), whereas the yield decreased by decreasing the amount of catalyst to 0.05 g (Table 1, entry 4).

Also, the effect of temperature on the conversion was checked, and the results obtained were tabulated in Table 1. It is obvious that at room temperature, a low product yield was formed (Table 1, entry 7). With increase in the temperature from room temperature to 70ºC, the product yields were found to increase. We obtained the best results at 50ºC (Table 1, entry 5).

The model reaction was also examined in the presence of [BNPs-Caff]HSO_4 at 50ºC in several solvents including EtOH, MeOH, $CHCl_3$, CH_3CN, THF, and DMF (Table 1 entries 9-14). Among all these solvents, H_2O was found to be the best one, affording the highest product yield (Table 1, entry 5). Moreover, when the reaction was carried out under solvent-free conditions, the target product was obtained with a low yield (Table 1, entry 15).

After optimization of the reaction conditions, a broad range of structurally-diverse aldehydes (**3**) were reacted with barbituric (**4**), ethyl acetoacetate (**2**), and hydrazine hydrate (**1**) in the presence of [BNPs-Caff]HSO_4 at 50 ºC to furnish the corresponding products in high yields and in short reaction times (Table 2). As shown in Table 2, variation in the electronic properties and the position of functional groups on the aromatic ring of the aldehyde did not show an obvious impact on the reaction yield.

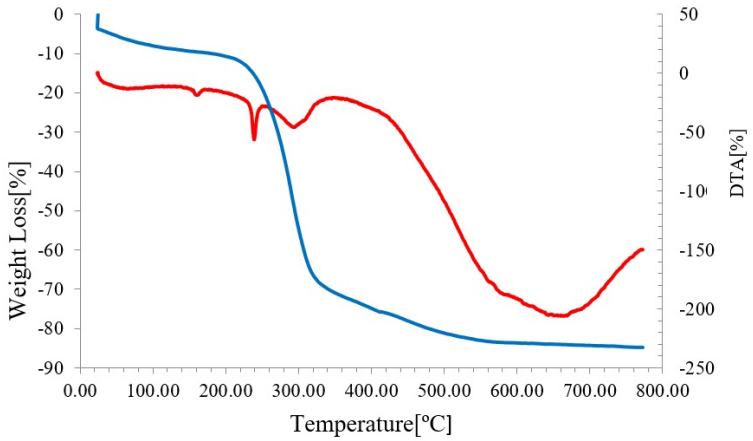


Fig. 5. TGA diagram of [BNPs-Caff]HSO_4 catalyst (blue line), DTA diagram of [BNPs-Caff]HSO_4 catalyst (red line).

Table 1. Investigation of catalyst effect, solvents, and temperature in the synthesis of pyranopyrazolopyrimidine **5a**.[a]

Entry	Solvent	Catalyst (g)	Temp(ºC)	Time (min)	Yield (%)[b]
1	H_2O	-	50	180	30
2	H_2O	-	70	180	32
3	H_2O	-	100	180	35
4	H_2O	0.05	50	70	87
5	H_2O	0.1	50	40	98
6	H_2O	0.3	50	40	98
7	H_2O	0.1	r.t	150	20
8	H_2O	0.1	70	40	97
9	EtOH	0.1	50	110	45
10	MeOH	0.1	50	110	75
11	$CHCl_3$	0.1	50	150	77
12	CH_3CN	0.1	50	110	87
13	THF	0.1	50	180	trace
14	DMF	0.1	50	180	20
15	neat	0.1	80	30	65

[a]Reaction conditions: Hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol) benzaldehyde (1.0mmol), barbituric acid (1.0 mmol), solvent (5 mL).
[b]Isolated yield.

Furthermore, the steric effects of the substituents at the ortho-position of the aromatic aldehyde did not have an obvious impact on the reaction yield. In addition, the presence of three electron-donating methoxy groups on the aromatic ring of the aldehyde afforded the desired product in 87% yield (Table 2, entry 16). Notably, [BNPs-Caff]HSO_4 efficiently catalyzed the reaction when hetero-aromatic aldehydes were used (Table 2, entries 18-20).

A Plausible mechanism for the synthesis of pyrazolopyranopyrimidine **5a** from ethyl acetoacetate, hydrazine hydrate, benzaldehyde, and barbituric acid catalyzed by [BNPs-Caff]HSO_4 is shown in Scheme 2.

3-Methyl-1H-pyrazol-5(4H)-one (I) was formed by condensation of ethyl acetoacetate and hydrazine, which was converted to its corresponding enolate form (II) in the presence of [BNPs-Caff]HSO_4. The acidic catalyst, played a major role for the formation of intermediate (III) by the Knoevenagel condensation of benzaldehyde and barbituric acid. Subsequently, intermediate (II) was reacted with Knoevenagel condensate (III) through a Michael addition reaction to produce intermediate (IV), which underwent an intramolecular cyclization by the nucleophilic addition of the enolate oxygen to the carbonyl group to afford intermediate (V). The catalyst [BNPs-Caff]HSO_4 could assist intermediate (V) to lose a water molecule and provide the target product 5a.

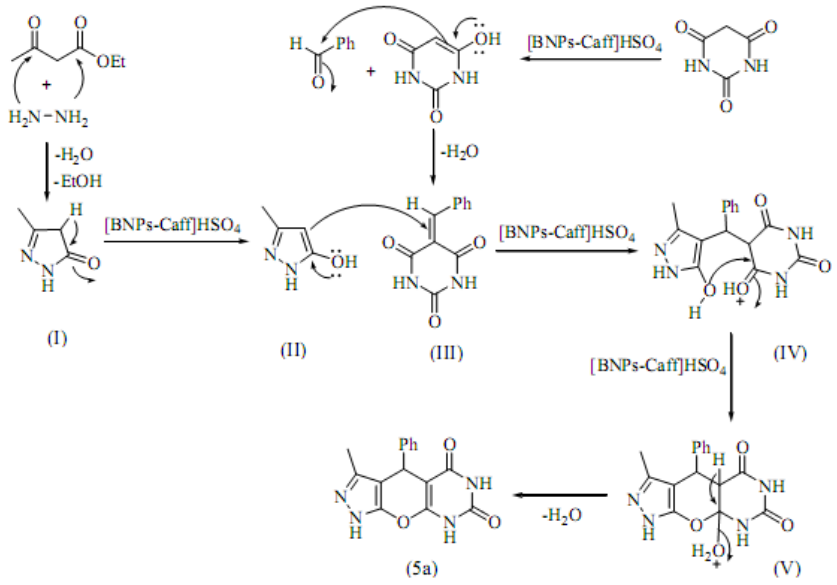
The catalyst separation from the product is a key problem within the development of a sustainable commercial process. It is of great interest to recover and reuse costly and/or toxic catalysts for economic and environmental reasons as well as to reduce the amount of the catalyst or its components in many products in order to respect the defined specifications. The reusability of [BNPs-Caff]HSO_4 was tested for the reaction of ethyl acetoacetate, hydrazine hydrate, barbituric acid, and benzaldehyde in water (5 mL) at 50ºC. After completion of the reaction, the mixture was cooled, and the resulting precipitate was filtered, dried, and dissolved in hot EtOH to separate the catalyst. Then, the catalyst was washed with acetone, dried, and successfully used for the next run under identical reaction conditions. The yields for five runs was 95, 93, 92, 90 and 88 %, respectively.

Shamroukh et al. [38] have studied the anti-bacterial activities of several pyrazolopyranotriazolo pyrimidines, which showed moderate anti-bacterial activities against *B. subtilis* and some other microorganisms. Products 5d, 5h, 5l, 5p, 5r, and 5s

Table 2. Synthesis of pyranopyrazolopyrimidines.[a]

Entry	Ar	Product	Time (min)	Yield (%)[b]	m.p. (ºC)		Ref.
					Found	Reported	
1	Ph	**5a**	40	95	217-219	218-220	[11]
2	4-OH-C_6H_4	**5b**	40	90	264-266	263-265	[12]
3	4-Me-C_6H_4	**5c**	55	87	201-203	200-201	[10]
4	4-MeO-C_6H_4	**5d**	60	92	226-228	228-230	[11]
5	2-MeO-C_6H_4	**5e**	50	85	231-233	230-231	[11]
6	4-Me_2N-C_6H_4	**5f**	50	93	258-260	260-262	[11]
7	4-Cl-C_6H_4	**5g**	45	92	220-222	222-223	[11]
8	2-Cl-C_6H_4	**5h**	40	90	224-226	223-225	[11]
9	2,4-$Cl_2C_6H_3$	**5i**	50	87	234-236	233-234	[11]
10	2,6-$Cl_2C_6H_3$	**5j**	80	90	194-196	-	-
11	4-Br-C_6H_4	**5k**	65	92	209-211	211-212	[11]
12	2-NO_2-C_6H_4	**5l**	85	90	208-210	208-209	[11]
13	3-NO_2-C_6H_4	**5m**	40	88	264-266	266-267	[11]
14	4-NO_2-C_6H_4	**5n**	40	95	233-235	233-234	[11]
15	4-CHO-C_6H_4	**5o**	55	85[c]	166-168	-	-
16	2,3,4-$(OMe)_3$-C_6H_2	**5p**	50	87	195-197	193-194	[11]
17	3,5-$(OMe)_2$-4-OH-C_6H_2	**5q**	70	93	240-242	-	-
18	2'-Furanyl	**5r**	75	87	288-290	-	-
19	2'-thiophenyl	**5s**	65	85	173-175	176-177	[11]
20	2-chloro quinoline	**5t**	45	94	235-237	-	-

[a]Reaction conditions: Hydrazin hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), aldehyde (1.0 mmol), barbituric acid (1.0 mmol), catalyst (0.1 g), H_2O (5 mL), 50ºC.
[b]Isolated yield.
[c]Disubstituted product.



Scheme 2. Plausible mechanism for synthesis of pyrazolopyranopyrimidine **5a**.

were screened for their *in vitro* anti-bacterial activity against the Gram-positive and Gram-negative bacteria strains including Micrococcus luteus (*M. luteus*), Staphylococcus aureus (*S. aureus*), and Bacillus subtilis (*B. subtilis*) using a well-diffusion method. DMSO, used as negative control, showed no activity against the above-mentioned bacterial strains. Penicillin G and tetracycline were used as the positive controls (Table 3). The pyranopyrazolopyrimidines 5d, 5h, 5l, 5p, 5r, and 5s were evaluated for their anti-bacterial activities at a concentration of 1000 µg/mL in DMSO. According to the results obtained, 5d, 5h, 5l, and 5p were active against all the three bacterial strains, and 5h had the highest anti-bacterial activity against *M. luteus*. Compound 5d was more active against S. aureus, and also showed a significant inhibition activity against *M. luteus* and *B. subtilis*. In addition, 5p showed a significant inhibition activity *against B. subtilis.*

A comparative study of the reaction conditions for the synthesis of pyranopyrazolopyrimidine **5a,** using the methods given in Table 4 and reported in the present paper, demonstrates the advantages of the present methodology. For example, most of the listed methodologies suffer from some limitations such as prolonged reaction times, and elevated temperatures.

4. Conclusion

We introduced a novel heterogeneous boehmite nanoparticles-supported ionic liquid (IL) catalyst, BNPs-3-propyl-imidazolopyridinium chloride ([BNPs-Caff]HSO_4, from caffeine and boehmite nanoparticles using a simple method. The catalytic activity of this IL catalyst was probed through a one-pot synthesis of pyrazolopyranopyrimidines *via* a one-pot four-component reaction of hydrazine hydrate, ethyl acetoacetate, barbituric acid, and an aldehyde. In addition, this methodology offered the competitiveness of recyclability of the catalyst, and the catalyst could be readily recovered by a simple filtration and reused for 5 cycles, and thus making the procedure environmentally more friendly. A number of synthesized compounds were screened for their *in vitro* anti-bacterial activities against the Gram-positive and Gram-negative bacteria using a well-diffusion method.

Acknowledgments

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Table 3. Antibacterial activity of pyranopyrazolopyrimidine (1000µg/mL) as zone of inhibition in milimeter.

Compound	*M. Luteus*	*S. Aureus*	*B. Subtilis*
5d	18	25	18
5h	21	17	11
5l	14	12	13
5p	10	13	15
5r	13	-	7
5s	10	-	-
DMSO[a]	-	-	-
Penicilline G[b]	65	47	18
Tetracycline[b]	50	33	37

[a]Negative control.
[b]Positive control.

Table 4. Comparison of protocols for synthesis of pyranopyrazolopyrimidine.

Entry	Catalyst	Solvent	temperature	Time	Yields (%)	Ref.
1	DABCO (20 mol %)	H_2O	reflux	20 min	99	[10]
2	Meglumine(0.1mmol)	H_2O	rt	15 min	90	[11]
3	TiO_2 NWs (10mol %)	EtOH/H_2O(1:1)	reflux	60min	95	[12]
4	OMWCNTs (0.005g)	EtOH/H2O(1:1)	reflux	70	94	[13]
4	Oleic acid	H_2O	reflux	12 h	82	[14]
5	MNPs@$DABCO^+Cl^-$	Solvent-free	80	5 min	95	[15]
6	[BNPs-Caff]HSO_4 (0.1gr)	H_2O	50	40 min	95	This work

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