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FULL PAPER

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Bi_2O_3/FAp, a sustainable catalyst for synthesis of dihydro-[1,2,4]triazolo[1,5-a]pyrimidine derivatives through green strategy

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The bismuth loaded on fluorapatite (Bi_2O_3/FAp) proved to be an excellent catalyst for the synthesis of novel dihydro-[1,2,4]triazolo[1,5-a]pyrimidine derivatives via a three-component reaction involving the mixture of 1*H*-1,2,4-triazol-5-amine, ethyl cyanoacetate or ethyl acetoacetate, and different benzaldehydes in ethanol at room temperature. The catalyst material was characterized by X-ray diffraction, Brunauer–Emmett–Teller surface area analysis, Fourier-transform infrared, scanning electron microscopy, energy-dispersive X-ray spectroscopy, and transmission electron microscopy techniques. The efficacy of Bi_2O_3/FAp as a heterogeneous catalyst was evaluated with the loading of different wt% of bismuth on FAp. The 2.5% bismuth on FAp performed extremely well as a catalyst with a high yield of products (92%–96%) in a short reaction time (25–35 min). The catalyst was recovered by simple filtration. It showed undiminished activity up to five runs. Simple work-up, room temperature reaction, short reaction time, high yields, no column chromatography, and good reusability of catalyst are the merits of the proposed protocol. In addition, this process offers 100% carbon efficiency and 98% atom economy with noteworthy fiscal and environmental benefits.

KEYWORDS

Bi_2O_3/FAp, dihydro-[1,2,4]triazolo-pyrimidine, ethanol medium, green methods, MCRs

1 | INTRODUCTION

Advances in the design of efficient reusable heterogeneous catalysts for organic synthesis and valued conversions of target bicyclic compounds obeying green conditions are cherished goals, with respect to the pharmaceutical industry and production.[1] In the past decade, heterogeneous catalysts gained importance in chemical science because of their high stability, activity, selectivity, and tunable properties. Heterogeneous catalysts offer a broad spectrum of applications, including diverse sustainable methods in synthetic chemistry, reaction intermediates for refinery operations, fine chemicals, and for other purposes.[2] Fluorapatite (FAp) is a cheap and eco-friendly material with the capability to form solid solutions and to accept varied cationic and anionic substituents.[3] In addition, because of the outstanding ion exchangeability with various metal ions, it can be used to formulate highly stable and supported metal catalysts with vastly dispersed and tunable acid–base properties.[4] Therefore, FAp $[Ca_{10}(PO_4)_6F_2]$ and metal-doped/modified FAp catalysts are becoming progressively valuable in organic synthesis as catalysts, primarily owing to their high stability,

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presence of both Lewis/Bronsted acidic and basic sites, and easy separation from reaction mixture through simple filtration.[5] Many FAp-based heterogeneous catalysts have demonstrated significant catalytic activity for the construction of C–C and C–N bond-forming organic reactions due to the presence of both acidic and basic sites.[6,7] In addition, FAp has a special position in many biomedical applications.[8] Among the various metal ions, bismuth (Bi^{3+}) occupies a distinct place as a catalyst due to its vacant d-shell and Lewis acid nature.[9] Moreover, as it helps to stabilize the intermediates in reactions, it has various applications as a catalyst in multicomponent condensation, oxidation, and cycloaddition reactions.[10,11]

Multicomponent reaction (MCR) is a powerful tool in synthetic organic chemistry and drug discovery programs, as it can be utilized for the creation of libraries of bioactive scaffolds. The development of combinatorial synthesis by utilization of MCRs has created a sustainable means for organic synthesis that focuses on the atom economy and environmental safety. MCRs with ecologically benign solvents and efficient, reusable heterogeneous catalysts are the utmost targets for the scientific community.

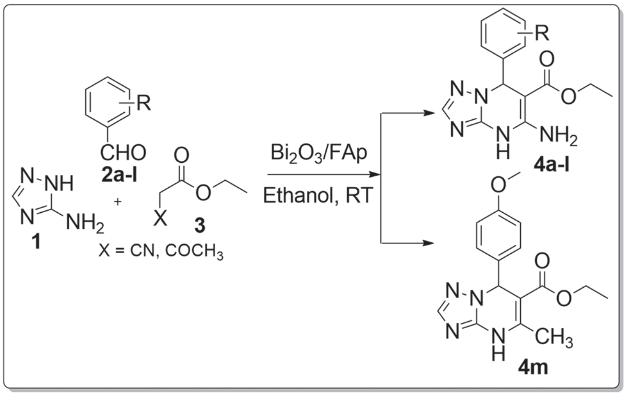
The dihydro-^{1,2,4}triazolo-pyrimidines are bicyclic *N*-heteroarenes and these structural analogs are versatile synthetic building blocks in various drug molecules.[12] Development of methods for dihydro-[1,2,4]triazolo-pyrimidines synthesis has received incredible attention of synthetic chemists for their broad spectrum of biological and pharmacological profiles, which include anticancer, antibacterial, antiproliferative, anti-HIV, and fungicidal activities.[13–18] Most synthetic protocols involved the MCR between active methylene substrate, aldehyde, and various amine compounds in the presence of different heterogeneous catalysts, bases, and solvents to synthesize bioactive core moieties.[19,20] In recent years, there is considerable interest toward the developing synthetic protocols for new dihydropyrimidine scaffolds. Various materials including $[DABCO](SO_3H)_2(Cl)_2$, $[DABCO](SO_3H)_2(HSO_4)_2$, $[H_2\text{-}DABCO][ClO_4]_2$, thiamine-HCl, $\gamma\text{-}Fe_2O_3@NaHSO_4$ nanocatalyst, and Nafion-H have been explored as catalysts in this regard.[21–25] Recently, Sumathi and Gopal accomplished Biginelli condensation of dihydropyrimidinone derivatives in a one-pot approach using bismuth-substituted FAp [$BiNaCa_4(PO_4)_3F$] at reflux condition. The use of hazardous acetonitrile solvent and nonreusability of the material were drawbacks associated with this protocol.[26] Not many studies on the use of bismuth-loaded FAp as a heterogeneous catalyst have been reported. Therefore, there is a void in finding of novel high-atom-economy green methodologies.

In our continued efforts to develop novel and green approaches, previously we have reported few efficient synthetic methods involving recyclable catalysts for different bioactive heterocycles.[27,28] Herein, we report the one-pot protocol for the synthesis of novel dihydro-[1,2,4]triazolo[1,5-a]pyrimidines by using an efficacious, recyclable Bi_2O_3/FAp heterogeneous catalyst in ethanol medium. The reaction proceeded with excellent catalytic activity with high yields for short reaction time (Scheme 1). The catalyst material was fully characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Brunauer–Emmett–Teller (BET), and Fourier-transform infrared (FT-IR) spectroscopic analysis.

2 | EXPERIMENTAL SECTION

2.1 | General remarks

All the chemicals and reagents used for the reaction were of analytical grade and utilized without any further purification. Bi_2O_3, $Ca(NO_3)_3 \cdot 4H_2O$, $Na_3PO_4 \cdot 12H_2O$, and NaF were purchased from Merck and Sigma-Aldrich dealers, Durban, South Africa. For the synthesized compounds, the structural elucidation was performed using nuclear magnetic resonance (NMR) spectral analysis by recording the spectral values of ^1H and ^{13}C NMR spectrum (Bruker AMX 400 MHz NMR spectrometer). Chemical shift values are reported in δ (ppm), with tetramethylsilane as the internal standard and dimethyl sulfoxide-d_6 as the solvent. Thin-layer chromatography (TLC)-aluminum plates coated with silica gel (Merck Kieselgel 60 F_{254}) were used to confirm the completion of reaction initially. The Bruker micro-TOF-Q II electrospray ionization (ESI) instrument functioning at ambient temperature was used for obtaining high-resolution mass spectrometry (HRMS) data. The JEOL JSM-6100 microscope and JEOL JEM-



SCHEME 1 Synthesis of dihydro-1,2,4-triazolo-pyrimidine derivatives (**4a–m**). RT, room temperature

1010 electron microscope were employed for obtaining SEM, energy-dispersive X-ray spectroscopy (EDX), and TEM morphology data. XRD data associated with the structural phases of the material were obtained using the Bruker D8 Advance instrument (Cu-K radiation source with a wavelength of 1.5406 Å). Materials were degassed by passing nitrogen overnight at 200 °C and Barrett–Joyner–Halenda (BJH) adsorption and desorption curves were obtained at −196 °C. Surface area, pore size, and pore volume of the material were established using a porosity and surface area analyzer (Micromeritics Tristar-II).

2.2 | Bi_2O_3/FAp catalyst preparation

Various weight percentages (1, 2.5, and 5 wt%) of bismuth-loaded FAp were prepared by adopting the procedure reported previously.[29] Trisodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$; 1.5 mmol) was dissolved in 25 mL of deionized water in 50 mL of the beaker. To this solution, sodium fluoride (0.5 mmol) was slowly added under continuous stirring at room temperature and the stirring continued for 20 min until a clear solution was obtained. Afterward, calcium nitrate tetrahydrate (2.5 mmol) was added into this mixture and again the mixture was stirred for 15 min. Lastly, the required measured amount of 99.999% of powder bismuth oxide (0.5 mmol) was added gradually and the mixture was further stirred for 6 h at 110 °C. The resultant suspensions were separated by centrifugation and washed several times with deionized water. The obtained samples were dried for 8 h in an oven at 120 °C. Furthermore, these materials were calcinated at 350 °C for 4 h under continuous airflow, to obtain the distinctive composition of Bi_2O_3/FAp materials.

2.3 | General procedure for the synthesis of dihydro-[1,2,4]triazolo-pyrimidine derivatives (4a–l)

A mixture of 1*H*-1,2,4-triazol-5-amine (**1**, 1 mmol), various chosen benzaldehydes (**2**, 1 mmol), ethyl cyanoacetate (**3**, 1 mmol), and 30 mg of 2.5% Bi_2O_3/FAp heterogeneous catalyst in absolute ethanol (5 mL) was mixed in a round-bottomed flask. The reaction mixture was continuously stirred for 25–35 min at room temperature. TLC was used for screening the reaction completion. After completion of the reaction, the catalyst material was retrieved from the reaction mixture by centrifugation and filtration. The retrieved dried catalyst was recycled for subsequent runs. The filtrate was concentrated under reduced vacuum pressure by rotatory evaporation, which resulted in the formation of solid products, and further recrystallized using hot ethanol to provide the desired pure products. The structures of all the synthesized novel derivatives were established by spectroscopic techniques (HRMS and ^{1}H and ^{13}C NMR) (Supplementary file).

3 | RESULTS AND DISCUSSION

3.1 | Characterization of the catalyst

The morphology of the as-prepared Bi_2O_3/FAp catalyst was established by SEM and TEM (Figure 1). Figure 1a,b shows the SEM micrograph and mapping of the bismuth loaded on the FAp (2.5% Bi_2O_3/FAp) catalyst. The FAp particles were hexagonal and showed irregular and lamellar arrangement with folded edges. Bismuth particles were widely dispersed on the surface of layered FAp. EDX spectrum (Figure 1c) was used to identify the elemental composition in the prepared material. The presence of Ca, P, F, and Bi elements in the resulting material was confirmed and the result matched well with the FAp material (Figure S1, **ESI**). The TEM micrograph (Figure 1d) showed the bismuth particles to be spherical, tightly grown, masked on the surface of FAp, and spread throughout the FAp circumference. The average size (diameter) of the particle was about 27 nm.

Figure 2 shows the XRD spectrum of the prepared 2.5% Bi_2O_3/FAp and FAp catalysts, with 2θ values ranging from 20° to 80° with overlying intense peaks of the crystalline phases. The intense and sharp diffraction peaks detected at 2θ values of 25.8°, 30.0°, 32.3°, 34.4°, 40.3°, 47.0°, 49.9°, 50.9°, 53.4°, and 56.2° were well indexed to the (002), (210), (211), (300), (310), (222), (213), (312), (004), and (322) plans of FAp, and well-matched with the standard FAp pattern (JCPDS no. 15-0876). In addition, other diffraction peaks identified at 26.2°, 33.3°, 42.5°, 44.3°, 45.7°, 52.5°, and 61.9° were indexed to the (120), (200), (122), (040), (041), (321) and (241) planes, respectively, and assigned to Bi_2O_3 (JCPDS no. 041-1449). Bi_2O_3/FAp was appropriately paired with the FAp material. The XRD data indicated the high degree of crystallinity of bismuth loaded onto FAp (Bi_2O_3/FAp).

Figure 3 illustrates the nitrogen adsorption–desorption isotherms of the Bi_2O_3/FAp composite, as obtained based on the BET analysis. The catalyst material showed stepwise adsorption and desorption hysteresis and was categorized as having the Type IV isotherm lying in the P/P_0 range from 0.05 to 1.0. The BET surface area, pore size, and pore volume were 54.1240 m^2/g, 197.075 Å, and 0.331 cm^3/g respectively. The inset in Figure 3 validates the prepared catalyst as a mesoporous

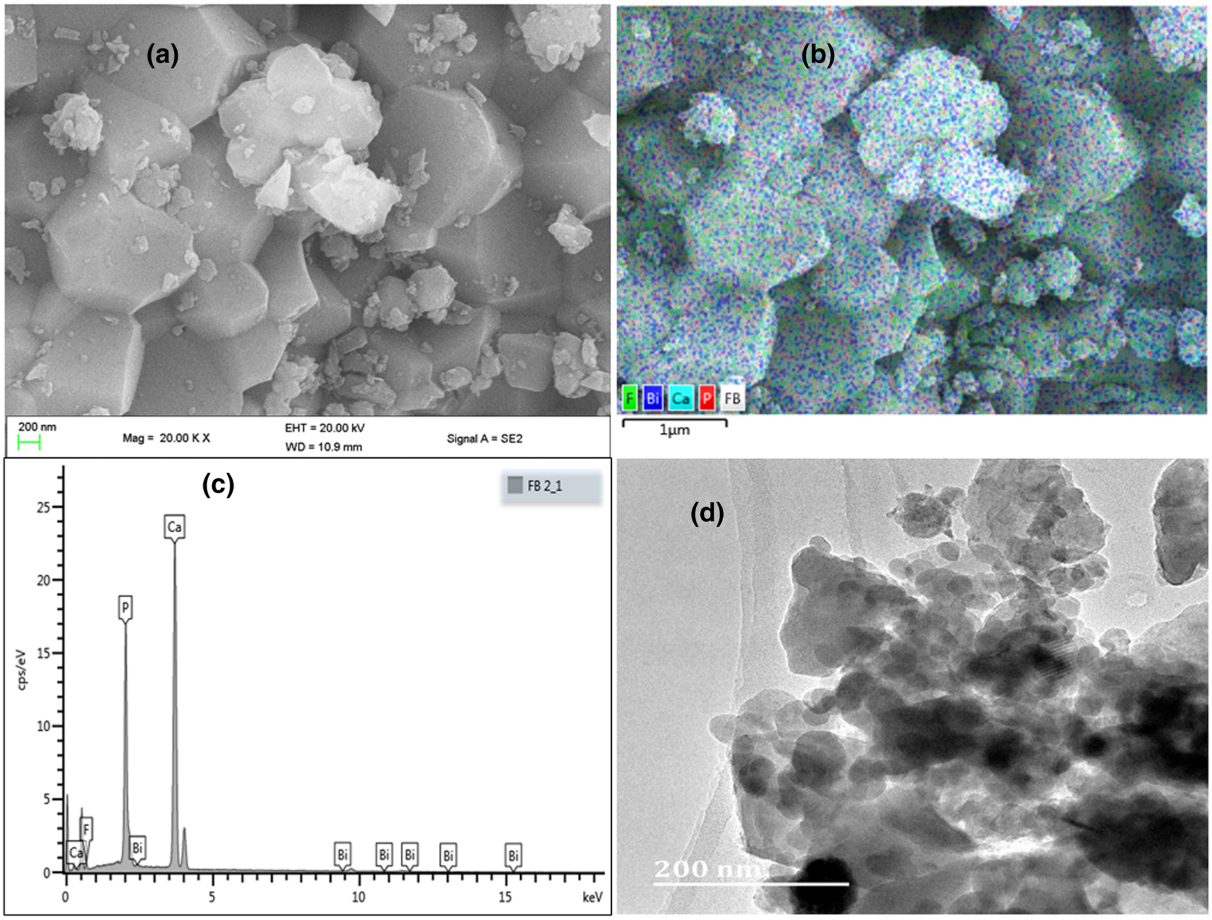


FIGURE 1 (a) Scanning electron microscopy (SEM) micrograph, (b) SEM mapping, (c) energy-dispersive X-ray spectroscopy spectrum, and (d) transmission electron microscopy micrograph of the 2.5% Bi_2O_3/FAp catalyst. FAp, fluorapatite

material. Greater specific surface area with 2.5% Bi_2O_3/FAp may have contributed to the higher catalytic activity observed, in the form of more active sites available for the reacting substrates and intermediates on the catalyst surface.

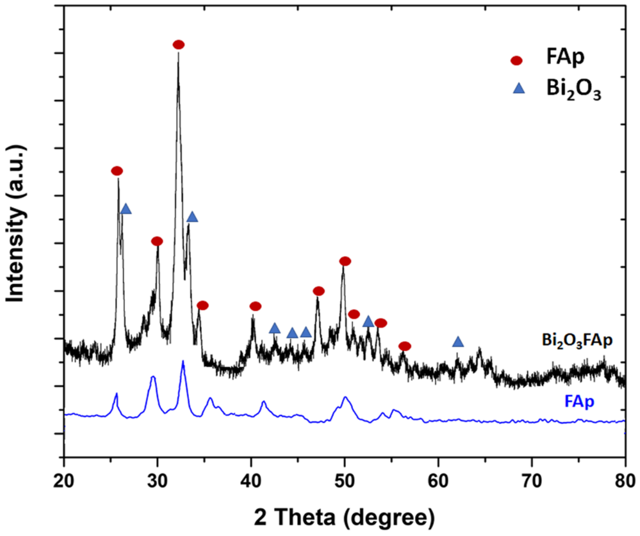


FIGURE 2 Powder X-ray diffractogram pattern of 2.5% Bi_2O_3/FAp and FAp materials. FAp, fluorapatite

Figure 4 presents the infrared spectra of the catalyst with the major characteristic absorption bands displayed at 1023, 599, and 564 cm^{-1}, which can be attributed to the stretching and bending absorbance of phosphate groups (PO_4^{3-}).[29] A prominent absorption band was observed at 1023 cm^{-1}, which was associated with the stretching vibration of P–O linkages of the PO_4^{3-} group. The absorption band at 599 and 564 cm^{-1} can be assigned to the triply degenerated bending asymmetric modes of the O–P–O bonds. In addition, the absorption peak corresponding to the carbonate group (CO_3^{2-}) was observed at 1450 cm^{-1}. These findings confirm that calcium phosphate and carbonate ions are present in the material.

Figure 5 illustrates the pyridine-adsorbed IR spectrum, which was used for identifying the kind of acidic sites on the surface of bismuth loaded on FAp. The strongest absorption band at 1431 cm^{-1} was assigned to Lewis acidic sites on the Bi_2O_3/FAp catalyst, whereas the small absorption frequency at 1480 cm^{-1} agrees to pyridine

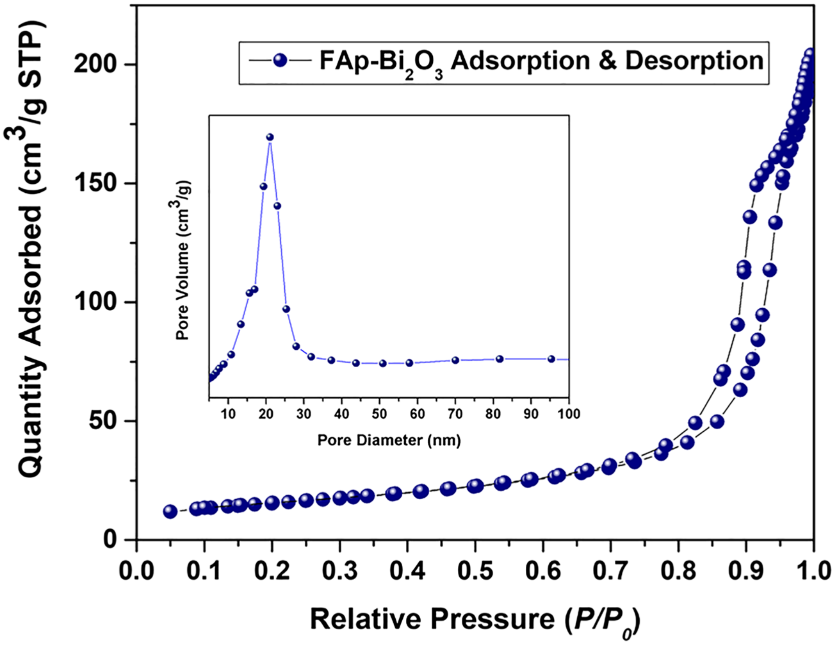


FIGURE 3 N_2 adsorption–desorption isotherm of the 2.5% Bi_2O_3/FAp catalyst. FAp, fluorapatite

adsorbed onto both Lewis and Brønsted acid sites, and the weak band at 1559 cm^{-1} corresponds to an apparent Brønsted acidic site.[30] Thus, the synthesized material was composed of strong Lewis acidic and weak Brønsted acidic sites. The catalyzed reaction can be assumed to occur as a result of the many Lewis acid sites on the Bi_2O_3/FAp catalyst surface.

3.2 | Catalytic activity

Initially, we focused on identifying a suitable catalyst for the model multicomponent condensation reaction involving 1*H*-1,2,4-triazol-5-amine (**1**), 4-methoxy benzaldehyde (**2a**), and ethyl cyanoacetate (**3**) as reactants (Scheme 1). Various acid, base, and metal oxide catalysts (30 mg per 1 mmol of aldehyde) were examined for the model reaction in ethanol medium, and the results are illustrated in Table 1. First, the reaction was carried out in the absence of the catalyst, during when the reaction progressed with trace and only low yields of desired product (**4a**) were obtained even after 24 h at both room temperature and under reflux condition (Table 1, Entries 1 and 2). Further, this synthetic protocol was performed using various organic and inorganic basic catalysts such as CS_2CO_3, K_2CO_3, NaOH, Et_3N, pyridine, and DABCO,

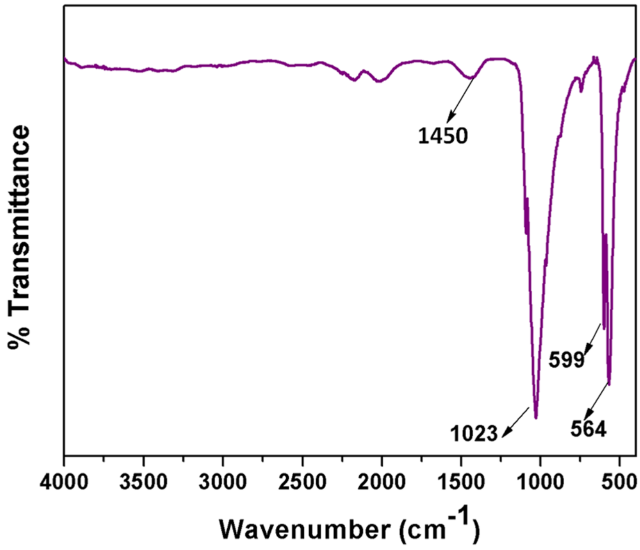


FIGURE 4 Fourier-transform infrared spectrum of the 2.5% Bi_2O_3/FAp catalyst. FAp, fluorapatite

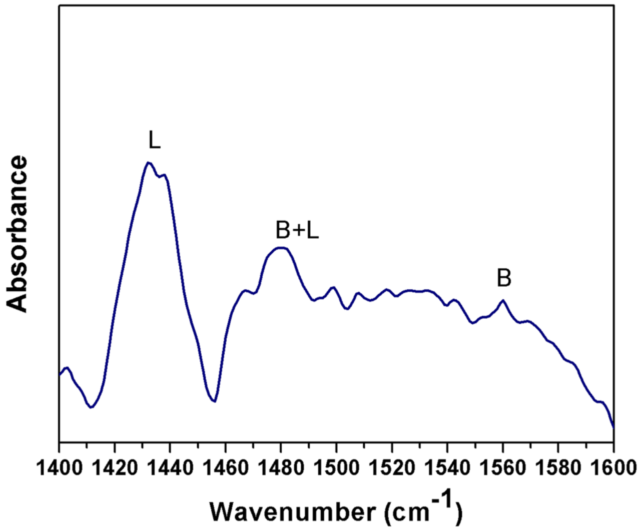


FIGURE 5 Pyridine infrared spectrum of the 2.5% Bi_2O_3/FAp catalyst. FAp, fluorapatite

TABLE 1 Screening of catalysts for the synthesis of dihydropyrimidine **4a**[a]

Entry	Catalyst	Conditions	Time (h)	% Yield[b]
1	–	Room temperature (RT)	24	Trace
2	–	Reflux	24	17
3	CS_2CO_3	RT	10	22
4	K_2CO_3	RT	8.0	18
5	NaOH	RT	6.0	39
6	Triethylamine	RT	10	19
7	Pyridine	RT	9.0	19
8	DABCO	RT	8.0	22
9	AcOH	RT	7.0	29
10	*p*-TSA	RT	10.0	32
11	HCl	RT	12.0	41
12	$HClO_4$–SiO_2	RT	4.5	46
13	H_2SO_4–SiO_2	RT	5.0	38
14	SiO_2	RT	7.5	44
15	ZnO_2	RT	3.0	51
16	Bi_2O_3	RT	2.5	66
17	Bi_2O_3	RT	2.5	69[c]
18	Bi_2O_3	RT	2.5	71[d]
19	Fluorapatite (FAp)	RT	1.0	69
20	1% Bi_2O_3/FAp	RT	0.50	87
21	2.5% Bi_2O_3/FAp	RT	0.50	96
22	5% Bi_2O_3/FAp	RT	0.50	92

[a] Reaction conditions: amine (**1**) (1 mmol), 4-methoxy benzaldehyde (**2a**) (1 mmol), ethyl cyanoacetate (**3**) (1 mmol), catalyst (30 mg per 1 mmol aldehyde), and solvent (5 mL).

[b] Isolated yields.

[c] 0.75 mg of Bi_2O_3.

[d] 1.5 mg of Bi_2O_3.

but again only low yield of the corresponding product (**4a**) was achieved (Table 1, Entries 3–8). Consequently, the reaction was performed in the presence of different Brønsted acid catalysts; however, again, only lower yields were obtained (Table 1, Entries 9–13). Then, the reaction was performed using various metal oxides (Table 1, Entries 14–16), with Bi_2O_3 giving a better yield (66%). In subsequent steps, the effect of increasing the amount of Bi_2O_3 was examined, but this did not increase the yield of the product (Table 1, Entries 17 and 18). FAp also provided a satisfactory yield of the desired product (Table 1, Entry 19). FAp exhibits an amphoteric feature having both Lewis acid and basic sites, with the Ca^{2+} accountable for the acidic sites, and F^- and P–O^- being liable for the basic sites.[31] This combination allows effective conversions, which explains the superior catalytic performance of FA. We further examined the efficacy of a modified FAp catalyst system (Bi_2O_3/FAp) with different weight percentages. The reaction was conducted with 1% bismuth loaded on an FAp catalyst. The reaction proceeded well with less reaction time (30 min), and produced the desired product in a good yield of 87% (Table 1, Entry 20). The increase in weight% of bismuth on FAp from 1% to 2.5%, accordingly increased the yield (96%) of the product (Table 1, Entry 21). With further increase in bismuth loading to 5%, the reaction proceeded smoothly, but with reduced yield (92%; Table 1, Entry 22). The obtained yield was lower than that with 2.5% of the catalyst. These differences in the catalytic efficiency of 1, 2.5, and 5 wt% of Bi_2O_3/FAp may be attributed to the distribution of active ions on the surface of supporting material, which influences the availability of active sites that accelerate the reaction and allows successful transformation. Many of the chemical reactions occur on the surface of the catalyst materials, and therefore, the nature, size, and distribution of particles on the catalyst surface have a distinct impact on their catalytic activity. In most cases, atoms on the particle surface act as Lewis acid centers, where the chemical reaction could be catalytically activated.[32,33] At 1% loading, the reaction time was longer due to the inadequate active sites present on the surface of the material, whereas at 5% loading, bismuth particles were highly agglomerated on the surface of FAp.[27] This is because at these loading rates several bismuth particles covered the active sites on the surface of the support material; eventually, the number of active sites available for the reaction to proceed is reduced. However, 2.5% loading of the Bi_2O_3/FAp catalyst system demonstrated greater catalytic activity for the dihydropyrimidine derivatives, compared with 1% and 5% loading of Bi_2O_3/FAp. This may be due to the wide and uniform dispersion of bismuth particles on the surface of layered FAp and more available active sites all over the FAp lattice (Figure 1). Evidently, metal-modified FAp often possesses improved tunable properties (stability and acidity) than its non-modified form[3,26]; thus, the Lewis acid nature of the highly efficient metal oxide (Bi_2O_3) loaded on the surface of supporting material (FAp) plays a vital role in organic synthesis.

Solvent plays a significant role in this condensed reaction and this could be attributed to the variation in the insolubility of the substrates and capability of solvents to swell the catalyst, thereby influencing its activity. A variety of polar-protic (MeOH, EtOH and H_2O), polar-aprotic

(CH_3CN, THF, and DMF), and non-polar (toluene) solvents were examined (Table 2, Entries 2–8), among which ethanol was found to be the superior medium for the reaction, which facilitated highest product yield. In addition, the model reaction was carried out under a catalyst-free condition in DMF solvent at 130 °C, for which no such improvement of the yield was noticed (Table 2, Entry 9). Under the solvent-free condition, no yield of product was noticed even after 24 h (Table 2, Entry 1). As ethanol is a green solvent, it is of significance from an eco-point of view. To optimize the required quantity of 2.5% Bi_2O_3/FAp, the reaction was studied by using 10, 20, 30, and 40 mg of the catalyst. The use of 10 mg of catalyst gave 73% yield in 60 min, 20 mg gave 91% yield in 40 min, 30 mg of catalyst offered 96% yield in 30 min, whereas with 40 mg of catalyst, the yield and reaction time remained unaltered (Table 3, Entries 1–4). Thus, 30 mg of catalyst was considered the optimum amount for the chosen reaction conditions.

Furthermore, we assessed the suitability of the recycled 2.5% of Bi_2O_3/FAp catalyst as recyclability is one of the vital criteria indicating catalyst efficiency. After completion of the reaction, the catalyst was separated from the reaction mixture by centrifugation and filtration. The acquired catalyst was further washed with ethyl acetate and desiccated in a heating oven for 2 h at 120 °C under vacuum. The recovered catalyst was reused for the next cycle of reaction performed under similar conditions (Figure 6). The recovered catalyst performed effectively up to the fifth cycle with similar efficacy in the MCR.

Subsequently, a hot filtration analysis was executed to study the heterogeneity of 2.5% of the Bi_2O_3/FAp catalyst for the synthesis of compound **4a**. After 15 min of reaction time, the Bi_2O_3/FAp catalyst was removed from the reaction mixture and the reaction in the left-over filtrate was continued under stirring and the same reaction conditions for up to 60 min. No substantial improvement in the yield of the product was observed in this reaction (Figure 7). These findings show that the Bi_2O_3/FAp material was stable and no leaching of metal content from the catalyst material occurred at the chosen reaction conditions. In addition, the EDX spectrum and TEM image of the recycled catalyst after the fifth run showed no significant changes in the elemental composition and morphology as compared with the fresh catalyst (**Figure S2, ESI**). The characterization data confirmed that there is no such erosion of the active material from the support, and the material proved to be of highly robust heterogeneous nature, preserving its crystal structure even after repeated use.

The efficiency of the prepared Bi_2O_3/FAp material in the current study was compared with the literature reported catalysts, in terms of the reaction conditions, time, and yields. The results are summarized in Table 4

TABLE 2 Effect of solvents on yield and reaction time[a]

Entry	Medium	Time (min)	%Yield
1	No solvent	1440	–[b]
2	MeOH	40	82
3	EtOH	30	96
4	Toluene	300	31
5	Tetrahydrofuran	240	48
6	CH_3CN	120	50
7	Dimethylformamide (DMF)	360	68
8	Water	90	53
9	DMF	30	51[c]

[a] Reaction conditions: amine (**1**) (1 mmol), 4-methoxy benzaldehyde (**2a**) (1 mmol), ethyl cyanoacetate (**3**) (1 mmol), 2.5% Bi_2O_3/fluorapatite (30 mg), and solvent (5 mL) at room temperature.

[b] No reaction observed.

[c] Reaction was carried out under catalyst-free conditions at 130 °C

TABLE 3 Optimization of 2.5% Bi_2O_3/fluorapatite catalyst quantity and reaction time[a]

Entry	Catalyst/mg	Time/min	Yield%
1	10	60	73
2	20	40	91
3	30	30	96
4	40	30	96

[a] Reaction conditions: amine (**1**) (1 mmol), 4-methoxy benzaldehyde (**2a**) (1 mmol), ethyl cyanoacetate (**3**) (1 mmol), and ethanol (5 mL) at room temperature.

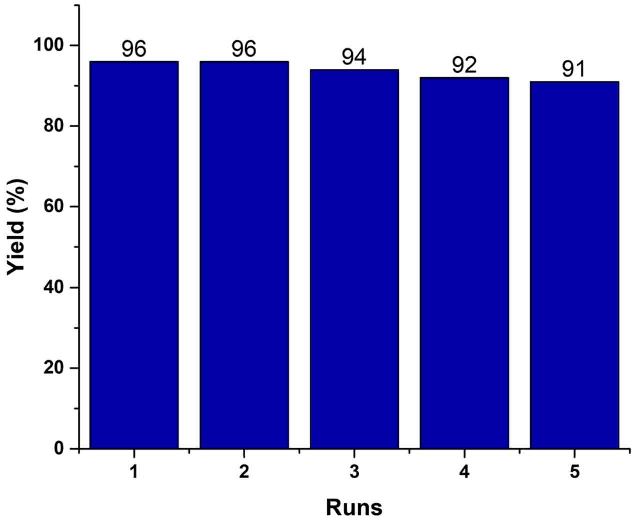


FIGURE 6 Recycling experiment of 2.5% Bi_2O_3/FAp catalyst for synthesis of dihydro-[1,2,4]triazolo[1,5-a]pyrimidine. FAp, fluorapatite

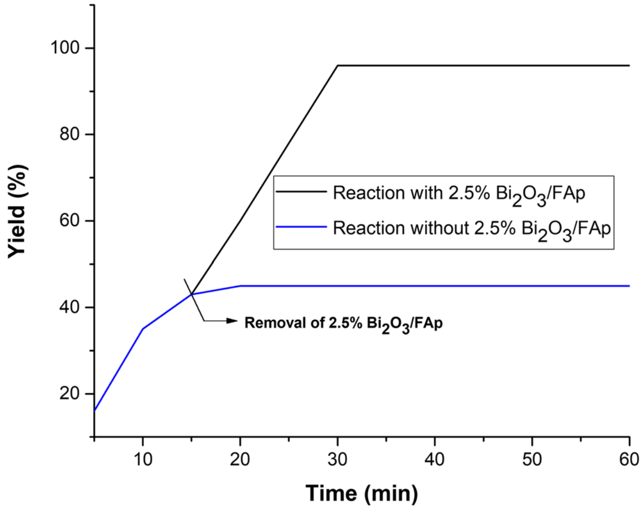


FIGURE 7 Hot filtration test results of the 2.5% Bi_2O_3/FAp catalyst for the synthesis of **4a**. FAp, fluorapatite

and the described catalyst gave higher yields with shorter reaction time at room temperature. Therefore, bismuth loaded on FAp is an adequate catalyst with high efficiency for the synthesis of dihydro-[1,2,4]triazolo-pyrimidine derivatives in comparison with catalysts reported in the literature.

Having the optimized the reaction conditions, we generalized the applicability of this procedure for the synthesis of a series of 13 dihydropyrimidine derivatives (**4a–m**) starting from 1*H*-1,2,4-triazol-5-amine (**1**), different benzaldehydes (**2a–l**), and ethyl cyanoacetate or ethyl acetoacetate (**3**) in ethanol using 2.5% of Bi_2O_3/FAp catalyst at room temperature (Table 5). Of the 13 derivatives, 12 were novel, with the remaining one being a known compound. All the reactions carried out gave high yields (92%–96%) of functionalized dihydropyrimidine derivatives within a short reaction time (25–35 min). The different electron-donating and electron-withdrawing

TABLE 4 Comparison of efficacy of Bi_2O_3/fluorapatite with other reported catalysts for the synthesis of dihydropyrimidine derivatives

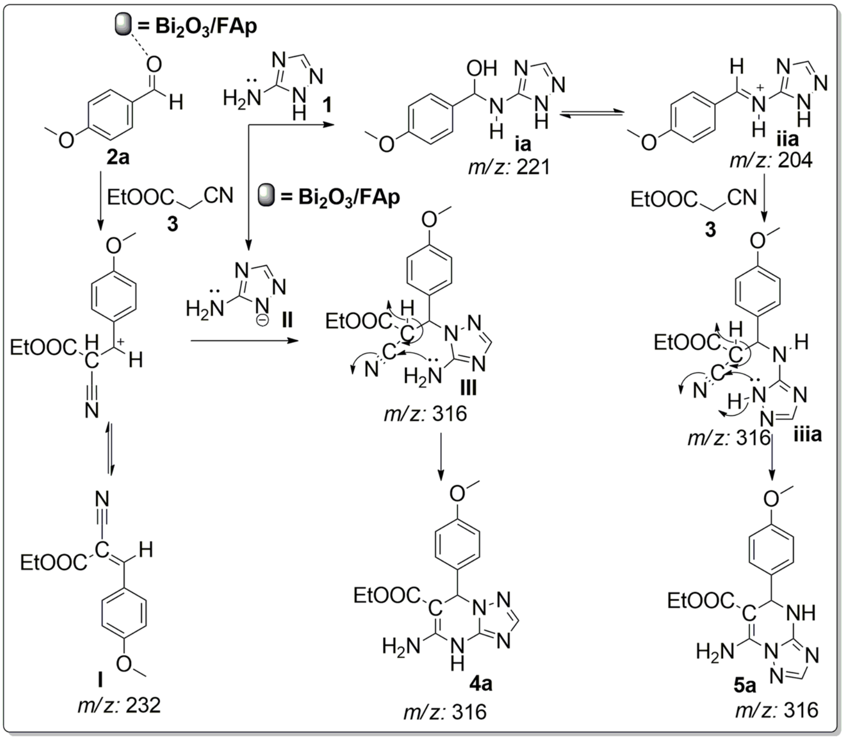
Catalyst	Solvent	Conditions	Time/min	% Yield[Ref]
DABCO-IL	Solvent free	100 °C	75–180	75–90[21]
DABCO-IL	H_2O	75 °C	25–60	78–95[22]
Thiamine-HCl	H_2O	Reflux	180–360	81–96[23]
γ-Fe_2O_3@$NaHSO_4$	Solvent free	100 °C	10–40	85–96[24]
Nafion-H	PEG-400	50 °C	30–50	86–94[25]
$BiNaCa_4(PO_4)_3F$	Acetonitrile	Reflux	90–420	37–90[26]
Catalyst free	Dimethylformamide	130–160 °C	15–20	6.0–82[14]
2.5% Bi_2O_3/fluorapatite	EtOH	Room temperature	25–35	92–96 [This work]

TABLE 5 Dihydro-[1,2,4]triazolo-pyrimidine derivatives obtained using 2.5% Bi_2O_3/fluorapatite catalyst[a]

Entry	R	X	Compound	Time/min	% Yield[b]	Melting point (°C)
1	4-OCH_3	CN	**4a**	30	96	186–188
2	3,4-OCH_3	CN	**4b**	28	95	192–194
3	4-$N(CH_3)_2$	CN	**4c**	35	92	179–181
4	3-OH,4-OCH_3	CN	**4d**	26	93	202–204
5	3,4-Di-OH	CN	**4e**	28	94	184–186
6	3-Indolyl	CN	**4f**	35	94	212–214
7	2,4,6-Tri-OCH_3	CN	**4g**	25	92	204–206
8	2-OCH_3	CN	**4h**	35	96	209–211
9	2-NO_2	CN	**4i**	30	94	186–188
10	4-OH,3-OCH_3	CN	**4j**	30	92	201–203
11	4-Cl	CN	**4k**	35	94	194–196
12	4-Br	CN	**4l**	26	95	182–184
13	4-OCH_3	$COCH_3$	**4m**	30	93	178–180[25]

[a] Reaction conditions: amine (**1**) (1 mmol), different substituted benzaldehydes (**2a–l**) (1 mmol), ethyl cyanoacetate (**3**) (1 mmol), 2.5% Bi_2O_3/fluorapatite (30 mg), and ethanol (5 mL) at room temperature.

[b] Isolated yields.



SCHEME 2 Proposed mechanism of dihydro-1,2,4-triazolo-pyrimidine derivatives (**4a–m**)

substituents on the aromatic phenyl ring did not show a marginal influence on the overall yields of the products. Both the active methylene compounds, ethyl cyanoacetate and ethyl acetoacetate, were well-tolerated and both reactions offered high conversions in the MCR. The newly synthesized analogs were characterized by spectroscopic techniques, HRMS, ^{1}H and ^{13}C NMR analysis (Supplementary file). For instance, compound **4a** displayed five sets of singlets in ^{1}H NMR: a characteristic singlet was observed at δ 5.22 ppm for one proton of the dihydropyrimidine moiety and the other four singlets appeared at δ 3.86, 6.45, 8.30, and 8.58 ppm, corresponding to the OCH_3, NH, CH, and NH_2 groups, respectively. In addition, one triplet (1.29 ppm) and one quartet (4.29 ppm) appeared due to the $–COOCH_2CH_3$ group, respectively. Two doublets were found at δ 8.08 and 7.14 ppm due to the four protons of the methoxy-substituted phenyl ring. The farthest downfield peak that appeared at δ 163.52 ppm belongs to the carbonyl carbon of the ester moiety of **4a** in ^{13}C NMR. In HRMS analysis, the molecular-ion peak was detected at $m/z = 338.1082$.

A suitable mechanistic pathway for the three-component condensation reaction for the construction of dihydropyrimidines (Scheme 2) is described. To investigate the nature of reaction intermediates, the reaction mixture was analyzed after 15 min of reaction time by LC–MS (**Figure S3, ESI**). Based on the presence of alkene (**I**) iminium ion (**2a**) intermediates in the reaction mixture and the final reaction product, a probable mechanism is proposed. The key step in this sequence involved the formation of Knoevenagel condensation compound (**I**) from the condensation of aldehyde (**2a**) and ethyl cyanoacetate (**3**). It is likely that in this reaction the aldehyde was adsorbed on the acidic sites of the catalyst to stimulate its C=O group. Simultaneously, the Lewis or Brønsted basic sites of the Bi_2O_3/FAp catalyst coordinating with 1*H*-1,2,4-triazol-5-amine (**1**) facilitated the generation of the other intermediate, the deprotonated 1,2,4-triazole-5-amine (**II**), which undergoes a Michael-type addition with Knoevenagel product (**I**) to give a transient intermediate (**III**). Finally, the intermediate (**III**), through consequent intramolecular cyclization and ring closure, results in the formation of the desired dihydro-[1,2,4]triazolo-pyrimidine derivative (**4a**). The alternative iminium ion mechanism **2a** → **ia** → **iia** does not constitute a major pathway. The proposed mechanism involving the Knoevenagel condensation and formation of intermediate is consistent with the reported literature.[34] Therefore, Bi_2O_3/FAp is an efficient catalyst in value-added organic conversions and this is probably due to its surface acidity and basicity. The synergetic effects of this complex enable smooth reaction.

4 | CONCLUSIONS

We reported the synthesis and characterization of a Bi_2O_3/FAp composite as a reusable heterogeneous catalyst for the synthesis of a series of biologically significant 1,2,4-triazole-fused dihydropyrimidine bicyclic systems in an ethanol medium at room temperature. The 2.5% Bi_2O_3/FAp composite exhibited excellent performance as a catalyst for the one-pot three-component synthesis of 12 novel dihydro-[1,2,4]triazolo[1,5-a]pyrimidine derivatives (**4a–l**), with 92%–96% yields achieved within 25–35 min of reaction time. The catalyst material was fully characterized by XRD, BET, FT-IR, SEM, EDX, and TEM techniques. The average size of Bi_2O_3 nanoparticles on 2.5% Bi_2O_3/FAp was 27 nm, as revealed by TEM data. Easily recovery of catalyst, reusability, short reaction time, excellent yields, mild conditions, and no hazardous solvents or column chromatography are the advantages of this method.

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