Novel Brönsted Acidic Ionic Liquids Confined in UiO-66 Nanocages for the Synthesis of Dihydropyrido[2,3-d]Pyrimidine Derivatives under Solvent-Free Conditions

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ABSTRACT: The effective and simple one-pot, three-component protocol for the synthesis of dihydropyrido[2,3-d]pyrimidine derivatives is presented using a triethylenediamine or imidazole Brönsted acidic, ionic-liquid-supported Zr metal–organic framework (TEDA/IMIZ-BAIL@UiO−66) as a green, novel, and retrievable heterogeneous catalyst under mild conditions. The multicomponent reactions of 6-amino-1,3-dimethyl uracil, various aromatic aldehydes, and acetyl acetone were conducted under solvent-free conditions so that dihydropyrido[2,3-d]pyrimidine derivatives can be obtained. It is possible to separate and purify the respective products easily using crystallization. We can recycle the catalysts six times without losing any major activity. Also, the characterization of the catalyst was done by energy-dispersive X-ray, field emission scanning electron microscopy, Fourier transform infrared, Brunauer−Emmett−Teller, X-ray diffraction, and thermogravimetric analysis analyses.

INTRODUCTION

Multicomponent reactions (MCRs) are very momentous reactions and extensively utilized in the synthesis of bioactive heterocyclic compounds.1 Moreover, MCRs pursue the green chemistry principles and protect reagents, time, and solvents. Thus, MCRs have engrossed much consideration for the generation of combinatorial libraries or structural scaffolds for detection of drugs.2

Uracil derivatives have been reported to contain a diversity of clinical and biological attributes.3 Additionally, pyrido[2,3-d]pyrimidines have gained great attention due to the varied range of pharmacological activities, including antibacterial,4 antihypertensive,5 antitumor,6 analgesic,7 and antimicrobial.8 They can also act as an adenosine kinase inhibitor,9 tyrosine kinase inhibitor,10 Abi kinase inhibitor,11 and calcium channel antagonist.12

Various approaches have been reported in the previous works for the synthesis of dihydropyrido[2,3-d]pyrimidine derivatives from aldehydes, 1,3-dicarbonyl compounds, and 1,3- dimethyl uracil condensation, such as reflux conditions13 and microwave irradiation,14 and using a nanomagnetic catalyst (Fe3O4@SiO2−SO3H),15 AcOH,16 thiourea dioxide,17 SBA−Pr−SO3H18 and H14[NaP5W9O31]−/SiO2−.19 Most of the reported procedures need long reaction times, reagents in stoichiometric amounts, and toxic solvents and cause low yields of the product.

Solvent-free reaction conditions are very important since they are efficient, clean, and cause reduction of organic solvent use.20

Metal–organic frameworks (MOFs) are crystalline porous compounds constructed from metal ions and organic linkers.

During recent years, there has been ever-growing attention in characterizing and preparing the metal–organic frameworks (MOFs) because of their high specific surface area and pore volume and low density.21 As a consequence, MOFs have been considered as promising candidate materials for several applications such as luminescence,22 nuclear waste partitioning,23,24 conductivity,25 radioactive remediation,26 removal of toxic27,28 materials, and drug delivery.29

Lately, ionic liquids (ILs), particularly acidic ones, have directed growing attention toward organic synthesis since they are able to offer an effective and green medium for organic reactions.30 Along with the application of ILs in organic transformations, they are also employed as reaction mediators for multicomponent reactions (MCRs).30

Organic reactions in acidic ionic liquid media have recently received significant attention of synthetic organic chemists; ionic liquids are environmentally friendly solvents with unique attributes such as high thermal stability, high ionic conductivity, nonflammability, nonvolatility, and miscibility with organic compounds, particularly with the heterocyclic compounds. Because of these beneficial properties, several works have been published over the last decades reporting the possibility to accomplish numerous organic reactions and catalyzed processes in ILs.31,32

The most significant benefit of MOFs compared to that of other porous materials is the easy tuning of their pore size/shapes as well as gas affinities by altering the organic linkers...
and metal complexes.\textsuperscript{33} Hence, it is desirable to combine ILs and MOFs for various applications like gas adsorption/separation and catalysis instead of utilizing the supported IL materials or bulk ILs.

Different synthetic approaches have been recently reported for biological products by the use of nanocatalysts.\textsuperscript{34−39} Here, we describe the synthesis of dihydropyrido[2,3-d]pyrimidine derivatives by a three-component condensation reaction of 6-amino-1,3-dimethyl uracil, aromatic aldehydes, and acetyl acetone using a triethylenediamine or imidazole Brönsted acidic, ionic-liquid-supported Zr metal–organic framework (TEDA/IMIZ-BAIL@UiO-66) as a green and recyclable catalyst under solvent-free conditions (Figure 1 and Scheme 1).

**Scheme 1. Synthesis of Dihydropyrido[2,3-d]pyrimidine Derivatives Using BAIL@UiO-66 under Solvent-Free Conditions**

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**RESULTS AND DISCUSSION**

In the primary tests, BAIL@UiO-66 was prepared, and its characterization was done by energy-dispersive X-ray (EDX), field emission scanning electron microscopy (FE-SEM), Fourier transform infrared (FT-IR), Brunauer–Emmett–Teller (BET), X-ray diffraction (XRD), and thermogravimetric analysis (TGA) analyses.

The stoichiometry and the chemical purity of the samples were examined by energy-dispersive analysis of X-ray (EDAX) investigation. The EDAX spectrum of Uio-66 (Figure 2a) indicates the presence of Zr, C, and O as the only basic components of Uio-66 MOF. The EDAX spectrum of TEDA/IMIZ-BAIL@UiO-66 (Figure 2b,c) indicates the elemental composition (Zr, C, O, N, and S) of micropores.

Field emission scanning electron microscopy (FE-SEM) is a helpful technique for specifying the size distribution, the shape of particles, and porosity. The particle size and the morphology of BAIL@UiO-66 MOF were specified using FE-SEM. As shown, the Uio-66 MOF and BAIL-functionalized Uio-66 materials displayed a spherical shape (Figure 3).

The FT-IR spectra of the bare Uio-66 nanostructure and BAIL-functionalized Uio-66 are shown in Figure 4. The two salient peaks at 1184 and 1540 cm\(^{-1}\) are corresponding to the symmetrical vibration and asymmetrical vibration of COO\(^{-}\), respectively. It reflects the presence of a dicarboxylate linker.\textsuperscript{40} The Zr-O band present between the carboxylic group of terephthalic acid and Zr(III) was clearly observed at 560 cm\(^{-1}\) in Uio-66. The presence of new bands at around 2800–3100 cm\(^{-1}\) was because of aliphatic C–H stretching vibrations and the sp\(^2\) C–H stretching vibration of the imidazole moiety. The peak observed at 1620 cm\(^{-1}\) indicates the C\(=\)N stretching vibration of the imidazole ring. The peak that is observed at 749 cm\(^{-1}\) represents the bending vibration of the imidazole ring. The peak observed at 1203 cm\(^{-1}\) along with a shoulder at 1400 cm\(^{-1}\) is assigned to the O\(\equiv\)S\(\equiv\)O symmetric and asymmetric stretching states. However, the bands at 1051 cm\(^{-1}\) are attributed to the S–O stretching vibration.

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**Figure 1.** Illustration of the incorporation of the ILs into the micropores of the MOF.

**Figure 2.** EDX spectra of Uio-66 MOF (a), IMIZ-BAIL@UiO-66 (b), and TEDA-BAIL@UiO-66 (C).
The powder X-ray diffraction (PXRD) patterns of the BAIL-functionalized UiO-66 materials represent that approximately all of the major diffraction peaks observed are in accordance with the pattern that was simulated and pure UiO-66 (Figure 5). From the results, it is clearly observed that the crystalline structure in the UiO-66 materials did not change in the BAIL functionalization process and stayed intact. The PXRD patterns indicate the essential peaks at around $2\theta = 7.3, 8.5, 12, 14.1, 14.7, 17.4, 18.6, 19.1, 22.2, 25.6, 28.1, 30.6, 33.1, 35.6, 37.4, 40.6, 43.4,$ and $44.6$°. These are corresponding to the (111), (200), (220), (311), (222), (400), (331), (420), (511), (600), (533), (711), (731), (820), (751), (664), and (933) Miller planes given in the PXRD pattern of the MOF and simulated UiO-66,$^{41,42}$ which proves that the framework is isostructural to the prototype UiO-66 Zr-MOF.

Nitrogen adsorption/desorption isotherms were employed for studying the specific surface area and pore volume distribution of nanostructures UiO-66 and BAIL@UiO-66 by the Brunauer−Emmett−Teller (BET) approach (Figure 6). The BAIL-functionalized UiO-66 catalysts presented a considerable reduction for the adsorbed N$_2$ at $P/P_0 > 0.1$ in comparison with pure UiO-66, $t$, especially the TEDA-BAIL@UiO-66 sample. The pure UiO-66 represented a BET surface area and a total pore volume of 1871 m$^2$ g$^{-1}$ and 0.904 cm$^3$ g$^{-1}$, while IMIZ-BAIL@UiO-66 and TEDA-BAIL@UiO-66 gave values of 1724 m$^2$ g$^{-1}$ and 0.892 cm$^3$ g$^{-1}$, and 1145 m$^2$ g$^{-1}$ and 0.551 cm$^3$ g$^{-1}$, respectively, as observed in Table 1. The reducing BET surface area and total pore volume are assigned to the embodiment of BAIL groups in the UiO-66 nanocages.
Nevertheless, the high surface areas, as well as the open cavities, were maintained benefiting the free diffusion of the product and reactant.

The BAIL-functionalized UiO-66 and UiO-66 exhibited three-stage weight loss in the TGA curves. The first weight loss step was observed at <150 °C and was assigned to the solvent loss from the framework. The second weight loss step at 150–350 °C was likely because of the decomposition of the immobilized ionic liquid moieties in the UiO-66 nanocages. The third weight loss step at >350 °C was assigned to the UiO-66 framework breakdown.

According to the data, the TEDA/IMIZ-BAIL@UiO-66 sample showed higher weight loss compared to the UiO-66 sample when both were heated up to 700 °C under Ar flow. Such behavior originates from the addition of the decomposed from TEDA/IMIZ-BAIL from UiO-66 in the analysis of IL-incorporated MOF sample. Onset and Endset temperatures were taken from the TGA measurement, which are provided in Table 2. The bulk IL results show that the decomposition initiates at 150 °C (specified by T onset) and IL totally disappears before reaching the temperature of 400 °C (specified by T endset). TGA measurements for UiO-66 were done using the same heating rate that was used for the bulk IL. It was observed that the decomposition of UiO-66 initiates at a temperature of 140 °C with about 50 wt % of the initial mass remaining in the pan following a a decrease of the slope curve to 700 °C. On the other hand, the TEDA/IMIZ-BAIL@UiO-66 sample showed a remaining mass of about 33 wt % of the initial mass. For the IL loading of about 24 wt % as given by BET measurements, it can be expected that about 26 wt % of the total mass remains in the pan following the temperature slope to 700 °C for this sample (it is about 50 wt % of the UiO-66 amount in the TEDA/IMIZ-BAIL@UiO-66 sample, since the bulk IL totally disappears at 700 °C). Nevertheless, the TGA profile of the TEDA/IMIZ-BAIL@UiO-66 sample shows a remaining mass of about 33 wt %, which is considerably less than the expected amount. In addition, the decomposition temperature that was obtained by this measurement was 135 °C, which is much lower than the decomposition temperature of bulk IL and pristine UiO-66.33–35 Figure 7 shows the thermogravimetric analysis (TGA) curves of UiO-66 and BAIL@UiO-66.

Table 2. Onset Temperatures, Endset Temperatures, and Weight Losses for UiO-66, TEDA/IMIZ-BAIL, and TEDA/IMIZ-BAIL-Incorporated UiO-66 Calculated from TGA Measurements (°C)

| sample                  | T onset (°C) | T endset (°C) | weight loss (%) |
|-------------------------|-------------|---------------|-----------------|
| UiO-66                  | 140         | 550           | 51.2            |
| TEDA/IMIZ-BAIL          | 150         | 350           | 26.3            |
| TEDA/IMIZ-BAIL@UiO-66   | 135         | 580           | 62.6            |

In early studies, for optimization of reaction conditions, the reaction of 6-amino-1,3-dimethyl uracil, 4-chlorobenzaldehyde, and acetyl acetone was selected as the model reaction for the one-pot synthesis of compound 4c. The reaction was run under solvent-free conditions at 100 °C (Scheme 2). The optimization of the reaction conditions was based on the solvent, catalyst, and various temperatures for the synthesis of dihydropyrido[2,3-d]pyrimidines.

Table 1. Measured BET Surface Areas and Pore Volumes of UiO-66 and BAIL@UiO-66

| sample           | BET surface area (m² g⁻¹) | pore volume (cm³ g⁻¹) |
|------------------|---------------------------|----------------------|
| UiO-66           | 1871                      | 0.904                |
| IMIZ-BAIL@UiO-66 | 1724                      | 0.892                |
| TEDA-BAIL@UiO-66 | 1145                      | 0.55                 |

Figure 7. TGA curves of the BAIL-functionalized UiO-66 and the UiO-66 MOF under an Ar atmosphere.

Our primary investigations were conducted using several catalysts such as MgO, CuI, CaO, TiO₂, ZnO, Cu (BDC), UiO-66, and BAIL@UiO-66, using each catalyst (0.01 g) separately, and all of the catalysts were investigated in the model reaction. From Figure 8, it was observed that BAIL@UiO-66 showed high activity compared with other catalysts, and the corresponding product was 4c obtained in very good yield and short reaction time (98% yield within 15 min) under solvent-free conditions.

Scheme 2. Model Reaction for the Synthesis of Dihydropyrido[2,3-d]pyrimidine 4c

Figure 8. Effect of various catalysts on the model reaction.

UiO-66 showed high activity compared with other catalysts, and the corresponding product was 4c obtained in very good yield and short reaction time (98% yield within 15 min) under solvent-free conditions.

Then, the model reaction was conducted using varying amounts of the BAIL@UiO-66 nanocomposite. The optimum
amount of BAIL@UiO-66 was 0.005 g, as shown in Figure 9. When this amount was increased, no change was observed in the reaction yield and time, while on reducing the catalyst amount, reduction in the product yield resulted. Therefore, the best level of BAIL@UiO-66 was chosen as 0.005 g in the model reaction (Figure 9).

Next, we conducted the model reaction for dihydropyrido-[2,3-\textit{d}]pyrimidine synthesis in the presence of BAIL@UiO-66 using different solvents under solvent-free conditions at varying temperatures. As shown in Table 3, under solvent-free conditions at 100 °C, the best outcomes were achieved (Table 3, entry 7). A temperature increase from 120 to 140 °C in this reaction showed no considerable impact on the product yield and time.

Some experiments were conducted, and a number of dihydropyrido-[2,3-\textit{d}]pyrimidines were prepared in high yields and short reaction times. It was seen that different aryl aldehydes presented high efficiency, giving high product yields with high purity. As observed in Table 4, aromatic aldehydes with electron-withdrawing groups like NO2 and Cl resulted in higher activity, giving high product yields compared with electron-donating groups like methyl and methoxy, as anticipated. In addition, sterically hindered aromatic aldehydes needed longer reaction times.

Then, to represent the advantages of the present work, the catalytic efficiency of BAIL@UiO-66 was shown in comparison with other catalysts in the model study. As observed in Table 5, BAIL@UiO-66 showed high activity compared with other catalysts and the corresponding product 4c generated in very good yield and short reaction time (15 min for a 98% yield) under solvent-free conditions at a temperature of 100 °C.

**Table 4. Synthesis of Dihydropyrido-[2,3-\textit{d}]pyrimidine Derivatives Using the BAIL@UiO-66 Catalyst**

| entry | R     | product | time (min) | yield (%) | mp (°C) | lit. mp (°C) |
|-------|-------|---------|------------|-----------|---------|--------------|
| 1     | H     | 4a      | 20         | 91        | >300    | >300         |
| 2     | 4-NO2 | 4b      | 14         | 95        | >300    | >300         |
| 3     | 4-Cl  | 4c      | 15         | 98        | >300    | >300         |
| 4     | 3,4-(CH3)2 | 4d | 16       | 88        | >300    | >300         |
| 5     | 3-NO2 | 4e      | 12         | 92        | >300    | >300         |
| 6     | 4-OCH3 | 4f     | 20         | 87        | >300    | >300         |
| 7     | 4-CH3 | 4g      | 10         | 90        | >300    | >300         |
| 8     | 3,4-(OCH3)2 | 4h | 18       | 89        | >300    | >300         |
| 9     | 4-CN  | 4i      | 17         | 93        | >300    | >300         |
| 10    | 3,4-(Cl)2 | 4j   | 13         | 95        | >300    | >300         |
| 11    | 5-Br,2-OH | 4k | 17       | 94        | >300    | b            |
| 12    | 2-OH,5-NO2 | 4l | 19       | 89        | >300    | >300         |

*Isolated yield. \*\*New products.

**Reuse of Catalyst.** For investigating the catalyst reusability, the model reaction was conducted again using the recovered TEDA/IMIZ-BAIL@UiO-66 nanocomposite under the optimized reaction conditions. When the reaction was completed (as specified by thin layer chromatography (TLC)), the residuals were dissolved in hot ethanol or CH2Cl2 and the catalyst was filtered. The recycled catalyst can be reused in six consecutive model reactions with no considerable activity loss (Figure 10).

**Proposed Mechanism.** Scheme 3 indicates a logical mechanism for the synthesis of dihydropyrido-[2,3-\textit{d}]-pyrimidines using BAIL@UiO-66 as a catalyst. The obtained results were tested experimentally together with the results obtained in the previous works.18,19 It is likely that BAIL@ UiO-66 serves as a Bronsted acid, increasing the carbonyl group’s electrophilicity on the acetyl acetone and aldehyde by a strong coordinate bond. It is believed that the first stage is the Bronsted acid-catalyzed Knoevenagel condensation between the aldehyde (2) and acetyl acetone (3) for producing adduct A that serves as a Michael acceptor. The 6-amino-1,3-dimethyl uracil 1 attacks adduct A in a Michael-type way for generating an open-chain intermediate, B. Subsequently, intramolecular cyclization, dehydration, and aromatization on the intermediate result in the ultimate product (4).

**CONCLUSIONS**

In conclusion, a Bronsted acidic, ionic-liquid-supported Zr metal–organic framework (BAIL@UiO-66) was successfully prepared and used as an effective heterogeneous and green catalyst for the synthesis of dihydropyrido-[2,3-\textit{d}]-pyrimidine derivatives by one-pot condensation of 6-amino-1,3-dimethyl uracil, different aromatic aldehydes, and acetyl acetone. The benefits of this approach include clean work-up and easy reusability of the catalyst, short reaction time, and high efficiency under solvent-free conditions. It is expected that this approach would be extensively applied in the combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

**EXPERIMENTAL SECTION**

**Materials and Instrumentation.** Chemical materials were supplied by Sigma-Aldrich and Merck and were of high purity. All of the them were of commercial reagent grade and were utilized with no further purification. The melting points were not corrected, and they were specified on the capillary tube on
Table 5. Comparison of the Catalytic Ability of Some Catalysts Reported in the Literature for the Synthesis of Dihydropyrido[2,3-d]pyrimidines (4c)α

| entry | catalyst | conditions | time/yield (%) | references |
|-------|----------|------------|---------------|------------|
| 1     | Wang and Merrifield resins | CH3COOH/microwave irradiation/rt | 8 h/75−88 | 13 |
| 2     | Fe3O4@SiO2−SO3H | H2O/stir. (75 °C) | 15 min/82−92 | 14 |
| 3     | thiourea dioxide | H2O/heating (110 °C) | 8 h/70−95 | 15 |
| 4     | SBA−Pr−SO3H | CH3CN/reflux | 8 h/90−95 | 16 |
| 5     | H2[NaP5W30O110]/SiO2 | H2O/reflux | 45 min/80−93 | 17 |
| 6     | BAIL@UiO-66 | solvent-free, 100 °C | 20 min/80−94 | 18 |
| 7     | BAIL@UiO-66 | solvent-free, 100 °C | 15 min/87−98 | 19 |

αBased on the three-component reaction of 6-amino-1,3-dimethyl uracil, 4-chlorobenzaldehyde, and acetyl acetone.

Figure 10. Reusability of the BAIL@UiO-66 catalyst.

Scheme 3. Proposed Mechanism for the Synthesis of Dihydropyrido[2,3-d]pyrimidines

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1H NMR and 13C NMR spectra were recorded on Bruker 400 and 100 MHz spectrometers, using DMSO-d6 as the solvent and tetramethylsilane as an internal standard. FT-IR spectra were recorded on Magna-IR spectrometer 550. The elemental analyses (C, H, N) were carried out using a Carlo Erba model EA 1108 analyzer. Powder X-ray diffraction (XRD) was conducted on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ = 1.5406 Å). Microscopic morphology of the samples was visualized by SEM (LEO 1455VP). The mass spectra were recorded on a Joel D-30 tool at an ionization potential of 70 eV. The compositional analysis was carried out using energy-dispersive analysis of X-ray (EDAX, Kevek, Delta Class I). Thermogravimetric analysis (TGA) was conducted on a Mettler Toledo TGA under argon, and it was heated from room temperature to 825 °C. Measurement of nitrogen adsorption–desorption isotherms was carried out at 196 °C using a Belsorp mini automatic adsorption device after degassing the samples at 150 °C for 5 h. The approximate sample weight was 10 mg in the TG experiment with a heating rate of 10 °C min⁻¹.

Preparation of UiO-66. The UiO-66 synthesis process is illustrated in Scheme 4. It was synthesized using a solvothermal approach based on the previous study, where 0.125 g of ZrCl4 was dissolved in 5 mL of N,N-dimethylformamide (DMF) and 1 mL of HCl (37%). Then, 0.123 g of terephthalic acid (H2BDC) was dissolved in 10 mL of DMF. The solutions were mixed in a 25 mL Teflon-lined autoclave, and they were heated at 80 °C for 16 h. The obtained product was collected by centrifugation at 5600 rpm for 15 min and then rinsed with DMF solvent from the product. Ultimately, the solids were dried at 80 °C overnight in a vacuum oven.

Preparation of TEDA/IMIZ-BAIL. TEDA/IMIZ-BAILs were prepared on the basis of the approach reported in previous studies with some changes. Triethylenediamine or imidazole (0.01 mol) and 1,4-butanediol (0.04 mol) were mixed in toluene (40 mL) and stirred magnetically for 72 h at 80 °C. Then, the white solid zwitterion (TEDA/IMIZ-BAIL precursor) was obtained, filtrated, and rinsed several times with ether. A stoichiometric amount of sulfuric acid was added to the zwitterion, and the obtained mixture was stirred for 6 h at 80 °C to form the ionic liquids. Finally, the BAIL phase was rinsed several times with toluene and diethyl ether for removal of non-ionic residues, and it was dried under vacuum at 110 °C (Scheme 5).

a Boetius melting point microscope. 1H NMR and 13C NMR spectra were recorded on Bruker 400 and 100 MHz spectrometers, using DMSO-d6 as the solvent and tetramethylsilane as an internal standard. FT-IR spectra were recorded on Magna-IR spectrometer 550. The elemental analyses (C, H, N) were carried out using a Carlo Erba model EA 1108 analyzer. Powder X-ray diffraction (XRD) was conducted on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ = 1.5406 Å). Microscopic morphology of the samples was visualized by SEM (LEO 1455VP). The mass spectra were recorded on a Joel D-30 tool at an ionization potential of 70 eV. The compositional analysis was carried out using energy-dispersive analysis of X-ray (EDAX, Kevek, Delta Class I). Thermogravimetric analysis (TGA) was conducted on a Mettler Toledo TGA under argon, and it was heated from room temperature to 825 °C. Measurement of nitrogen adsorption–desorption isotherms was carried out at 196 °C using a Belsorp mini automatic adsorption device after degassing the samples at 150 °C for 5 h. The approximate sample weight was 10 mg in the TG experiment with a heating rate of 10 °C min⁻¹.
Preparation of TEDA/IMIZ-BAIL@UiO-66. The method for the preparation of the novel and robust Brønsted acidic, ionic-liquid-functionalized UiO-66 MOF is shown in Scheme 6. Briefly, UiO-66 (1.0 g) was dehydrated under vacuum at 110 °C for 12 h. In a round-bottom flask, UiO-66 was suspended in anhydrous toluene (30 mL), followed by the addition of N-heterocyclic compounds including triethylenediamine or imidazole (5 mmol). The reaction mixture was refluxed under stirring at 80 °C for 12 h. After reaction completion, the solvent was separated by filtration and the excess of triethylenediamine/imidazole was removed by washing with toluene. Next, the product was dispersed in 30 mL of anhydrous toluene. During vigorous stirring, equivalent molar ratio 1,4-butane sultone (5 mmol) was introduced into the solution and the mixture was refluxed at 80 °C for 12 h. The final solid was gathered by filtration and dried under vacuum at 110 °C for 3 h. Next, the white solid was suspended in 20 mL of ethanol accompanied by addition of an equivalent amount of concentrated H2SO4 (98%) drop-by-drop at 50 °C for 24 h. Finally, the catalyst was separated by filtration and dried under vacuum at 50 °C for 12 h.

General Procedure for the Synthesis of Dihydropyrido[2,3-d]pyrimidines (4a–4l). A mixture of 6-amino-1,3-dimethyl uracil (1 mmol), acetyl acetone (1 mmol), aldehyde (1 mmol), and BAIL@UiO-66 (0.005 g) was heated at 100 °C for 10–15 min. After completion of the
reaction as determined by thin layer chromatography (TLC) (eluent: hexane/ethyl acetate, 4:1), the reaction mixture was cooled to room temperature and the solid obtained was dissolved in dichloromethane; the catalyst was insoluble in CH₂Cl₂ and separated by simple filtration. The solvent was evaporated, and the residue was recrystallized from ethanol to afford the pure product.

All of the products were characterized and identified with mp, ¹H NMR, ¹³C NMR, and FT-IR spectroscopy techniques. Spectral data of the new products are given below.

_Spectral Data of the New Compounds._

6-Acetyl-5-(5-bromo-2-hydroxyphenyl)-1,3,7-trimethyl-5,8-dihydropyrido-[2,3-d]pyrimidine-2,4(1H,3H)-dione (4k). White solid, mp: >300 °C. ¹H NMR (400 MHz, DMSO-d₆) δ: 3.03 (s, 3H, CH₃), 3.14 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.16 (s, 3H, CH₃), 4.65 (s, 1H, CH), 7.41 (d, 1H, J = 7.8 Hz, ArH), 7.23 (d, 1H, J = 7.7 Hz, ArH), 6.75 (d, 1H, J = 7.4 Hz, ArH), 9.08 (s, 1H, NH) 9.65 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 18.41, 27.34, 29.51, 30.23, 32.65, 79.11, 112.47, 117.65, 123.82, 125.71, 135.24, 147.87, 148.26, 151.35, 153.27, 163.41, 195.62. FT-IR (KBr): 3028, 2956, 1708, 1683, 1541, 1523, 1513 cm⁻¹; anal. calcd for C₁₈H₁₈BrN₃O₄: C 51.44, H 4.32, Br 19.01, N 10.00, O 20.43. Found C 51.40, H 4.38, Br 19.03, N 10.02, O 20.38; MS (EI) (m/z): 419.05 (M⁺).

6-Acetyl-5-(2-hydroxy-5-nitrophenyl)-1,3,7-trimethyl-5,8-dihydropyrido-[2,3-d]pyrimidine-2,4 (1H,3H)-dione (4l). White solid, mp: >300 °C. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.87 (s, 3H, CH₃), 4.79 (s, 1H, CH), 7.03 (s, 2H, NH₂), 7.21–7.25 (d, 1H, J = 7.8 Hz, ArH), 9.08–9.10 (d, 1H, J = 7.6 Hz, ArH), 10.90 (s, 1H, OH), 12.02 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-d₆) δ: 18.41, 27.34, 29.51, 30.23, 32.65, 79.11, 112.47, 117.65, 123.82, 125.71, 135.24, 147.87, 148.26, 151.35, 153.27, 163.41, 195.62. FT-IR (KBr): 3425, 3302, 2580, 2198, 1666, 1400, 1254 cm⁻¹; anal. calcd for C₁₄H₁₁N₅O₄: C 53.68, H 3.54, N 22.36, O 20.43. Found C 53.64, H 3.48, N 22.32 O 20.38; MS (EI) (m/z): 313.08 (M⁺).

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**Notes**

The authors declare no competing financial interest.

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