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Triethylammonium Hydrogen Sulfate [Et_3NH][HSO_4]-Catalyzed Rapid and Efficient Multicomponent Synthesis of Pyrido[2,3-*d*]pyrimidine and Pyrazolo[3,4-*b*]pyridine Hybrids

Chetan Jadhav, Amol Nipate, Asha Chate, and Charansingh Gill*

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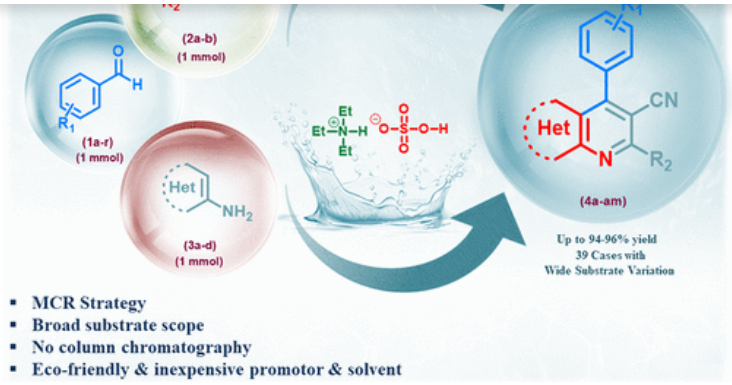
SUBJECTS: Aldehydes, Catalysts, Reaction products, Salts, Solvents

Abstract



An operationally simple, one-pot multicomponent reaction has been developed for the assembly of pyrido[2,3-*d*]pyrimidine and pyrazolo[3,4-*b*]pyridine derivatives (**4a**–**4am**) in excellent yields (92–94%) with high purity. The reactions were easy to perform simply by mixing of electron-rich amino heterocycles (including aminouracils and aminopyrazoles), aldehyde, and acyl acetonitrile in the presence of $[Et_3NH][HSO_4]$ under solvent-free conditions. The remarkable feature of the present approach is that the ionic liquid possesses dual solvent-catalytic engineering capability. Results of this study revealed that 1 mmol of the ionic liquid catalyst under solvent-free conditions at 60 °C is the best reaction parameter for the construction of fused pyridine and pyrimidine derivatives in excellent yields. The present methodology showed good results under gram-scale conditions, thereby indicating its applicability in industrial as well as academic settings in the near future.

Introduction

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Green chemistry possesses the spirit of sustainable development and is attracting increasing interest in the 21st century. In the chemical world, strategies for increasing sustainability often require the redesign of reactions and modifications of existing chemical processes aiming, among other things, at the reduction of chemicals used as solvents in a wide range of industrial applications. In this context, ionic liquids (ILs) have emerged as intriguing modern materials in science and technology. In order to understand and explore the interesting and unique properties including high chemical and thermal stability, low volatility, ability to dissolve a wide range of material polarity, nonflammability, negligible vapor pressure, potential recyclability, immiscibility with many organic solvents, and possibly

carbon−heteroatom and carbon−carbon bond-forming reactions lie at the heart of organic synthesis. Multicomponent reactions (MCRs) have been recognized as valuable tools in modern organic synthesis for the drug discovery process and the total synthesis of natural products. (26−29) MCRs can provide access to a library of complex structures in a straightforward manner, and diversity can be achieved for building up compound libraries by simply varying each component. (30,31) Over the past four decades, there has been a huge development in three- and four-component reactions, and great endeavor continues to be made to expand new MCRs. (32−35)

Pyrazole and its hybrids are gaining significance in organic and medicinal chemistry. (36) They have shown an extensive spectrum of biological and pharmacological activities, such as anti-inflammatory, (37) antidepressant, (38) antitumor, (39) antibacterial, (40) and antihyperglycemic. (41) Especially, pyrazole nuclei have been recognized to have the widest range of activities, for example, pyrazolo[3,4-*b*]pyridines are useful for the treatment of a wide variety of mental and physical illnesses, such as anorexia nervosa, Alzheimer's disease, depression, drug and alcohol withdrawal symptoms, gastrointestinal disease, hemorrhage stress, drug addiction, and infertility. (42) Heterocycles containing pyrimidine moieties are of great interest because of several pharmacological activities like antiviral agents, (44) while others are known as anticancer agents inhibiting tyrosine kinases or dihydrofolate reductases. (43) Pyrazolo-[3,4-*b*]pyridine hybrids are generally synthesized by the reaction of 5-aminopyrazole and substituted α,β-unsaturated nitriles in organic solvents using triethylamine as a catalyst, (45,46) but most of them suffer from drawbacks, such as lower yields and use of organic solvents.

In continuation of our interest toward the development of a useful green synthetic procedure, (47−52) herein, we report an efficient and green one-pot three-component strategy for the synthesis of fused pyridine derivatives (including pyrido[2,3-*d*]pyrimidine and pyrazolo[3,4-*b*]pyridine) by the three-component reaction of substituted aromatic/heteroaromatic aldehyde, acyl acetonitrile, and electron-rich amino heterocycles (including aminopyrazoles and aminouracils) in ionic liquids without any catalyst.

Results and Discussion

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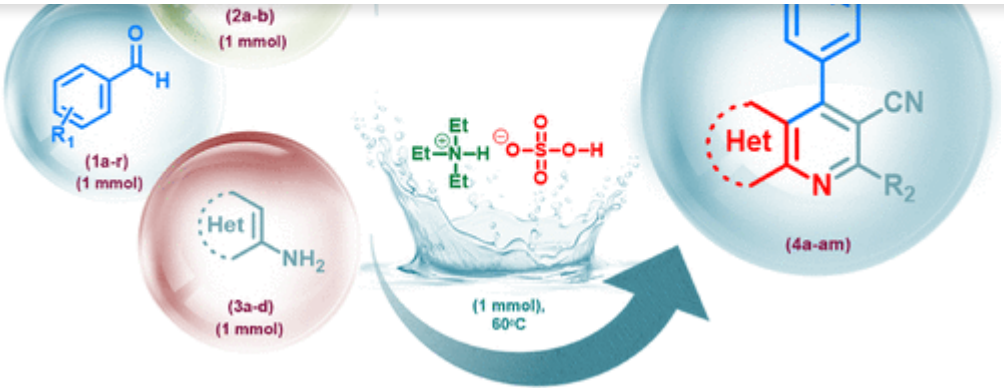
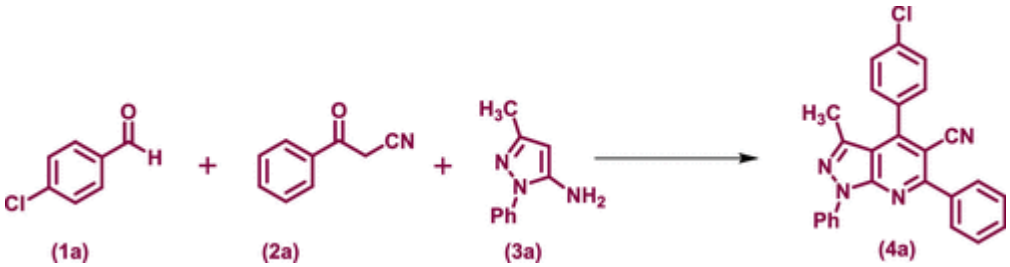
Herein, we disclosed an efficient and green route for the synthesis of fused pyridine hybrids by employing electron-rich amino heterocycles (including aminopyrazoles and aminouracils), heteroaryl aldehyde, and acyl acetonitrile in the presence of $[Et_3NH][HSO_4]$ ionic liquid as the



Scheme 1. Synthesis of Pyrido[2,3-*d*]pyrimidine and Pyrazolo[3,4-*b*]pyridine Hybrids in Ionic Liquid $[Et_3NH][HSO_4]$

To avoid drawbacks such as toxicity and volatility that various organic solvents inherently have, we employed ionic liquids into the three-component reaction as a green medium. Preliminary investigations on the title reaction were performed using the three-component reaction of 4-chloro benzaldehyde (**1a**), 3-oxo-3-phenylpropanenitrile (**2a**), and 3-methyl-1-phenyl-1*H*-pyrazole-5-amine (**3a**) as model substrates to optimize the reaction conditions (Scheme 2).

Scheme 2



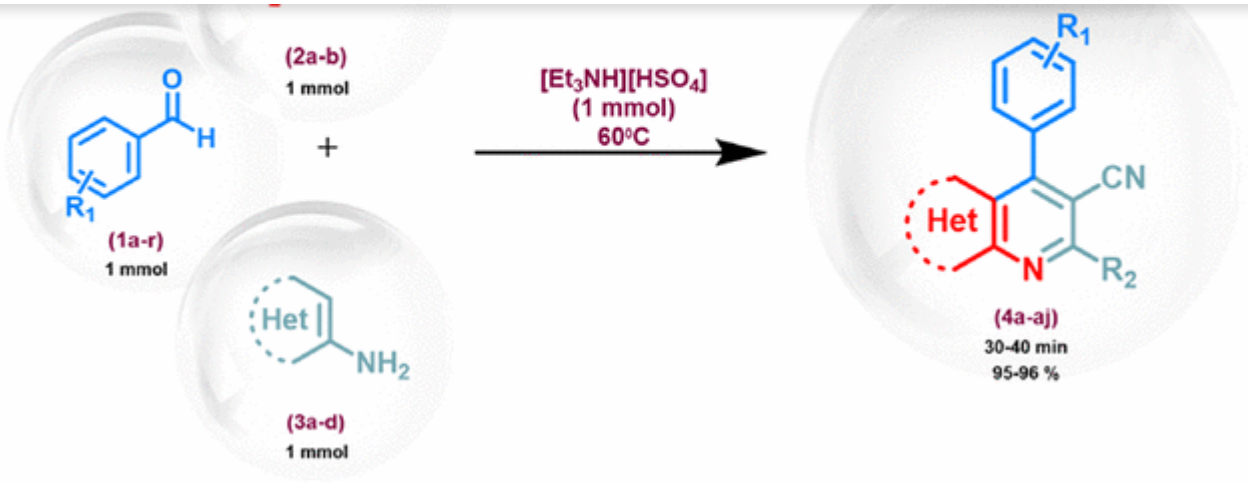
Scheme 2. Model Reaction

The model reaction was carried out in the presence of different ILs (Table 1). It was observed that all of the investigated ILs were capable of catalyzing the synthesis of the desired 4-(4-chlorophenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**4a**). However, the yield of the corresponding fused pyridine derivative was excellent in the presence of $[Et_3NH][HSO_4]$ (Table 1, entry 11). Then, various reaction parameters, such as the reaction time, temperature, and amount of IL, were checked (Table 1). The outcomes showed that a significantly increased yield of the desired fused pyridine hybrid was obtained by carrying out the reaction with 1:1:1:1 molar ratios of 4-chloro benzaldehyde (**1a**), 3-oxo-3-

2	EtOH	60	18 h	20
3	[bmim]BF_4 (1)	60	30 min	70
4	[Bmim]Br (1)	60	30 min	78
5	[bmim]NO_3 (1)	60	30 min	80
6	[bpy][FeCl] (1)	60	30 min	80
7	[$DBUH^+$] [Im^-] (1)	60	30 min	70
8	[DBUH][OAc] (1)	60	30 min	65
9	piperidine ammonium acetate (1)	60	30 min	75
10	ChCl:2$ZnCl_2$ (1)	60	30 min	75
11	[Et_3NH][HSO_4] (1)	60	30 min	96
12	[Et_3NH][HSO_4] (1.1)	60	30 min	96
13	[Et_3NH][HSO_4] (0.8)	60	30 min	88
14	[Et_3NH][HSO_4] (1)	80	30 min	96
15	[Et_3NH][HSO_4] (1)	50	30 min	70

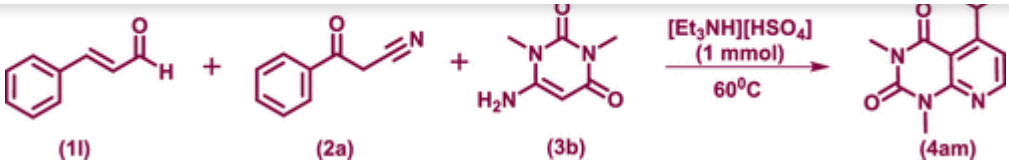
[a]4-Chloro benzaldehyde (**1a**), 3-oxo-3-phenylpropanenitrile (**2a**), and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3a**).
[b]Isolated yield.

To get the optimum reaction, conditions were then tested for the synthesis of other fused pyridine derivatives by using 18 aldehydes (**1a**−**1r**), two acyl acetonitrile (**2a** and **2b**), and four electron-rich amino heterocycles (**3a**−**3d**) (see the Supporting Information, Figure S1). The corresponding pyrido[2,3-*d*]pyrimidine and pyrazolo[3,4-*b*]pyridine derivatives (**4a**−**4am**) were



[a]Aldehydes (**1a**−**1r**) (1 mmol), acyl acetonitriles (**2a** and **2b**) (1 mmol), electron-rich amino heterocycles (**3a**−**3d**) (1 mmol), and $[Et_3NH][HSO_4]$-IL (1 mmol).
[b]All reactions were heated at 60 °C till completion as indicated by TLC.
[c]Isolated yield.

Furthermore, we conducted the multicomponent reaction of cinnamaldehyde (**1r**), 3-oxo-3-phenyl-propenonitrile (**2a**), and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**3b**) as shown in Scheme 3. The result revealed that α,β-unsaturated aldehydes were found to be

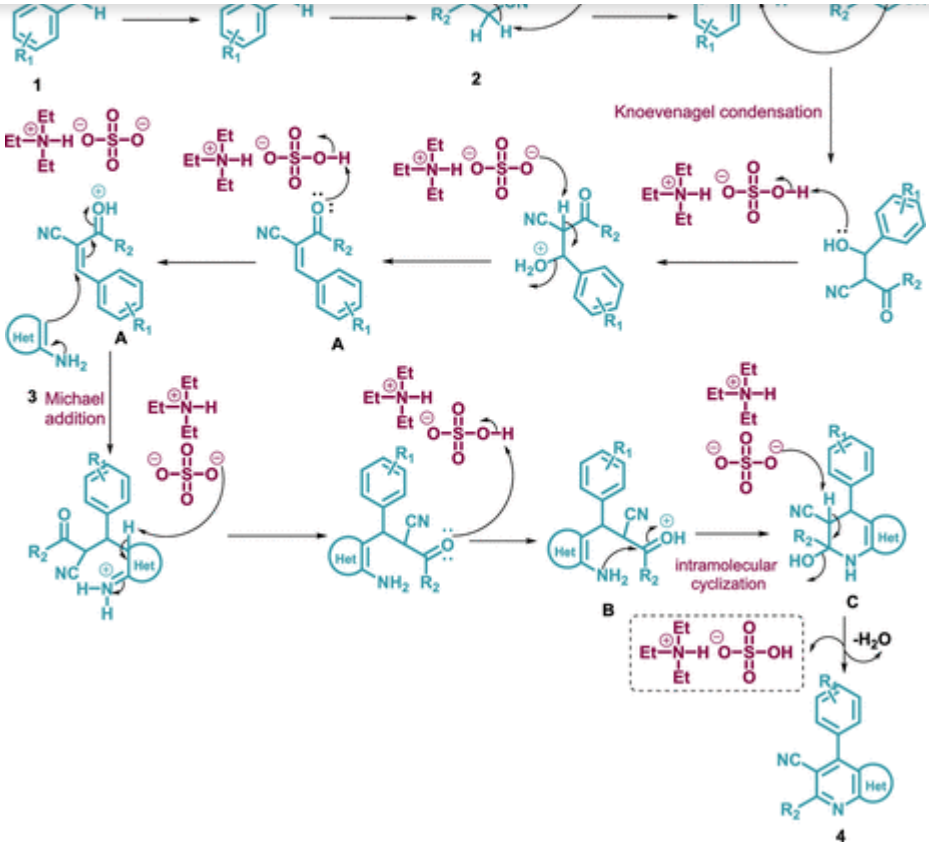


Scheme 3. Reaction of Cinnamaldehyde, 6-Amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, and 3-Oxo-3-phenyl-propanenitrile

Under the optimized reaction conditions, we examined a series of pyrido[2,3-*d*]pyrimidine and pyrazolo[3,4-*b*]pyridine to probe the scope of this $[Et_3NH][HSO_4]$-catalyzed, three-component transformation. The structural diversity of the starting materials is summarized in Table 2, and a wide variety of aryl aldehydes containing electron-donating and electron-withdrawing groups at the meta or para position, aliphatic aldehydes, and heteroaromatic aldehydes were reacted with acyl acetonitriles containing para electron-withdrawing substituents and electron-rich amino heterocycles shown in the Supporting Information (Figure S1) to afford the corresponding pyrido[2,3-*d*]pyrimidine and pyrazolo[3,4-*b*]pyridine hybrids in excellent yields. It is important to note that the ortho-substituted aldehydes 2-bromobenzaldehyde and 2-methoxy benzaldehyde and the para-substituted acyl acetonitriles and electron-rich amino heterocycles stably afforded the expected products under the same reaction parameters. The heteroaromatic aldehydes furfural and thiophene-2-carbaldehyde took part in the reaction, smoothly affording the expected products in excellent yields. The results show that $[Et_3NH][HSO_4]$ is an efficient catalyst for the preparation of a large series of fused pyridine in excellent yields (Table 2). It was also found that meta-substituted acyl acetonitriles with electron-donating groups (4-Me and 4-MeO) did not take part in the reaction to give the corresponding fused pyridine.

It is evident from the literature that ILs containing hydrogen sulfate exhibit Brønsted acid properties in various organic transformations. (17,53,54) Accordingly, a plausible mechanism for this IL-catalyzed three-component synthesis of pyrazolo[3,4-*b*]pyridine and pyrido[2,3-*d*]pyrimidine derivatives is proposed in Scheme 4. First, a sequence of reaction involving Knoevenagel condensation of aldehyde **1** with acyl acetonitrile **2** is proposed to give the intermediate **A**. Michael addition of electron-rich amino heterocycles **3** to **A** should then occur to provide intermediate **B**, which undergoes intramolecular heterocyclization and dehydration to give **C**. In the last step, oxidation of intermediate **C** takes place to form product **4**.

Scheme 4



Scheme 4. Proposed Mechanism for the Synthesis of Pyrazolo[3,4-*b*]pyridine and Pyrido[2,3-*d*]pyrimidine Hybrids

The reusability of the catalyst is a significant advantage particularly for commercial applications and was also explored in the model reaction. To test the reusability of the catalyst, after completion of the reaction, cold water was added to the reaction mixture, and the products were isolated by filtration. The ionic liquid was recovered by removing the water under reduced pressure and was reused at least five times without any appreciable decrease in yield (Figure 1). The IR spectrum of the recovered $[Et_3NH][HSO_4]$ (after five cycles) corresponded with that of the fresh sample. As confirmed in Figure 2, the IR spectrum shown by the recovered catalyst was proven to be almost identical to that of the fresh one.

Figure 1

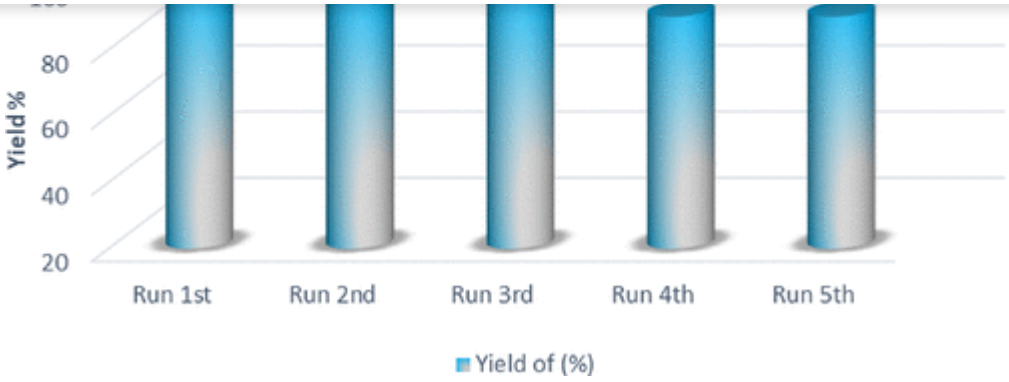


Figure 1. Recycling of the IL in the synthesis of **4a**.

Figure 2

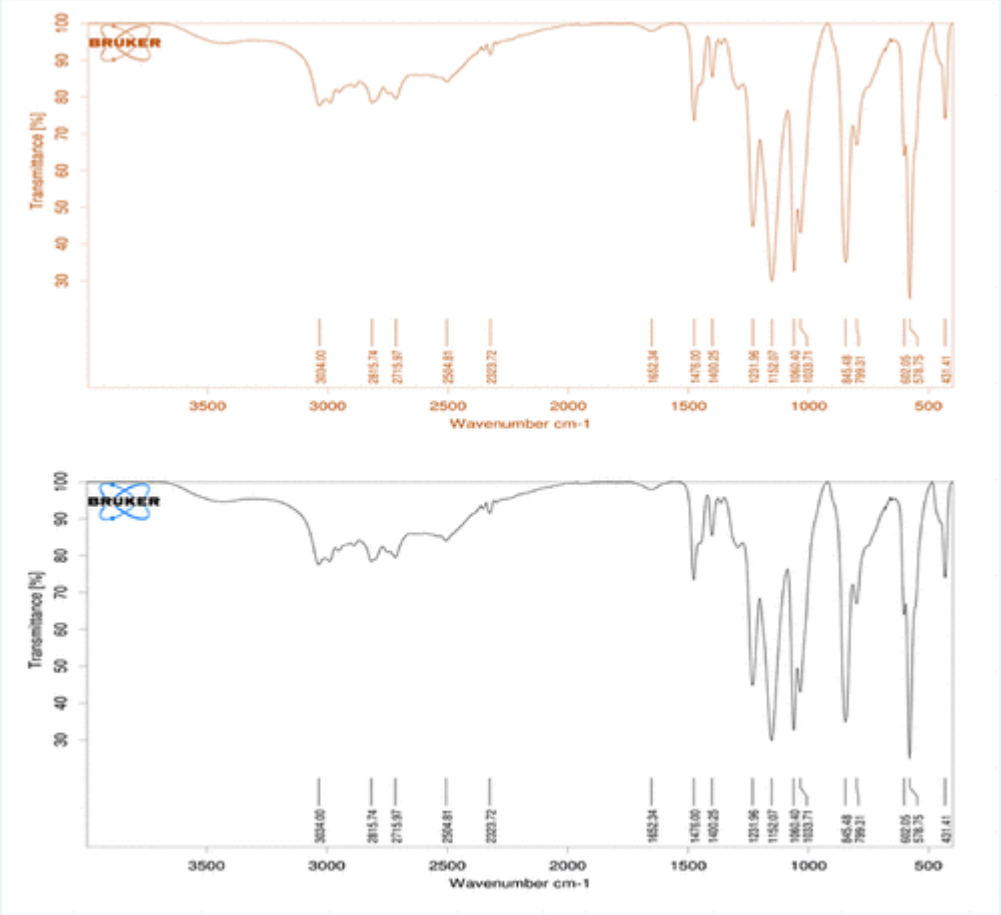


Figure 2. IR spectra of the reuse and recovery of $[Et_3NH][HSO_4]$ (black spectrum: fresh; orange spectrum: after five recycles).

five cycles.

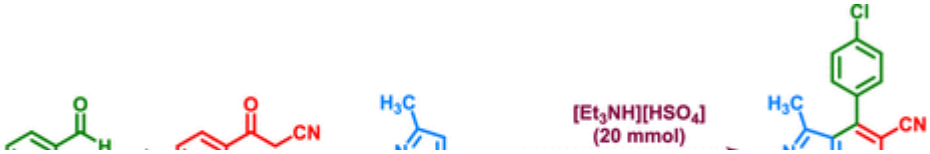
Table 3. Comparative Study with a Reported Method for the Synthesis of Fused Pyridine Derivatives

entry	catalyst and solvent	temperature	time (min)	yield (%)	refere
1	[Bmim]Br, solvent-free	80 °C	4–5 h	72–98	(24)
2	$[Et_3NH][HSO_4]$, solvent-free	60 °C	30–45 min	90–96	this w

In comparison with other reported catalysts for pyrazolo[3,4-*b*]pyridine and pyrido[2,3-*d*]pyrimidine derivatives (Table 3), $[Et_3NH][HSO_4]$ as a catalyst as well as a solvent is among the best ones in terms of operational simplicity, shorter reaction time, good to excellent yields, extensive substrate range with high functional group tolerance, and recyclability. For example, Shi et al. reported an efficient one-pot synthesis of fused pyridine derivatives in which [Bmim]Br solvent-free at 80 °C offered up to 72–90% conversion after prolonged duration (4–7 h) (Table 3, entry 1). In our case, catalyst $[Et_3NH][HSO_4]$ solvent-free at 60 °C offered up to 90–96% conversion only in a very short duration (30–45 min) (Table 3, entry 2). In addition to the abovementioned advantages, $[Et_3NH][HSO_4]$ is readily available, eco-friendly, inexpensive, and safer. Also, it was used as a greener solvent, and furthermore, the reusability of the catalyst was studied for up to five cycles.

Furthermore, to evaluate the reaction productivity and the catalytic potency, we have conducted the gram-scale (20 mmol) reaction under the optimized reaction condition, which provided the desired 4-(4-chlorophenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **4a** in 94.5% yield in 30 min (Scheme 5). We have noted that our large-scale experimental results are nearly similar to the small-scale 1 mmol (Table 2, entry 1) reaction with respect to yield and time to obtain the desired product.

Scheme 5



In conclusion, the ability of $[Et_3NH][HSO_4]$ ILs to act as solvents and catalysts for the synthesis of pyrazolo[3,4-*b*]pyridine and pyrido[2,3-*d*]pyrimidine derivatives is noted. These ILs that act as alternative solvents and catalysts are cheap, rapidly and easily prepared, satisfactorily biodegradable, recyclable, and not harmful to the environment compared to conventional solvents. The final products were obtained in high purity and in satisfactory yields in short reaction times. The developed methodology is environmentally friendly with green chemistry credentials as the ILs can be recycled and reused while they present remarkable biodegradability potential in a short time period. In addition, the present methodology showed good results under gram-scale conditions, thereby indicating its applicability in industrial as well as academic settings in the near future.

Experimental Section

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General Remarks

Melting points (m.p.) of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin-Elmer RXI spectrometer in KBr and ^{1}H NMR and ^{13}C NMR on a Bruker DRX-300 and Bruker Avance II 400 spectrometer using tetramethyl silane (TMS) as the internal standard and DMSO-d_6/$CDCl_3$ as the solvent, respectively. Thin-layer chromatography (TLC) was conducted on silica-gel $HSGF_{254}$. High-resolution mass spectra (HRMS) were obtained using a time-of-flight mass spectrometry instrument. Starting products, like substituted aldehydes and aminouracils and aminopyrazoles, and acyl acetonitrile (80%) were purchased from Sigma-Aldrich and were used without further purification. Other chemicals were of commercial grade and used without further purification.

General Procedure for Preparation of Triethylammonium Hydrogen Sulfate $[Et_3NH][HSO_4]$-IL (55)

Sulfuric acid (98%) (9.8 g, 0.1 mmol) was dropped into the triethylamine (10.1 g, 0.1 mmol) at 60 °C in 1 h. After the addition, the reaction mixture was stirred for an additional period of 1 h at 70 °C to ensure that the reaction had proceeded to completion. Then, the traces of water were removed by heating the residue at 80 °C in a high vacuum until the weight of the residue remained constant. The yield of $[Et_3NH][HSO_4]$ was 99% (19.8 g).^{1}H NMR (DMSO-d_6): δ (ppm) 1.18 (t, 3H), 3.10 (m, 2H), 8.89 (s, 1H) (5).

were isolated by filtration. The ionic liquid was recovered by removing the water under reduced pressure and was reused.

Spectral Data

3-Methyl-1,6-diphenyl-4-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4a)

m.p.: 231–233 °C. IR (KBr) v: 2221, 1596, 1572, 1506, 1491, 1437, 1343, 1127, 1091, 1017, 839, 774, 757, 705 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.18 (3H, s, CH_3), 7.26–7.35 (1H, m, ArH), 7.47–7.60 (9H, m, ArH), 7.99–8.01 (2H, m, ArH), 8.28 (2H, d, J = 8.0 Hz, ArH). HRMS [found: m/z 420.1143 (M^+); calcd for $C_{26}H_{16}{}^{35}Cl_2N_4$ M: 420.1442].

2-Amino-5-(4-chlorophenyl)-4-oxo-7-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4b)

m.p.: 252–254 °C. IR (KBr) v: 3322, 3149, 3059, 2216,1696, 1668, 1596, 1541, 1487, 1455, 1431, 1386, 1356, 1281, 1214, 1090, 1017, 909, 827, 801, 785, 718 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 7.40–7.43 (2H, m, ArH), 7.50–7.57 (7H, m, ArH + NH_2), 7.88–7.96 (2H, m, ArH), 11.22 (1H, s, NH). HRMS [found: m/z 373.0729 (M^+); calcd for $C_{20}H_{12}{}^{35}ClN_5O$ M: 373.0730].

5-(4-Chlorophenyl)-1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4c)

m.p.: >300 °C. IR (KBr) v: 2222, 1712, 1666, 1583, 1554, 1495, 1477, 1440, 1410, 1362, 1287, 1087, 1020, 779, 752, 721, 697 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.19 (3H, s, CH_3), 3.69 (3H, s, CH_3), 7.43 (2H, dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, ArH), 7.58 (2H, dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, ArH), 7.62–7.64 (3H, m, ArH), 8.03 (2H, d, J = 7.2 Hz, ArH). HRMS [found: m/z 402.0886 (M^+); calcd for $C_{22}H_{15}{}^{35}ClN_4O_2$ M: 402.0884].

2-Amino-4-oxo-7-phenyl-5-*p*-tolyl-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4d)

m.p.: 249–250 °C. IR (KBr) v: 3323, 3060, 2224, 1701, 1665, 1539,1455, 1431, 1386, 1357, 1280, 1209, 1103, 908, 828, 789, 717, 694 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.43 (3H, s, CH_3), 7.28 (5H, s, ArH), 7.58–7.60 (4H, m, ArH + NH_2), 7.89–7.99 (2H, m, ArH), 11.18 (1H, s, NH). ^{13}C NMR (DMSO-d_6) (δ, ppm): 21.65, 108.74, 114.13, 118.04, 128.48, 128.97, 129.69,

(2H, m, ArH), 8.22 (2H, d, J = 8.4 Hz, ArH). HRMS [found: m/z 400.1688 (M^+); calcd for $C_{27}H_{20}N_4$ M: 400.1688].

1,3-Dimethyl-2,4-dioxo-7-phenyl-5-*p*-tolyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4f)

m.p.: >300 °C. IR (KBr) v: 2222, 1713, 1668, 1553, 1478, 1409, 1362, 1286, 1097, 817, 752, 716, 698 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.41 (3H, s, CH_3), 3.17 (3H, s, CH_3), 3.67 (3H, s, CH_3), 7.25–7.31 (4H, m, ArH), 7.61–7.62 (3H, m, ArH), 8.00–8.02 (2H, m, ArH). HRMS [found: m/z 382.1435 (M^+); calcd for $C_{23}H_{18}N_4O_2$ M: 382.1430].

7-(4-Chlorophenyl)-1,3-dimethyl-2,4-dioxo-5-(4-methylphenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4g)

m.p.: >300 °C. IR (KBr) v: 2220, 1718, 1670, 1578, 1550, 1496, 1475, 1411, 1363, 1285, 1092, 1012, 844, 812 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.44 (3H, s, CH_3), 3.21 (3H, s, CH_3), 3.71 (3H, s, CH3), 7.28–7.34 (4H, m, ArH), 7.73 (2H, d, J = 8.0 Hz, ArH), 8.08 (2H, d, J = 8.4 Hz, ArH). HRMS [found: m/z 416.1001 (M^+); calcd for $C_{23}H_{17}{}^{35}ClN_4O_2$ M: 416.1040].

3-Methyl-1,6-diphenyl-4-(3,4-methylenedioxylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4h)

m.p.: 216–218 °C. IR (KBr) v: 2220, 1584, 1570, 1506, 1489, 1467, 1442, 1385, 1272, 1236, 1197, 1037, 931, 779, 758, 708 cm^{-1}; ^1H NMR ($CDCl_3$) (δ, ppm): 2.25 (3H, s, CH_3), 6.12 (2H, d, J = 10.8 Hz, OCH_2O), 6.99–7.03 (3H, m, ArH), 7.32 (1H, t, J = 7.6 Hz, ArH), 7.49–7.55 (5H, m, ArH), 7.99–8.01 (2H, m, ArH), 8.29 (2H, d, J = 8.0 Hz, ArH). HRMS [found: m/z 430.1428 (M^+); calcd for $C_{27}H_{18}N_4O_2$ M: 430.1430].

5-(3,4-Methylenedioxyphenyl)-1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4i)

m.p.: 269–270 °C. IR (KBr) v: 2223, 1718, 1670, 1554, 1502, 1477, 1439, 1362, 1244, 1080, 1037, 822, 752, 713, 696 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.16 (3H, s, CH_3), 3.63 (3H, s, CH_3), 6.10 (2H, s, OCH_2O), 6.82–6.86 (1H, m, ArH), 6.93–6.95 (1H, m, ArH), 6.98–7.03 (1H, m, ArH), 7.56–7.61 (3H, m, ArH), 7.98–8.00 (2H, m, ArH). HRMS [found: m/z 412.1179 (M^+); calcd for $C_{23}H_{16}N_4O_4$ M: 412.1172].

3-Methyl-1,6-diphenyl-4-(4-bromophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4k)

m.p.: 244–246 °C. IR (KBr) v: 2223, 1595, 1571, 1507, 1489, 1433, 1340, 1196, 1124, 1012, 834, 774, 753, 699 cm^{-1}; ^1H NMR ($CDCl_3$) (δ, ppm): 2.19 (3H, s, CH_3), 7.33 (1H, t, J = 7.2 Hz, ArH), 7.42 (2H, d, J = 8.0 Hz, ArH), 7.50–7.56 (5H, m, ArH), 7.75 (2H, d, J = 8.0 Hz, ArH), 7.99–8.02 (2H, m, ArH), 8.29 (2H, d, J = 8.0 Hz, ArH). HRMS [found: m/z 464.0643(M^+); calcd for $C_{26}H_{17}{}^{79}BrN_4$ M: 464.0637].

5-(4-Bromophenyl)-1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4l)

m.p.: >300 °C. IR (KBr) v: 2222, 1713, 1666, 1553, 1476, 1410, 1362, 1287, 1072, 1011, 752, 697 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.18 (3H, s, CH_3), 3.69 (3H, s, CH_3), 7.36 (2H, d, J = 8.4 Hz, ArH), 7.61–7.64 (3H, m, ArH), 7.71 (2H, d, J = 8.4 Hz, ArH), 8.01–8.03 (2H, m, ArH). HRMS [found: m/z 446.0375 (M^+); calcd for $C_{22}H_{15}{}^{79}BrN_4O_2$ M: 446.0378].

5-(4-Bromophenyl)-7-(4-chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4m)

m.p.: 177–178 °C. IR (KBr) v: 3446, 3177, 2224, 1714, 1641, 1574, 1557, 1490, 1385, 1261, 1204, 1092, 1072, 1010, 833, 815, 750, 705 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 7.31–7.36 (2H, m, ArH), 7.63–7.70 (4H, m, ArH), 7.86–7.92 (2H, m, ArH), 11.50 (1H, s, NH), 12.26 (1H, s, NH). HRMS [found: m/z 451.9676 (M^+); calcd for $C_{20}H_{10}{}^{79}Br^{35}ClN_4O_2$ M: 451.9676].

5-(3,4-Dimethoxyphenyl)-1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4n)

m.p.: 226–227 °C. IR (KBr) v: 2223, 1717, 1674, 1564, 1517, 1467, 1405, 1351, 1281, 1260, 1138, 1020, 789, 750, 697 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.20 (3H, s, CH_3), 3.68 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.94 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, ArH), 7.03 (1H, d, J = 2.0 Hz, ArH), 7.07 (1H, d, J = 8.4 Hz, ArH), 7.61–7.64 (3H, m, ArH), 8.01–8.03 (2H, m, ArH). ^{13}C NMR (DMSO-d_6) (δ, ppm): 28.96, 30.77, 104.39, 107.73, 116.95, 127.08, 128.07, 129.29, 129.36, 130.01, 130.66, 131.93, 133.29, 137.02, 139.24, 151.31, 152.84, 157.21, 159.40, 163.52. HRMS [found: m/z 428.1483 (M^+); calcd for $C_{24}H_{20}N_4O_4$ M: 428.1485].

tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4p)

m.p.: 246–248 °C. IR (KBr) v: 2222, 1714, 1668, 1552, 1516, 1473, 1441, 1409, 1361, 1253, 1176, 1097, 833, 752 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.20 (3H, s, CH_3), 3.69 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 7.06 (2H, d, J = 8.8 Hz, ArH), 7.35 (2H, d, J = 8.8 Hz, ArH), 7.62–7.65 (3H, m, ArH), 8.03 (2H, dd, J_1 = 2.0 Hz, J_2 = 7.2 Hz, ArH). HRMS [found: m/z 398.1378 (M^+); calcd for $C_{23}H_{18}N_4O_3$ M: 398.1379].

7-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4q)

m.p.: >300 °C. IR (KBr) v: 2221, 1717, 1669, 1610, 1577, 1549, 1515, 1472, 1363, 1298, 1253, 1176, 1092, 1035, 840, 816, 752 cm^{-1}; ^1H NMR(DMSO-d_6) (δ, ppm): 3.18 (3H, s, CH_3), 3.67 (3H, s, CH_3), 3.85 (3H, s, OCH3), 7.04 (2H, d, J = 8.4 Hz, ArH), 7.32 (2H, d, J = 8.4 Hz, ArH), 7.69 (2H, d, J = 8.4 Hz, ArH), 8.04 (2H, d, J = 8.4 Hz, ArH). HRMS [found: m/z 432.0988 (M^+); calcd for $C_{23}H_{17}{}^{35}ClN_4O_3$ M: 432.0989].

3-Methyl-1,6-diphenyl-4-(2-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4r)

m.p.: 226–228 °C. IR (KBr) v: 2223, 1575, 1557, 1526, 1503, 1429, 1383, 1345, 1196, 1127, 795, 762, 708 cm^{-1}; ^1H NMR ($CDCl_3$) (δ, ppm): 2.03 (3H, s, CH_3), 7.34 (1H, t, J = 7.6 Hz, ArH), 7.51–7.57 (6H, m, ArH), 7.82 (1H, t, J = 8.0 Hz, ArH), 7.90 (1H, t, J = 7.2 Hz, ArH), 8.02–8.04 (2H, m, ArH), 8.29 (2H, d, J = 8.4 Hz, ArH), 8.41 (1H, d, J = 8.4 Hz, ArH). HRMS [found: m/z 431.1383 (M^+); calcd for $C_{26}H_{17}N_5O_2$ M: 431.1382].

3-Methyl-1-phenyl-6-(4-chlorophenyl)-4-(2-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4s)

m.p.: 201–202 °C. IR (KBr) v: 2223, 1581, 1566, 1524, 1506, 1438, 1345, 1096, 1012, 792, 754 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.00 (3H, s, CH_3), 7.39–7.43 (1H, m, ArH), 7.59–7.63 (2H, m, ArH), 7.69–7.72 (2H, m, ArH), 7.86–7.88 (1H, m, ArH), 7.99–8.02 (3H, m, ArH), 8.07–8.11 (1H, m, ArH), 8.22 (2H, d, J = 8.0 Hz, ArH), 8.49 (1H, d, J = 8.0 Hz, ArH). ^{13}C NMR (DMSO-d_6) (δ, ppm): 13.98, 101.34, 113.69, 117.31, 118.35, 121.87, 126.12, 127.48, 128.87, 129.49, 130.07, 131.87, 132.48, 132.77, 135.55, 136.21, 136.66, 138.69, 144.13, 147.60, 150.20, 159.13. HRMS [found: m/z 465.1005 (M^+); calcd for $C_{26}H_{16}{}^{35}ClN_5O_2$ M: 465.0993].

ArH). HRMS [found: *m*/*z* 420.1144 (M^+); calcd for $C_{26}H_{17}{}^{35}ClN_4$ M: 420.1142].

5-(3-Chlorophenyl)-1,3-dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4u)

m.p.: 270–272 °C. IR (KBr) v: 2225, 1717, 1668, 1557, 1479, 1409, 1394, 1358, 1108, 1019, 818, 781, 750, 706 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.19 (3H, s, CH_3), 3.69 (3H, s, CH_3), 7.36 (1H, dd, J_1 = 1.6 Hz, J_2 = 6.8 Hz, ArH), 7.51–7.59 (3H, m, ArH), 7.62–7.64 (3H, m, ArH), 8.03–8.04 (2H, m, ArH). HRMS [found: *m*/*z* 402.0884 (M^+); calcd for $C_{22}H_{15}{}^{35}ClN_4O_2$ M: 402.0884].

3-Methyl-1,6-diphenyl-4-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4v)

m.p.: 186–188 °C. IR (KBr) v: 2220, 1596, 1574, 1506, 1434, 1342, 1197, 1128, 1058, 771, 756, 703 cm^{-1}; ^1H NMR ($CDCl_3$) (δ, ppm): 2.12 (3H, s, CH_3), 7.33 (1H, t, *J* = 7.6 Hz, ArH), 7.44 (1H, dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, ArH), 7.50–7.58 (7H, m, ArH), 7.64 (1H, d, *J* = 8.0 Hz, ArH), 8.03–8.06 (2H, m, ArH), 8.31 (2H, d, *J* = 8.0 Hz, ArH). HRMS [found: *m*/*z* 420.1140 (M^+); calcd for $C_{26}H_{17}{}^{35}ClN_4$ M: 420.1142].

3-Methyl-1,6-diphenyl-4-(2-nitro-4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4w)

m.p.: 275–276 °C. IR (KBr) v: 2220, 1584, 1563, 1525, 1505, 1435, 1380, 1341, 1295, 1074, 845, 763, 711 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.07 (3H, s, CH_3), 7.39–7.43 (1H, m, ArH), 7.59–7.64 (5H, m, ArH), 7.97–7.99 (2H, m, ArH), 8.10 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, ArH), 8.15 (1H, d, *J* = 2.0 Hz, ArH), 8.23 (2H, d, *J* = 8.4 Hz, ArH), 8.52 (1H, d, *J* = 8.8 Hz, ArH). HRMS [found: *m*/*z* 465.0995 (M^+); calcd for $C_{26}H_{16}{}^{35}ClN_5O_2$ M: 465.0993].

3-Methyl-1,6-diphenyl-4-(4-dimethylaminophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4x)

m.p.: 210–212 °C. IR (KBr) v: 2219, 1607, 1564, 1526, 1506, 1436, 1369, 1206, 1171, 969, 824, 796, 757 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.22 (3H, s, CH_3), 3.05 (6H, s, $(CH_3)_2N$), 6.91 (2H, d, *J* = 8.8 Hz, ArH), 7.35–7.39 (1H, m, ArH), 7.52–7.60 (7H, m, ArH), 7.93–7.95 (2H, m, ArH), 8.22 (2H, d, *J* = 8.4 Hz, ArH). HRMS [found: *m*/*z* 429.1960 (M^+); calcd for $C_{28}H_{23}N_5$ M: 429.1953].

ArH), 7.96−7.98 (2H, m, ArH), 8.20 (2H, d, J = 8.0 Hz, ArH). HRMS [found: m/z 463.1576 (M^+); calcd for $C_{28}H_{22}{}^{35}ClN_5$ M: 463.1564].

3-Methyl-1,6-diphenyl-4-(thiophen-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4z)

m.p.: 191−192 °C. IR (KBr) v: 2223, 1574, 1558, 1527, 1506, 1487, 1433, 1412, 1349, 1196, 1118, 777, 758, 708 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 2.25 (3H, s, CH_3), 7.38−7.44 (2H, m, ArH), 7.59−7.64 (6H, m, ArH), 7.96−7.99 (2H, m, ArH), 8.03−8.05 (1H, m, ArH), 8.23 (2H, d, J = 8.4 Hz, ArH). ^{13}C NMR (DMSO-d_6) (δ, ppm): 14.82, 103.16, 114.58, 117.85, 121.53, 127.14, 128.40, 129.14, 129.88, 130.06, 130.74, 130.86, 131.78, 132.76, 138.15, 138.76, 144.34, 145.95, 150.10, 160.71. HRMS [found: m/z 392.1095 (M^+); calcd for $C_{24}H_{16}N_4S$ M: 392.1096].

1,3-Dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4am)

m.p.: 177−178 °C. IR (KBr) v: 1717, 1669, 1585, 1551, 1498, 1465, 1422, 1378, 1355, 1283, 1240, 1175, 1003, 844, 762, 719, 703 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 3.19 (3H, s, CH_3), 3.62 (3H, s, CH_3), 7.09 (1H, d, J = 4.8 Hz, ArH), 7.31−7.32 (2H, m, ArH), 7.40−7.42 (3H, m, ArH), 8.67 (1H, d, J = 4.8 Hz, ArH).

Supporting Information

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University, Aurangabad 431004, Maharashtra, India;
https://orcid.org/0000-0002-3419-8233; Email: chgill16@gmail.com

Authors

Chetan Jadhav - *Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India*

Amol Nipate - *Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India*

Asha Chate - *Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India*

Notes

The authors declare no competing financial interest.
(C.J.) This work is dedicated to my beloved parents.

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