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RESEARCH ARTICLE

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Efficient One-Pot Three-Component Synthesis of Fused Pyridine Derivatives in Ionic Liquid

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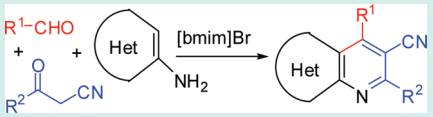
Supporting Information

ABSTRACT: An efficient one-pot synthesis of fused pyridine derivatives (including pyrazolo[3,4-*b*]pyridine and pyrido[2,3-*d*]pyrimidine) by three-component reaction of aldehyde, acyl acetonitrile, and electron-rich amino heterocycles (including aminopyrazole and aminouracils) in ionic liquid is reported. This new protocol has the advantages of environmental friendliness, higher yields, shorter reaction times, and convenient operation.



KEYWORDS: one-pot synthesis, pyridine derivatives, multicomponent reactions, ionic liquid

INTRODUCTION

Multicomponent reactions (MCRs) in which several reactions are combined into one synthetic operation have been used extensively to form carbon−carbon bonds in the synthetic chemistry.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedure step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. Thus, they are perfectly amenable to automation for combinatorial synthesis.[2] In the past decade, there have been tremendous development in three- and four-component reactions and great effort continue to be made to develop new MCRs.[3]

Pyrazole and its derivatives are gaining importance in medicinal and organic chemistry. They have displayed broad spectrum of pharmacological and biological activities, such as antibacterial, antidepressant, antihyperglycemic, anti-inflammatory, and antitumor.[4] In particular, condensed pyrazoles are known for various biological activities, for example, pyrazolo[3,4-*b*]pyridines are useful for treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhaged stress, drug and alcohol withdrawal symptoms, drug addition and infertility.[5] Pyrido[2,3-*d*]-pyrimidines represent a heterocyclic ring system of considerable interest because of several biological activities associated with this scaffold. Some analogues have been found to act as anticancer agents inhibiting dihydrofolate reductases or tyrosine kinases,[6] while others are known as antiviral agents.[7] Pyrazolo-[3,4-*b*]pyridine derivatives are general prepared by reaction of 5-aminopyrazole and substituted α,β-unsaturated nitriles in organic solvent using triethylamine as catalyst,[8] but most of them suffer from drawbacks, such as lower yields and use of organic solvent.

Room temperature ionic liquids (RTILs), especially those based on 1-alkyl-3-methylimidazolium cations, have shown great promise as an attractive alterative to conventional organic solvents, and more attention has been currently focused on organic reactions promoted by ionic liquids.[9] They are nonvolatile, recyclable, nonexplosive, easily operable, and thermally robust.[10] There are many reports concerning the applications of ionic liquid in organic reactions, such as Friedel−Crafts reactions,[11] Diels−Alder reactions,[12] Heck reactions,[13] Pechmann condensations,[14] Biginelli reactions,[15] Beckmann rearrangements,[16] and other reactions.[17] As part of our current studies on the developments of new routes to heterocyclic systems in ionic liquid,[18] we herein described a facile synthesis of fused pyridine derivatives (including pyrazolo[3,4-*b*]pyridine and pyrido[2,3-*d*]pyrimidine) by three-component reaction of aldehyde, acyl acetonitrile, and electron-rich amino heterocycles (including aminopyrazole and aminouracils) in ionic liquid without any catalyst.

RESULTS AND DISCUSSION

To avoid the disadvantages such as volatility and toxicity than many organic solvents inherently have, we employed RTILs into the three-component reaction as a green medium. Initially, the three-component reaction of 4-methylbenzaldehyde **1**{*1*}, 3-oxo-3-phenylpropanenitrile **2**{*1*}, and 3-methyl- 1-phenyl-1*H*-pyrazol-5-amine **3**{*1*} as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 1). The effects of solvents and reaction temperature were evaluated for this model reaction, and the results are summarized in Table 1. The ionic liquid [bmim]Br provided higher yields and shorter reaction times than those using organic solvents (Table 1, entry 8 vs entries 1−5). The bmim bromide also proved to be slightly superior to the

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Scheme 1. Model Reaction

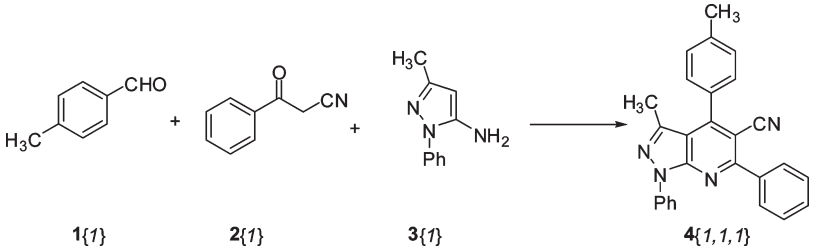

Table 1. Optimization of Reaction Conditions

entry	solvent	T (°C)	time (h)	isolated yield (%)
1	acetone	60	24	32
2	acetonitrile	70	18	59
3	ethanol	80	10	73
4	chloroform	60	25	55
5	DMF	100	8	81
6	[bmim]PF_6	90	6.5	89
7	[bmim]BF_4	90	6	90
8	[bmim]Br	90	5	93
9	[bmim]Br	r.t.	20	53
10	[bmim]Br	40	14	68
11	[bmim]Br	60	8	79
12	[bmim]Br	80	5	93

analogous hexafluorophosphate or tetrafluoroborate ionic liquids for this reaction (Table 1, entries 6 and 7). The yield of product **4**{*1,1,1*} was improved and the reaction time was shortened as the temperature was increased from room temperature to 80 °C, with no further improvement observed at 90 °C (Table 1, entries 8−12). Therefore, the most suitable reaction temperature is 80 °C.

The optimized reaction conditions were then tested for library construction with eighteen aldehydes **1**{*1*−*18*}, three acyl acetonitriles **2**{*1*−*3*}, and four electron-rich amino heterocycles **3**{*1*−*4*} (Figure 1). The corresponding fused pyridine derivatives **4** were obtained in good yields at 80 °C in ionic liquid [bmim]Br without any catalyst. The results are summarized in Table 2. The protocol was effective with aromatic aldehydes having either electron-withdrawing (nitro, halide) or electron-donating groups (hydroxyl, alkoxyl) and also with heterocyclic aldehydes and aliphic aldehydes.

α,β-Unsaturated aldehydes were found to be incompatible with the three-component assembly reaction, as noted for the combination of 3-phenylacrylaldehyde **1**{*18*}, 3-oxo-3-phenylpropanenitrile **2**{*1*}, and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **3**{*2*}. In this case, the desired tetrahydropyrido[2,3-*d*]pyrimidine was not obtained. Instead, an efficient side reaction between **1**{*18*} and **3**{*2*} occurred to give1,3-dimethyl-5-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was observed (Table 2, entry 46).

The structures of all products **4** were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data as well as HRMS analysis. The structure of **4**{*13,2,1*} was further confirmed by X-ray diffraction analysis. The molecular structure of **4**{*13,2,1*} is shown in Figure 2.

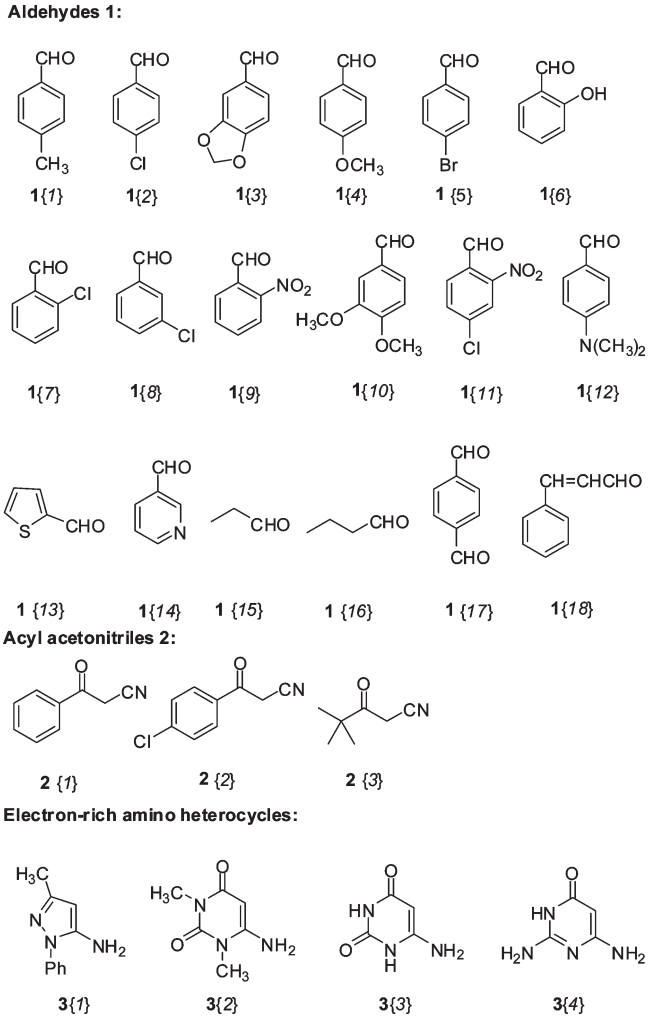

Figure 1. Diversity of reagents.

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compounds **4** could be explained by the reaction sequence in Scheme 2. First, a Knoevenagel condensation reaction 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 cyclization and dehydration to give **C**. In the last step, the intermediate product **C** is aromatized to product **4**.

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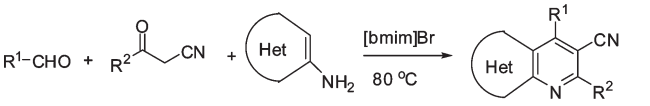
Table 2. Synthesis of Fused Pyridine Derivatives 4 in Ionic Liquid [bmim]Br



1{*1-18*} 2{*1-3*} 3{*1-3*} 4{*1(1-18),2(1-3),3(1-3)*}

entry	products	time (h)	isolated yield (%)	mp (°C)
1	4{*1,1,1*}	5	93	210−212
2	4{*1,1,2*}	5	92	>300
3	4{*1,1,4*}	5	94	249−250
4	4{*1,2,1*}	5	96	210−211
5	4{*1,2,2*}	5	92	>300
6	4{*1,3,1*}	4	86	197−199
7	4{*2,1,1*}	5	95	231−233
8	4{*2,1,2*}	5.5	88	>300
9	4{*2,1,4*}	5.5	98	252−254
10	4{*2,2,1*}	5.5	93	244−246
11	4{*2,2,2*}	5	90	>300
12	4{*2,3,1*}	4	85	180−182
13	4{*3,1,1*}	5.5	94	216−218
14	4{*3,1,2*}	5	90	269−270
15	4{*4,1,1*}	4.5	98	206−208
16	4{*4,1,2*}	5	94	246−248
17	4{*4,2,2*}	5	88	>300
18	4{*5,1,1*}	5.5	95	244−246
19	4{*5,1,2*}	5.5	98	>300
20	4{*5,2,3*}	5	93	177−178
21	4{*5,2,4*}	5.5	97	266−268
22	4{*6,1,1*}	4.5	98	204−206
23	4{*7,1,1*}	6	82	186−188
24	4{*8,1,1*}	6	98	176−178
25	4{*8,1,2*}	7	90	270−272
26	4{*9,1,1*}	6.5	92	226−228
27	4{*9,2,1*}	5.5	93	201−202
28	4{*10,1,1*}	4	92	192−194
29	4{*10,1,2*}	4.5	92	226−227
30	4{*11,1,1*}	5.5	91	275−276
31	4{*12,1,1*}	4.5	96	210−212
32	4{*12,2,1*}	4.5	92	265−267
33	4{*13,1,1*}	5	95	191−192
34	4{*13,1,2*}	5	90	257−258
35	4{*13,2,1*}	5	80	210−212
36	4{*13,2,2*}	5	90	275−276
37	4{*14,1,1*}	5	83	174−176
38	4{*14,1,2*}	6	85	269−270
39	4{*14,2,1*}	5	89	201−203
40	4{*14,2,2*}	6	81	246−248
41	4{*15,1,1*}	4.5	98	138−139
42	4{*15,2,1*}	4.5	89	200−202
43	4{*16,1,1*}	4.5	91	156−158
44	4{*16,2,1*}	4.5	92	163−164
45	4{*17,1,2*}	5	90	>300
46	4{*18,0,2*}[a]	5	72	177−178

[a] The product is 1,3-dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione.

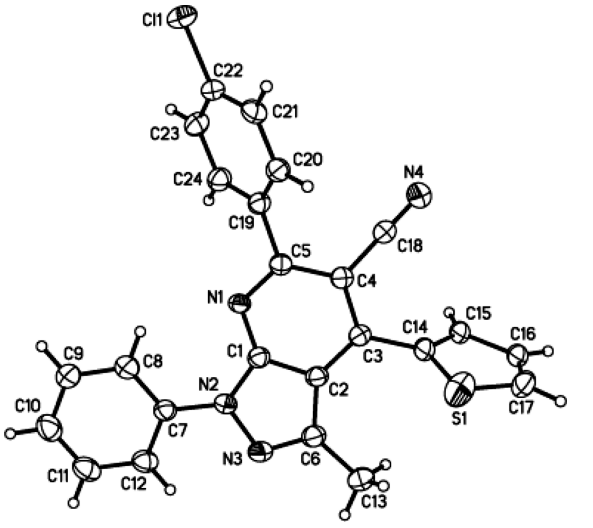
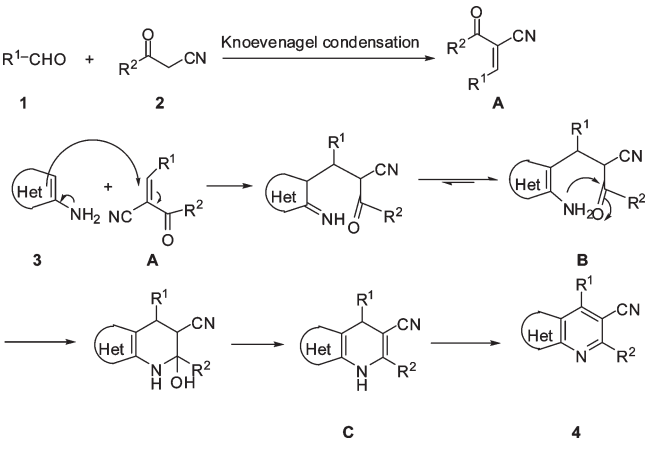


Figure 2. Crystal structure of 4{*13,2,1*}.

Scheme 2. Proposed Mechanism for the Synthesis of Fused Pyridines 4



CONCLUSION

We have described an efficient one-pot three-component reaction of aldehyde, acyl acetonitrile, and electron-rich amino heterocycles, such as 5-aminopyrazole or 6-aminopyrimidine-2,4-dione, for the synthesis of pyrazolo[3,4-*b*] pyridine and pyrido[2,3-*d*]pyrimidine derivatives in ionic liquid. This method has the advantages of higher yields, milder reaction conditions, shorter reaction time, convenient procedure, and environmental friendliness. Given the large number of commercially available building blocks, the present method should be applicable to synthesis of libraries with high diversity.

EXPERIMENTAL PROCEDURES

General Information. Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR were determined on Varian-300 MHz or Varian-400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in parts per million downfield from internal

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standard TMS. High-resolution mass spectra (HRMS) were obtained using a time-of-flight mass spectrometry (TOF-MS) instrument. X-ray crystallographic analysis was performed with a Rigaku Mercury CCD/AFC diffractometer.

General Procedure for the Synthesis of Fused Pyridine Derivatives 4. A dry 50 mL flask was charged with aldehyde **1** (1 mmol), acyl acetonitrile **2** (1 mmol), electron-rich amino heterocycles **3** (1 mmol), and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 80 °C for 4−7 h to complete the reaction (monitored by TLC), then 50 mL water was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give **4**.

3-Methyl-1,6-diphenyl-4-(4-methylphenyl)-1H-pyrazolo[3,4-b]-pyridine-5-carbonitrile 4{1,1,1}. mp: 210−212 °C. IR (KBr) ν: 2221, 1583, 1559, 1506, 1433, 1418, 1385, 1340, 1196, 1176, 1127, 775, 758, 706 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.10 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.38 (t, J = 7.2 Hz, 1H, ArH), 7.45 (d, J = 8.0 Hz, 2H, ArH), 7.56−7.61 (m, 7H, ArH), 7.94−7.96 (m, 2H, ArH), 8.22 (d, J = 8.4 Hz, 2H, 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-(4-methylphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile 4{1,1,2}. mp: >300 °C. IR (KBr) ν: 2222, 1713, 1668, 1553, 1478, 1409, 1362, 1286, 1097, 817, 752, 716, 698 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.41 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 7.25−7.31 (m, 4H, ArH), 7.61−7.62 (m, 3H, ArH), 8.00−8.02 (m, 2H, ArH). HRMS [Found m/z 382.1435 (M^+); Calcd for $C_{23}H_{18}N_4O_2$ M, 382.1430].

2-Amino-4-oxo-7-phenyl-5-(4-methylphenyl)-3,4-dihydro-pyrido[2,3-d]pyrimidine-6-carbonitrile 4{1,1,4}. mp: 249−250 °C. IR (KBr) ν: 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: 2.43 (s, 3H, CH_3), 7.28 (s, 5H, ArH), 7.58−7.60 (m, 4H, ArH+NH_2), 7.89−7.99 (m, 2H, ArH), 11.18 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 21.66, 108.74, 114.13, 118.04, 128.48, 128.97, 129.69, 130.92, 134.85, 137.99, 138.17, 138.33, 141.37, 156.47, 158.73, 162.98, 164.96. HRMS [Found m/z 353.1277(M^+); Calcd for $C_{20}H_{12}{}^{35}ClN_5O$ M, 353.1277].

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and spectroscopic characterization for compounds **4** and the X-ray crystallographic information for compound **4**{*13,2,1*}. This information is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

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Author Contributions

Zhibin Huang and Daqing Shi conceived and designed the experiments, Yao Zhou and Yu Hu performed the experiments, Daqing Shi and Zhibin Huang co-wrote the manuscript and supporting information.

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