# One-pot synthesis of pyrano[2,3-*d*]pyrimidine derivatives in ionic liquid medium

**Yu-Ling Li[a,b], Bai-Xiang Du[a,b], Xiang-Shan Wang[a,b]*, Da-Qing Shi[a,b] and Shu-Jiang Tu[a,b]**

[a]*Department of Chemistry, Xuzhou Normal University, Xuzhou, Jiangsu, 221116, China*

[b]*The Key Laboratory of Biotechnology on Medical Plant, Jiangsu, Xuzhou 221116, China*

In this paper, a series of pyrano[2,3-*d*]pyrimidine derivatives have been synthesised by the reaction of aromatic aldehydes, malononitrile and pyrimidine-4,6-diol in ionic liquid [bmim$^+$][$BF_4^-$] at 80 °C. The structures of the products were characterised by IR, $^1$H NMR spectra. Compared with other methods, ionic liquid is a green solvent, which has the advantages of easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

**Keywords:** ionic liquid, green chemistry, pyrano[2,3-*d*]pyrimidine, synthesis

Heterocycles are of great value in the design and discovery of new biologically active compounds. Pyrano[2,3-*d*]pyrimidines are annulated uracils which have received considerable attention over the past years due to their wide range of biological activity. Compounds with these ring systems have diverse pharmacological activity such as antitumour,[1] cardiotonic,[2] hepatoprotactive,[3] antihypertensive,[3] anti-bronchitic[4] and antimicrobial activity.[5]

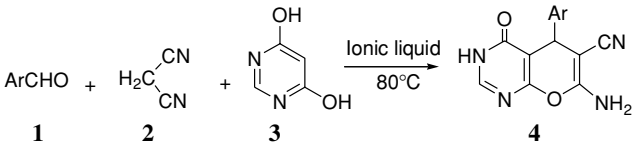
Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As a result, a number of reports have appeared[6] which usually require drastic conditions, long reaction times and complex synthetic pathways and often react in organic solvents. Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

Recently, the use of ionic liquids as environmentally benign solvents for a broad range of chemical processes has been advocated.[7] This is due to a number of intriguing properties of ionic liquids: high thermal and chemical stability, negligible vapor pressure, nonflammability, and high capacity.[8] Room temperature ionic liquids, especially those based on the 1,3-dialkylimidazolium cations, have been shown to be good 'solvents' for a wide range of inorganic and organic reactions.[9] A nice feature of ionic liquid is that yields can be optimised by changing the anions or properties of the cation. In addition, several ionic liquids show enhancement in reaction rates and selectivity, compared to organic solvents with the added benefit of the ease of recovery and reuse of these ionic liquids.

In view of the emerging importance of room temperature ionic liquids as novel reaction media, we report in this paper a novel three-component one-pot synthesis of well functionalised pyrano[2,3-*d*] pyrimidines in ionic liquid medium (Scheme 1). When three components of aromatic aldehyde **1**, malononitrile **2** and pyrimidine-4,6-diol **3** were treated in ionic liquids [bmim$^+$][$BF_4^-$] at 80°C for a few hours (Scheme 1), the pyrano[2,3-*d*]pyrimidine derivatives **4** were obtained in high yields (85–95%) (Table 1).

As the first step, in an effort to optimise the reaction conditions, we performed a series of reactions showed in Scheme 1 utilising a variety of ionic liquids. A summary of the optimisation experiment is provided in Table 1. It turned out that at room temperature, no reaction took (Table 1, entries 1 and 2). In addition, different ionic liquids were further studied, from Table 1, we could conclude that the ionic liquid [bmim$^+$][$BF_4^-$] was the best reaction media for this reaction.

In order to demonstrate the efficiency and scope of the present method, we applied this ionic liquid to the reaction of variety of aromatic aldehydes with pyrimidine-4,6-diol and malononitrile. The results are summarized in Table 2. Data from




**1** **2** **3** **4**

**Scheme 1**

**Table 1** Synthesis of **4a** in ionic liquid under different reaction conditions[a]

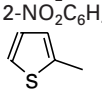
| Entry | Temperature/°C | ionic liquid | Time/h | Yield[b]/% |
|---|---|---|---|---|
| 1 | R.t. | [bmim$^+$][$BF_4^-$] | 3 | 0 |
| 2 | R.t. | [bmim$^+$][$PF_6^-$] | 3 | 0 |
| 3 | 80 | [bmim$^+$]Br$^-$ | 3 | 60 |
| 4 | 80 | [emim$^+$]Br$^-$ | 3 | 55 |
| 5 | 80 | [emim$^+$][$BF_4^-$] | 3 | 82 |
| 6 | 80 | [bmim$^+$][$BF_4^-$] | 2 | 92 |
| 7 | 80 | [bmim$^+$][$PF_6^-$] | 3 | 80 |

[a]Reaction condition: 10 ml ionic liquid, 2 mmol 4-chlorobenzaldehyde, 2 mmol pyrimidine-4,6-diol, 2.5 mmol malononitrile.
[b]Isolated yields.

Table 2 demonstrated that the reactions proceeded smoothly to give **4** in high yields under the optimised conditions. All the products were characterised by their melting points, $^1$H NMR and IR spectra.

Since the ionic liquid is likely to be the most expensive among all the components in the reaction system, we examined the recycling [bmim$^+$][$BF_4^-$] for the reaction. At completion monitored by TLC, the reaction mixture was allowed to cool

**Table 2** Synthesis of **4** in ionic liquid [bmim$^+$][$BF_4^-$][a]

| Entry | Ar | Time/h | Products | Yields/%[b] |
|---|---|---|---|---|
| **1** | 4-Cl$C_6H_4$ | 2 | **4a** | 92 |
| **2** | 3,4-$(CH_3)_2C_6H_3$ | 4 | **4b** | 90 |
| **3** | 4-F$C_6H_4$ | 2 | **4c** | 85 |
| **4** | 2-$NO_2$-4-Cl$C_6H_3$ | 3 | **4d** | 88 |
| **5** | 2-$NO_2C_6H_4$ | 2 | **4e** | 87 |
| **6** |  | 2 | **4f** | 95 |
| **7** | 3,4-$Cl_2C_6H$ | 2 | **4g** | 86 |
| **8** | 4-Br$C_6H_4$ | 2 | **4h** | 89 |
| **9** | 2-Cl$C_6H_4$ | 2 | **4i** | 85 |
| **10** | 3-Cl$C_6H_4$ | 3 | **4j** | 87 |
| **11** | 2,4-$Cl_2C_6H_3$ | 2 | **4k** | 89 |
| **12** | 3,4-$(CH_3O)_2C_6H_3$ | 4 | **4l** | 85 |
| **13** | 3-$NO_2C_6H_3$ | 2 | **4m** | 87 |

[a]Reaction condition: 10 ml ionic liquid, 2 mmol aromatic aldehyde and 2 mmol pyrimidine-4,6-diol, 2.5 mmol malononitrile, 80 °C.
[b]Isolated yields.

* Correspondent. E-mail: ylli1972@yahoo.com

**Table 3** Study on the reuse of ionic liquid [bmim$^+$][$BF_4^-$][a]

| Round | Temperature/°C | Reaction time/h | Yield/%[b] |
|---|---|---|---|
| 1 | 80 | 2 | 92 |
| 2 | 80 | 2 | 91 |
| 3 | 80 | 2 | 91 |
| 4 | 80 | 2 | 90 |
| 5 | 80 | 2 | 89 |
| 6 | 80 | 2 | 88 |

[a]Reaction condition: 10 ml ionic liquid, 2 mmol 4-chlorobenzaldehyde and 2 mmol pyrimidine-4,6-diol, 2.5 mmol malononitrile, 80 °C.
[b]Isolated yields.

to room temperature, the solid of the products was isolated by filtration, the filtrate of the ionic liquid [bmim$^+$][$BF_4^-$] could be recovered easily by drying at 80°C *in vacuo* for several hours. Investigations using 4-chlorobenzaldehyde, pyrimidine-4,6-diol and malononitrile as model substrates showed that successive reuse of the recovery ionic liquid [bmim$^+$][$BF_4^-$]. The results are summarised in Table 3. [bmim$^+$][$BF_4^-$] could be reused repeatedly, without loss of its effect. Even in the sixth round the yield of the product **4a** is fairly good.

In conclusion, with high yields and mild conditions, we think that the present work described here in providing a useful method for the preparation of pyrano[2,3-*d*]pyrimidine derivatives. Compared with other methods, this new method has the advantages of easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

## Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. $^1$H NMR spectra were obtained for solution in DMSO-$d_6$ with $Me_4Si$ as internal standard using a Bruker-400 spectrometer.

*General procedure for preparation of ionic liquid*
*1-Butyl-3-methylimidazolium bromide [bmim$^+$]Br:* In a three-necked, 500 ml round-bottomed flask equipped with reflux condenser, 100-ml dropping funnel, and magnetic stirrer, 22.96 g (0.28 mol) of 1-methylimidazole was diluted under Ar in 250 ml of hexane and 39.00 g (0.29 mol) of bromobutane. The solution was then refluxed for 30 min. the mixture was concentrated at 80 °C under reduced pressure. The product was obtained by drying the residual liquid at 80 °C *in vacuo*.

*1-Butyl-3-methylimidazolium tetrafluorate [bmim$^+$][$BF_4^-$]:* A solution of [bmim$^+$]Br$^-$ (26.30 g, 0.12 mol) in acetone (50 ml), was added dropwise to a rapidly stirring solution of $NaBF_4$(13.20 g, 0.12 mol) in acetone (50 ml). The mixture was stirred at room temperature for 96 h, the solid was filtered off and washed with acetone. The filtrate was concentrated at 50 °C under reduced pressure. The product [bmim$^+$][$BF_4^-$] was obtained by drying the residual liquid at 80 °C *in vacuo*.

*1-Butyl-3-methylimidazolium hexafluorophosphate [bmim$^+$][$PF_6^-$]:* A solution of [bmim$^+$]Br$^-$ (6.57 g, 30 mmol) was cooled to 0 °C and to this was added slowly $HPF_6$ (4.5 ml of a 60% solution in water, 30.5 mmol). The mixture was allowed to warm to room temperture and stirred for 16 h. After separation, the viscous liquid product was washed with water until the washings were neutral, the product [bmim$^+$][$PF_6^-$] was obtained by drying the liquid at 80 °C *in vacuo*.

*General procedure for preparation of* **4**
A dry 50 ml flask was charged with aromatic aldehyde **1** (2 mmol), malononitrile **2** (2.5 mmol), and pyrimidine-4,6-diol **3** (2 mmol) and ionic liquid [bmim$^+$][$BF_4^-$] (10 ml). The mixture was stirred at 80°C for 2–4 h to complete the reaction (monitored by TLC), then cooled to room temperature. The solid was filtered off and washed with water. The filtrate of ionic liquid [bmim$^+$][$BF_4^-$] was then recovered for reuse by drying at 80 °C several hours *in vacuo*. The crude product was purified by recrystallisation from DMF to give **4**.

*7-Amino-5-(4-chlorophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6- carbonitrile* (**4a**): M.p. 254–256 °C. IR (KBr, ν, cm$^{-1}$): 3427, 3307, 3163, 2186, 1661, 838; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.44 (s, 1H, CH), 7.22 (d, 2H, *J* =8.0 Hz, ArH), 7.23 (s, 2H, $NH_2$), 7.37 (d, 2H, *J* =8.0 Hz, ArH), 8.16 (s, 1H, ArH), 11.50(s, 1H, NH). Anal.calcd for $C_{14}H_9ClN_4O_2$: C 55.92, H 3.02, N 18.63; found C 56.11, H 3.16, N 18.74.

*7-Amino-5-(3,4-dimethylphenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4b**): M.p. 265–266 °C. IR (KBr, ν, cm$^{-1}$): 3401, 3329, 3142, 2182, 1686; $^1$H NMR (DMSO-$d_6$, δ, ppm): 2.16 (s, 3H, $CH_3$), 2.18 (s, 3H, $CH_3$), 4.31 (s, 1H, CH), 6.88 (d, 1H, *J* = 7.6 Hz, ArH), 6.92 (s, 1H, ArH), 7.04 (d, 1H, *J* = 7.6 Hz, ArH), 7.12 (s, 2H, $NH_2$), 8.12 (s, 1H, ArH), 12.75 (s, 1H, NH). Anal. calcd for $C_{16}H_{14}N_4O_2$: C 65.30, H 4.79, N 19.04; found C 65.21, H 4.94, N 18.95.

*7-Amino-5-(4-fluorophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4c**): M.p. 253–255 °C. IR (KBr, ν, cm$^{-1}$): 3432, 3333, 3160, 2189, 1656; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.44 (s, 1H, CH), 7.10–7.25 (m, 4H, ArH), 7.20 (s, 2H, $NH_2$), 8.14 (s, 1H, ArH), 12.74(s, 1H, NH). Anal. calcd for $C_{16}H_9FN_4O_2$: C 59.16, H 3.19, N 19.17; found C 58.98, H 3.32, N 19.35.

*7-Amino-5-(4-chloro-2-nitrophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4d**): M.p. 269–270 °C. IR (KBr, ν, cm$^{-1}$): 3406, 3349, 3158, 2183, 1667, 843; $^1$H NMR (DMSO-$d_6$, δ, ppm): 5.23 (s, 1H, CH), 7.39 (s, 2H, $NH_2$), 7.45 (d, 1H, *J* = 2.0 Hz, ArH), 7.56 (dd, 1H, *J* = 8.8 Hz, *J′* = 2.0 Hz, ArH), 7.92 (d, 1H, *J* = 8.8 Hz, ArH), 8.17 (s, 1H, ArH), 12.75 (s, 1H, NH). Anal.calcd for $C_{14}H_8ClN_5O_4$: C 48.64, H 2.33, N 20.26; found C 48.43, H 2.48, N 20.42.

*7-Amino-4a,5-dihydro-5-(2-nitrophenyl)-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4e**): M.p. 261–263 °C. IR (KBr, ν, cm$^{-1}$): 3398, 3306, 3169, 2188, 1670; $^1$H NMR (DMSO-$d_6$, δ, ppm): 5.22 (s, 1H, CH), 7.33 (s, 2H, $NH_2$), 7.40 (dd, 1H, *J* = 8.0 Hz, *J′* = 1.2 Hz, ArH), 7.44–7.48 (m, 1H, ArH), 7.64–7.68 (m, 1H, ArH), 7.85 (dd, 1H, *J* = 8.0 Hz, *J′* = 1.2 Hz, ArH), 8.15 (s, 1H, ArH), 12.72 (s, 1H, NH). Anal.calcd for $C_{14}H_9N_5O_4$: C 54.02, H 2.91, N 22.50; found C 54.23, H 2.78, N 22.32.

*7-Amino-4a,5-dihydro-4-oxo-5-(2-thienyl)-4H-pyrano[2,3-d]pyrimidine-6- carbonitrile* (**4f**): M.p. 244–246 °C. IR (KBr, ν, cm$^{-1}$): 3385, 3325, 3196, 2204, 1664; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.77 (s, 1H, CH), 6.92–6.96 (m, 2H, ArH), 7.29 (s, 2H, $NH_2$), 7.35 (dd, 1H, *J* = 4.8 Hz, *J′* = 1.2 Hz, ArH), 8.16 (s, 1H, ArH), 12.82 (s, 1H, NH). Anal.calcd for $C_{12}H_8N_4O_4S$: C 52.93, H 2.96, N 20.58; found C 52.73, H 2.88, N 20.32.

*7-Amino-5-(3,4-dichlorophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6- carbonitrile* (**4g**): M.p. 281–283 °C. IR (KBr, ν, cm$^{-1}$): 3403, 3325, 3172, 2194, 1682, 840, 803; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.50 (s, 1H, CH), 7.20 (dd, 1H, *J* = 8.4 Hz, *J′* = 2.4 Hz, ArH), 7.29 (s, 2H, $NH_2$), 7.47 (d, 1H, *J* = 2.4 Hz, ArH), 7.58 (d, 1H, *J* = 8.4 Hz, ArH), 8.17 (s, 1H, ArH), 11.52 (s, 1H, NH). Anal. calcd for $C_{14}H_8Cl_2N_4O_2$: C 50.17, H 2.41, N 16.72; found C 50.28, H 2.46, N 16.67.

*7-Amino-5-(4-bromophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4h**): M.p. 250–252 °C. IR (KBr, ν, cm$^{-1}$): 3413, 3343, 3245, 2191, 1684, 834; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.42 (s, 1H, CH), 7.16 (d, 2H, *J* = 8.4 Hz, ArH), 7.23 (s, 2H, $NH_2$), 7.50 (d, 2H, *J* = 8.4 Hz, ArH), 8.16 (s, 1H, ArH), 11.50 (s, 1H, NH). Anal. calcd for $C_{14}H_9BrN_4O_2$: C 48.72, H 2.63, N 16.23; found C 48.62, H 2.71, N 16.33.

*7-Amino-5-(2-chlorophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4i**): M.p. 263–265 °C. IR (KBr, ν, cm$^{-1}$): 3411, 3338, 3198, 2195, 1661, 746; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.91 (s, 1H, CH), 7.18–7.19 (m, 3H, ArH + $NH_2$), 7.24–7.28 (m, 2H, ArH), 7.38 (dd, 1H, *J* = 7.6 Hz, *J′* = 1.6 Hz, ArH), 8.16 (s, 1H, ArH), 11.48(s, 1H, NH). Anal.calcd for $C_{14}H_9ClN_4O_2$: C 55.92, H 3.02, N 18.63; found C 55.77, H 2.94, N 18.59.

*7-Amino-5-(3-chlorophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4j**): M.p. 277–278 °C. IR (KBr, ν, cm$^{-1}$): 3421, 3317, 3140, 2187, 1684, 803; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.46 (s, 1H, CH), 7.17 (d, 1H, *J* = 7.6 Hz, ArH), 7.23–7.37 (m, 5H, ArH + $NH_2$), 8.16 (s, 1H, ArH), 11.50(s, 1H, NH). Anal.calcd for $C_{14}H_9ClN_4O_2$: C 55.92, H 3.02, N 18.63; found C 56.17, H 3.15, N 18.49.

*7-Amino-5-(2,4-dichlorophenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4k**): M.p. 257–259 °C. IR (KBr, ν, cm$^{-1}$): 3412, 3305, 3162, 2187, 1691, 841; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.90 (s, 1H, CH), 7.23 (s, 2H, $NH_2$), 7.24 (d, 1H, *J* = 8.0 Hz, ArH), 7.36 (dd, 1H, *J* = 8.0 Hz, *J′* = 2.0 Hz, ArH), 7.55 (d, 1H, *J* = 2.0 Hz, ArH), 8.17 (s, 1H, ArH), 11.60(s, 1H, NH). Anal.calcd for $C_{14}H_8Cl_2N_4O_2$: C 50.17, H 2.41, N 16.72; found C 50.28, H 2.45, N 16.57.

*7-Amino-5-(3,4-dimethoxyphenyl)-4a,5-dihydro-4-oxo-4H-pyrano[2,3-d]pyrimidine-6- carbonitrile* (**4l**): M.p. 279–280 °C. IR (KBr, ν, $cm^{-1}$): 3397, 3289, 3194, 2197, 1690, 799; $^1$H NMR (DMSO-$d_6$, δ, ppm): 3.71 (s, 3H, $CH_3O$), 3.72 (s, 3H, $CH_3O$), 4.37 (s, 1H, CH), 6.66 (dd, 1H, $J$ = 8.4 Hz, $J'$ = 2.0 Hz, ArH), 6.80 (d, 1H, $J$ = 2.0 Hz, ArH), 6.88(d, 1H, $J$ = 8.4 Hz, ArH), 7.13 (s, 2H, $NH_2$), 8.13 (s, 1H, ArH), 11.42(s, 1H, NH). Anal.calcd for $C_{16}H_{14}N_4O_4$: C 58.89, H 4.32, N 17.17; found C 58.91, H 4.28, N 17.26.

*7-Amino-4a,5-dihydro-5-(3-nitrophenyl)-4-oxo-4H-pyrano[2,3-d]pyrimidine-6-carbonitrile* (**4m**): M.p. 273–275 °C. IR (KBr, ν, $cm^{-1}$): 3421, 3305, 3158, 2179, 1687, 827; $^1$H NMR (DMSO-$d_6$, δ, ppm): 4.67 (s, 1H, CH), 7.34 (s, 2H, $NH_2$), 7.63 (t, 1H, $J$ = 7.6 Hz, ArH), 7.71–7.74 (m, 1H, ArH), 8.04–8.05 (m, 1H, ArH), 8.10–8.13 (m, 1H, ArH), 8.18 (s, 1H, ArH), 11.58 (s, 1H, NH). Anal.calcd for $C_{14}H_9N_5O_4$: C 54.02, H 2.91, N 22.50; found C 53.91, H 3.03, N 22.67.

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