# An Efficient Synthesis of Pyrido[2,3-*d*]pyrimidine Derivatives in Ionic Liquid



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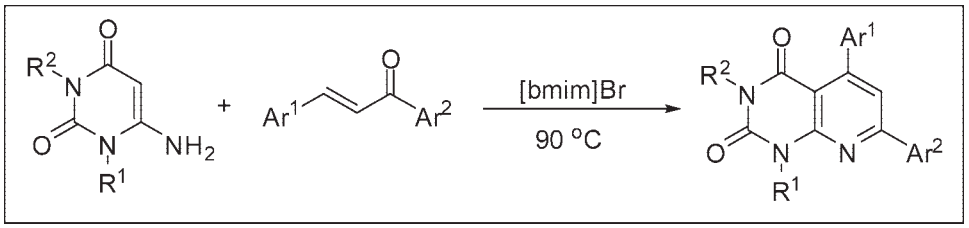


A series of 5,7-diarylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones was synthesized *via* the reaction of 6-aminopyrimidine-2,4-dione and α,β-unsaturated ketones in ionic liquid without using any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure over traditional methods.

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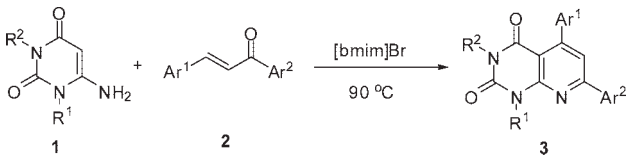
## INTRODUCTION

The importance of uracil and its annulated derivatives is well recognized by synthetic [1] as well as biological [2] chemists. With the development of clinically useful anticancer and antiviral drugs [3], there has recently been remarkable interest in the synthetic manipulations of uracils [4]. Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, which include antitumor [5], antibacterial [6], anti-inflammatory [7], antifungal [8], and antileishmaniasis [9] properties, and also act as cyclin-dependent kinase 4 inhibitors [10]. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. Broom *et al*. [11] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracile in protic solvent but obtained uncyclized condensed acetylenic adduct when the reaction was carried in DMF [12]. Wawzonek reported the synthesis of pyrido[2,3-*d*]pyrimidine-2,4-diones by the acid- and base-catalyzed condensation of 6-amino-1,3-dimethyluracil with α,β-unsaturated carbonyl compounds [13]. Bhuyan *et al*. [14] reported the synthesis of pyrido[2,3-*d*]pyrimidines from the reaction of arylidenemalononitrile with 6-aminouracil in refluxing 1-propanol, but in this reaction, benzylmalononitrile was obtained as by-product and the amount of arylidenemalononitrile needed was in excess. Quiroga *et al* [15] reported the synthesis of prrido[2,3-*d*]pyrimidines by the reaction of 6-amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone and α,β-unsaturated ketones in boiling DMF. Recently, Bagley *et al*. [16] reported a new method for the synthesis of pyrido[2,3-*d*]pyrimidines by the reaction of 2,6-diaminopyrimidin-4-one and butynones in a range of different solvents at room temperature or 60°C. Quiroga *et al*. [17] reported the synthesis of pyrido[2,3-d]pyrimidines *via* a selective cyclocondensation reaction between 6-aminopyrimidines and the Mannich bases, propiophenone hydrochlorides. Devi *et al*. [18] reported a novel three-component one-pot synthesis of pyrido[2,3-*d*]pyrimidines using microwave heating. These methods usually require harsh conditions, using organic solvents, long reaction times and complex synthetic pathways.

The ionic liquids have been the subject of considerable current interest as environmentally benign reaction media in organic synthesis because of their unique properties of nonvolatility, nonflammability, and recyclability, among others [19]. Numerous chemical reaction, such as polymerization [20], hydrogenation [21], regioselective alkylation [22], Friedel-Crafts reactions [23], dimerization of alkenes [24], Diels-Alder reactions [25], Michael reactions [26], Cross-coupling reactions [27], and some enzymic reactions [28] can be carried out in ionic liquid. As part of our current studies on the development of new routes to heterocyclic systems [29], we herein describe a facile synthesis of pyrido[2,3-

**Scheme 1**




1 2 3

*d*]pyrimidine derivatives by the reaction of 6-aminopyrimidine-2,4-dione and α,β-unsaturated ketones in ionic liquid without using any catalyst (Scheme 1).

## RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optimal solvent, the reaction of 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1a** and 1-(4-chlorophenyl)-3-(4-methylphenyl)prop-2-en-1-one **2a** was examined using ionic liquid such as [bmim]Br, [bmim]$BF_4$, [bmim]$PF_6$, acetone, acetonitrile, ethanol, chloroform, and DMF as solvent, respectively, at different temperature for the synthesis of **3a**. The results are summarized in Table 1.

It can be seen from Table 1 that the reactions using ionic liquids (Table 1, entries 6–8) as the solvents resulted in higher yields and shorter reaction times than those using organic solvents (Table 1, entries 1–5). On the basis of the obtained results, [bmim]Br was found to be superior in terms of cheap and yield. To optimize the reaction temperature, the reactions were carried out at different temperature ranging from room temperature to 90°C. We found that the yield of the product **3a** was improved and the reaction time was shortened, as the temperature was increased to 90°C (Table 1, entries 8–12). Therefore, the most suitable reaction temperature is to 90°C. Under these optimized reaction conditions, a series of pyrido[2,3-*d*]pyrimidine derivatives **3** were synthesized. The results are summarized in Table 2.

As shown in Table 2, this protocol can be applied not only to the aromatic rings of α,β-unsaturated ketones with electron-withdrawing groups (such as halide and nitro groups), but also to α,β-unsaturated ketones with electron-donating groups (such as alkyl and alkoxyl groups). Therefore, we concluded that the electronic nature of the substituents of aromatic rings of α,β-unsaturated ketones has no significant effect on this reaction.

In this study, all the products **3** were characterized by mp, IR, and $^1$H NMR spectral data as well as HRMS analysis.

Although the detailed mechanism of above reaction remains not to be fully clarified, the formation of compounds **3** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded *via* a reaction sequence of Michael addition, cyclization, dehydration and aromatization. First, the Michael addition reaction of 6-aminopyrimidine- 2,4-dione **1** to α,β-unsaturated ketones **2** give the intermediate product **4**, which on intermolecular cyclization and dehydration gave rise to **5**. In the last step, the intermediate product **5** aromatized to product **3**.

In conclusion, we have developed an efficient synthesis of 5,7-diarylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones *via* the reaction of 6-aminopyrimidine-2,4-dione and α,β-unsaturated ketones in ionic liquid without any catalyst. This protocol has the advantages of easier work-up, milder reaction conditions, high yields, and environmentally benign procedure over traditional methods.

## EXPERIMENTAL

Commercial solvents and reagents were used as received. Melting points were uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in $cm^{-1}$. $^1$H NMR was determined on Varian-400 MHz spectrometer in DMSO-$d_6$ or $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using TOF-MS instrument.

**General procedure for the synthesis of pyrido[2,3-*d*]pyrimidines derivatives 3.** A dry 50 mL flask was charged with 6-aminopyrimidine-2,4-dione 1 (1 mmol), α,β-unsaturated ketones 2 (1 mmol), and ionic liquid [bmim]Br (2 mL). The mixture was stirred at 90°C for 5–7.5 h to complete the reaction (monitored by TLC), then 50 mL $H_2O$ was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give 3.

***7-(4-Chlorophenyl)-1,3-dimethyl-5-p-tolylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3a).*** Mp: 238–239°C; IR (potassium bromide): 3074, 2950, 1707, 1665, 1594, 1576, 1545, 1515, 1420, 1403, 1362, 1281, 1257, 1091, 1003, 834, 821, 784, 750

**Table 1**

Solvent and reaction temperature optimization for the synthesis of **3a**[a].

| Entry | Solvent | Reaction temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | acetone | reflux | 15 | 43 |
| 2 | acetonitrile | reflux | 10 | 58 |
| 3 | ethanol | reflux | 8.5 | 72 |
| 4 | chloroform | reflux | 13 | 52 |
| 5 | DMF | 100 | 7 | 88 |
| 6 | [bmim]Br | 90 | 5 | 96 |
| 7 | [bmim]$BF_4$ | 90 | 6 | 90 |
| 8 | [bmim]$PF_6$ | 90 | 6.5 | 88 |
| 9 | [bmim]Br | r.t. | 18 | 47 |
| 10 | [bmim]Br | 40 | 16 | 62 |
| 11 | [bmim]Br | 60 | 10 | 73 |
| 12 | [bmim]Br | 80 | 6.5 | 81 |

[a] 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1 mmol), 1-(4-chlorophenyl)-3-(4-methylphenyl)prop-2-en-1-one (1 mmol), and 2 mL solvent.

**Table 2**

Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **3** in ionic liquid.

| Entry | $R^1$ | $R^2$ | $Ar^1$ | $Ar^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| **3a** | $CH_3$ | $CH_3$ | 4-$CH_3C_6H_4$ | 4-$ClC_6H_4$ | 5 | 96 |
| **3b** | $CH_3$ | $CH_3$ | 3,4-$Cl_2C_6H_3$ | 4-$MeOC_6H_4$ | 6 | 92 |
| **3c** | $CH_3$ | $CH_3$ | 4-$NO_2C_6H_4$ | 4-$MeOC_6H_4$ | 6 | 92 |
| **3d** | $CH_3$ | $CH_3$ | 4-$BrC_6H_4$ | 4-$ClC_6H_4$ | 6.5 | 90 |
| **3e** | $CH_3$ | $CH_3$ | 3,4-$Cl_2C_6H_3$ | 4-$ClC_6H_4$ | 7.5 | 93 |
| **3f** | $CH_3$ | $CH_3$ | 4-$MeC_6H_4$ | 4-$MeOC_6H_4$ | 5 | 88 |
| **3g** | $CH_3$ | $CH_3$ | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 6 | 87 |
| **3h** | $CH_3$ | $CH_3$ | 4-$MeC_6H_4$ | 4-$MeC_6H_4$ | 5 | 90 |
| **3i** | $CH_3$ | H | 3,4-$OCH_2OC_6H_3$ | 4-$MeOC_6H_4$ | 5 | 90 |
| **3j** | $CH_3$ | H | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 5 | 96 |
| **3k** | H | H | 3,4-$OCH_2OC_6H_3$ | 4-$MeOC_6H_4$ | 5 | 92 |
| **3l** | H | H | 4-$ClC_6H_4$ | 4-$BrC_6H_4$ | 6 | 98 |
| **3m** | H | H | 4-$MeC_6H_4$ | Naphthalene-2-yl | 7 | 98 |

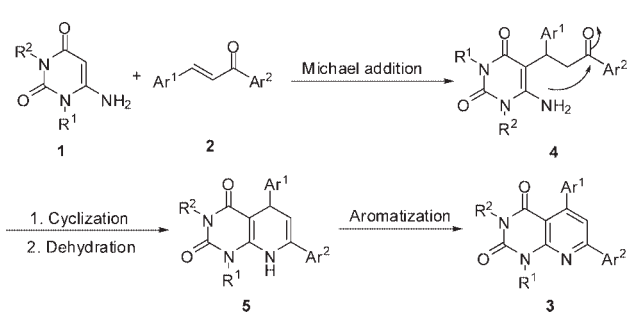
$cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.38 (s, 3H, $CH_3$), 3.18 (s, 3H, $CH_3$), 3.68 (s, 3H, $CH_3$), 7.21–7.29 (m, 4H, ArH), 7.55–7.61 (m, 3H, ArH), 8.27 (d, $J$ = 8.4 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 391.1089($M^+$); Calcd for $C_{22}H_{18}^{35}ClN_3O_2$: M 391.1088].

***5-(3,4-Dichlorophenyl)-7-(4-methoxyphenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3b).*** Mp: 295–296°C; IR (potassium bromide): 1706, 1670, 1578, 1543, 1472, 1422, 1367, 1253, 1221, 1178, 1132, 1027, 832, 753 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.20 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 7.09 (d, $J$ = 8.8 Hz,2H, ArH), 7.38 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H, ArH), 7.66 (s, 1H, ArH), 7.69 (d, $J$ = 8.4 Hz, 2H, ArH), 8.28 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 441.0646 ($M^+$); Calcd for $C_{22}H_{17}^{35}Cl_2N_3O_3$: M 441.0647].

***7-(4-Methoxyphenyl)-1,3-dimethyl-5-(4-nitrophenyl) pyrido[2,3-d]pyrimidine-2,4-(1H,3H)-dione (3c).*** Mp: >300°C; IR (potassium bromide): 1705, 1665, 1587, 1548, 1510, 1418, 1368, 1268, 1245, 1178, 1130, 838, 752 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.19 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 7.09 (d, $J$ = 8.8 Hz, 2H, ArH), 7.65–7.68 (m, 3H, ArH), 7.66 (s, 1H, ArH), 8.27–8.30 (m, 4H, ArH). HRMS [Found: *m*/*z*: 418.1276 ($M^+$); Calcd for $C_{22}H_{18}N_4O_5$: M 418.1277].

***5-(4-Bromophenyl)-7-(4-chlorophenyl)-1,3-dimethyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)- dione (3d).*** Mp: 264–266°C; IR (potassium bromide): 1707, 1668, 1593, 1576, 1547, 1490, 1420, 1363, 1282, 1258, 1178, 1003, 832, 804, 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.38 (s, 3H, $CH_3$), 3.87 (s, 3H, $CH_3$), 7.22 (d, $J$ = 8.8 Hz, 2H, ArH), 7.39 (s, 1H, ArH), 7.48 (d, $J$ = 8.8 Hz, 2H, ArH), 7.59 (d, $J$ = 8.4 Hz, 2H, ArH), 8.07 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 455.0039 ($M^+$); Calcd for $C_{21}H_{15}^{79}Br^{35}ClN_3O_2$: M 455.0036].

**Scheme 2**




***5-(3,4-Dichlorophenyl)-7-(4-chlorophenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3e).*** Mp: 254–256°C; IR (potassium bromide): 1710, 1672, 1575, 1548, 1475, 1421, 1365, 1218, 1089, 1008, 841, 753 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.20 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 7.39 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.4 Hz, 1H, ArH), 7.61 (d, $J$ = 8.8 Hz,2H, ArH), 7.69–7.71 (m, 2H, ArH), 7.76 (s, 1H, ArH), 8.23 (d, $J$ = 8.8 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 445.0152 ($M^+$); Calcd for $C_{21}H_{14}^{35}Cl_3N_3O_2$: M 445.0152].

***7-(4-Methoxyphenyl)-1,3-dimethyl-5-p-tolylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3f).*** Mp: 259–260°C; IR (potassium bromide): 1700, 1655, 1604, 1554, 1519, 1423, 1367, 1246, 1225, 1176, 1036, 834, 818, 751 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.38 (s, 3H, $CH_3$), 3.18 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 7.04–7.09 (m, 2H, ArH), 7.20–7.30 (m, 4H, ArH), 7.53 (s, 1H, ArH), 8.20–8.27 (m, 2H, ArH). HRMS [Found: *m*/*z*: 387.1583 ($M^+$); Calcd for $C_{23}H_{21}N_3O_3$: M 387.1583].

***5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3g).*** Mp: 279–280°C; IR (potassium bromide): 1702, 1657, 1607, 1579, 1557, 1519, 1423, 1366, 1249, 1226, 1174, 1087, 1029, 833, 751 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.19 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 7.08 (d, $J$ = 8.0 Hz, 2H, ArH), 7.41 (dd, $J_1$ = 2.0 Hz, $J_2$ = 7.6 Hz, 2H, ArH), 7.48 (dd, $J_1$ = 2.0 Hz, $J_2$ = 7.6 Hz, 2H, ArH), 7.59 (s, 1H, ArH), 8.26 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 407.1037 ($M^+$); Calcd for $C_{22}H_{18}^{35}ClN_3O_3$: M 407.1037].

***1,3-Dimethyl-5,7-di(p-tolyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3h).*** Mp: 217–219°C; IR (potassium bromide): 1704, 1661, 1590, 1546, 1515, 1418, 1363, 1260, 1220, 819, 755 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.43 (s, 6H, 2 × $CH_3$), 3.39 (s, 3H, $CH_3$), 3.88 (s, 3H, $CH_3$), 7.27–7.32 (m, 6H, ArH), 7.44 (s, 1H, ArH), 8.03 (d, $J$ = 8.0 Hz, 2H, ArH). HRMS [Found: *m*/*z*: 371.1634 ($M^+$); Calcd for $C_{23}H_{21}N_3O_2$: M 371.1634].

***5-(3,4-Methylenedioxyphenyl)-7-(4-methoxyphenyl)-1-methylpyrido[2,3-d]pyrimidine-2,4 (1H, 3H)-dione (3i).*** Mp: 308–309°C; IR (potassium bromide): 3299, 1707, 1687, 1577, 1550, 1502, 1484, 1441, 1376, 1255, 1229, 1180, 1106, 1028,

931, 842, 765 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.68 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 6.08 (s, 2H, $OCH_2O$), 6.91 (d, $J$ = 8.0 Hz, 1H, ArH), 6.96 (d, $J$ = 8.0 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 7.08 (d, $J$ = 8.0 Hz, 2H, ArH), 7.52 (s, 1H, ArH), 8.24 (d, $J$ = 8.0 Hz, 2H, ArH), 11.39 (s, 1H, NH). HRMS [Found: $m/z$: 403.1166 ($M^+$); Calcd for $C_{22}H_{17}N_3O_5$: M 403.1168].

***5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-1-methyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3j).*** Mp: >300°C; IR (potassium bromide): 3172, 1707, 1692, 1579, 1543, 1485, 1448, 1386, 1363, 1262, 1242, 1179, 1032, 981, 833 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.65 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 7.06–7.10 (m, 2H, ArH), 7.41–7.50 (m, 4H, ArH), 7.56 (s, 1H, ArH), 8.23–8.28 (m, 2H, ArH), 11.44 (s, 1H, NH). HRMS [Found: $m/z$: 393.0881 ($M^+$); Calcd for $C_{21}H_{16}^{35}ClN_3O_3$: M 393.0880].

***5-(3,4-Methylenedioxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3k).*** Mp: 317–318°C; IR (potassium bromide): 3294, 1723, 1705, 1593, 1578, 1549, 1441, 1406, 1362, 1253, 1183, 1094, 1037, 932, 871, 827, 804 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 3.83 (s, 3H, $OCH_3$), 6.07 (s, 2H, $OCH_2O$), 6.91–6.96 (m, 2H, ArH), 7.01 (s, 1H, ArH), 7.06 (d, $J$ = 8.4 Hz, 2H, ArH), 7.44 (s, 1H, ArH), 8.17 (d, $J$ = 8.4 Hz, 2H, ArH), 11.13 (s, 1H, NH), 11.59 (s, 1H, NH). HRMS [Found: $m/z$: 389.1024 ($M^+$); Calcd for $C_{21}H_{15}N_3O_5$: M 389.1012].

***7-(4-Bromophenyl)-5-(4-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3l).*** Mp: >300°C; IR (potassium bromide): 3180, 1714, 1590, 1575, 1553, 1484, 1403, 1361, 1260, 1008, 828, 766 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 7.46–7.48 (m, 4H, ArH), 7.59 (s, 1H, ArH), 7.75 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.4Hz,2H, ArH), 8.17 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.8 Hz, 2H, ArH), 11.28 (s, 1H, NH), 11.77 (s, 1H, NH). HRMS [Found: $m/z$: 426.9724 ($M^+$); Calcd for $C_{19}H_{11}^{79}Br^{35}ClN_3O_2$: M 426.9723].

***7-(Naphthalen-2-yl)-5-p-tolylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (3m).*** Mp: 302–304°C; IR(potassium bromide): 3412, 3170, 3056, 1721, 1692, 1594, 1553, 1506, 1409, 1389, 1262, 1197, 860, 747 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ: 2.40 (s, 3H, $CH_3$), 7.25 (d, $J$ = 7.6 Hz, 2H, ArH), 7.38 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.0 Hz, 2H, ArH), 7.59–7.63 (m, 2H, ArH), 7.70 (d, $J$ = 1.6 Hz, 1H, ArH), 7.99 (d, $J$ = 8.0 Hz, 1H, ArH), 8.04–8.09 (m, 2H, ArH), 836 (d, $J$ = 8.8 Hz, 1H, ArH), 8.83 (s, 1H, ArH), 11.22 (s, 1H, NH), 11.74 (s, 1H, NH). HRMS [Found: $m/z$: 379.1345 ($M^+$); Calcd for $C_{24}H_{17}N_3O_2$: M 379.1321].

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## REFERENCES AND NOTES

[1] (a) Bradshaw, T. K.; Hutchison, D. W. Chem Soc Rev 1977, 6, 43; (b) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. Tetrahedron 1980, 36, 865; (c) Prajapati, D.; Bhuyan, P. J.; Sandhu, J. S. J Chem Soc Perkin Trans I 1988, 607; (d) Bhuyan, P. J.; Borah, H. N.; Sandhu, J. S. J Chem Soc Perkin Trans I 1999, 3083.

[2] (a) Marumoto, R.; Furukawa, Y. Chem Pharm Bull 1997, 25, 2974; (b) Griengl, R.; Wack, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. J Med Chem 1987, 30, 1199; (c) Clercq, E. D.; Bernaerts, R. J Biol Chem 1987, 262, 14905; (d) Jones, A. S.; Sayers, J. R.; Walker, R. T.; Clercq, E. D. J Med Chem 1988, 31, 268; (e) Mitsuya, H.; Yarchoan, R.; Broder, S. Science 1990, 249, 1533; (f) Pontikis, R.; Monneret, C. Tetrahedron Lett 1994, 35, 4351.

[3] (a) Heidelberger, C.; Arafield, F. J Cancer Res 1963, 23, 1226; (b) Baba, M.; Pauwels, R.; Herdwig, P.; Clercq, E. D.; Desmyster, J.; Vandepulfe, M. Biochem Biophys Res Commun 1987, 142, 128; (c) Clercq, E. D. J Med Chem 1986, 29, 1561; (d) Clercq, E. D. Anticancer Res 1986, 6, 549; (e) Jones, A. S.; Verhalst, G.; Walker, R. T. Tetrahedron Lett 1979, 20, 4415.

[4] (a) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. J Org Chem 1981, 46, 846; (b) Su, T. L.; Huang, J. T.; Burchanal, J. H.; Watanabe, K. A.; Fox, J. J. J Med Chem 1986, 29, 709; (c) Prajapati, D.; Sandhu, J. S. Synthesis 1988, 342.

[5] (a) Broom, A. D.; Shim, J. L.; Anderson, G. L. J Org Chem 1976, 41, 1095; (b) Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. J Med Chem 1980, 23, 327.

[6] (a) Matsumoto, J.; Minami, S. J Med Chem 1975, 18, 74; (b) Suzuki, N. Chem Pharm Bull 1980, 28, 761; (c) Oakes, V.; Rydon, H. N. J Chem Soc 1956, 4433; (d) Degraw, J. I.; Kisliuk, R. L.; Gaumont, Y.; Baugh, C. M. J Med Chem 1974, 17, 470; (e) Zakharov, A. V.; Gavrilov, M. Y.; Novoselova, G. N.; Vakhrin, M. I.; Konshin, M. E. Khim Farm Zh 1996, 30, 39.

[7] Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. Khim Farm Zh 1991, 25, 26.

[8] Heckler, R. E.; Jourdan, G. P.; Eur. Pat. Appl. EP 414386 A1 27, 1991; Chem Abstr 1991, 115, 71630.

[9] Agarwal, A.; Ashutosh, R.; Goyal, N.; Chauhan, P. M. S.; Gupta, S. Bioorg Med Chem 2005, 13, 6678.

[10] Vander Wel, S. N.; Harvey, P. J.; McNamara, D. J.; Repine, J. T.; Keller, P. R.; Quin, J., III; Booth, R. J.; Elliott, W. L.; Dobrusin, E. M.; Fry, D. W.; Toogood, P. L. J Med Chem 2005, 48, 2371.

[11] Broom, A. D.; Shim, J. L.; Anderson, C. L. J Org Chem 1976, 41, 1095.

[12] Shim, J. L.; Neiss, R.; Broom, A. D. J Org Chem 1972, 37, 578.

[13] Wawzonek, S. J Org Chem 1976, 41, 3149.

[14] Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. J Org Chem 1990, 55, 568.

[15] Quiroga, J.; Insuasty, B.; Sanchez, A.; Nogueras, M.; Meier, H. J Heterocycl Chem 1992, 29, 1045.

[16] Bagley, M. C.; Hughes, D. D.; Lloyd, R.; Powers, V. E. C. Tetrahedron Lett 2001, 42, 6585.

[17] Quiroga, J.; Insuasty, H.; Insuasty, B.; Abonía, R.; cobo, J.; Sánchez, A.; Nogueras, M. Tetrahedron 2002, 58, 4873.

[18] Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. Tetrahedron Lett 2003, 44, 8307.

[19] (a) Welton, T. Chem Rev 1999, 99, 2071; (b) Wasserscheid, P.; Keim, W. Angew Chem Int Ed 2000, 39, 3773; (c) Sheldon, R. Chem Commun 2001, 2399; (d) Wilkes, J. S. Green Chem 2002, 4, 73; (e) Yao, Q. Org Lett 2002, 4, 2197; (f) Zerth, H. M.; Leonard, N. M.; Mohan, R. S. Org Lett 2003, 5, 55; (g) Su, C.; Chen, Z. C.; Zheng, Q. G. Synthesis 2003, 555; (h) Rajagopal, R.; Jarikote, D. V.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V. Tetrahedron Lett 2003, 44, 1815; (i) Kumar, A.; Pawar, S. S. J Org Chem 2004, 69, 1419.

[20] Abdul-Sada, A. A. K.; Ambler, P. W.; Hodgson, P. K. G.; Seddon, K. R.; Stewark, N. J. World Pat. WO9521871, 1995.

[21] (a) Chauvin, Y.; Mussman, L.; Olivier, H. Angew Chem Int Ed Engl 1995, 38, 3097; (b) Fisher, T.; Sethi, A.; Wellton, T.; Woolf, J. Tetrahedron Lett 1999, 40, 293; (c) Asams, C. J.; Earle, M. J.; Seddon, K. R. Chem Commun 1999, 25; (d) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. Chem Commun 1999, 1043; (e) Monteiro, A. L.; Zimn, F. K.; de Souza, R. F.; Dupont, J. Tetrahedron:

Asymmetry 1997, 8, 177; (f) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. Polyhedron 1996, 15, 1217.

[22] (a) Badri, M.; Brunet, J. J.; Perron, R. Tetrahedron Lett 1992, 33, 4435; (b) Earle, M. J.; McCormac, P. B.; Seddon, K. R. Chem Commun 1998, 2245.

[23] (a) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. J Org Chem 1986, 54, 480; (b) Luer, G. D.; Bartalk, D. E. J Org Chem 1982, 47, 1238; (c) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. Chem Commun 1998, 2097.

[24] Ellis, B.; Keim, W.; Wasserscheid, P. Chem Commun 1999, 337.

[25] Earle, M. J.; McCormac, P. B.; Seddon, K. R. Green Chem 1999, 1, 23.

[26] Corey, E. J.; Zhang, F. Y. Org Lett 2000, 2, 1097.

[27] (a) Kaufmann, D. E.; Nouroozian, M.; Henze, H. Synlett 1996, 1091; (b) Bohm, V. P. W.; Herrmann, W. A. Chem Eur J 2000, 6, 1017; (c) Carmichael, A. J.; Earle, M. J.; Holberey, J. D.; McCormac, P. B.; Seddon, K. R. Org Lett 1999, 1, 997; (d) Zim, D.; de Souza, R. F.; Dupont, J.; Monteiro, A. L. Tetrahedron Lett. 1998, 39, 7071; (e) Song, L. E.; Roh, E. J Chem Commun 2000, 837.

[28] Schoefer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. Chem Commun 2001, 425.

[29] (a) Shi, D. Q.; Dou, G. L.; Li, Z. Y.; Ni, S. N.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Tetrahedron 2007, 63, 9764; (b) Shi, C. L.; Shi, D. Q.; Kim, S. H.; Huang, Z. B.; Ji, S. J.; Ji, M. Tetrahedron 2008, 64, 2425; (c) Shi, D. Q.; Dou, G. L.; Shi, C. L.; Li, Z. Y.; Ji, S. J. Synthesis 2007, 3117; (d) Shi, D. Q.; Dou, G. L.; Ni, S. N.; Shi, J. W.; Li, X. Y.; Wang, X. S.; Wu, H.; Ji, S. J. Synlett 2007, 2509; (e) Shi, D. Q.; Niu, L. H.; Shi, J. W.; Wang, X. S.; Ji, S. J. J Heterocycl Chem 2007, 44, 1083; (f) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S. J Heterocycl Chem 2008, 45, 653; (g) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S.; Ji, S. J. J Heterocycl Chem 2008, 45, 693; (h) Shi, D. Q.; Yang, F.; Ni, S. N. J Heterocycl Chem 2009, 46, 469; (i) Dou, G. L.; Wang, M. M.; Huang, Z. B.; Shi, D. Q. J Heterocycl Chem 2009, 46, 645; (j) Shi, D. Q.; Niu, L. H.; Yao, H.; Jiang, H. J Heterocycl Chem 2009, 46, 237.