Clean synthesis of pyrido[2,3-*d*]pyrimidines in aqueous media

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The reaction of substituted cinnamonitriles and 4-amino-2,6-dihydroxypyrimidine or 2,4-diamino-6-hydroxypyrimidine in water in the presence of triethylbenzylammonium chloride (TEBA) as catalyst affords a clean synthesis of pyrido[2,3-*d*]pyrimidine derivatives.

Keywords: clean synthesis, pyrido[2,3-*d*]pyrinidine, aqueous media

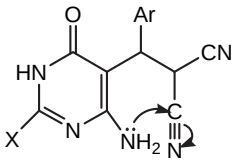
The need to reduce the amount of toxic waste and by products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.[1] One of the most promising approaches uses water as the reaction medium.[2] Breslow,[3] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions.[4] The aqueous medium with respect to organic solvent is less expensive, less dangerous and environment-friendly. Generally, the low solubiblity[5] of most reagents in water is not an obstacle to the reactivity, which on the contrary, is reduced with the use of cosolvents.

Pyrido[2,3]pyrimidines are annelated uracils which have received considerable attention over the past years due to their wide range of biological activity. Compounds with this ring systems have diverse pharmacological activity such as antitumour,[6] cardiotonic,[7] hepatoprotactive,[7] antihypertensive,[7] antibronchitic[8] and antifungal activity.[9] Therefore, for the preparation of these complex molecules large efforts has been directed towards the synthetic manipulation of uracils. As a result, a number of reports have appeared in literature[10] which usually require forcing conditions, long reaction times, complex synthetic pathways and using an organic solvent. Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles. Based on our previous studies on the use of water as solvent for carrying out carbon–carbon forming reactions under heterogeneous catalysis,[11] we report here a novel synthesis of well functionalised pyrido[2,3-*d*] pyrimidines using water as reaction medium.

When substituted cinnamonitriles **1** were treated with 4-amino-2,6-dihydroxypyrimidine **2** in water at 90 °C and in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA) for 6–16 h, the products 7-amino-5-aryl-6-cyanopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **3** were obtained in good yields (Scheme 1). The results are summarised in Table 1.

Treatment of substituted cinnamonitriles **1** with 2,4-diamino-6-hydroxypyrimidine **4** under the same reaction conditions gave the 2,7-diamino-5-aryl-6-cyanopyrido[2,3-*d*]pyrimidine-4(3*H*)-ones **5** (Scheme2). These results are summarised in Table **2**.

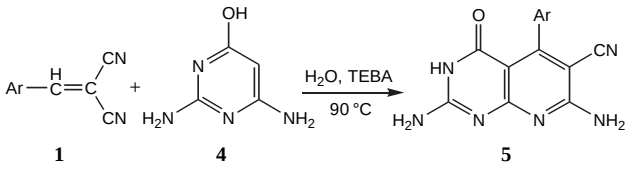
The structures of the compounds **4** and **5** were ascertained by spectroscopic data and elemental analysis. A reasonable mechanism for the formation of the products **4** and **5** is outlined in Scheme 3. The reaction occurs via an initial formation of the Michale adduct, from the Michael addition of substituted cinnamonitrile and 4-amino-2,6- dihydroxypyrimidine or 2,4-diamno-6-hydroxpyrimidine. The Michael adduct then cyclizes, isomerizates and subsequently losses a hydrogen molecule to afford the fully aromatised compound. This type of hydrogen loss is well precedented.[12]



Scheme 1

Table 1 The synthesis of 7-amino-5-aryl-6-cyanopyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione in aqueous media

Entry	Ar	Reaction times/h	Isolated yield/%
3a	4-ClC_6H_4	16	88
3b	2-ClC_6H_4	10	66
3c	2,4-$Cl_2C_6H_3$	6	72
3d	4-BrC_6H_4	9	99
3e	4-FC_6H_4	6	76
3f	3,4-$(CH_3O)_2C_6H_3$	10	78
3g	3,4-$Cl_2C_6H_3$	10	84
3h	3-$NO_2C_6H_4$	8	88
3i	4-$NO_2C_6H_4$	12	78
3j	4-$CH_3OC_6H_4$	6	70



1 **4** **5**

Scheme 2

Table 2 The synthesis of 2,7-diamino-5-aryl-6-cyanopyrido [2,3-*d*]pyrimidine-4(3*H*)-one in aqueous media

Entry	Ar	Reaction times/h	Isolated yield/%
5a	2-ClC_6H_4	5	99
5b	4-ClC_6H_4	6	86
5c	4-BrC_6H_4	5	74
5d	4-$NO_2C_6H_4$	6	90
5e	4-HOC_6H_4	7	86
5f	2,4-$Cl_2C_6H_3$	5	76
5g	3,4-$(CH_3)_2C_6H_3$	5	81

In summary, the conversion of substituted cinnamonitriles and 4-amino-2,6-dihydroxypyrimidine or 2,4-diamino-6-hydroxypyrimidine to pyrido[2,3-*d*]pyrimidine derivatives have been efficiently performed in water as a solvent and by using a catalytic amount of TEBA. Compared the previous methods, this new protocol has the advantages of good yields, low cost, simple operation and environmentally benign procedure.

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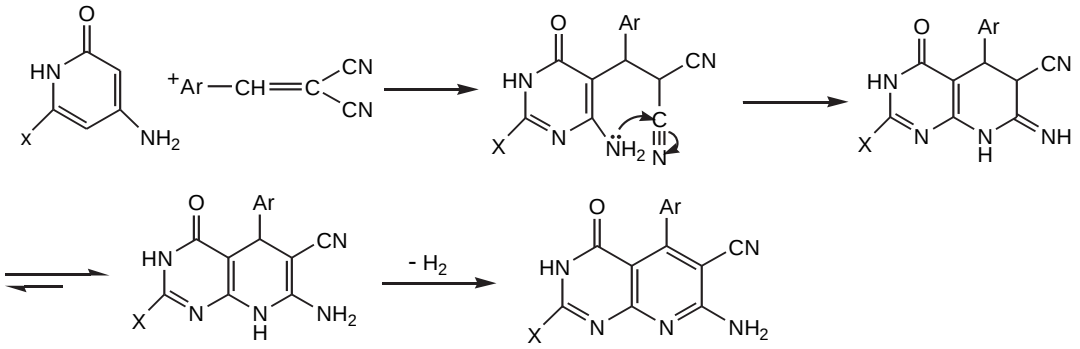

Scheme 3

Experimental

Melting points are uncorrected. IR Spectra were recorded on a FT IR-8101 Spectrameter in KBr with absorptions in cm^{-1}. ^1H NMR spectra were determined on an Inova-400MHz spectrometer using DMSO-d_6 solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Microanalyses were carried out on a Perkin-Elmer 2400 II elemental analyzer.

General procedure for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives **3** and **5**. A mixture of the substituted cinnamonitriles **1** (2 mmol), 4-amino-2,6-dihydroxy- pyrimidine **2** or 2,4-diamino-6-hydroxypyrimidine **4** (2 mmol) and TEBA (0.15 g) in H_2O (10 ml) was stirred for 5–16 h at 90 °C, then cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water and recrystallised from DMF to give pure **3** to **5**.

7-Amino-5-(4-chlorophenyl)-6-cyanopyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3a**): M.p. >300 °C; IR, ν: 3398, 3330, 3169, 3090, 2224, 1706, 1645, 1590, 1556, 1495, 1442, 1409, 1375, 1299, 1260, 1200, 1144, 1092, 1018, 877, 803, 771, 711, 680 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.30 (2H, d, *J* = 8.4 Hz, ArH), 7.48 (2H, d, *J* = 8.4 Hz, ArH), 7.66 (2H, s, NH_2), 10.95 (1H, s, NH), 11.47 (1H, s, NH); Anal. calcd for $C_{14}H_8ClN_5O_2$: C 53.60, H 2.57, N 22.33; found C 53.81, H 2.53, N 22.54.

7-Amino-5-(2-chlorophenyl)-6-cyanopyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3b**): M.p. >300 °C; IR, ν: 3386, 3325, 3164, 2921, 2223, 1717, 1673, 1648, 1598, 1563, 1484, 1439, 1381, 1306, 1258, 1204, 1154, 1100, 1057, 1028, 808, 763, 707 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.28–7.31 (1H, m, ArH), 7.39–7.46 (2H, m, ArH), 7.52–7.54 (1H, m, ArH), 7.76 (2H, s, NH_2), 11.01 (1H, s, NH), 11.55 (1H, s, NH); Anal. calcd for $C_{14}H_8ClN_5O_2$: C 53.60, H 2.57, N 22.33; found C 53.75, H 2.51, N 22.19.

7-Amino-6-cyano-5-(2,4-dichlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3c**): M.p. >300 °C; IR, ν: 3385, 3334, 3156, 3081, 2924, 2800, 2223, 1717, 1651, 1636, 1598, 1560, 1485, 1440, 1383, 1306, 1257, 1205, 1145, 1100, 1056, 1026, 906, 877, 826, 802, 756, 711 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.36 (1H, d, *J* = 8.4 Hz, ArH), 7.52 (1H, d, *J* = 8.4 Hz, ArH), 7.74 (1H, s, ArH), 7.81 (2H, s, NH_2), 11.05 (1H, s, NH), 11.60 (1H, s, NH); Anal. calcd for $C_{14}H_7Cl_2N_5O_2$: C 48.30, H 2.03, N 20.12; found C 48.18, H 2.13, N 20.25.

7-Amino-6-cyano-5-(4-bromophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3d**): M.p. >300 °C; IR, ν: 3400, 3329, 3172, 3083, 2931, 2803, 2221, 1716, 1698, 1645, 1592, 1545, 1491, 1441, 1410, 1374, 1298, 1264, 1199, 1143, 1105, 1073, 1014, 876, 801, 768, 706 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.24 (2H, d, *J* = 8.4 Hz, ArH), 7.62 (2H, d, *J* = 8.4 Hz, ArH), 7.68 (2H, s, NH_2), 10.95 (1H, s, NH), 11.50 (1H, s, NH); Anal. calcd for $C_{14}H_8BrN_5O_2$: C 46.95, H 2.25, N 19.55; found C 47.12, H 2.18, N 19.77.

7-Amino-6-cyano-5-(4-fluorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3e**): M.p. >300 °C; IR, ν: 3362, 3334, 3147, 3015, 2802, 2229, 1734, 1674, 1646, 1606, 1566, 1512, 1440, 1387, 1302, 1224, 1160, 1097, 1028, 877, 832, 808, 756 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.24–7.27 (2H, m, ArH), 7.30–7.35 (2H, m, ArH), 7.66 (2H, s, NH_2), 10.94 (1H, s, NH), 11.48 (1H, s, NH); Anal. calcd for $C_{14}H_8FN_5O_2$: C 56.57, H 2.71, N 23.56; found C 56.62, H 2.63, N 23.49.

7-Amino-6-cyano-5-(3,4-dimethoxyphenyl)pyrido[2,3-d] pyrimidine-2,4(1H,3H)-dione (**3f**): M.p. >300 °C; IR, ν: 3397, 3348, 3188, 3090, 2838, 2222, 1703, 1646, 1597, 1553, 1439, 1412, 1363, 1258, 1183, 1142, 1023, 801, 767 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.72 (3H, s, CH_3O), 3.82 (3H, s, CH_3O), 6.81 (1H, d, *J* = 8.4 Hz, ArH), 6.89 (1H, s, ArH), 6.98 (1H, d, *J* = 8.4 Hz, ArH), 7.58 (2H, s, NH_2), 10.89 (1H, s, NH), 11.41 (1H, s, NH); Anal. calcd for $C_{16}H_{13}N_5O_4$: C 56.64, H 3.86, N 20.64; found C 56.78, H 3.81, N 20.47.

7-Amino-6-cyano-5-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3g**): M.p. >300 °C; IR, ν: 3396, 3328, 3187, 3090, 2818, 2223, 1715, 1699, 1645, 1592, 1560, 1478, 1440, 1372, 1302, 1261, 1203, 1138, 1103, 1035, 947, 899, 803, 733, 702, 685 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.30 (1H, d, *J* = 8.0 Hz, ArH), 7.63 (1H, s, ArH), 7.71 (1H, d, *J* = 8.0 Hz, ArH), 7.74 (2H, s, NH_2), 11.01 (1H, s, NH), 11.54 (1H, s, NH); Anal. calcd for $C_{14}H_7Cl_2N_5O_2$: C 48.30, H 2.03, N 20.12; found C 48.57, H 1.94, N 20.25.

7-Amino-6-cyano-5-(3-nitrophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3h**): M.p. >300 °C; IR, ν: 3401, 3326, 3188, 3090, 2803, 2227, 1724, 1702, 1646, 1598, 1560, 1532, 1485, 1447, 1370, 1340, 1304, 1205, 1099, 1030, 924, 847, 803, 737, 703, 682 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.73–7.81 (4H, m, ArH, NH_2), 8.21–8.22 (1H, m, ArH), 8.30–8.32 (1H, m, ArH), 11.02 (1H, s, NH), 11.56 (1H, s, NH); Anal. calcd for $C_{14}H_8N_6O_4$: C 51.86, H 2.49, N 25.92; found C 52.03, H 2.52, N 26.07.

7-Amino-6-cyano-5-(4-nitrophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3i**): M.p. >300 °C; IR, ν: 3609, 3535, 3321, 3199, 3081, 2848, 2227, 1706, 1666, 1589, 1553, 1522, 1450, 1381, 1348, 1208, 1151, 1108, 1018, 926, 887, 852, 812, 770, 750, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.59 (2H, d, *J* = 6.8 Hz, ArH), 7.80 (2H, s, NH_2), 8.29 (2H, d, *J* = 6.8 Hz, ArH), 11.03 (1H, s, NH), 11.56 (1H, s, NH); Anal. calcd for $C_{14}H_8N_6O_4$: C 51.86, H 2.49, N 25.92; found C 52.05, H 2.53, N 25.89.

7-Amino-6-cyano-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**3j**): M.p. >300 °C; IR, ν: 3403, 3329, 3189, 3078, 2220, 1702, 1646, 1593, 1550, 1515, 1438, 1374, 1308, 1255, 1180, 1028, 875, 802 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.82 (3H, s, CH_3O), 6.96 (2H, d, *J* = 8.0 Hz, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 7.58 (2H, s, NH_2), 10.88 (1H, s, NH), 11.42 (1H, s, NH); Anal. calcd for $C_{15}H_{11}N_5O_3$: C 58.25, H 3.58, N 22.64; found C 58.37, H 3.52, N 22.70.

2,7-Diamino-6-cyano-5-(2-chlorophenyl)pyrido[2,3-d]pyrimidine-4(3H)-one (**5a**): M.p. >300 °C; IR, ν: 3463, 3333, 3177, 2189, 1661, 1556, 1458, 1389, 1300, 1205, 1135, 1035, 811, 786, 755 cm^{-1}; ^1H NMR(DMSO-d_6) δ: 6.92 (2H, s, NH_2), 7.25–7.28 (1H, m, ArH), 7.33 (2H, s, NH_2), 7.36–7.44 (2H, m, ArH), 7.50–7.52 (1H, m, NH), 10.78 (1H, s, NH); Anal. calcd for $C_{14}H_9ClN_6O$: C 53.77, H 2.90, N 26.87; found C 53.85, H 2.81, N 26.96.

2,7-Diamino-6-cyano-5-(4-chlorophenyl)pyrido[2,3-d]pyrimidine-4(3H)-one (**5b**): M.p. >300 °C; IR, ν: 3501, 3394, 3318, 3056, 2214, 1681, 1668, 1615, 1549, 1492, 1428, 1309, 1195, 1088, 1026, 916, 877, 812, 683 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 6.82 (2H, s, NH_2), 7.22 (2H, s, NH_2), 7.27 (2H, d, *J* = 8.4 Hz, ArH), 7.45 (2H, d, *J* = 8.4 Hz, ArH), 10.64 (1H, s, NH); Anal. calcd for $C_{14}H_9ClN_6O$: C 53.77, H 2.90, N 26.87; found C 53.63, H 2.82, N 26.98.

2,7-Diamino-6-cyano-5-(4-bromophenyl)pyrido[2,3-d]pyrimidine-4(3H)-one (**5c**): M.p. >300 °C; IR, ν: 3389, 3197, 3150, 3078, 2214, 1685, 1667, 1615, 1546, 1489, 1428, 1309, 1195, 1071, 1012, 916, 876, 810 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.21 (2H, d, *J* = 8.0 Hz, ArH), 7.28 (2H, s, NH_2), 7.59 (2H, d, *J* = 8.0 Hz, ArH)), 10.70 (1H, s, NH); Anal. calcd for $C_{14}H_9BrN_6O$: C 47.08, H 2.54, N 23.53; found C 47.27, H 2.49, N 23.68.

2,7-Diamino-6-cyano-5-(4-nitrophenyl)pyrido[2,3-d]pyrimidine-4(3H)-one (**5d**): M.p. >300 °C; IR, ν: 3446, 3343, 3187, 2170, 1670, 1550, 1515, 1472, 1439, 1385, 1346, 1301, 1216, 1106, 916, 885, 816, 742 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.35 (2H, s, NH_2), 7.55 (2H, d, *J* = 8.8 Hz, ArH), 8.26 (2H, d, *J* = 8.8 Hz, ArH), 10.70 (1H, s, NH);

Anal. calcd for $C_{14}H_9N_7O_3$: C 52.02, H 2.81, N 30.33; found C 52.27, H 2.73, N 30.17.

2,7-Diamino-6-cyano-5-(4-hydroxyphenyl)pyrido[2,3-d] pyrimidine-4(3H)-one (**5e**): M.p. >300 °C; IR, ν: 3381, 3181, 3140, 2820, 2213, 1696, 1667, 1636, 1613, 1549, 1515, 1425, 1388, 1309, 1266, 1223, 1196, 1173, 1106, 917, 877, 835, 813 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 6.75 (2H, d, J = 8.0 Hz, ArH), 7.04 (2H, d, J = 8.0 Hz, ArH), 7.08 (2H, s, NH_2), 9.55 (1H, s, OH), 10.58 (1H, s, NH); Anal. calcd for $C_{14}H_{10}N_6O_2$: C 57.14, H 3.43, N 28.56; found C 57.28, H 3.36, N 28.63.

2,7-Diamino-6-cyano-5-(2,4-dichlorophenyl)pyrido[2,3-d] pyrimidine-4(3H)-one (**5f**): M.p. >300 °C; IR, ν: 3368, 3190, 3098, 2886, 2222, 1673, 1626, 1555, 1479, 1433, 1340, 1199, 1143, 1104, 1054, 921, 878, 816, 797cm^{-1}; ^1H NMR (DMSO-d_6) δ: 6.90 (2H, s, NH_2), 7.33 (1H, d, J = 8.4 Hz, ArH), 7.35 (2H, s, NH_2), 7.49 (1H, d, J = 8.4 Hz, ArH), 7.70 (1H, s, ArH), 10.76 (1H, s, NH); Anal. calcd for $C_{14}H_8Cl_2N_6O$: C 48.44, H 2.32, N 24.21; found C 48.27, H 2.39, N 24.06.

2,7-Diamino-6-cyano-5-(3,4-dichlorophenyl)pyrido[2,3-d] pyrimidine-4(3H)-one (**5g**): M.p. >300 °C; IR, ν: 3510, 3407, 3195, 3031, 2878, 2206, 1694, 1665, 1612, 1547, 1500, 1472, 1423, 1306, 1188, 1099, 961, 878, 832, 811 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.24 (3H, s, CH_3), 2.28 (3H, s, CH_3), 6.78 (2H, s, NH_2), 6.93 (1H, d, J = 8.4 Hz, ArH), 6.98 (1H, s, ArH), 7.11–7.17 (3H, m, ArH, NH_2), 10.56 (1H, s, NH); Anal. calcd for $C_{16}H_{14}N_6O$: C 62.74, H 4.61, N 27.44; found C 62.83, H 4.54, N 27.56.

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