Efficient Synthesis of 2-Substituted Pyrido[3,2-*d*]pyrimidines Involving S_NAr and Palladium-Catalyzed Cross-Coupling Reactions

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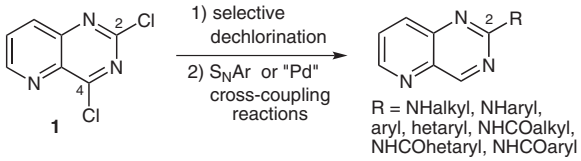
Abstract: The efficient and original synthesis of various 2-substituted pyrido[3,2-*d*]pyrimidines is reported. Starting from 2,4-dichloropyrido[3,2-*d*]pyrimidine, a regioselective pallado-dehalogenation led to 2-chloropyrido[3,2-*d*]pyrimidine, which was used in S_NAr and palladium-catalyzed cross-coupling reactions in order to afford highly functionalized products in very good yields.

Key words: arylations, amination, palladium

Pyridopyrimidine moieties are scaffolds present in a great number of biologically active drugs and very promising PDGF, EGFR, DHFR, p38 MAP kinase, PI3 kinase, tyrosine kinase, adenosine kinase, and cyclin-dependant kinases inhibitors.[1–8] Hence, the synthesis of pyridopyrimidine derivatives provides an interesting challenge in medicinal chemistry. Nevertheless, synthetic methods leading to pyrido[3,2-*d*]pyrimidine regioisomers are scarcely reported.

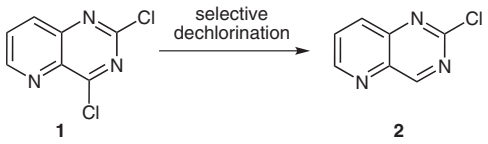
Our group has recently developed original strategies to design 2,4-disubstituted pyrido[3,2-*d*]pyrimidines.[9,10] Starting from **1** (Scheme 1), we have shown that S_NAr, Stille and Suzuki palladium-catalyzed reactions occurred regioselectively at C4 and then at C2, indicating a strong electronic difference between the two halogenated centers.[11] Interestingly, the chlorine differentiation led to 2,4-disubstituted pyrido[3,2-*d*]pyrimidines.



Scheme 1

In this paper, we report efficient methods affording 2-substituted pyrido[3,2-*d*]pyrimidines from 2-chloropyrido[3,2-*d*]pyrimidine (**2**). In a first step, we engaged compound **1** in a regioselective reduction of the C4–Cl bond by using tributyltin hydride in the presence of tetrakis(triphenylphosphine)palladium(0) in toluene at 100 °C (Scheme 2).[10]

We are now able to crystallize this starting material and an X-ray crystal structure analysis of **2** formally established its structure (Figure 1).[12]



Scheme 2 *Reagents and conditions*: Bu_3SnH (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), toluene, 100 °C, 1 h, 86%.

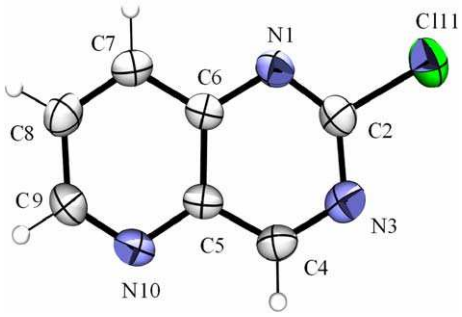


Figure 1 ORTEP representation of compound **2**

In order to study the versatility of **2** as a building block, we carried out a wide range of S_NAr and cross-coupling reactions. The first S_NAr was a direct amination (Table 1). Reaction of **2** with a mixture of aqueous ammonia and tetrahydrofuran in a sealed tube at 80 °C led after 12 hours to the desired derivative **3a** in 69% yield (entry 1). Condensations of alkyl- and arylamines were then performed in refluxing 1,4-dioxane (entries 2–7).

Derivatives **3b** and **3c** were easily obtained from butylamine and 4-methoxybenzylamine in 80% and 92% yields, respectively. Starting indiscriminately from aniline and 4-methoxy- or 4-chloroaniline, the reactions gave the desired compounds **3d–f** in high yields in few hours (entries 2–6).

Nevertheless, the use of 2-chloroaniline proved to be more tricky. In fact, compound **3g** was isolated after 48 hours in only 65% yield (entry 7). The increase in the re-

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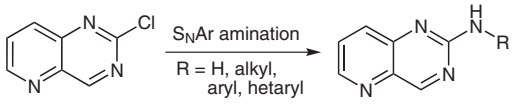
Table 1 Amination of 2-Chloropyrido[3,2-*d*]pyrimidine (**2**)[a]



2 **3**

Entry	Product	R	Time (h)	Yield[b] (%)
1	**3a**	H	12	69
2	**3b**	Bu	4	80
3	**3c**	4-$MeOC_6H_4CH_2$	4	92
4	**3d**	Ph	4	79
5	**3e**	4-$MeOC_6H_4$	3	84
6	**3f**	4-ClC_6H_4	3	81
7	**3g**	2-ClC_6H_4	48	65

[a] Reaction conditions: for R = H, NH_4OH, THF, sealed tube, 80 °C; for R …H, RNH_2 (1.2 equiv), 1,4-dioxane, reflux.
[b] Yields are given for isolated product after flash chromatography.

action time is due to steric hindrance, which affects directly the C2 S_NAr.

The second aim of this work was the use of **2** in Suzuki and Stille palladium-catalyzed reactions (Table 2).[9,10] All reactions were quenched after full disappearance of the starting material **2** and were carried out with only 5 mol% of tetrakis(triphenylphosphine)palladium(0). Other components were fitted to the nature of the coupling process.

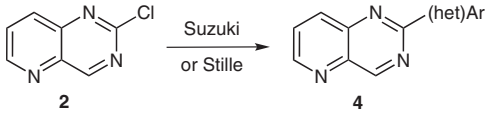
Our previous report proved the efficiency of Suzuki reactions between **2** and (het)arylboronic acids in nonaqueous conditions to give 2-(het)arylpyrido[3,2-*d*]pyrimidines **4a–c** (entries 1–3). Alternatively, we used the corresponding tributylstannyl derivatives in order to achieve Stille reactions to give **4a–c** (entries 4–6). To prevent degradation, the amount of stannyl derivatives was slightly increased and lithium chloride addition proved to be necessary.

Unfortunately, the reaction time increased to 24 hours and the product yield of 2-(het)arylpyrido[3,2-*d*]pyrimidines **4a–c** decreased notably compared to the Suzuki coupling reactions. Using the sensitive 2-(tributylstannyl)pyridine, no reaction occurred and the starting material **2** was fully recovered (entry 7). Whatever the chosen Suzuki or Stille conditions, 2-(het)arylpyrido[3,2-*d*]pyrimidines **4** were obtained independently of electronic and steric effects. In our hands, Stille-type reactions proved to be less efficient.

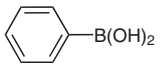
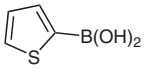
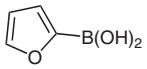
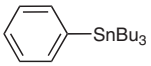
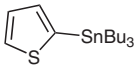
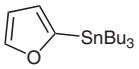
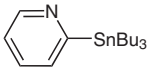
The last palladium-catalyzed reaction investigated was the unusual Buchwald-type reaction. The great interest of this method is to prepare new 2-amidopyrido[3,2-*d*]pyrimidines in one step. Reactions were also carried out with 5 mol% of palladium(II) acetate and 10 mol% of Xantphos as a catalytic system[13] in refluxing 1,4-dioxane (Table 3).

In this study, the alkyl, aryl, and hetaryl primary amides (Table 3, entries 1–5) were successfully introduced by C2 chlorine displacement after a few minutes and compounds **5a–e** were isolated in good yields. These reactions were also independent of the amide substitution.

Table 2 (Het)Arylation of 2-Chloropyrido[3,2-*d*]pyrimidine (**2**)[a]

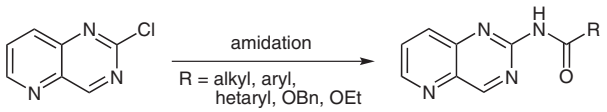


2 **4**

Entry	Reactant	Product	(Het)Ar	Time (h)	Yield[b] (%)
1		**4a**	Ph	3	86
2		**4b**	2-thienyl	2	85
3		**4c**	2-furyl	3	87
4		**4a**	Ph	24	56
5		**4b**	2-thienyl	24	46
6		**4c**	2-furyl	24	69
7		**4d**	2-pyridyl	24	–[c]

[a] Reaction conditions: Suzuki reaction (het)$ArB(OH)_2$ (1.2 equiv), Na_2CO_3 (2 equiv), $Pd(PPh_3)_4$ (0.05 equiv), toluene–EtOH (2:1), 100 °C; Stille reaction (het)$ArSnBu_3$ (1.25 equiv), $Pd(PPh_3)_4$ (0.05 equiv), LiCl (2.8 equiv), DMF, 90 °C.
[b] Yields are given for isolated products.
[c] Starting material was recovered.

Table 3 Amidation of 2-Chloropyrido[3,2-*d*]pyrimidine (**2**)[a]



2 **5**

Entry	Product	R	Time (min)	Yield[b] (%)
1	**5a**	Ac	15	88
2	**5b**	Ph	15	81
3	**5c**	4-ClC_6H_4	15	68
4	**5d**	3-pyridyl	10	74
5	**5e**	pyrazin-2-yl	20	92
6	**5f**	OBn	15	71
7	**5g**	OEt	45	72

[a] Reaction conditions: $RCONH_2$ (1.2 equiv), K_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.05 equiv), Xantphos (0.1 equiv), 1,4-dioxane, reflux.
[b] Yields are given for isolated products.

To complete this work, we employed **2** in reaction with benzylcarbamate. The reaction was achieved in a few minutes and compound **5f** was isolated in 71% yield. With the very electron-rich ethylcarbamate, the reaction time slightly increased to 45 minutes, but without any incidence on the yield of **5g**.

Herein, we have described the original regioselective dechlorination procedure of 2,4-dichloropyrido[3,2-*d*]pyrimidine (**1**) using palladium-catalyzed Stille-type coupling reaction with tributyltin hydride. Furthermore, we have studied the reactivity of 2-chloropyrido[3,2-*d*]pyrimidine (**2**) via aminations (S_NAr), (het)arylations, and amidations, cross-coupling reactions (Suzuki, Stille, and Buchwald), and found it to act as a versatile building block for the direct introduction of the pyrido[3,2-*d*]pyrimidin-2-yl moiety.

^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance DPX250 (250.19 MHz ^{1}H, 62.89 MHz ^{13}C) or Bruker Avance II (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometers using tetramethylsilane as the internal standard, chemical shifts are reported in parts par million (ppm, δ units). Coupling constants are reported in units of hertz (Hz) if applicable. Infrared spectra were recorded using a Ge ATR instrument. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer. Exact mass were performed in CRMPO, Rennes, France. Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed on silica gel 60 (40–63 mesh). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F254 precoated plates. Visualization was done with ultraviolet light. Reactions requiring anhydrous conditions were performed under argon. All solvents were freshly distilled under argon prior to use. Chemical reagents and solvents were obtained from either Aldrich or Acros Organics. PE = petroleum ether (boiling range 40–60 °C).

2-Aminopyrido[3,2-*d*]pyrimidine (3a); Typical Procedure

A soln of **2** (100 mg, 0.6 mmol) in THF (5 mL) and aq NH_3 soln (5 mL) was heated at 80 °C in a sealed tube for 12 h. The mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. After extraction with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2–MeOH, 95:5) to give **3** (69% yield) as a yellow solid; mp 214–215 °C.

IR (ATR-Ge): 3329, 3160, 2290, 1659, 1581, 1465, 1364, 1174, 939, 816 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.11 (br s, 2 H, NH_2), 7.66 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 7.82 (d, *J* = 8.6 Hz, 1 H, H8), 8.59 (dd, *J* = 1.4, 4.1 Hz, 1 H, H6), 9.13 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 128.6 (CH), 132.7 (CH), 135.9 (C_q), 146.4 (CH), 148.0 (C_q), 160.8 (C_q), 163.0 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_7H_7N_4$: 147.0671; found: 147.0667.

2-(Alkylamino)- or 2-(Arylamino)pyrido[3,2-*d*]pyrimidines 3b–g; General Procedure

To a soln of **2** (100 mg, 0.6 mmol) in 1,4-dioxane (6 mL) was added the amine (1.2 equiv). The reaction was refluxed for the desired time (Table 1). The mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. After extraction with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography to afford the desired compounds **3b**–**g**.

2-(Butylamino)pyrido[3,2-*d*]pyrimidine (3b)

From **2**, flash chromatography (CH_2Cl_2–MeOH, 99:1) gave **3b** (80% yield) as a yellow solid; mp 85–86 °C.

IR (ATR-Ge): 3242, 2853, 1609, 1584, 1404, 1348, 1174, 1087, 934, 811 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.38–1.53 (m, 2 H, CH_2), 1.61–1.73 (m, 2 H, CH_2), 3.51–3.59 (m, 2 H, CH_2), 5.88 (s, 1 H, NH), 7.53 (dd, *J* = 4.1, 8.5 Hz, 1 H, H7), 7.88 (d, *J* = 8.5 Hz, 1 H, H8), 8.60 (dd, *J* = 1.6, 4.1 Hz, 1 H, H6), 9.17 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.9 (CH_3), 20.2 (CH_2), 31.6 (CH_2), 41.6 (CH_2), 128.2 (CH), 133.5 (CH), 136.8 (C_q), 146.6 (CH), 148.5 (C_q), 159.6 (C_q), 163.2 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}N_4$: 203.1297; found: 203.1294.

2-(4-Methoxybenzylamino)pyrido[3,2-*d*]pyrimidine (3c)

From **2**, flash chromatography (CH_2Cl_2–MeOH, 98:2) gave **3c** (92% yield) as a yellow solid; mp 143–144 °C.

IR (ATR-Ge): 1607, 1585, 1541, 1508, 1246, 1180, 1021, 818, 726 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.79 (s, 3 H, OCH_3), 4.69 (d, *J* = 5.6 Hz, 2 H, CH_2), 6.03 (s, 1 H, NH), 6.86 (d, *J* = 8.5 Hz, 2 H, H_{arom}), 7.33 (d, *J* = 8.5 Hz, 2 H, H_{arom}), 7.54 (dd, *J* = 4.1, 8.5 Hz, 1 H, H7), 7.89 (d, *J* = 8.5 Hz, 1 H, H8), 8.62 (dd, *J* = 1.5, 4.1 Hz, 1 H, H6), 9.11 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 45.5 (CH_2), 55.4 (CH_3), 114.2 (2 CH), 128.3 (CH), 129.2 (2 CH), 130.8 (C_q), 133.7 (CH), 137.1 (C_q), 147.0 (CH), 148.5 (C_q), 159.1 (C_q), 159.4 (C_q), 163.5 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_4O$: 267.1246; found: 267.1242.

2-(Phenylamino)pyrido[3,2-*d*]pyrimidine (3d)

From **2**, flash chromatography (CH_2Cl_2–MeOH, 99:1) gave **3d** (79% yield) as a white solid; mp 166–167 °C.

IR (ATR-Ge): 1604, 1585, 1545, 1449, 1393, 1250, 818, 745 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 7.5 Hz, 1 H, H_{arom}), 7.39 (t, *J* = 7.5 Hz, 2 H, H_{arom}), 7.62 (dd, *J* = 4.1, 8.5 Hz, 1 H, H7), 7.72 (s, 1 H, NH), 7.80–7.84 (m, 2 H, H_{arom}), 8.02–8.06 (m, 1 H, H8), 8.73 (dd, *J* = 1.6, 4.1 Hz, 1 H, H6), 9.30 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 119.4 (2 CH), 123.3 (CH), 128.6 (CH), 129.1 (2 CH), 134.4 (CH), 137.4 (C_q), 139.3 (C_q), 147.9 (C_q), 148.2 (CH), 156.9 (C_q), 163.4 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_4$: 223.0984; found: 223.0981.

2-(4-Methoxyphenylamino)pyrido[3,2-*d*]pyrimidine (3e)

From **2**, flash chromatography (PE–EtOAc, 98:2) gave **3e** (84% yield) as a yellow solid; mp 179–180 °C.

IR (ATR-Ge): 1615, 1541, 1449, 1231, 1172, 1036, 818, 719 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 6.95 (d, *J* = 8.8 Hz, 2 H, H_{arom}), 7.59 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 7.67–7.71 (m, 3 H, NH, H_{arom}), 7.98 (d, *J* = 8.6 Hz, 1 H, H8), 8.69 (m, 1 H, H6), 9.27 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 114.4 (2 CH), 121.7 (2 CH), 128.5 (CH), 132.3 (C_q), 134.2 (CH), 137.3 (C_q), 147.8 (CH), 148.1 (C_q), 156.0 (C_q), 157.2 (C_q), 163.4 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_4O$: 253.1089; found: 253.1084.

2-(4-Chlorophenylamino)pyrido[3,2-*d*]pyrimidine (3f)
From **2**, flash chromatography (PE–EtOAc, 98:2) gave **3f** (81% yield) as a yellow solid; mp 179–180 °C.

IR (ATR-Ge): 1589, 1537, 1489, 1456, 1405, 1239, 818, 722 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.39 (d, *J* = 8.8 Hz, 2 H, H_{arom}), 7.80 (dd, *J* = 4.1, 8.5 Hz, 1 H, H7), 8.00–8.10 (m, 3 H, NH, H_{arom}), 8.74–8.76 (m, 1 H, H8), 9.35 (s, 1 H, H6), 10.26 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 120.2 (2 CH), 125.3 (C_q), 128.3 (2 CH), 129.0 (CH), 133.5 (CH), 136.5 (C_q), 139.1 (C_q), 146.9 (C_q), 148.1 (CH), 156.4 (C_q), 162.9 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}{}^{35}ClN_4$: 257.0594; found: 257.0598.

2-(2-Chlorophenylamino)pyrido[3,2-*d*]pyrimidine (3g)
From **2**, flash chromatography (PE–EtOAc, 98:2) gave **3g** (65% yield) as a yellow solid; mp 90–91 °C.

IR (ATR-Ge): 3411, 2920, 2357, 1584, 1528, 1439, 1302, 1223, 1032, 934, 816 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.00 (dt, *J* = 1.5, 7.6 Hz, 1 H, H_{arom}), 7.31–7.43 (m, 2 H, H_{arom}), 7.63 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 7.96 (br s, 1 H, NH), 8.05 (d, *J* = 8.6 Hz, 1 H, H8), 8.75 (dd, *J* = 1.5, 4.1 Hz, 1 H, H6), 8.85 (dd, *J* = 1.3, 8.3 Hz, 1 H, H_{arom}), 9.31 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 120.1 (CH), 122.6 (C_q), 123.2 (CH), 127.6 (CH), 128.6 (CH), 129.2 (CH), 134.4 (CH), 135.9 (C_q), 137.5 (C_q), 147.6 (C_q), 148.6 (CH), 156.4 (C_q), 163.4 (CH).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}{}^{35}ClN_4$: 257.0594; found: 257.0593.

2-Phenyl- and 2-Hetarylpyrido[3,2-*d*]pyrimidines 4; General Procedures
Suzuki cross-coupling: To an argon-degassed soln of **2** (100 mg, 0.6 mmol) in toluene (6 mL) and EtOH (3 mL) was added successively (het)arylboronic acid (1.2 equiv), Na_2CO_3 (2 equiv), and $Pd(PPh_3)_4$ (35 mg, 0.05 equiv). The reaction was heated at 100 °C under vigorous stirring for the time given in Table 2. After complete disappearance of **2**, H_2O (10 mL) was added. After extraction with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography to afford the expected compound.

Stille cross-coupling: A soln of **2** (100 mg, 0.6 mmol), the (het)ArSnBu_3 (1.25 equiv) and LiCl (2.8 equiv) in DMF (7 mL) was degassed with argon (bubbling) over 15 min. $Pd(PPh_3)_4$ (34 mg, 0.05 equiv) was added in 1 portion and the mixture was immerged in a pre-heated oil bath (90 °C) for the time given in Table 2. After the disappearance of **2**, the mixture was cooled to r.t. and the volatiles were concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (10 mL) and sat. KF soln (20 mL) was added. After filtration and extraction, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The crude material was purified by flash chromatography to afford the compounds.

2-Phenylpyrido[3,2-*d*]pyrimidine (4a)
From **2**, flash chromatography (PE–EtOAc, 80:20) gave **4a** as a beige solid; mp 99–100 °C.

IR (ATR-Ge): 3022, 2367, 1563, 1447, 1385, 1261, 1169, 1067, 934, 797 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.51–7.55 (m, 3 H, H_{Ph}), 7.75 (dd, *J* = 4.1, 8.5 Hz, 1 H, H7), 8.34 (dd, *J* = 1.5, 8.5 Hz, 1 H, H8), 8.59–8.63 (m, 2 H, H_{Ph}), 8.98 (dd, *J* = 1.5, 4.1 Hz, 1 H, H6), 9.67 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 128.5 (CH), 128.8 (2 CH), 128.9 (2 CH), 131.1 (CH), 136.6 (CH), 137.3 (C_q), 139.4 (C_q), 146.9 (C_q), 151.8 (CH), 161.6 (C_q), 161.9 (CH).

MS (IS): *m*/*z* = 208.0 [M + H]$^+$.

2-(2-Thienyl)pyrido[3,2-*d*]pyrimidine (4b)
From **2**, flash chromatography (PE–EtOAc, 80:20) gave **4b** as a beige solid; mp 131–132 °C.

IR (ATR-Ge): 3084, 1570, 1527, 1449, 1421, 1385, 1261, 1210, 964, 823 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.16–7.19 (m, 1 H, H_{het}), 7.53 (dd, *J* = 1.2, 5.0 Hz, 1 H, H_{het}), 7.73 (dd, *J* = 4.1, 8.8 Hz, 1 H, H7), 8.14 (dd, *J* = 1.2, 3.8 Hz, 1 H, H_{het}), 8.26 (dd, *J* = 1.6, 8.8 Hz, 1 H, H8), 8.93 (dd, *J* = 1.6, 4.1 Hz, 1 H, H6), 9.55 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 128.6 (2 CH), 130.2 (CH), 130.8 (CH), 136.0 (CH), 139.0 (C_q), 143.0 (C_q), 146.9 (C_q), 151.4 (CH), 158.3 (C_q), 161.9 (CH).

MS (IS): *m*/*z* = 214.0 [M + H]$^+$.

2-(2-Furyl)pyrido[3,2-*d*]pyrimidine (4c)
From **2**, flash chromatography (PE–EtOAc, 70:30) gave **4c** as a brown solid; mp 110–111 °C.

IR (ATR-Ge): 3073, 1582, 1533, 1452, 1417, 1359, 1267, 1199, 953, 821 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.54 (dd, *J* = 1.8, 3.5 Hz, 1 H, H_{het}), 7.42 (d, *J* = 3.5 Hz, 1 H, H_{het}), 7.62 (d, *J* = 0.7 Hz, 1 H, H_{het}), 7.69 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 8.29 (d, *J* = 8.6 Hz, 1 H, H8), 8.89 (dd, *J* = 1.5, 4.1 Hz, 1 H, H6), 9.51 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 112.7 (CH), 115.4 (CH), 128.9 (CH), 136.4 (CH), 139.2 (C_q), 146.1 (CH), 147.0 (C_q), 151.8 (CH), 152.1 (C_q), 154.6 (C_q), 162.4 (CH).

MS (IS): *m*/*z* = 198.0 [M + H]$^+$.

2-(Acylamino)pyrido[3,2-*d*]pyrimidines 5a–g; General Procedure
To an argon-degassed soln of **2** (100 mg, 0.6 mmol) in 1,4-dioxane (5 mL) was added successively the amide or carbamate (1.2 equiv), K_2CO_3 (2.0 equiv), $Pd(OAc)_2$ (0.05 equiv), and Xantphos (0.1 equiv), the mixture was heated at reflux for 15 to 45 min (Table 3). The mixture was cooled to r.t. and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel) to afford the desired compounds **5a–g**.

***N*-(Pyrido[3,2-*d*]pyrimidin-2-yl)acetamide (5a)**
From **2**, flash chromatography (EtOAc–MeOH, 99:1) gave **5a** (88% yield) as a white solid; mp 200–201 °C.

IR (ATR-Ge): 1678, 1604, 1530, 1449, 1320, 1014, 826, 726 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.66 (s, 3 H, CH_3), 7.76 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 8.23 (d, *J* = 8.6 Hz, 1 H, H8), 8.94 (dd, *J* = 1.4, 4.1 Hz, 1 H, H6), 9.31 (s, 1 H, NH), 9.56 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.8 (CH_3), 129.3 (CH), 135.7 (CH), 138.7 (C_q), 147.8 (C_q), 151.0 (CH), 154.7 (C_q), 164.2 (CH), 172.0 (C_q).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_9H_9N_4O$: 189.0776; found: 189.0774.

_N_-(Pyrido[3,2-*d*]pyrimidin-2-yl)benzamide (5b)
From **2**, flash chromatography (PE–EtOAc, 50:50) gave **5b** (81% yield) as a white solid; mp 170–171 °C.

IR (ATR-Ge): 1703, 1604, 1515, 1467, 1397, 1235, 833, 730 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.48–7.63 (m, 3 H, H_{Ph}), 7.74–7.79 (m, 1 H, H7), 8.01 (d, *J* = 7.1 Hz, 2 H, H_{Ph}), 8.30 (d, *J* = 8.6 Hz, 1 H, H8), 8.93–8.95 (m, 1 H, H6), 9.08 (s, 1 H, NH), 9.51 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 127.7 (2 CH), 128.9 (CH), 129.0 (2 CH), 132.7 (CH), 134.2 (C_q), 135.7 (CH), 138.3 (C_q), 147.6 (C_q), 151.0 (CH), 154.5 (C_q), 163.8 (CH), 165.1 (C_q).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{11}N_4O$: 251.0933; found: 251.0937.

4-Chloro-_N_-(pyrido[3,2-*d*]pyrimidin-2-yl)benzamide (5c)
From **2**, flash chromatography (EtOAc–MeOH, 98:2) gave **5c** (68% yield) as a yellow solid; mp 196–197 °C.

IR (ATR-Ge): 1707, 1585, 1464, 1250, 1095, 925, 833, 748 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 7.78 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 7.95 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 8.30 (d, *J* = 8.6 Hz, 1 H, H8), 8.95–8.98 (m, 2 H, NH, H6), 9.52 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 129.0 (CH), 129.2 (2 CH), 129.3 (2 CH), 132.5 (C_q), 135.7 (CH), 138.3 (C_q), 139.1 (C_q), 147.6 (C_q), 151.0 (CH), 154.4 (C_q), 163.8 (CH), 164.2 (C_q).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}{}^{35}ClN_4O$: 285.0543; found: 285.0548.

_N_-(Pyrido[3,2-*d*]pyrimidin-2-yl)nicotinamide (5d)
From **2**, flash chromatography (CH_2Cl_2–MeOH, 99:1) gave **5d** (74% yield) as a yellow solid; mp 211–212 °C.

IR (ATR-Ge): 1711, 1585, 1471, 1408, 1298, 1257, 1099, 826, 722 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 7.57 (dd, *J* = 4.9, 7.8 Hz, 1 H, H_{Het}), 7.96 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 8.27–8.36 (m, 2 H, H_{het}, H8), 8.78 (d, *J* = 3.8 Hz, 1 H, H_{het}), 9.01 (dd, *J* = 1.4, 4.1 Hz, 1 H, H6), 9.14 (s, 1 H, H_{het}), 9.62 (s, 1 H, H4), 11.62 (s, 1 H, NH).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 123.5 (CH), 129.5 (CH), 130.0 (C_q), 134.9 (CH), 136.0 (CH), 137.7 (C_q), 146.8 (C_q), 149.2 (CH), 151.3 (CH), 152.6 (CH), 154.9 (C_q), 163.2 (CH), 164.5 (C_q).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{10}N_5O$: 252.0885; found: 252.0885.

_N_-(Pyrido[3,2-*d*]pyrimidin-2-yl)pyrazine-2-carboxamide (5e)
From **2**, flash chromatography (CH_2Cl_2–MeOH, 98:2) gave **5e** (92% yield) as a beige solid; mp 263–264 °C.

IR (ATR-Ge): 1718, 1515, 1460, 1401, 1231, 1135, 1021, 888, 722 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 7.99 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 8.33 (d, *J* = 8.6 Hz, 1 H, H8), 8.84–8.85 (m, 1 H, H_{het}), 8.99 (d, *J* = 2.5 Hz, 1 H, H_{het}), 7.99 (dd, *J* = 1.4, 4.1 Hz, 1 H, H6), 9.34 (d, *J* = 1.3 Hz, 1 H, H_{het}), 9.64 (s, 1 H, H4), 10.90 (br s, 1 H, NH).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_9N_6O$: 253.0838; found: 253.0833.

Benzyl _N_-(Pyrido[3,2-*d*]pyrimidin-2-yl)carbamate (5f)
From **2**, flash chromatography (CH_2Cl_2–MeOH, 99:1) gave **5f** (71% yield) as a white solid; mp 161–162 °C.

IR (ATR-Ge): 3186, 2986, 1756, 1604, 1538, 1454, 1399, 1212, 1060, 826 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 5.31 (s, 2 H, CH_2), 7.35–7.48 (m, 5 H, H_{arom}), 7.73 (dd, *J* = 4.1, 8.5 Hz, 1 H, H7), 8.26 (dd, *J* = 1.5, 8.5 Hz, 1 H, H8), 8.32 (br s, 1 H, NH), 8.91 (dd, *J* = 1.5, 4.1 Hz, 1 H, H6), 9.49 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 67.7 (CH_2), 128.6 (CH), 128.7 (2 CH), 128.8 (2 CH), 128.9 (CH), 135.5 (CH), 135.6 (C_q), 138.1 (C_q), 147.7 (C_q), 150.7 (CH), 151.6 (C_q), 154.3 (C_q), 163.9 (CH).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_4O_2$: 281.1039; found: 281.1032.

Ethyl _N_-(Pyrido[3,2-*d*]pyrimidin-2-yl)carbamate (5g)
From **2**, flash chromatography (CH_2Cl_2–acetone, 95:5) gave **5g** (72% yield) as a white solid; mp 204–205 °C.

IR (ATR-Ge): 3206, 2976, 1752, 1604, 1534, 1481, 1402, 1206, 1066, 827 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.36 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.75 (dd, *J* = 4.1, 8.6 Hz, 1 H, H7), 8.29 (d, *J* = 8.6 Hz, 1 H, H8), 8.73 (br s, 1 H, NH), 8.92 (dd, *J* = 1.4, 4.1 Hz, 1 H, H6), 9.53 (s, 1 H, H4).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.7 (CH_3), 62.1 (CH_2), 128.9 (CH), 135.6 (CH), 138.1 (C_q), 147.8 (C_q), 150.6 (CH), 151.8 (C_q), 154.4 (C_q), 163.8 (CH).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{11}N_4O_2$: 219.0882; found: 219.0876.

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(12) Crystallographic study: The structure of compound **2** has been established by X-ray crystallography (Figure 1). Colorless single crystals of **2** were obtained by slow evaporation from MeOH–$CHCl_3$ (20:80). The unit cell dimensions were determined using the least-squares fit from 25 reflections ($25° < \theta < 35°$). Intensities were collected with an Enraf-Nonius CAD-4 diffractometer using the CuKα radiation and a graphite monochromator up to $\theta = 45°$. The data were collected to relatively low resolution, i.e. no reflections were observed for $\theta > 45°$ with λ_{Cu}. The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[14a] The structure was solved by direct methods SHELX 86[2] and refined using SHELX 97[2] suite of programs.[14b,c] Crystallographic data for the structure **2** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication (CCDC 718788): Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk.

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