Acetic Acid Mediated Coupling of 2-Aminonicotinamides with Ortho Esters: A Convenient, Scalable Synthesis of 2,3-Substituted Pyrido[2,3-*d*]pyrimidines

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Abstract: Substituted pyrido[2,3-*d*]pyrimidines are synthesized in good to excellent yields by treatment of various 2-aminonicotinamides with triethyl orthopropionate or triethyl orthoacetate in the presence of acetic acid.

Key words: pyrido[2,3-*d*]pyrimidines, 2-aminonicotinamides, acetic acid, oxazin-4-one

The development of methodology for synthesis of heterocycles is an important area of interest, as their structures form the basis of many pharmaceutically active products. In particular, quinazolinones draw significant attention due to their vast array of biological activities ranging from anticonvulsants to antihypertensives.[1] While a significant number of papers have been published describing different approaches to quinazolinones,[2] the pyrido[2,3-*d*]pyrimidines have attracted far less attention. Nevertheless, the synthesis of this heterocycle poses a significant challenge. In analyzing methods toward quinazolinone synthesis, a common approach involves the functionalization of anthralinic acids. However, application of quinazolinone synthesis methodology using 2-aminonicotinic acids in place of anthralinic acids is generally unsuccessful. Diminished reactivity is observed with 2-aminonicotinic acids since the amidine moiety tends to exhibit low nucleophilicity towards a variety of electrophiles. To address this inherent reactivity issue, we have recently employed the aza-Wittig reaction[3] to the synthesis of pyrido[2,3-*d*]pyrimidines (Figure 1).[4,5] While iminophosphoranes[6] may exhibit greater reactivity, they are also moisture-sensitive and generally can not be isolated in large amounts without risk of decomposition.

A second approach to the pyrido[2,3-*d*]pyrimidines involves the reaction of oxazin-4-ones with amines under dehydrating conditions (Figure 1).[7] However, the generation of oxazin-4-ones tend to be low-yielding owing to the poor reactivity of 2-aminonicotinic acids. In addition, when these reactions are conducted on a larger scale, we have found that oxazin-4-ones are prone to hydrolysis.[8] Consequently, there appears to be a lack of reliable, high-yielding methods that generate pyrido[2,3-*d*]pyrimidines on scale.

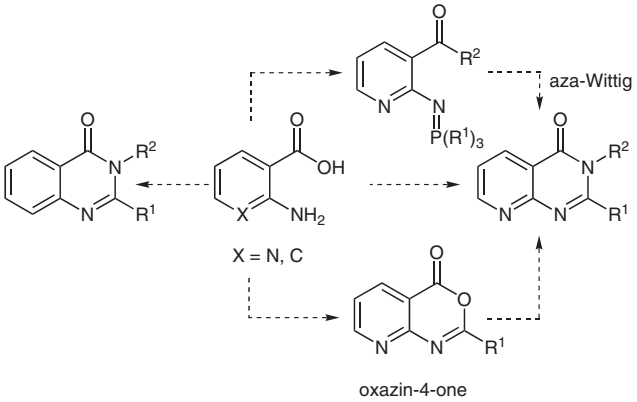

Figure 1 Common approaches to pyrido[2,3-*d*]pyrimidines

As part of our program targeting biologically active N-containing heterocycles, we required an efficient synthesis of 2,3-substituted pyrido[2,3-*d*]pyrimidines. Attempts at utilizing conventional methods afforded low yields and required difficult purification procedures in order to reject unwanted side products. Hence, we were required to develop a synthesis of pyrido[2,3-*d*]pyrimidines that circumvents issues of scale and yield.

Our approach began with investigating pyrido[2,3-*d*]pyrimidine formation by direct reactions with 2-aminonicotinamides. While isolated examples of the reaction between 2-aminonicotinamide itself and triethylorthoformate can be found in the literature,[9] to the best of our knowledge, there are no reports of N-substituted 2-aminonicotinamides participating with orthoacetates or orthopropionates to directly afford the corresponding 2,3-substituted pyrido[2,3-*d*]pyrimidines. Herein we present our efforts toward a generalized method to this class of compound.

Based on an initial lead utilizing PPTS (pyidinium *p*-toluenesulfonate), we screened different acids and were pleased to find that the treatment of 2-aminonicotinamides with triethyl orthopropionate and acetic acid afforded the desired compound in 97% yield (Table 1).

Using 2-amino-*N*-(4-iodophenyl)nicotinamide (**1**) as our test substrate, we found that acetic acid effected the transformation, yielding full conversion into the desired compound **2**. Further optimization of reaction stoichiometries led to lowering of the number of equivalents of acetic acid and triethyl orthopropionate (Table 2).

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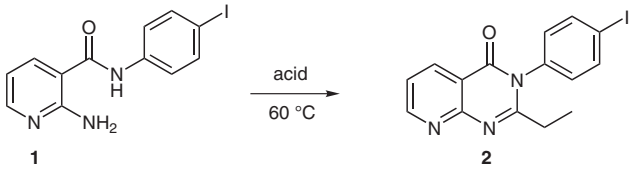
Table 1 Influence of Different Acids in Pyrido[2,3-*d*]pyrimidine Formation

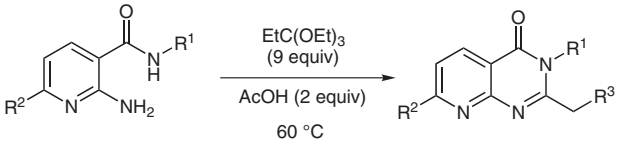


1 2

Entry	Solvent/Reagent	Acid	Yield (%)
1	triethyl orthopropionate	PPTS	40[a]
2	triethyl orthopropionate	H_2SO_4	<5
3	triethyl orthopropionate	AcOH	97[b]
4	triethyl orthopropionate	HCl	<5
5	triethyl orthopropionate	TFA	72[b]
6	propionyl chloride	–	–
7[c]	triethyl orthopropionate	–	–

[a] Isolated yield.
[b] HPLC assay yield.
[c] Control experiment.

Table 2 Acetic Acid Mediated Synthesis of 2,3-Substituted Pyrido[2,3-*d*]pyrimidines

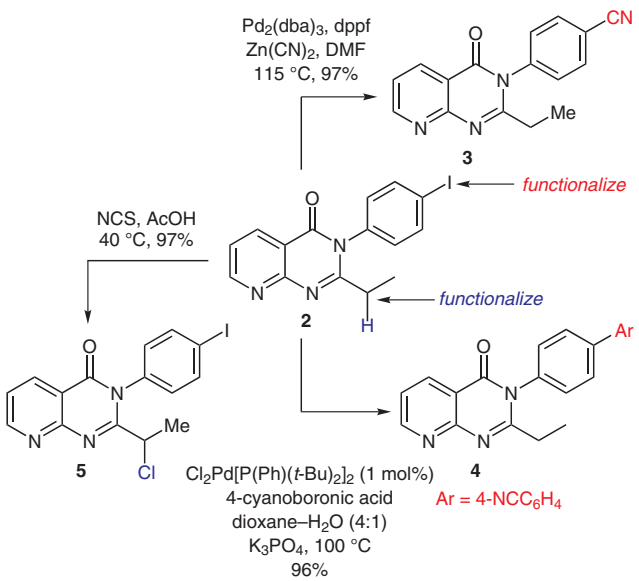


Entry	R^1	R^2	R^3	Yield (%)
1	4-IC_6H_4	H	H	83[a]
2	4-IC_6H_4	H	Me	92[b]
3	2-$MeSC_6H_4$	H	Me	95
4	2-$MeOC_6H_4$	H	Me	74
5	4-FC_6H_4	Cl	Me	71
6	2-naphthyl	H	Me	77
7	*c*-Pr	H	Me	60
8	2-MeC_6H_4	H	Me	79
9	3,5-$Me_2C_6H_4$	H	H	76[a]
10	3,5-$Me_2C_6H_4$	H	Me	86
11	4-NCC_6H_4	Me	Me	57[c]
12	4-NCC_6H_4	OMe	Me	95
13	4-$CF_3CH_2OC_6H_4$	H	Me	69

[a] Triethyl orthoacetate was used in place of triethyl orthopropionate.
[b] Reaction conducted on 950 g scale.
[c] Reaction conducted at 100 °C.

With regard to reaction scope, aromatic groups are well tolerated affording pyrido[2,3-*d*]pyrimidines in moderate to excellent yields. N-Ortho substitutions are also compatible, providing desired pyrido[2,3-*d*]pyrimidines in good yield (entries 4 and 7). Alkyl substituents on the amide do not make good substrates. For example, cyclization of the nicotinamide derived from *n*-hexylamine affords a mixture of starting material, a product resulting from coupling of triethyl orthopropionate to the amidine of the nicotinamide, and approximately 20% of the desired cyclized product.[10] Interestingly, nicotinamides derived from cyclopropylamine (entry 7) participate well in the reaction suggesting that even substituents with poor π-character will undergo the reaction. Substituents on the pyridine ring (entries 5, 11, 12) required more forcing conditions. To test the scalability of the method, a reaction with amide **1** was conducted on a 950 g scale. An excellent yield of 92% (980 g) of the desired pyrido[2,3-*d*]pyrimidine (**2**) (entry 2) was obtained in this scaled-up reaction.

Pyrido[2,3-*d*]pyrimidines can be elaborated as shown in Scheme 1. Palladium-catalyzed cyanation of **2** afforded benzonitrile **3** in 97% yield.[11] Utilizing 1% $Cl_2Pd[P(Ph)(t\text{-}Bu)_2]_2$, our recently developed catalyst,[12] 4-cyanoboronic acid was also successfully cross-coupled to afford biaryl **4** in 96% yield. Finally, halogenation at the 2-ethyl position with NCS generated the secondary chloride **5** and opens the possibility to eliminate to the olefin or conduct nucleophilic displacements to further build molecular complexity.



Scheme 1 Elaboration of 2,3-substituted pyrido[2,3-*d*]pyrimidines

In conclusion, we have developed a synthesis of 2,3-substituted pyrido[2,3-*d*]pyrimidines starting from 2-aminonicotinamides under mildly acidic conditions. We have demonstrated that the reaction can be run reliably on a large scale and products of the reaction can be elaborated to different functionalized pyrido[2,3-*d*]pyrimidines in excellent yields.

NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR. Chemical shifts are reported in δ (ppm) referenced to $CHCl_3$, DMSO, or DMF. All starting materials necessary for the preparation of 2,3-disubstituted pyrido[2,3-*d*]pyrimidines were derived from EDC coupling of the respective amines with 2-aminonicotinic acids. $Cl_2Pd[P(t\text{-}Bu)_2Ph]_2$ was prepared according to a literature procedure.[12]

Pyrido[2,3-*d*]pyrimidines; General Procedure

To a solution or slurry of the 2-aminonicotinamide (**1**; 5.0 mmol) in triethyl orthopropionate (45 mmol, 9 mL) [or triethyl orthoacetate (7.75 mL, 45 mmol) for Table 2, entries 1 and 9] was added glacial AcOH (10 mmol, 0.55 mL). The mixture was heated to 60 °C for 4 h at which time the HPLC analysis revealed full consumption of starting material. Two different workups were employed.

Workup A: The mixture was diluted with aq 1 M HCl (5 mL) and stirred for 5 min. The solution was made basic by the addition of concd NH_4OH and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Silica gel chromatography of the crude material (hexanes–EtOAc, 30:70) afforded the desired pyrido[2,3-*d*]pyrimidines (Table 2).

Workup B: The mixture was diluted with hexanes (50 mL) and filtered to afford the desired pyrido[2,3-*d*]pyrimidines (Table 2).

3-(4-Iodophenyl)-2-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 1)

Workup B. Silica gel chromatography of the sticky solid (hexanes–EtOAc, 30:70 → 100 EtOAc) afforded the title compound; yield: 1.51 g (83%).

IR (neat): 3063, 2982, 1681, 1593, 1566, 1431, 1274, 1003, 788 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (dd, *J* = 1.8, 4.5 Hz, 1 H), 8.48 (d, *J* = 7.8 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.54 (dd, *J* = 4.7, 7.9 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.7, 157.6, 157.2, 156.0, 138.4, 137.2, 135.9, 130.6, 122.1, 115.5, 95.7, 24.3.

EI: *m*/*z* calcd for $C_{14}H_{10}IN_3O$: 362.9869; found [M + H]: 363.9952.

2-Ethyl-3-[3-(methylthio)phenyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 3)

Workup B; yield: 1.42 g (95%).

IR (neat): 3059, 2984, 2933, 1690, 1573, 1562, 1432, 1247, 801, 705 cm^{-1}.

^{1}H NMR (400 MHz, DMF-d_7): δ = 9.04 (dd, *J* = 2.2, 4.7 Hz, 1 H), 8.55 (dd, *J* = 1.9, 7.8 Hz, 1 H), 7.59 (m, 3 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.7 Hz, 1 H), 2.59 (s, 3 H), 2.50 (m, 2 H), 1.23 (t, *J* = 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, DMF-d_7): δ = 163.1, 162.2, 158.6, 156.8, 141.6, 139.2, 136.7, 130.8, 127.3, 126.6, 125.8, 123.0, 116.8, 29.2, 15.1, 10.9

EI: *m*/*z* calcd for $C_{16}H_{15}N_3OS$: 297.09358; found [M + H]: 298.10086.

2-Ethyl-3-(2-methoxyphenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 4)

Workup A. Silica gel chromatography of the crude material (hexanes–EtOAc, 30:70) afforded the title compound; yield: 1.07 g (76%).

IR (neat): 2977, 2942, 2844, 1682, 1583, 1496, 1431, 1241, 1023, 790 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (dd, *J* = 2.2, 4.7 Hz, 1 H), 8.59 (dd, *J* = 2.1, 7.8 Hz, 1 H), 7.50 (dt, *J* = 1.8, 8.2 Hz, 1 H), 7.40 (dd, *J* = 4.5, 7.8 Hz, 1 H), 7.21 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.12 (m, 2 H), 3.79 (s, 3 H), 2.47 (m, 2 H), 1.30 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.4, 161.2, 157.1, 155.8, 154.0, 135.8, 130.8, 129.5, 124.7, 122.1, 120.8, 115.2, 112.3, 55.6, 28.0, 10.1.

EI: *m*/*z* calcd for $C_{16}H_{15}N_3O_2$: 281.11643; found [M + H]: 282.12406.

7-Chloro-2-ethyl-3-(4-fluorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 5)

Conducted on a 2.9 mmol scale. Workup A. Silica gel chromatography using CH_2Cl_2–acetone (98:2 → 4:1); yield: 630 mg (71%).

IR (film): 2090, 3010, 1683, 1603, 1579, 1593, 1557, 1507, 1424, 1368 1259, 1211 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 8.3 Hz, 1 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 7.30–7.23 (m, 4 H), 2.48 (q, *J* = 7.3 Hz, 2 H), 1.29 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 162.5 (d, *J* = 147 Hz), 157.6, 157.5, 138.9 (d, *J* = 4.5 Hz), 132.1, 129.8 (d, *J* = 8.7 Hz), 123.2, 117.4, 117.2, 114.4, 29.7, 10.6.

EI: *m*/*z* calcd for $C_{15}H_{11}ClFN_3O$: 303.0653; found [M + H]: 304.0655.

2-Ethyl-3-(naphthalene-2-yl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 6)

Workup B; yield: 1.15 g (77%).

IR (neat): 3058, 2984, 2934, 1690, 1585, 1431, 1368, 1248, 797 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.0 (s, 1 H), 8.52 (d, *J* = 7.4 Hz, 1 H), 8.07 (m, 4 H), 7.60 (m, 4 H), 2.43 (m, 2 H), 1.16 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 161.3, 157.3, 156.0, 136.0, 134.5, 133.1, 132.7, 129.4, 128.1, 127.8, 127.4, 127.2, 126.9, 126.2, 122.3, 115.7, 29.1, 10.5.

EI: *m*/*z* calcd for $C_{19}H_{15}N_3O$: 301.12151; found [M + H]: 302.12879.

3-Cyclopropyl-2-ethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 7)

Reaction conducted on a 2.8 mmol scale. Workup B. Silica gel chromatography of the crude material (hexanes–EtOAc, 50:50 → 100 EtOAc); yield: 0.39 g (60%).

IR (neat): 3066, 2975, 2997, 2921, 1681, 1586, 1566, 1429, 1037, 808, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (dd, *J* = 1.9, 4.5 Hz, 1 H), 8.52 (dd, *J* = 1.9, 7.8 Hz, 1 H), 7.35 (dd, *J* = 4.5, 8.1 Hz, 1 H), 3.11 (q, *J* = 7.3 Hz, 2 H), 2.94 (m, 1 H), 1.46 (t, *J* = 7.3 Hz, 3 H), 1.34 (q, *J* = 7.2 Hz, 2 H), 0.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 162.6, 156.7, 155.4, 135.7, 121.8, 115.6, 27.6, 26.7, 10.6, 9.8.

EI: *m*/*z* calcd for $C_{12}H_{13}N_3O$: 215.10586; found [M + H]: 216.11322.

2-Ethyl-3-(*o*-tolyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 8)

Work-up A. Silica gel chromatography (hexanes–EtOAc, 30:70 → 100 EtOAc); yield: 1.05 g (79%).

IR (neat): 3057, 2982, 2939, 1681, 1589, 1578, 1432, 1368, 1252, 903, 794 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (dd, *J* = 2.3, 4.7 Hz, 1 H), 8.60 (dd, *J* = 1.9, 7.8 Hz, 1 H), 7.41 (m, 4 H), 7.15 (d, *J* = 7.4 Hz, 1 H), 2.40 (m, 2 H), 2.10 (s, 3 H), 1.30 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 161.9, 157.8, 156.2, 136.8, 135.8, 135.4, 131.7, 129.9, 128.0, 127.7, 122.2, 115.9, 29.2, 17.4, 10.7.

EI: *m*/*z* calcd for $C_{16}H_{15}N_3O$: 265.12151; found [M + H]: 266.12870.

2-Methyl-3-(3,5-dimethylphenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 9)

Workup A. Silica gel chromatography (hexanes–EtOAc, 30:70 → 100 EtOAc) afforded the title compound; yield: 1.0 g (76%).

IR (neat): 3065, 2997, 2921, 1683, 1586, 1566, 1427, 1039, 809, 701 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.97 (dd, *J* = 1.7, 4.5 Hz, 1 H), 8.48 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.54 (dd, *J* = 4.5, 7.9 Hz, 1 H), 7.16 (s, 1 H), 7.07 (s, 2 H), 2.34 (s, 6 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8, 158.0, 157.2, 155.9, 138.9, 137.2, 135.9, 130.4, 125.6, 122.1, 115.3, 24.2, 20.7.

EI: *m*/*z* calcd for $C_{16}H_{15}N_3O$: 265.12151; found [M + H]: 266.12879.

2-Ethyl-3-(3,5-dimethylphenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 10)

Workup A. Silica gel chromatography (hexanes–EtOAc, 30:70 → 100 EtOAc) afforded the title compound; 1.2 g (86%).

IR (neat): 3074, 2935, 2831, 1681, 1584, 1565, 1431, 1273, 1026, 801, 710 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (d, *J* = 2.7 Hz, 1 H), 8.48 (d, *J* = 3.5 Hz, 1 H), 7.54 (dd, *J* = 4.5, 7.6 Hz, 1 H), 7.16 (s, 1 H), 7.06 (s, 2 H), 2.40 (q, *J* = 7.3 Hz, 2 H), 2.34 (s, 6 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.9, 161.2, 157.1, 155.8, 138.9, 136.7, 135.9, 130.4, 125.8, 122.1, 155.5, 28.8, 20.6, 10.4.

EI: *m*/*z* calcd for $C_{17}H_{17}N_3O$: 279.13716; found [M + H]: 280.14444.

4-(2-Ethyl-7-methyl-4-oxopyrido[2,3-*d*]pyrimidin-3(4*H*)-yl)benzonitrile (Table 1, Entry 11)

Reaction conducted at 100 °C on a 27 mmol scale. Workup A. Silica gel chromatography using CH_2Cl_2–acetone (98:2 → 4:1) afforded the title compound; 4.5 g (57%).

IR (film): 3010 (br), 1701, 1681, 1592, 1567, 1503, 1411, 1373, 1270 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.04 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.04 Hz, 1 H), 2.75 (s, 3 H), 2.42 (q, *J* = 7.3 Hz, 2 H), 1.30 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 162.1, 160.1, 157.0, 140.8, 136.2, 133.7, 129.5, 122.6; 117.4, 113.7, 112.9, 29.5, 25.3, 10.6.

EI: *m*/*z* calcd for $C_{17}H_{14}N_4O$: 290.1168; found [M + H]: 291.1250.

4-(2-Ethyl-7-methoxy-4-oxopyrido[2,3-*d*]pyrimidin-3(4*H*)-yl)benzonitrile (Table 1, Entry 12)

Reaction conducted on a 3.1 mmol scale. Workup A. Silica gel chromatography using CH_2Cl_2–acetone (98:2 → 4:1) afforded the title compound; yield: 0.91 g (95%).

IR (film): 2090, 3010, 1685, 1673, 1606, 1587, 1566, 1505, 1483, 1422, 1381, 1368, 1350, 1293, 1207 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.6 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 1 H), 4.10 (s, 3 H), 2.48 (q, *J* = 7.4 Hz, 2 H), 1.24 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 161.7, 161.0, 157.6, 140.9, 138.0, 133.6, 129.5, 117.4, 113.7, 112.4, 109.6, 54.4, 29.5, 11.4.

EI: *m*/*z* calcd for $C_{17}H_{14}N_4O_2$: 306.1117; found: 307.1199.

2-Ethyl-3-[4-(2,2,2-trifluoroethoxy)phenyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (Table 1, Entry 13)

Workup A. Silica gel chromatography (hexanes–EtOAc, 30:70 → 100 EtOAc) afforded the title compound; yield: 1.07 g (76%).

IR (neat): 3066, 2988, 2942, 1681, 1587, 1509, 1433, 1237, 1157, 1070, 966, 793, 656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (dd, *J* = 1.9, 4.5 Hz, 1 H), 8.51 (dd, *J* = 2.0, 7.8 Hz, 1 H), 7.35 (dd, *J* = 4.5, 7.8 Hz, 1 H), 7.15 (d, *J* = 8.8 Hz, 2 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 4.36 (q, *J* = 8.0 Hz, 2 H), 2.43 (q, *J* = 7.3 Hz, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 161.8, 157.9, 157.6, 156.3, 136.7, 130.9, 129.6, 122.2, 116.3, 65.8 (q, *J* = 36.2 Hz), 29.7, 10.9.

EI: *m*/*z* calcd for $C_{17}H_{14}F_3N_3O_2$: 349.30717; found [M + H]: 350.11146.

Large Scale Preparation of 2-Ethyl-3-(4-iodophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (2)

A 20 L reactor was charged with 2-amino-*N*-(4-iodophenyl)nicotinamide (**1**; 950 g, 2.8 mol) under N_2. Triethyl orthopropionate (5.0 L, 25.2 mol) was added and the stirring was commenced (no exotherm observed). AcOH (320 mL, 5.6 mol) was added and the mixture was heated to 60 °C for 3.5 h. The HPLC analysis at this time revealed full conversion to the desired product. The mixture was cooled to 20 °C, charged slowly with heptanes (8.0 L), and stirred for an additional 15 min before filtering through a sintered glass funnel (porosity D). The filter cake was washed with heptanes (6.0 L) and air dried (2–3 h). The filter cake was transferred to a vacuum oven and dried (40 °C/2 Torr, 12 h) to afford **2**; yield: 980 g (92%).

IR (neat): 3060, 2982, 2936, 2873, 1682, 1590, 1566, 1431, 1271, 1115, 1008, 797, 707 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (dd, *J* = 2.1, 4.5 Hz, 1 H), 8.48 (dd, *J* = 2.0, 7.8 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.55 (dd, *J* = 4.5, 7.9 Hz, 1 H), 7.30 (d, *J* = 8.5 Hz, 2 H), 2.37 (q, *J* = 7.2 Hz, 2 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.9, 160.8, 157.2, 155.9, 138.5, 136.8, 135.9, 130.9, 122.2, 115.6, 95.8, 29.0, 10.4.

EI: *m*/*z* calcd for $C_{15}H_{12}IN_3O$: 377.00251; found [M + H]: 378.01106.

Elaboration of Pyrido[2,3-*d*]pyrimidines

4-(2-Ethyl-4-oxopyrido[2,3-*d*]pyrimidin-3(4*H*)-yl)benzonitrile (3)

To a slurry of iodide **2** (37.7 g, 100 mmol) in degassed DMF (95 mL) was added dppf (443 mg, 0.8 mmol) and $Zn(CN)_2$ (6.1 g, 52 mmol). $Pd_2(dba)_3$ (366 mg, 0.4 mmol) was then added and the mixture was heated to 115 °C for 3 h. After that, the HPLC analysis revealed full conversion. The solution was cooled to r.t., poured into H_2O (0.5 L), and stirred for 0.5 h before filtering. The filter cake was reslurried in toluene (100 mL) and filtered to afford **3**; yield: 27.7 g (97%).

IR (neat): 3442, 3256, 2223, 1682, 1610, 1583, 1566, 1504, 1432, 1250, 1005, 815, 683 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00 (dd, *J* = 1.7, 4.5 Hz, 1 H), 8.50 (dd, *J* = 1.7, 7.8 Hz, 1 H), 8.10 (d, *J* = 8.2 Hz, 2 H), 7.76 (d, *J* = 8.2 Hz, 2 H), 7.56 (dd, *J* = 4.5, 7.9 Hz, 1 H), 2.34 (q, *J* = 7.3 Hz, 2 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8, 160.3, 157.2, 156.1, 141.3, 135.9, 133.8, 130.1, 122.3, 118.2, 115.6, 112.2, 29.0, 10.3.

EI: *m*/*z* calcd for $C_{16}H_{12}N_4O$: 276.10111; found [M + H]: 277.10825.

3-(4-Cyanophenyl)-2-ethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (4)

To a mixture of the iodide **2** (1.89 g, 5 mmol), 4-cyanophenylboronic acid (822 mg, 5.75 mmol), and K_3PO_4 (2.13 g, 10 mmol) in dioxane–H_2O (20:5 mL) was added $Cl_2Pd[P(Ph)(t\text{-}Bu)_2]_2$ (31 mg, 0.05 mmol). The slurry was heated to 100 °C for 3 h. After that, the HPLC analysis revealed full conversion. To the mixture was added H_2O (20 mL), MTBE (50 mL), and filtered. The filter cake was washed with H_2O (20 mL), MTBE (20 mL), and hexanes (20 mL). The solids were transferred to a vacuum oven and dried to constant mass; yield: 1.70 g (96%).

IR (neat): 3073, 3011, 2225, 1676, 1592, 1567, 1433, 1258, 1002, 791, 720 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00 (dd, *J* = 1.9, 4.7 Hz, 1 H), 8.52 (dd, *J* = 2.0, 7.8 Hz, 1 H), 8.0 (m, 6 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.56 (dd, *J* = 4.7, 7.9 Hz, 1 H), 2.43 (q, *J* = 7.4 Hz, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMF-d_7): δ = 161.5, 158.1, 156.3, 144.3, 139.8, 139.2, 138.3, 136.2, 133.3, 129.9, 128.7, 128.3, 122.5, 119.0, 116.3, 111.3, 67.0, 10.3.

EI: *m*/*z* calcd for $C_{22}H_{16}N_4O$: 352.13241; found [M + H]: 353.14016.

2-(1-Chloroethyl)-3-(4-iodophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (5)

To a solution of the iodide **2** (3.77 g, 10 mmol) in AcOH (10 mL) was added NCS (1.46 g, 11 mmol) and the mixture was heated to 40 °C for 12 h. The mixture was diluted with H_2O (100 mL) and filtered. The solids were washed with aq sat. $NaHCO_3$ (20 mL), H_2O (20 mL), and dried in a vacuum oven to constant mass to afford **5**; yield: 4.05 g (97%).

IR (neat): 3074, 3012, 1676, 1592, 1567, 1433, 1371, 1259, 1002, 791 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.04 (d, *J* = 4.3 Hz, 1 H), 8.54 (d, *J* = 7.9 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 7.63 (dd, *J* = 4.5, 7.8 Hz, 1 H), 7.40 (d, *J* = 7.2 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 4.68 (q, *J* = 6.5 Hz, 1 H), 1.81 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.7, 157.2, 156.6, 156.3, 138.5, 138.1, 136.1, 135.3, 131.8, 130.8, 123.3, 116.3, 96.4, 53.2, 21.7. Restricted rotation observed.

EI: *m*/*z* calcd for $C_{15}H_{11}ClIN_3O$: 410.96353; found [M + H]: 411.97116.

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