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Preparation of 2-Aminopyridoimidazoles and 2-Aminobenzimidazoles via Phosphorus Oxychloride-Mediated Cyclization of Aminoureas

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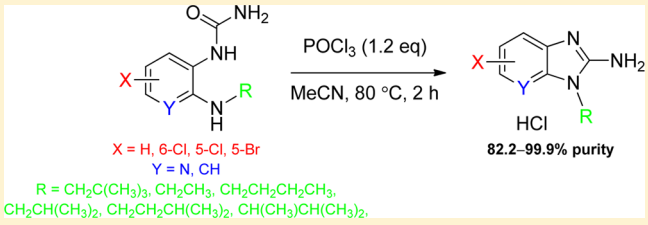
Supporting Information

ABSTRACT: The novel preparation of 2-aminopyridoimidazoles and 2-aminobenzimidazoles via the cyclization of (2-aminopyridin-3-yl)urea and (2-aminophenyl)urea substrates in the presence of phosphorus oxychloride is described. This methodology is demonstrated for a range of urea substrates with aminoimidazole products obtained in good yields and with excellent levels of purity.

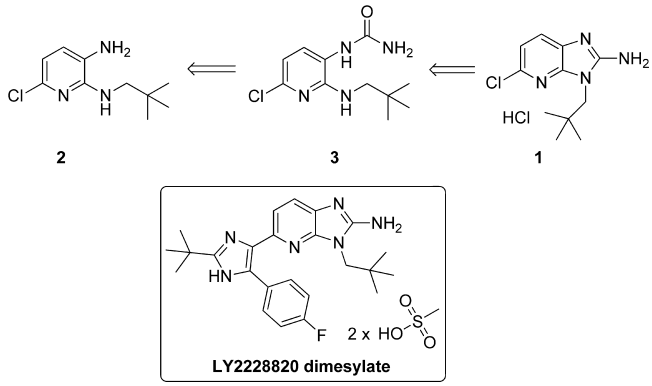


The 2-aminoimidazole moiety is an important pharmacophore in medicinal chemistry. This ring structure is found in a variety of pharmacologically active compounds and in several classes of marine natural products,[1] many of which exhibit a broad range of biological functions including serotonergic and histaminergic receptor anatagonism[2] in addition to antiviral, antibacterial, and anticancer activities.[3]

As a result of their interesting biological properties, several strategies for the synthesis of 2-aminoimidazoles have been reported in the literature. Predominant among these is the condensation of α-aminocarbonyls with cyanamide[4] or α-haloketones with *N*-acetylguanidine;[5] however, these reactions are typically pH-sensitive, require unstable precursors, and are limited to the preparation of minimally substituted 2-aminoimidazole motifs. A second common approach involves the modification of an existing imidazole scaffold,[6] although this method can be hampered by the requirement for several protection/deprotection steps.

As part of our studies toward the synthesis of LY2228820 dimesylate (see Scheme 1), a selective inhibitor of p38 mitogen-activated protein kinase that is currently under clinical investigation for the treatment of human malignancies,[7] we wished to access the 2-aminoimidazole **1**. Preparation of **1** was initially conducted by cyclization of diamine **2** in the presence of cyanogen bromide (Scheme 2), following literature procedures.[8,9] Using this method, the hydrobromide salt of **1**

Scheme 1. Alternative Synthetic Strategy for the Synthesis of 2-Aminoimidazole 1



was obtained as a white solid in good yield (76%) following crystallization in methanol/methyl *tert*-butyl ether (MTBE).

We wished to circumvent the use of cyanogen bromide for the synthesis of **1**, and therefore, an alternative more environmentally benign process was sought. It was postulated that conversion of **2** to the corresponding urea **3** and treatment

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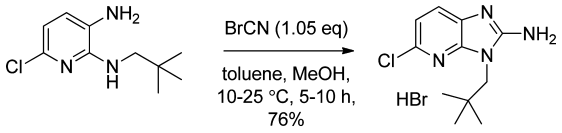
Scheme 2. Synthesis of 2-Aminoimidazole 1 with Cyanogen Bromide



2 1

of this compound with phosphoryl oxychloride may induce cyclization to provide the desired aminoimidazole **1** as a hydrochloride salt (Scheme 1).

To test this proposed synthetic approach, access to compound **3** was first required. Synthesis of **3** was achieved as shown in Scheme 3, beginning from commercially available 2,6-dichloro-3-nitropyridine (X = 6-Cl, Y = N) that was converted to 6-chloro-*N*-neopentyl-3-nitropyridin-2-amine **4** by treatment with neopentylamine [R = $CH_2C(CH_3)_3$] and triethylamine in MTBE. Nitropyridine **4** was then hydrogenated to provide diamine **2**, which was immediately carried forward to the next synthetic step to avoid the formation of potential oxidation side products. Conversion of **2** to the novel urea **3** was accomplished using previously described chemistry[10] involving reaction with potassium cyanate and hydrochloric acid in ethanol/water at room temperature to provide the targeted urea **3** in good yield (69%) and without the need for further purification.

With the required urea **3** now in hand, our strategy for the synthesis of 2-aminoimidazole **1** was explored. Thus, phosphoryl oxychloride (1.2 equiv) was added dropwise to a solution of **3** in acetonitrile at room temperature. The resultant solution was heated to 80 °C for 2 h, water was added, and the reaction mixture cooled to give a slurry that was filtered to isolate an off-white solid. Subsequent analysis determined that the isolated solid was the desired 2-aminoimidazole **1**, obtained in high yield (79%) and excellent purity (99.9%) (Table 1, entry 1).

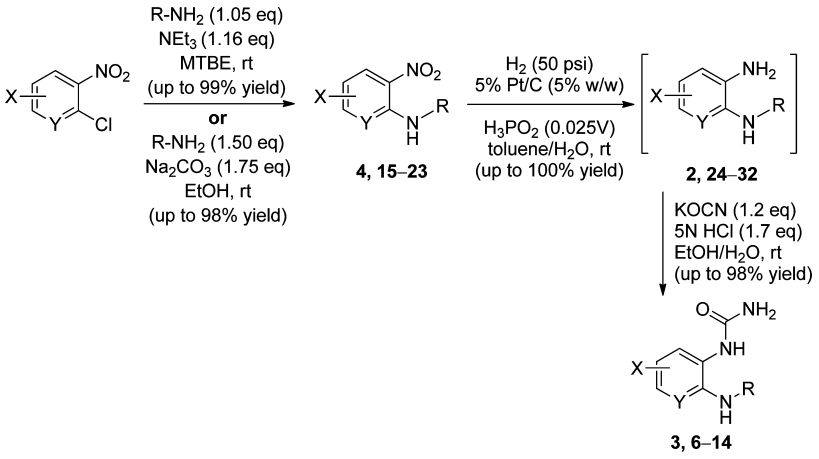
The procedure described above was the result of a limited optimization study. Initial success was seen in neat phosphoryl oxychloride (3 mL/g of substrate) at 100 °C. Employment of toluene as a solvent allowed the use of as little as 1.5 equiv of phosphoryl oxychloride. For ease of isolation, the solvent was switched to acetonitrile. Isopropyl acetate, *n*-butyl acetate, and anisole have also been demonstrated to be competent solvents. Thionyl chloride and oxalyl chloride produced complicated mixtures of products in limited experimentation.

A significant side product was observed during early optimization studies by HPLC analysis of reaction mixtures. The level of this side product was found to increase if reaction time was prolonged. We tentatively assigned the side product as the phosphoramidic acid **5** (Figure 1) based on LC-MS analysis. After reaction completion, the addition of water at 80 °C, followed by a 1 h of stirring at this temperature, was found to revert this side product to release 2-aminoimidazole **1**.

We next wished to extend this novel methodology to include the cyclization of a range of urea substrates featuring modifications of the amine substituent (R), the electronic properties of the pyridine ring (X), and the nature of the aromatic structure (Y). For this purpose, nine novel ureas (**6**–**14**) were targeted comprising five amine variants [R = ethyl (**6**), *n*-butyl (**7**), *iso*-butyl (**8**), *iso*-pentyl (**9**), and 1,2-dimethylpropyl (**10**)], one disubstituted pyridine (**11**), two 5-substituted halide compounds (**12** and **13**), and a benzylurea substrate (**14**). These compounds were prepared as previously described for the synthesis of our original urea substrate **3** (Scheme 3), starting from commercially available 2,6-dichloro-3-nitropyridine (synthesis of **6**–**10**), *N*-neopentyl-3-nitropyridin-2-amine (synthesis of **11**), 5-chloro- and 5-bromo-2-chloro-3-nitropyridine (synthesis of **12** and **13**, respectively), and 2,4-dichloro-1-nitrobenzene (synthesis of **14**).

Conversion of each of **24**–**32** to the novel urea substrates **6**–**14**, respectively, was achieved as previously described for the synthesis of **3** (potassium cyanate and hydrochloric acid in ethanol/water at room temperature). While highly efficient reactions were observed using this methodology for the synthesis of the amine varied compounds (**6**–**10**) and benzylurea **14**, the formation of several side products was noted by ^{1}H NMR analysis for reactions of the substrates (**11**–**13**) in which the electronic properties of the aromatic ring had been altered relative to our original urea substrate **3**. These side

Scheme 3. Preparation of Urea Substrates 3, 6–14 for 2-Aminoimidazole Synthesis[a]



[a]**2**, **3**, **4**: R = $CH_2C(CH_3)_3$, X = 6-Cl, Y = N; **6**, **15**, **24**: R = CH_2CH_3, X = 6-Cl, Y = N; **7**, **16**, **25**: $CH_2CH_2CH_2CH_3$, X = 6-Cl, Y = N; **8**, **17**, **26**: R = $CH_2CH(CH_3)_2$, X = 6-Cl, Y = N; **9**, **18**, **27**: R = $CH_2CH_2CH(CH_3)_2$, X = 6-Cl, Y = N; **10**, **19**, **28**: R = $CH(CH_3)CH(CH_3)_2$, X = 6-Cl, Y = N; **11**, **20**, **29**: R = $CH_2C(CH_3)_3$, X = H, Y = N; **12**, **21**, **30**: R = $CH_2C(CH_3)_3$, X = 5-Cl, Y = N; **13**, **22**, **31**: R = $CH_2C(CH_3)_3$, X = 5-Br, Y = N; **14**, **23**, **32**: R = $CH_2C(CH_3)_3$, X = 6-Cl, Y = C.

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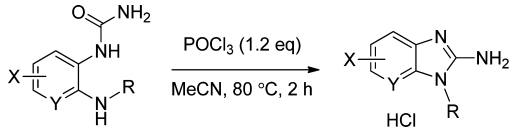
Table 1. Synthesis of 2-Aminoimidazoles



entry	urea	R	X	Y	aminoimidazole	yield (%)[a]	purity (%)[b]
1	**3**	$CH_2C(CH_3)_3$	6-Cl	N	**1**	79	99.9
2	**6**	CH_2CH_3	6-Cl	N	**33**	69	99.2
3	**7**	$CH_2CH_2CH_2CH_3$	6-Cl	N	**34**	74	98.2
4	**8**	$CH_2CH(CH_3)_2$	6-Cl	N	**35**	67	99.7
5	**9**	$CH_2CH_2CH(CH_3)_2$	6-Cl	N	**36**	64	99.6
6	**10**	$CH(CH_3)CH(CH_3)_2$	6-Cl	N	**37**	70	99.2
7	**11**	$CH_2C(CH_3)_3$	H	N	**38**	14[c]	82.2
8	**12**	$CH_2C(CH_3)_3$	5-Cl	N	**39**	57	95.7
9	**13**	$CH_2C(CH_3)_3$	5-Br	N	**40**	56	99.1
10	**14**	$CH_2C(CH_3)_3$	6-Cl	CH	**41**	76	98.1

[a]Percentage isolated by filtration of reaction mixture upon reaction completion. [b]As determined by HPLC analysis. [c]An additional 43% of **38** (purity = 81.9%) was isolated from mother liquor by extraction with ethyl acetate/water.

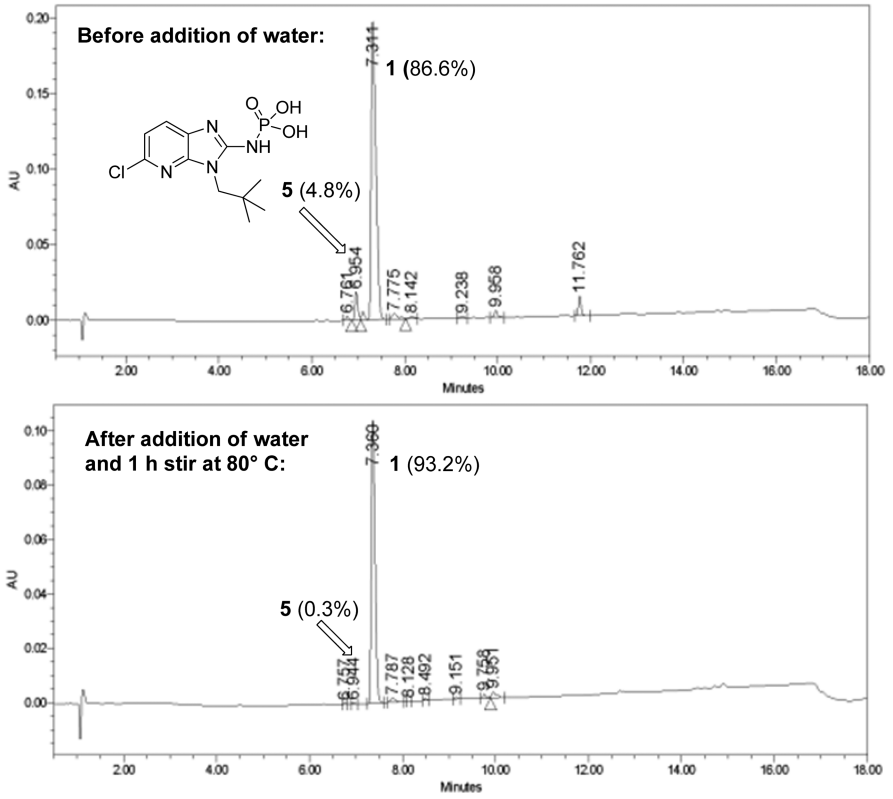


Figure 1. Phosphoramidic acid side product **5**. HPLC conditions: Zorbax SB-C8 (4.6 mm ID × 75 mm, 3.5 μm) column under the following conditions: mobile phase A, 0.1% H_3PO_4 in H_2O; mobile phase B, 0.1% H_3PO_4 in acetonitrile; flow rate 1.5 mL/min; gradient 0.0 min (5% B), 15.0 min (90% B), 15.1 min (90% B), 16.1 min (5% B), 18.0 min (5% B); wavelength 225 nm; 40 °C.

products were successfully removed by chromatographic purification, providing the required urea derivatives in high purity for subsequent synthesis of the corresponding 2-aminoimidazoles.

Cyclization of the novel ureas **6**–**14** in the presence of phosphorus oxychloride was next conducted using the optimized reaction conditions identified in our earlier studies for the synthesis of 2-aminoimidazole **1**. This novel methodology was found to be efficient for a range of straight-chain and branched amine variants (Table 1, entries 2–6), with the aminoimidazole products **33**–**37** obtained in good yields and with excellent levels of purity (>98% by HPLC analysis). Successful cyclization was also recorded for reaction of the urea precursors **12** and **13** (Table 1, entries 8 and 9), in which the halide substituent (X = Cl, Br) is present at the 5-position of the pyridine ring, albeit with slightly reduced yields observed relative to reactions of our 6-chloro-substituted ureas **3** and **6**–**10**. Significantly, this novel methodology was also found to be applicable to the synthesis of benzimidazoles; thus, benzylurea **14** underwent efficient phosphorus oxychloride-mediated cyclization to provide the novel product **41** in excellent yield and purity (Table 1, entry 10).

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In contrast to the other urea substrates (**3**, **6**−**10**, **12**−**14**) examined in this study that underwent efficient cyclization in the presence of phosphorus oxychloride (Table 1, entries 1−6 and 8−10), urea **11**, in which no halide substituent is present on the pyridine ring, was found to produce a mixture of reaction products. While the previously prepared 2-aminoimidazoles (**1**, **33**−**37**, and **39**−**41**) were readily isolated as precipitates from their respective reaction mixtures, only a minor amount (14%) of product **38** was obtained in this manner for reaction of **11** (Table 1, entry 7) and a reduced level of purity (82.2%) was recorded relative to the other 2-aminoimidazole products synthesized. Mass recovery was improved by extraction of the mother liquor with ethyl acetate/water; however, while the aqueous extract was found to contain the hydrochloride salt of **38**, purity was again low (81.9%) with significant quantities of additional side products observed by ^{1}H NMR analysis.

In conclusion, the phosphorus oxychloride-mediated cyclization of aminoureas provides an effective route to 2-aminopyridoimidazoles and 2-aminobenzimidazoles, obviating the use of hazardous reagents such as cyanogen bromide. This methodology has been demonstrated for a range of urea substrates with 2-aminoimidazole products obtained in good yields and with excellent levels of purity.

EXPERIMENTAL SECTION

All reactions were carried out under an inert atmosphere. NMR spectra were recorded on a 300, 400, or 500 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. COSY and HETCOR correlations were used to confirm the NMR peak assignments of all novel compounds. Infrared (IR) spectra were obtained as films on NaCl plates or as KBr disks, and wavelengths are reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was performed on a TOF instrument in electrospray ionization (ESI) mode; samples were made up in acetonitrile or acetonitrile/water. Elemental analysis was performed using a PerkinElmer 240 and Exeter Analytical CE440 elemental analysers. Flash column chromatography was carried out using Kieselgel 60, 0.040−0.063 mm. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (60 PF254). HPLC analysis of aminoimidazole products was carried out using a Zorbax RX-C8 (4.6 mm ID × 250 mm, 5 μm) column under the following conditions: mobile phase A, 0.1% H_3PO_4 in H_2O; mobile phase B, 0.1% H_3PO_4 in acetonitrile; flow rate 1.5 mL/min; gradient 0.0 min (5% B), 15.0 min (90% B), 15.5 min (90% B), 16.5 min (5% B), 20.0 min (5% B); wavelength 254 nm; 40 °C.

General Procedure for Synthesis of Nitropyridin-2-amines 4, 15−19, 21, and 22. Amine (5.20 mmol) was added dropwise to a solution of nitropyridine substrate (5.18 mmol) and triethylamine (0.84 mL, 6.01 mmol) in methyl *tert*-butyl ether (12 mL) at −5 °C. The reaction mixture was stirred overnight at room temperature and then washed with water (20 mL) and brine (20 mL × 3). The organic phase was dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude nitropyridin-2-amines **4**, **15**−**19**, **21**, and **22**. The nitropyridin-2-amines **15**, **18**, **21**, and **22** were utilized without further purification; **19** was purified by column chromatography on silica gel using hexane as eluent, while **4**, **16**, **17**, were recrystallized from 2-propanol.

*6-Chloro-N-neopentyl-3-nitropyridin-2-amine (**4**).* Starting from 2,6-dichloro-3-nitropyridine (1.00 g, 5.18 mmol), triethylamine (0.84 mL, 6.01 mmol), and 2,2-dimethylpropan-1-amine (0.61 mL, 5.20 mmol). Recrystallization from 2-propanol yielded **4** as a yellow solid (1.13 g, 89.5%); ν_{max}(KBr)/cm^{-1} 3378.3, 2958.4, 1609.2, 1571.4, 1519.5, 1595.8, 1235.6; δ_H(500 MHz, DMSO-d_6) 0.95 (9H, s, 3 × CH_3), 3.41 (2H, d, *J* 6.2, CH_2), 6.79−6.76 (1H, m, aromatic H), 8.45−8.41 (1H, m, aromatic H), 8.53 (1H, t, *J* 5.7, aromatic H); δ_C(125.8 MHz, DMSO-d_6) 27.2 (3 × CH_3), 32.1 (C), 51.5 (CH_2), 111.6 (aromatic CH), 126.6 (aromatic C), 138.7 (aromatic CH), 152.2 (aromatic C), 155.2 (aromatic C); HRMS (ESI+): Exact mass calculated for $C_{10}H_{15}ClN_3O_2$ $(M + H)^+$ 244.0853. Found 244.0844.

*6-Chloro-N-ethyl-3-nitropyridin-2-amine (**15**).* Starting from 2,6-dichloro-3-nitropyridine (1.00 g, 5.18 mmol), triethylamine (0.84 mL, 6.01 mmol), and ethanamine (0.45 mL, 5.44 mmol). Yellow solid (1.03 g, 99.0%), Found: C, 41.61; H, 3.96; N, 21.19; $C_7H_8ClN_3O_2$ requires C, 41.70; H, 4.00; N, 20.84%; mp 76−80 °C; ν_{max}(KBr)/cm^{-1} 3383.3, 2970.2, 1608.1, 1569.2, 1234.7; δ_H(400 MHz) 1.32 (3H, t, *J* 7.3, CH_3), 3.66 (2H, dq, *J* 7.3/5.5, CH_2), 6.60 (1H, d, *J* 8.6, aromatic H), 8.32 (1H, bs, NH), 8.35 (1H, d, *J* 8.6, aromatic H); δ_C(75.5 MHz) 14.6 (CH_3), 36.5 (CH_2), 111.7 (aromatic CH), 126.7 (aromatic C), 137.7 (aromatic CH), 152.2 (aromatic C), 156.9 (aromatic C).

*6-Chloro-N-butyl-3-nitropyridin-2-amine (**16**).* Starting from 2,6-dichloro-3-nitropyridine (2.00 g, 10.36 mmol), triethylamine (1.68 mL, 12.02 mmol), and butan-1-amine (1.08 mL, 10.88 mmol). Recrystallization from 2-propanol yielded **16** as a yellow solid (2.34 g, 98.4%), Found: C, 47.21; H, 5.30; N, 18.66; $C_9H_{12}ClN_3O_2$ requires C, 47.07; H, 5.27; N, 18.30%; mp 37−39 °C; ν_{max}(KBr)/cm^{-1} 3396.4, 2956.4, 1608.2, 1571.9, 1235.2; δ_H(400 MHz) 0.98 (3H, t, *J* 6.9, CH_3), 1.45 (2H, sym m, *J* 7.5, CH_2), 1.68 (2H, qu, *J* 7.5, CH_2), 3.62 (2H, sym m, *J* 5.5, CH_2), 6.59 (1H, d, *J* 8.6, aromatic H), 8.34 (1H, d, *J* 8.6, aromatic H), 8.35 (1H, bs, NH); δ_C(75.5 MHz) 13.8 (CH_3), 20.1 (CH_2), 31.3 (CH_2), 41.3 (CH_2), 111.7 (aromatic CH), 127.8 (aromatic C), 137.7 (aromatic CH), 152.3 (aromatic C), 156.9 (aromatic C).

*6-Chloro-N-isobutyl-3-nitropyridin-2-amine (**17**).* Starting from 2,6-dichloro-3-nitropyridine (2.50 g, 12.95 mmol), triethylamine (2.09 mL, 15.03 mmol), and 2-methylpropan-1-amine (1.35 mL, 13.60 mmol). Recrystallization from 2-propanol yielded **17** as a yellow solid (2.49 g, 83.5%), mp 63−65 °C; ν_{max}(KBr)/cm^{-1} 3376.4, 2959.6, 1607.8, 1572.1, 1211.2; δ_H(400 MHz) 1.02 (6H, d, *J* 6.8, 2 × CH_3), 1.92−2.05 (1H, sym m, CH), 3.45−3.48 (2H, m, CH_2), 6.59 (1H, d, *J* 8.6, aromatic H), 8.35 (1H, d, *J* 8.6, aromatic H), 8.45 (1H, bs, NH); δ_C(75.5 MHz) 20.2 (2 × CH_3), 28.2 (CH), 48.8 (CH_2), 111.6 (aromatic CH), 126.5 (aromatic C), 137.7 (aromatic CH), 152.5 (aromatic C), 156.8 (aromatic C); HRMS (ES+): Exact mass calculated for $C_9H_{13}ClN_3O_2$ $(M + H)^+$ 230.0696. Found: 230.0683.

*6-Chloro-N-isopentyl-3-nitropyridin-2-amine (**18**).* Starting from 2,6-dichloro-3-nitropyridine (2.50 g, 12.95 mmol), triethylamine (2.09 mL, 15.03 mmol), and 3-methylbutan-1-amine (1.58 mL, 13.60 mmol). Yellow oil (2.97 g, 94.2%), Found: C, 49.60; H, 5.86; N, 17.49; $C_{10}H_{14}ClN_3O_2$ requires C, 49.29; H, 5.79; N, 17.24%; ν_{max}(film)/cm^{-1} 3383.7, 2957.8, 1606.3, 1570.9, 1235.2; δ_H(400 MHz) 0.98 (6H, d, *J* 6.5, 2 × CH_3), 1.54−1.62 (2H, m, CH_2), 1.71 (1H, sym m, *J* 6.6, CH), 3.63 (2H, sym m, *J* 5.5/1.8, CH_2), 6.60 (1H, d, *J* 8.6, aromatic H), 8.33 (1H, bs, NH), 8.35 (1H, d, *J* 8.6, aromatic H); δ_C(75.5 MHz) 22.5 (2 × CH_3), 25.9 (CH), 38.1 (CH_2), 39.9 (CH_2), 111.6 (aromatic CH), 126.5 (aromatic C), 137.7 (aromatic CH), 152.3 (aromatic C), 156.9 (aromatic C).

*6-Chloro-N-(3-methylbutan-2-yl)-3-nitropyridin-2-amine (**19**).* Starting from 2,6-dichloro-3-nitropyridine (1.00 g, 5.18 mmol), triethylamine (0.84 mL, 6.01 mmol), and 3-methylbutan-2-amine (0.63 mL, 5.44 mmol). Purification by column chromatography (eluent = 100% hexane) yielded **19** as a yellow oil (1.00 g, 79.0%), ν_{max}(film)/cm^{-1} 3372.4, 2964.3, 1603.2, 1570.7, 1492.9, 1261.5; δ_H(400 MHz) 0.98 (3H, d, *J* 10.8, CH_3), 1.00 (3H, d, *J* 10.8, CH_3), 1.23 (3H, d, *J* 6.4, CH_3), 1.83−1.95 (1H, sym m, CH), 4.27−4.36 (1H, sym m, CH), 6.57 (1H, d, *J* 8.6, aromatic H), 8.34 (1H, d, *J* 8.6, aromatic H), 8.38 (1H, bs, NH); δ_C(75.5 MHz) 17.4, 18.48, 18.54 (3 × CH_3), 32.9, 52.0 (2 × CH), 111.5 (aromatic CH), 126.2 (aromatic C), 137.8 (aromatic CH), 152.0 (aromatic C), 156.9 (aromatic C); HRMS (ES+): Exact mass calculated for $C_{10}H_{15}ClN_3O_2$ $(M + H)^+$ 244.0853. Found: 244.0844.

*5-Chloro-N-neopentyl-3-nitropyridin-2-amine (**21**).* Starting from 2,5-dichloro-3-nitropyridine (2.00 g, 10.36 mmol), triethylamine (1.68 mL, 12.02 mmol), and 2,2-dimethylpropan-1-amine (1.22 mL, 10.36 mmol). Orange solid (2.27 g, 89.5%), mp 72−74 °C; ν_{max}(KBr)/cm^{-1} 3394.2, 2958.9, 1610.3, 1567.3, 1204.6; δ_H(300 MHz) 1.01 (9H, s, 3 ×

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CH_3), 3.49 (2H, d, *J* 5.7, CH_2), 8.34 (1H, d, *J* 2.4, aromatic H), 8.41 (1H, d, *J* 2.4, aromatic H), 8.39 (1H, bs, NH); δ_C(75.5 MHz) 27.4 (3 × CH_3), 31.9 (C), 52.4 (CH_2), 117.5 (aromatic C), 127.1 (aromatic C), 134.1 (aromatic CH), 151.6 (aromatic C), 154.5 (aromatic CH); HRMS (ES+): Exact mass calculated for $C_{10}H_{15}ClN_3O_2$ $(M + H)^+$ 244.0853. Found: 244.0841.

*5-Bromo-N-neopentyl-3-nitropyridin-2-amine (**22**).* Starting from 5-bromo-2-chloro-3-nitropyridine (2.00 g, 8.42 mmol), triethylamine (1.36 mL, 9.77 mmol), and 2,2-dimethylpropan-1-amine (0.99 mL, 8.42 mmol). Orange solid (2.20 g, 90.7%), mp 66−68 °C; ν_{max}(KBr)/cm^{-1} 3394.3, 2959.4, 1603.5, 1565.9, 1203.6; δ_H(300 MHz) 1.01 (9H, s, 3 × CH_3), 3.48 (2H, d, *J* 6.0, CH_2), 8.38 (1H, bs, NH), 8.41 (1H, d, *J* 2.4, aromatic H), 8.54 (1H, d, *J* 2.1, aromatic H); δ_C(75.5 MHz) 27.4 (3 × CH_3), 32.0 (C), 52.4 (CH_2), 104.0 (aromatic C), 127.8 (aromatic C), 136.8 (aromatic CH), 151.8 (aromatic C), 156.4 (aromatic CH); HRMS (ES+): Exact mass calculated for $C_{10}H_{15}BrN_3O_2$ $(M + H)^+$ 288.0348. Found: 288.0345.

General Procedure for Synthesis of Nitropyridin-2-amine 20 and 2-Aminonitrobenzene 23. Amine (30.30 mmol) was added dropwise to a suspension of nitropyridine or nitrobenzene substrate (20.18 mmol) and sodium carbonate (3.74 g, 35.31 mmol) in EtOH (35 mL) at room temperature and stirred overnight. The resultant slurry was concentrated, diluted with water, and slowly neutralized with concentrated hydrochloric acid to pH = 7. The suspension was cooled to 0 °C for 1 h, and the observed solid was collected by vacuum filtration and washed with ice-cold water. If no solid was observed, the reaction mixture was instead extracted with ethyl acetate to obtain the desired amine product.

*N-Neopentyl-3-nitropyridin-2-amine (**20**).* Starting from 2-chloro-3-nitropyridine (3.20 g, 20.18 mmol), 2,2-dimethylpropan-1-amine (3.57 mL, 30.30 mmol), and sodium carbonate (3.74 g, 35.31 mmol). Yellow oil (4.14 g, 98.1%). Found: C, 57.43; H, 7.25; N, 19.91; $C_{10}H_{15}N_3O_2$ requires C, 57.40; H, 7.23; N, 20.08%; ν_{max}(film)/cm^{-1} 3393.2. 2959.5, 1611.6, 1574.4, 1510.8, 1503.7, 1234.2; δ_H(300 MHz) 1.03 (9H, s, 3 × CH_3), 3.50 (2H, d, *J* 5.7, CH_2), 6.60 (1H, dd, *J* 8.3/4.6, aromatic CH), 8.38−8.45 (2H, m, aromatic H), 8.44 (1H, bs, NH); δ_C(75.5 MHz) 27.5 (3 × CH_3), 31.9 (C), 52.3 (CH_2), 111.4 (aromatic CH), 127.8 (aromatic C), 135.4 (aromatic CH), 153.3 (aromatic C), 155.9 (aromatic CH).

*5-Chloro-N-neopentyl-2-nitroaniline (**23**).* Starting from 2,4-dichloro-1-nitrobenzene (5.00 g, 26.01 mmol), 2,2-dimethylpropan-1-amine (4.60 mL, 39.10 mmol), and sodium carbonate (4.83 g, 45.63 mmol). Recrystallization from hexane yielded **23** as a bright yellow solid (5.16 g, 81.7%), mp 92−94 °C; ν_{max}(KBr)/cm^{-1} 3375.2, 2960.6, 1614.5, 1566.7, 1492.7, 1243.1; δ_H(400 MHz) 1.07 (9H, s, 3 × CH_3), 3.05 (2H, d, *J* 5.2, CH_2), 6.58 (1H, dd, *J* 9.1/2.1, aromatic H), 6.85 (1H, d, *J* 2.1, aromatic H), 8.12 (1H, d, *J* 9.1, aromatic H), 8.27 (1H, bs, NH); δ_C(75.5 MHz) 27.6 (3 × CH_3), 31.7 (C), 54.9 (CH_2), 113.3 (aromatic CH), 115.6 (aromatic CH), 128.3 (aromatic CH), 131.1 (aromatic C), 142.9 (aromatic C), 146.4 (aromatic C); HRMS (ES+): exact mass calculated for $C_{11}H_{16}ClN_2O_2$ $(M + H)^+$ 243.0882. Found: 243.0889.

General Procedure for Hydrogenations. A mixture of platinum on activated carbon (0.76 g, 3.90 mmol, 5% w/w, 5% on carbon), water (2.5 mL), and hypophosphorous acid (0.21 mL, 1.89 mmol) was added to a solution of nitro **4**, **15**−**23** (20.52 mmol) in toluene (50 mL). The reaction mixture was hydrogenated at 50 psi overnight at room temperature. The crude reaction mixture was filtered over Celite with absolute ethanol as eluent. The mother liquor was evaporated under reduced pressure to provide **2**, **24**−**32**.

*6-Chloro-N2-neopentylpyridine-2,3-diamine (**2**).* Starting from **4** (5.00 g, 20.52 mmol), Pt/C (0.76 g, 3.90 mmol), and hypophosphorous acid (0.21 mL, 1.89 mmol). Dark brown solid (4.21 g, 96.2%); δ_H(300 MHz) 0.99 (9H, s, 3 × CH_3), 3.10 (2H, bs, 2 × NH), 3.26 (2H, s, CH_2), 4.37 (1H, bs, NH), 6.46 (1H, d, *J* 7.7, aromatic H), 6.80 (1H, d, *J* 7.7, aromatic H).

*6-Chloro-N2-ethylpyridine-2,3-diamine (**24**).* Starting from **15** (3.00 g, 14.88 mmol), Pt/C (0.55 g, 2.83 mmol, 5%), and hypophosphorous acid (0.15 mL, 1.37 mmol). Dark blue solid (2.53 g, 99.5%); δ_H(400 MHz) 1.26 (3H, t, *J* 7.2, CH_3), 2.35 (3H, 3 × NH), 3.46 (2H, q, *J* 7.2, CH_2), 6.48 (1H, d, *J* 7.7, aromatic H), 6.79 (1H, d, *J* 7.7, aromatic H).

*6-Chloro-N2-butylpyridine-2,3-diamine (**25**).* Starting from **16** (1.50 g, 6.53 mmol), Pt/C (0.24 g, 1.24 mmol, 5%), and hypophosphorous acid (0.066 mL, 0.60 mmol). Dark blue oily solid (1.22 g, 93.7%); δ_H(400 MHz) 0.96 (3H, t, *J* 7.3, CH_3), 1.43 (2H, sym m, *J* 7.3, CH_2), 1.61 (2H, qu, *J* 7.4, CH_2), 2.85 (3H, 3 × NH), 3.42 (2H, t, *J* 7.2, CH_2), 6.47 (1H, d, *J* 7.7, aromatic H), 6.79 (1H, d, *J* 7.7, aromatic H).

*6-Chloro-N2-isobutylpyridine-2,3-diamine (**26**).* Starting from **17** (1.50 g, 6.53 mmol), Pt/C (0.24 g, 1.24 mmol, 5%), and hypophosphorous acid (0.066 mL, 0.60 mmol). Dark blue solid (1.27 g, 97.6%); δ_H(400 MHz) 0.99 (6H, d, *J* 6.7, 2 × CH_3), 1.82−1.99 (1H, m, CH), 3.04 (2H, bs, NH_2), 3.26 (2H, d, *J* 6.9, CH_2), 4.31 (1H, bs, NH), 6.46 (1H, d, *J* 7.7, aromatic H), 6.78 (1H, d, *J* 7.7, aromatic H).

*6-Chloro-N2-isopentylpyridine-2,3-diamine (**27**).* Starting from **18** (1.50 g, 6.16 mmol), Pt/C (0.23 g, 1.17 mmol, 5%), and hypophosphorous acid (0.062 mL, 0.57 mmol). Dark blue oily solid (1.30 g, 98.6%); δ_H(400 MHz) 0.96 (6H, d, *J* 7.1, 2 × CH_3), 1.52 (2H, q, *J* 7.1, CH_2), 1.72 (1H, sym m, *J* 6.7, CH), 3.17 (3H, bs, 3 × NH), 3.43 (2H, t, *J* 7.4, CH_2), 6.47 (1H, d, *J* 7.7, aromatic H), 6.78 (1H, d, *J* 7.7, aromatic H).

*6-Chloro-N2-(3-methylbutan-2-yl)pyridine-2,3-diamine (**28**).* Starting from **19** (1.50 g, 6.16 mmol), Pt/C (0.23 g, 1.17 mmol, 5%), and hypophosphorous acid (0.062 mL, 0.57 mmol). Dark blue oil (1.31 g, 99.5%); δ_H(400 MHz) 0.93 (3H, d, *J* 6.8, CH_3), 0.96 (3H, d, *J* 6.8, CH_3), 1.14 (3H, d, *J* 6.8, CH_3), 1.75−1.91 (1H, m, CH), 3.37 (3H, bs, 3 × NH), 4.01−4.10 (1H, m, CH), 6.43 (1H, d, *J* 8.0, aromatic H), 6.79 (1H, d, *J* 8.0, aromatic H).

*N2-Neopentylpyridine-2,3-diamine (**29**).* Starting from **20** (1.50 g, 7.17 mmol), Pt/C (0.27 g, 1.36 mmol, 5%), and hypophosphorous acid (0.072 mL, 0.66 mmol). Dark blue solid (1.19 g, 92.3%); δ_H(400 MHz) 1.01 (9H, s, 3 × CH_3), 3.28 (2H, s, CH_2), 4.49 (1H, bs, NH), 6.48 (1H, dd, *J* 7.7/5.2, aromatic CH), 6.83 (1H, dd, *J* 7.4/1.5, aromatic H), 7.71 (1H, dd, *J* 5.2/1.3, aromatic H).

*5-Chloro-N2-neopentylpyridine-2,3-diamine (**30**).* Starting from **21** (1.50 g, 6.16 mmol), Pt/C (0.23 g, 1.17 mmol, 5%), and hypophosphorous acid (0.062 mL, 0.57 mmol). Dark black solid (1.31 g, 99.5%); δ_H(400 MHz) 0.99 (9H, s, 3 × CH_3), 3.25 (2H, s, CH_2), 6.83 (1H, d, *J* 2.0, aromatic H), 7.65 (1H, d, *J* 2.4, aromatic H).

*5-Bromo-N2-neopentylpyridine-2,3-diamine (**31**).* Starting from **22** (1.50 g, 5.21 mmol), Pt/C (0.19 g, 0.99 mmol, 5%), and hypophosphorous acid (0.052 mL, 0.48 mmol). Dark black solid (1.34 g, 99.5%); δ_H(400 MHz) 0.99 (9H, s, 3 × CH_3), 3.25 (2H, s, CH_2), 6.95 (1H, d, *J* 2.4, aromatic H), 7.73 (1H, d, *J* 2.0, aromatic H).

*5-Chloro-N1-neopentylbenzene-1,2-diamine (**32**).* Starting from **23** (1.50 g, 6.18 mmol), Pt/C (0.23 g, 1.17 mmol, 5%), and hypophosphorous acid (0.062 mL, 0.57 mmol). Dark blue oily solid (1.29 g, 98.4%); δ_H(400 MHz) 1.03 (9H, s, 3 × CH_3), 2.84 (2H, s, CH_2), 3.01 (3H, bs, 3 × NH), 6.57−6.65 (3H, m, 3 × aromatic H).

General Procedure for Synthesis of Ureas. A solution of potassium cyanate (2.09 g, 25.30 mmol) in water (5 mL) and aqueous hydrochloric acid (7.16 mL, 35.82 mmol, 5 N) were added dropwise separately over 1 h to diamine **2**, **24**−**32** (21.06 mmol) in ethanol (15 mL) at room temperature. A staggered addition was employed where an excess of aqueous hydrochloric acid was maintained in the reaction mixture throughout the addition process. The reaction mixture was stirred for 30 min, after which water (15 mL) was added, and the resultant mixture was stirred for a further 2 h. The reaction slurry was filtered, and the cake was washed with toluene and dried under vacuum overnight to give the crude urea products **3**, **6**−**14**.[11] The ureas **3**, **6**−**10**, and **14** were utilized without further purification, while **11**−**13** were purified by column chromatography on silica gel using 10% ethyl acetate in hexane as eluent.

*1-[6-Chloro-2-(neopentylamino)pyridin-3-yl]urea (**3**).* Starting from **2** (4.50 g, 21.06 mmol), potassium cyanate (2.09 g, 25.30 mmol), and hydrochloric acid (7.16 mL, 35.82 mmol, 5 N). Gray solid (3.74 g, 69.0%); ν_{max}(KBr)/cm^{-1} 3267.9, 2960.2, 1662.4, 1613.6, 1538.9, 1514.4, 1432.8; δ_H(500 MHz, DMSO-d_6) 0.94−0.90 (9H, m, 3

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× CH_3), 3.16 (2H d, *J* 5.8, CH_2), 5.96 (1H, d, *J* 5.8, NH), 5.98 (2H, bs, NH_2), 6.50 (1H, d, *J* 7.9, aromatic CH), 7.44 (1H, d, *J* 7.9, aromatic CH), 7.85 (1H, bs, NH); δ_C(125.8 MHz, DMSO-d_6) 27.41 (3 × CH_3), 32.01 (C), 51.81 (CH_2), 109.9 (aromatic CH), 119.4 (aromatic C), 132.7 (aromatic CH), 142.1 (aromatic C), 152.6 (aromatic C), 156.6 (CO); HRMS (ESI+): exact mass calculated for $C_{11}H_{18}ClN_4O$ $(M + H)^+$ 257.1164. Found: 257.1157.

1-[6-Chloro-2-(ethylamino)pyridin-3-yl]urea (**6**). Starting from **24** (2.60 g, 15.15 mmol), potassium cyanate (1.51 g, 18.18 mmol), and hydrochloric acid (5.15 mL, 25.8 mmol, 5 N). Gray solid (2.59 g, 80.0%), mp 163−165 °C; ν_{max}(KBr)/cm^{-1} 3442.8, 1654.2, 1601.9, 1543.3, 1495.9; δ_H(400 MHz, DMSO-d_6) 1.16 (3H, t, *J* 7.2, CH_3), 3.30 (2H, q, *J* 7.2, CH_2), 6.03 (2H, bs, 2 × NH), 6.37 (1H, bs, NH), 6.49 (1H, d, *J* 8.0, aromatic H), 7.69 (1H, d, *J* 8.0, aromatic H), 8.29 (1H, bs, NH); δ_C(75.5 MHz) 14.5 (CH_3), 35.7 (CH_2), 109.6 (aromatic CH), 120.1 (aromatic C), 130.0 (aromatic CH), 141.0 (aromatic C), 150.9 (aromatic C), 156.4 (CO); HRMS (ES+): exact mass calculated for $C_8H_{12}ClN_4O$ $(M + H)^+$ 215.0700. Found: 215.0696.

1-[6-Chloro-2-(butylamino)pyridin-3-yl]urea (**7**). Starting from **25** (1.20 g, 6.01 mmol), potassium cyanate (0.60 g, 7.21 mmol), and hydrochloric acid (2.04 mL, 10.22 mmol, 5 N). Light gray solid (1.41 g, 96.3%), mp 145−148 °C; ν_{max}(KBr)/cm^{-1} 3407.3, 3277.2, 1666.4, 1608.5, 1550.0, 1501.5, 1437.8; δ_H(400 MHz) 0.91 (3H, t, *J* 7.3, CH_3), 1.36 (2H, sym m, *J* 7.4, CH_2), 1.54 (2H, qu, *J* 7.4, CH_2), 3.23−3.30 (2H, m, CH_2), 5.98 (2H, bs, 2 × NH), 6.20 (1H, bt, *J* 5.0, NH), 6.50 (1H, d, *J* 7.9, aromatic H), 7.57 (1H, d, *J* 7.9, aromatic H), 7.92 (1H, bs, NH); δ_C(75.5 MHz) 13.8 (CH_3), 19.7 (CH_2), 30.9 (CH_2), 40.6 (CH_2), 109.7 (aromatic CH), 119.7 (aromatic C), 131.3 (aromatic CH), 141.7 (aromatic C), 151.6 (aromatic C), 156.5 (CO); HRMS (ES+): exact mass calculated for $C_{10}H_{16}ClN_4O$ $(M + H)^+$ 243.0997. Found: 243.1001.

1-[6-Chloro-2-(isobutylamino)pyridin-3-yl]urea (**8**). Starting from **26** (1.99 g, 9.99 mmol), potassium cyanate (0.99 g, 11.99 mmol), and hydrochloric acid (3.40 mL, 16.98 mmol, 5 N). Gray solid (2.08 g, 85.6%), mp 165−167 °C; ν_{max}(KBr)/cm^{-1} 3455.9, 3265.7, 2954.0, 1663.0, 1595.2; δ_H(300 MHz, DMSO-d_6) 0.91 (6H, d, *J* 6.7, 2 × CH_3), 1.81−1.98 (1H, m, CH), 3.07−3.12 (2H, m, CH_2), 6.03 (2H, bs, NH_2), 6.29 (1H, bt, *J* 5.2, NH), 6.49 (1H, d, *J* 7.9, aromatic H), 7.58 (1H, d, *J* 7.9, aromatic H), 8.08 (1H, bs, NH); δ_C(75.5 MHz, DMSO-d_6) 20.8 (CH_3), 27.9 (CH), 49.1 (CH_2), 110.1 (aromatic CH), 120.2 (aromatic C), 131.8 (aromatic CH), 142.1 (aromatic C), 152.2 (aromatic C), 157.0 (CO); HRMS (ES+): Exact mass calculated for $C_{10}H_{16}ClN_4O$ $(M + H)^+$ 243.1013. Found: 243.1006.

1-[6-Chloro-2-(isopentylamino)pyridin-3-yl]urea (**9**). Starting from **27** (2.60 g, 12.17 mmol), potassium cyanate (1.21 g, 14.60 mmol), and hydrochloric acid (4.14 mL, 20.68 mmol, 5 N). Light gray solid (2.57 g, 82.5%), mp 167−169 °C; ν_{max}(KBr)/cm^{-1} 3447.9 3200.5, 1666.9, 1610.1, 1538.3, 1420.2, 1358.3; δ_H(400 MHz, DMSO-d_6) 0.92 (6H, d, *J* 6.6, 2 × CH_3), 1.45 (2H, q, *J* 7.1, CH_2), 1.65 (1H, sym m, *J* 6.6, CH), 3.44 (2H, t, *J* 7.4, CH_2), 5.93 (2H, bs, 2 × NH), 6.08 (1H, bs, NH), 6.51 (1H, d, *J* 7.9, aromatic H), 7.53 (1H, d, *J* 7.9, aromatic H), 7.73 (1H, bs, NH); δ_C(75.5 MHz) 22.1 (CH_3), 22.5 (CH), 37.9 (CH_2), 39.0 (CH_2), 109.7 (aromatic CH), 119.7 (aromatic C), 131.6 (aromatic CH), 141.8 (aromatic C), 151.8 (aromatic C), 156.5 (CO); HRMS (ES+): exact mass calculated for $C_{11}H_{18}ClN_4O$ $(M + H)^+$ 257.1169. Found: 257.1166.

1-[6-Chloro-2-{(3-methylbutan-2-yl)amino}pyridin-3-yl]urea (**10**). Starting from **28** (2.07 g, 9.68 mmol), potassium cyanate (0.96 g, 11.61 mmol), and hydrochloric acid (3.29 mL, 16.45 mmol, 5 N). Dark gray solid (2.09 g, 84.1%), mp 134−136 °C; ν_{max}(KBr)/cm^{-1} 3381.0, 2963.9, 1662.6, 1609.0, 1498.6; δ_H(300 MHz, DMSO-d_6) 0.90 (6H, t, *J* 6.8, 2 × CH_3), 1.08 (3H, d, *J* 6.6, CH_3), 1.73−1.86 (1H, sym m, CH), 3.97−3.82 (1H, sym m, CH), 5.73 (1H, bd, *J* 7.9, NH), 5.94 (2H, bs, NH_2), 6.49 (1H, d, *J* 7.9, aromatic H), 7.50 (1H, d, *J* 7.9, aromatic H), 7.77 (1H, s, NH); δ_C(75.5 MHz) 17.4, 18.3, 18.9 (3 × CH_3), 32.9, 51.3 (2 × CH), 110.8 (aromatic CH), 115.2 (aromatic C), 137.7 (aromatic CH), 148.9 (aromatic C), 154.9 (aromatic C), 157.8 (CO); HRMS (ES+): Exact mass calculated for $C_{11}H_{18}ClN_4O$ $(M + H)^+$ 257.1169. Found: 257.1160.

1-[2-(Neopentylamino)pyridin-3-yl]urea (**11**). Starting from **29** (3.50 g, 19.52 mmol), potassium cyanate (1.94 g, 23.43 mmol), and hydrochloric acid (6.64 mL, 33.20 mmol, 5 N). Purification by column chromatography (eluent = 10% ethyl acetate in hexane) gave **11** as a gray solid (0.74 g, 16.9%), mp 163−165 °C; ν_{max}(KBr)/cm^{-1} 3412.7, 3257.5, 2957.6, 1743.6, 1661.6, 1610.8, 1538.6, 1465.3, 1369.6; δ_H(400 MHz, DMSO-d_6) 0.92 (9H, s, 3 × CH_3), 3.22 (2H, d, *J* 5.9, CH_2), 5.60 (1H, bt, *J* 5.3, NH), 5.92 (2H, bs, NH_2), 6.49 (1H, dd, *J* 7.5/5.0, aromatic CH), 7.41 (1H, d, *J* 7.5, aromatic CH), 7.76 (1H, d, *J* 7.5, aromatic CH), 7.81 (1H, bs, NH); δ_C(75.5 MHz) 27.9 (3 × CH_3), 32.4 (C), 52.2 (CH_2), 111.9 (aromatic CH), 120.9 (aromatic C), 130.6 (aromatic CH), 142.7 (aromatic CH), 153.3 (aromatic C) 157.3 (CO); HRMS (ES+): exact mass calculated for $C_{11}H_{19}N_4O$ $(M + H)^+$ 223.1559. Found: 223.1556.

1-[5-Chloro-2-(neopentylamino)pyridin-3-yl]urea (**12**). Starting from **30** (2.19 g, 10.26 mmol), potassium cyanate (1.02 g, 12.31 mmol), and hydrochloric acid (3.49 mL, 17.44 mmol, 5 N). Purification by column chromatography (eluent = 10% ethyl acetate in hexane) gave **12** as a gray solid (0.51 g, 19.3%), mp 159−160 °C; ν_{max}(KBr)/cm^{-1} 3462.5, 3239.3, 2954.6, 1664.1, 1590.4, 1529.3, 1425.1, 1359.2; δ_H(300 MHz, DMSO-d_6) 0.92 (9H, s, 3 × CH_3), 3.23 (2H, d, *J* 6.0, CH_2), 5.74 (1H, bt, *J* 5.9, NH), 6.06 (2H, bs, NH_2), 7.66 (1H, d, *J* 2.4, aromatic CH), 7.73 (1H, d, *J* 2.4, aromatic CH), 7.95 (1H, bs, NH); δ_C(75.5 MHz, DMSO-d_6) 27.9 (3 × CH3), 32.5 (C), 52.2 (CH2), 117.2 (aromatic C), 122.2 (aromatic C), 128.2 (aromatic CH), 139.2 (aromatic CH), 150.9 (aromatic C) 156.8 (CO); HRMS (ES+): exact mass calculated for $C_{11}H_{18}N_4OCl$ $(M + H)^+$ 257.1169. Found: 257.1160.

1-[5-Bromo-2-(neopentylamino)pyridin-3-yl]urea (**13**). Starting from **31** (2.10 g, 8.13 mmol), potassium cyanate (0.81 g, 9.76 mmol), and hydrochloric acid (2.77 mL, 13.83 mmol, 5 N). Purification by column chromatography (eluent = 10% ethyl acetate in hexane) gave **13** as a gray solid (0.72 g, 29.5%), mp 165−167 °C; ν_{max}(KBr)/cm^{-1} 3469.3, 3234.5, 2954.2, 1666.5, 1586.3, 1537.7, 1497.1, 1424.7; δ_H(400 MHz, DMSO-d_6) 0.86 (9H, s, 3 × CH_3), 3.16 (2H, d, *J* 5.8, CH_2), 5.93 (1H, bt, *J* 5.7, NH), 6.12 (2H, bs, NH_2), 7.69 (1H, d, *J* 2.0, aromatic CH), 7.79 (1H, d, *J* 2.0, aromatic CH), 8.36 (1H, bs, NH); δ_C(75.5 MHz, DMSO-d_6) 28.1 (3 × CH_3), 32.6 (C), 52.4 (CH_2), 104.7 (aromatic C), 123.1 (aromatic C), 128.3 (aromatic CH), 140.2 (aromatic CH), 150.0 (aromatic C) 157.0 (CO); HRMS (ES+) exact mass calculated for $C_{11}H_{18}N_4OBr$ $(M + H)^+$ 301.0664. Found: 301.0668.

1-[4-Chloro-2-(neopentylamino)phenyl]urea (**14**). Starting from **32** (1.80 g, 8.46 mmol), potassium cyanate (0.84 g, 10.15 mmol), and hydrochloric acid (2.88 mL, 14.39 mmol, 5 N). Dark red solid (2.12 g, 98.0%), mp 105−107 °C; ν_{max}(KBr)/cm^{-1} 3304.2, 1959.6, 1656.7, 1604.7, 1531.1, 1476.9; δ_H(400 MHz) 1.00 (9H, s, 3 × CH_3), 2.89 (2H, s, CH_2), 4.65 (2H, bs, 2 × NH), 5.95 (1H, bs, NH), 6.62 (1H, dd, *J* 8.2/2.3, aromatic H), 6.69 (1H, d, *J* 2.3, aromatic H), 7.04 (1H, d, *J* 8.2, aromatic H); δ_C(75.5 MHz) 27.9 (3 × CH_3), 32.2 (C), 56.5 (CH_2), 110.7 (aromatic CH), 115.5 (aromatic CH), 124.6 (aromatic C), 126.3 (aromatic CH), 129.8 (aromatic C), 144.8 (aromatic C), 157.5 (CO); HRMS (ES+): exact mass calculated for $C_{12}H_{19}ClN_3O$ $(M + H)^+$ 256.1217. Found: 256.1215.

General Procedure for Synthesis of 2-Aminoimidazoles. Phosphoryl oxychloride (1.61 mL, 17.29 mmol) was added dropwise to a solution of urea **3**, **6**−**14** (14.41 mmol) in acetonitrile (29 mL) at room temperature. The resultant solution was heated under reflux at 80 °C for 2 h. Water (15 mL) was added to the reaction mixture, and the mixture was heated at 80 °C for a further 1 h. The resulting mixture was cooled to room temperature, and the slurry was filtered. The cake was washed with water and dried under vacuum overnight to give 2-aminoimidazoles **1**, **33**−**41**.

5-Chloro-3-neopentyl-3H-imidazo[4,5-b]pyridin-2-amine hydrochloride (**1**). Starting from **3** (3.70 g, 14.41 mmol) and phosphoryl oxychloride (1.61 mL, 17.29 mmol). Off-white solid (3.14 g, 78.9%, 99.9% pure by HPLC analysis); ν_{max}(KBr)/cm^{-1} 2962.9, 1680.2, 1599.1, 1512.2, 1473.3, 1458.0, 1420.2; δ_H(500 MHz, DMSO-d_6) 0.98 (9H, s, 3 × CH_3), 3.96 (2H, s, CH_2), 7.34 (1H, d, *J* 8.3, aromatic CH), 7.78 (1H, d, *J* 8.3, aromatic CH), 9.11 (2H, bs, NH_2); δ_C(125.8 MHz,

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DMSO-d_6) 27.5 (3 × CH_3), 34.3 (C), 51.5 (CH_2), 118.8 (aromatic CH), 121.9 (aromatic CH), 122.8 (aromatic C), 142.1 (aromatic C), 144.2 (aromatic C), 152.2 (aromatic C); HRMS (ESI+): exact mass calculated for $C_{11}H_{16}ClN_4$ $(M + H)^+$ 239.1058. Found: 239.1053.

*5-Chloro-3-ethyl-3H-imidazo[4,5-b]pyridin-2-amine hydrochloride (**33**).* Starting from **6** (1.26 g, 5.87 mmol) and phosphoryl oxychloride (0.66 mL, 7.04 mmol). Light gray solid (0.94 g, 68.7%, 99.2% pure by HPLC analysis), mp 237−239 °C; ν_{max}(KBr)/cm^{-1} 3020.5, 1677.9, 1603.9, 1518.0, 1422.7; δ_H(400 MHz, DMSO-d_6) 1.30 (3H, t, *J* 7.2, CH_3), 4.17 (2H, q, *J* 7.2, CH_2), 7.38 (1H, d, *J* 8.2, aromatic H), 7.81 (1H, d, *J* 8.2, aromatic H), 9.26 (2H, bs, NH_2); δ_C(75.5 MHz, DMSO-d_6) 13.4 (CH_3), 36.9 (CH_2), 119.3 (aromatic CH), 122.5 (aromatic CH), 122.9 (aromatic C), 143.1 (aromatic C), 143.5 (aromatic C), 151.2 (aromatic C); HRMS (ES+): exact mass calculated for $C_8H_{10}ClN_4$ $(M + H)^+$ 197.0594. Found: 197.0589.

*5-Chloro-3-butyl-3H-imidazo[4,5-b]pyridin-2-amine hydrochloride (**34**).* Starting from **7** (1.20 g, 4.94 mmol) and phosphoryl oxychloride (0.55 mL, 5.93 mmol). Brown solid (0.96 g, 74.2%, 98.2% pure by HPLC analysis), mp 179−181 °C; ν_{max}(KBr)/cm^{-1} 2959.2, 1681.6, 1523.7, 1428.8; δ_H(400 MHz, DMSO-d_6) 0.77 (3H, t, *J* 7.4, CH_3), 1.19 (2H, sym m, *J* 7.6, CH_2), 1.55 (2H, qu, *J* 7.6, CH_2), 3.95 (2H, t, *J* 7.4, CH_2), 7.21 (1H, d, *J* 8.2, aromatic H), 7.63 (1H, d, *J* 8.2, aromatic H), 8.84 (2H, bs, NH_2); δ_C(75.5 MHz, DMSO-d_6) 14.0 (3 × CH_3), 19.6 (CH_2), 19.9 (CH_2), 41.5 (CH_2), 119.3 (aromatic CH), 122.6 (aromatic CH), 123.2 (aromatic C), 142.9 (aromatic C), 143.9 (aromatic C), 151.6 (C); HRMS (ES+): exact mass calculated for $C_{10}H_{14}ClN_4$ $(M + H)^+$ 225.0907. Found: 225.0905.

*5-Chloro-3-isobutyl-3H-imidazo[4,5-b]pyridin-2-amine (**35**).* Starting from **8** (1.00 g, 4.12 mmol) and phosphoryl oxychloride (0.46 mL, 4.94 mmol). Light brown solid (0.72 g, 67.3%, 99.7% pure by HPLC analysis), mp 236−238 °C; ν_{max}(KBr)/cm^{-1} 2964.2, 1679.7, 1601.9, 1420.4; δ_H(400 MHz, DMSO-d_6) 0.91 (6H, d, *J* 6.8, 2 × CH_3), 2.13−2.27 (1H, sym m, CH), 3.95 (2H, d, *J* 7.6 CH_2), 7.35 (1H, d, *J* 8.4, aromatic H), 7.80 (1H, d, *J* 8.4, aromatic H), 9.17 (2H, bs, NH_2); δ_C(150 MHz, DMSO-d_6) 19.3 (2 × CH_3), 26.9 (CH), 47.9 (CH_2), 118.9 (aromatic CH), 122.1 (aromatic CH), 122.4 (aromatic C), 142.4 (aromatic C), 143.6 (aromatic C), 151.2 (C); HRMS (ES+): Exact mass calculated for $C_{10}H_{14}ClN_4$ $(M + H)^+$ 225.0907. Found: 225.0905.

*5-Chloro-3-isopentyl-3H-imidazo[4,5-b]pyridin-2-amine (**36**).* Starting from **9** (1.20 g, 4.67 mmol) and phosphoryl oxychloride (0.52 mL, 5.61 mmol). Cream solid (0.82 g, 64.1%, 99.6% pure by HPLC analysis), mp 224−226 °C; ν_{max}(KBr)/cm^{-1} 2961.8, 1675.6, 1600.4, 1522.3, 1420.5; δ_H(400 MHz, DMSO-d_6) 0.96 (6H, d, *J* 5.7, 2 × CH_3), 1.54−1.62 (3H, m, CH and CH_2), 4.12 (2H, t, *J* 6.8, CH_2), 7.36 (1H, d, *J* 8.2, aromatic H), 7.79 (1H, d, *J* 8.2, aromatic H), 9.05 (2H, bs, NH_2); δ_C(75.5 MHz, DMSO-d_6) 22.6 (2 × CH_3), 25.6 (CH), 36.2 (CH_2), 40.3 (CH_2), 119.4 (aromatic CH), 122.5 (aromatic CH), 123.0 (aromatic C), 143.2 (aromatic C), 143.8 (aromatic C), 151.4 (C); HRMS (ES+): exact mass calculated for $C_{11}H_{16}ClN_4$ $(M + H)^+$ 239.1063. Found: 239.1057.

*5-Chloro-3-(3-methylbutan-2-yl)-3H-imidazo[4,5-b]pyridin-2-amine hydrochloride (**37**).* Starting from **10** (1.25 g, 4.86 mmol) and phosphoryl oxychloride (0.54 mL, 5.83 mmol). Black solid (0.93 g, 69.9%, 99.2% pure by HPLC analysis), mp 89−92 °C; ν_{max}(KBr)/cm^{-1} 3107.6, 2971.8, 1674.4, 1422.6; δ_H(400 MHz, DMSO-d_6) 0.77 (3H, d, *J* 6.8, CH_3), 1.11 (3H, d, *J* 6.8, CH_3), 1.65 (3H, d, *J* 6.8, CH_3), 2.58−2.68 (1H, sym m, CH), 4.34−4.45 (1H, sym m, CH), 7.43 (1H, d, *J* 8.0, aromatic H), 7.87 (1H, d, *J* 8.4, aromatic H), 9.20 (2H, bs, NH_2); δ_C(150 MHz, DMSO-d_6) 15.84, 19.36, 19.42 (3 × CH_3), 30.7, 57.6 (2 × CH), 118.8 (aromatic CH), 122.2 (aromatic CH), 122.7 (aromatic C), 141.9 (aromatic C), 142.9 (aromatic C), 150.9 (C); HRMS (ES+): Exact mass calculated for $C_{11}H_{16}ClN_4$ $(M + H)^+$ 239.1063. Found: 239.1059.

*3-Neopentyl-3H-imidazo[4,5-b]pyridin-2-amine hydrochloride (**38**).* Starting from **11** (0.70 g, 3.15 mmol) and phosphoryl oxychloride (0.35 mL, 3.78 mmol). Light brown solid (0.10 g, 13.6%, 82.2% pure by HPLC analysis), δ_H(400 MHz, DMSO-d_6); 1.06 (9H, s, 3 × CH_3), 4.11 (2H, s, CH_2), 7.36 (1H, dd, *J* 7.9/5.0, aromatic H), 7.84 (1H, dd, *J* 7.9/1.3, aromatic H), 8.28 (1H, dd, *J* 5.0/1.3, aromatic H), 9.14 (2H, bs, NH_2); δ_C(75.5 MHz, DMSO-d_6) 27.5 (3 × CH_3), 34.4 (C), 51.1 (CH_2), 118.9 (aromatic CH), 119.1 (aromatic CH), 124.4 (aromatic C), 141.4 (aromatic CH), 144.9 (aromatic C), 152.3 (C); HRMS (ES+): Exact mass calculated for $C_{11}H_{17}N_4$ $(M + H)^+$ 205.1453. Found: 205.1443. Note: Mother liquor was extracted with ethyl acetate and water; aqueous layer was isolated and concentrated to give **38** as a red oily solid (0.34 g, 42.5%, 81.9% pure by HPLC analysis). Evidence for the presence of a phosphorus byproduct was observed by ^1H and ^{31}P NMR analysis for both samples of **38** isolated (not detected by HPLC analysis).

*6-Chloro-3-neopentyl-3H-imidazo[4,5-b]pyridin-2-amine (**39**).* Starting from **12** (0.47 g, 1.81 mmol) and phosphoryl oxychloride (0.20 mL, 2.18 mmol). Brown solid (0.28 g, 57.0%, 95.7% pure by HPLC analysis), mp > 240 °C; ν_{max}(KBr)/cm^{-1} 3079.4, 2963.5, 1687.1, 1623.8, 1513.6, 1470.2; δ_H(400 MHz, DMSO-d_6) 0.99 (9H, s, 3 × CH_3), 4.03 (2H, s, CH_2), 7.89 (1H, d, *J* 2.1, aromatic H), 7.94 (1H, d, *J* 2.1, aromatic H), 9.32 (2H, bs, NH_2); δ_C(75.5 MHz, DMSO-d_6) 28.0 (3 × CH_3), 34.8 (C), 51.9 (CH_2), 119.2 (aromatic CH), 124.3 (aromatic C), 126.3 (aromatic C), 140.6 (aromatic CH), 143.9 (aromatic C), 152.9 (C); HRMS (ES+): Exact mass calculated for $C_{11}H_{16}ClN_4$ $(M + H)^+$ 239.1063. Found: 239.1057.

*6-Bromo-3-neopentyl-3H-imidazo[4,5-b]pyridin-2-amine (**40**).* Starting from **13** (0.52 g, 1.72 mmol) and phosphoryl oxychloride (0.19 mL, 2.07 mmol). Light brown solid (0.31 g, 56.2%, 99.1% pure by HPLC analysis), mp > 240 °C; ν_{max}(KBr)/cm^{-1} 3119.2, 2961.2, 1700.2, 1617.5, 1588.9, 1476.2; δ_H(400 MHz, DMSO-d_6) 0.94 (9H, s, 3 × CH_3), 3.62 (2H, s, CH_2), 7.48 (1H, d, *J* 1.8, aromatic H), 8.03 (1H, d, *J* 1.8, aromatic H); δ_C(75.5 MHz, DMSO-d_6) 28.5 (3 × CH_3), 34.2 (C), 50.8 (CH_2), 111.9 (aromatic C), 117.4 (aromatic CH), 124.5 (aromatic C), 139.9 (aromatic CH), 144.6 (aromatic C), 154.7 (C); HRMS (ES+): Exact mass calculated for $C_{11}H_{16}BrN_4$ $(M + H)^+$ 283.0558. Found: 283.0553.

*6-Chloro-1-neopentyl-1H-benzo[d]imidazol-2-amine hydrochloride (**41**).* Starting from **14** (1.00 g, 3.91 mmol) and phosphoryl oxychloride (0.44 mL, 4.69 mmol). Off-white solid (0.89 g, 83.1%, 99.0% pure by HPLC analysis), 98.1% pure by HPLC analysis), mp 220−222 °C; ν_{max}(KBr)/cm^{-1} 3108.6, 1668.0, 1515.8, 1480.7, 1401.4; δ_H(400 MHz, DMSO-d_6) 0.99 (9H, s, 3 × CH_3), 4.02 (2H, s, CH_2), 7.27 (1H, dd, *J* 8.5/1.8, aromatic H), 7.38 (1H, d, *J* 8.5, aromatic H), 7.72 (1H, d, *J* 1.8, aromatic H), 8.68 (2H, bs, NH_2); δ_C(75.5 MHz, DMSO-d_6) 27.9 (CH_3), 35.4 (C), 52.7 (CH_2), 112.0 (aromatic CH), 113.3 (aromatic CH), 123.6 (aromatic CH), 127.1 (aromatic C), 129.4 (aromatic C), 133.4 (aromatic C), 152.4 (C); HRMS (ES+): exact mass calculated for $C_{12}H_{17}ClN_3$ $(M + H)^+$ 238.1111. Found: 238.1102.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral and analytical data: copies of ^1H and ^{13}C NMR spectra and HPLC profiles of all novel 2-aminoimidazoles (**1**, **33**−**41**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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