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Research and Development of an Efficient Process for the Construction of the 2,4,5-Substituted Pyridines of NK-1 Receptor Antagonists

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Abstract:

Roche has identified a 2,4,5-trisubstituted pyridine template for a new class of potent NK_1 receptor antagonists. Previous strategies for construction of the pyridine core of these NK-1 receptor antagonists involved functionalization of a 2,5-disubstituted pyridine. We now report on construction of the pyridine core from commodity components. Shestopalov reported the synthesis of *trans*-4′-aryl-5′-cyano-1′,2′,3′,4′-tetrahydro-6′-hydroxy-2′-oxo-1,3′-bipyridinium inner salts from 1-(2-amino-2-oxoethyl)pyridinium chloride, aromatic aldehydes, and ethyl cyanoacetate in the presence of a base. Reaction of these salts with phosphorus oxychloride affords 4-aryl-3-cyano-2,6-dichloropyridines. These are efficiently converted to nicotinamide precursors of the Roche NK-1 receptor antagonists by regioselective displacement of one chlorine by an amine, hydrogenolysis of the remaining chlorine, and nitrile hydrolysis.

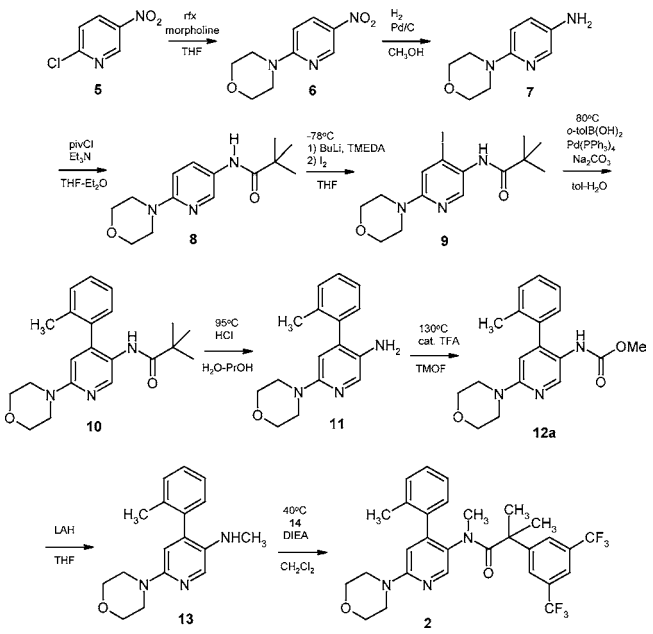
Introduction

The tachykinin neuropeptides, substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), are neurotransmitters or neuromodulatory agents. Each of these structurally related neuropeptides has a preferred receptor: the NK_1 receptor for SP, the NK_2 receptor for NKA, and the NK_3 receptor for NKB. The NK_1 and NK_2 receptors are widely distributed in the central nervous system (CNS) and peripheral tissue; NK_3 may be more localized in the CNS.

In recent years, many small-molecule NK-1 receptor antagonists have been identified, and clinical trials have highlighted their therapeutic potential for treatment of depression and anxiety and for control of chemotherapy-induced nausea and vomiting.[1] The Roche NK-1 receptor antagonists are nicotinamides such as **1** and "inverse nicotinamides" such as **2**−**4**[2] (Figure 1).

Previous strategies for construction of antagonists **2**−**4** involved functionalization of a 2,5-disubstituted pyridine. To illustrate, the Discovery Chemistry synthesis of **2** (Scheme 1) begins with 2-chloro-5-nitropyridine (**5**). Morpholine displacement, nitro group reduction, and pivaloylation affords pivalamide **8**. Regioselective lithiation provides access to the 4-iodopyridine **9**, which is used in a Suzuki coupling with an arylboronic acid. Amide hydrolysis, N-methylation via the methyl carbamate **12a**, and acylation with α,α-dimethyl-3,5-bis(trifluoromethyl)benzeneacetyl chloride (**14**) complete the sequence.[2b]

Scheme 1. **Discovery Chemistry route from 2-chloro-5-nitropyridine 5 to 2**



While the Discovery Chemistry route provided rapid access to **2**, the lithiation required a low temperature (−78 °C) and an excess (3−4 equiv) of butyllithium and the Suzuki coupling partner was relatively expensive *o*-tolylboronic acid.

The Process Chemistry group demonstrated that the Discovery Chemistry methyl carbamates such as **12a** are also accessible via Hofmann rearrangement of a nicotinamide (Scheme 2). 6-Chloronicotinic acid **15** is converted to the *tert*-butylamide via the acid chloride. The 4-aryl substituent is introduced by 1,4-addition of *o*-tolylmagnesium chloride followed by dihydropyridine oxidation. After chlorine displacement by morpholine or 1-methylpiperazine, the *tert*-butyl group is cleaved, the amide **19** is subjected to Hofmann rearrangement, and the isocyanate is trapped with methanol.[3]

While the Process Chemistry route provided larger quantities of the Roche NK-1 receptor antagonists for clinical evaluation, 6-chloronicotinic acid **15** is a value-added starting material. 6-Chloronicotinic acid **15** is likely prepared from 6-hydroxynicotinic acid, prepared by microbial oxidation of

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(1) (a) Albert, J. S. *Expert Opin. Ther. Pat.* **2004**, *14*, 1421. (b) Duffy, R. A. *Expert Opin. Emerging Drugs* **2004**, *9*, 9.

(2) (a) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. EP1035115 (9/13/00). (b) Ballard, T. M.; Higgins, G. A.; Hoffmann, T.; Poli, S. M.; Sleight, A. EP1103545 (5/30/01). (c) Hoffmann, T.; Bös, M.; Stadler, H.; Schnider, P.; Hunkeler, W.; Godel, T.; Galley, G.; Ballard, T. M.; Higgins, G. A.; Poli, S. M.; Sleight, A. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1362.

(3) (a) Hilpert, H.; Hoffmann-Emery, F.; Rimmler, G.; Rogers-Evans, M.; Stahr, H. W.; Waldmeier, P. EP1103546 (5/30/01). (b) Hoffmann-Emery, F.; Hilpert, H.; Scalone, M.; Waldmeier, P. *J. Org. Chem.* **2006**, *71*, 2000.

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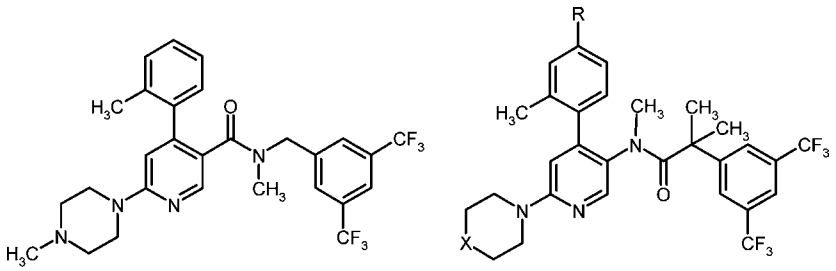
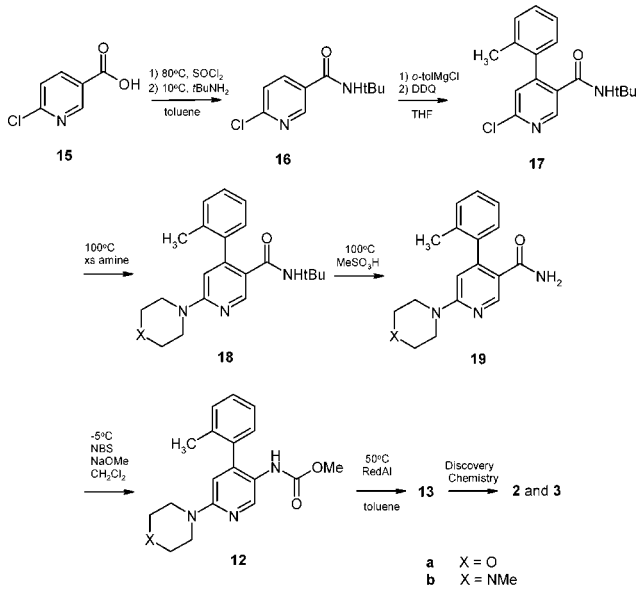


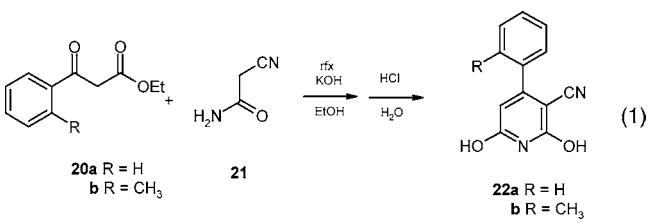
Figure 1. **Roche NK-1 receptor antagonists.**

Scheme 2. **Process Chemistry route from 6-chloronicotinic acid 15 to 2 and 3**



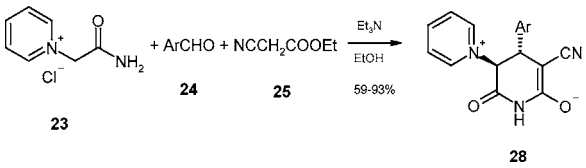
nicotinic acid. In addition, the throughput for the 1,4-addition is poor since *o*-tolylmagnesium chloride is used in excess (typically 3−5 equiv) as a 1 M THF solution. Finally, the dihydropyridine oxidation using manganese dioxide, potassium permanganate, manganese(III) acetate dihydrate, or DDQ requires a byproduct separation and oxidant regeneration.

We now report on an alternative construction of the Process Chemistry nicotinamides such as **19** from commodity components. There are many methods for pyridine ring construction, including the Hantzsch, Kröhnke, and Guareschi−Thorpe syntheses. 3-Cyano-2,6-dihydroxy-4-phenylpyridine (**22a**) was constructed by a Guareschi−Thorpe synthesis in 1980 (eq 1).[4] Ethyl benzoylacetate **20a** and cyanoacetamide **21** are readily available, but the yield is low (42%). Attempted extension of this method to construction of 3-cyano-2,6-dihydroxy-4-(2-methylphenyl)pyridine (**22b**) met with only limited success.



(1)

Shestopalov reported the synthesis of *trans*-4′-aryl-5′-cyano-1′,2′,3′,4′-tetrahydro-6-hydroxy-2-oxo-1,3′-bipyridinium inner salts **28** from 1-(2-amino-2-oxoethyl)pyridinium chloride **23**, an aromatic aldehyde **24**, and ethyl cyanoacetate **25** in the presence of a base (eq 2).[5]



(2)

We have found that reaction of Shestopalov pyridinium inner salts such as **28** with phosphorus oxychloride provides 4-aryl-3-cyano-2,6-dichloropyridines **29** which can be efficiently converted to the nicotinamides **19**. The nicotinamides **19** can then be converted via the Process Chemistry route methylamines such as **13** to the Roche NK-1 receptor antagonists **2**, **3**, and **4** (Scheme 3). The Shestopalov pyridine ring construction is detailed in Scheme 4.

Pyridine Ring Construction

The Shestopalov ring construction shown in Scheme 4 is the end result of three sequential reactions: Knoevenagel condensation of aldehyde **24** with methyl cyanoacetate **26**, Michael addition of the pyridinium ylid from **23** to the condensation product **27**, and cyclization of the Michael adduct.

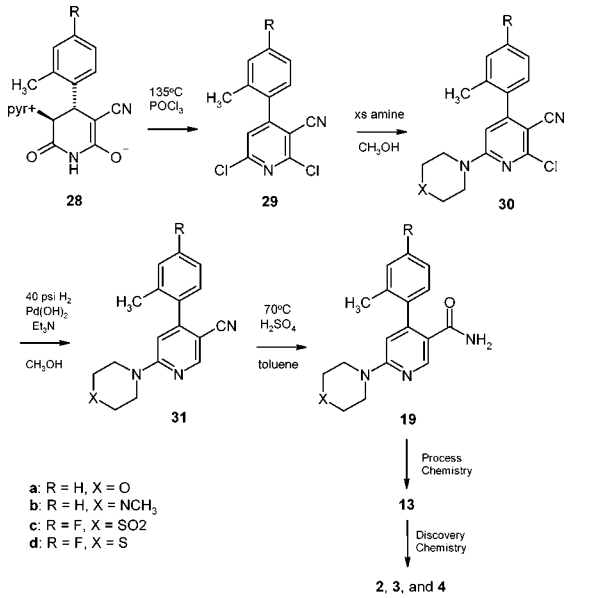
The Knoevenagel condensation is fast: condensation of aldehyde **24** and methyl cyanoacetate **26** in isopropanol is complete in less than 1 h at 25 °C. The Michael addition to **27** is also fast: the Michael adduct precipitates during triethylamine addition to a mixture of the Knoevenagel product **27** and pyridinium salt **23** in methanol at 25 °C. The cyclization is relatively slow, perhaps because of the limited solubility of the Michael adduct: the precipitate after 6 h at 25 °C consists of a mixture of the Michael adduct and cyclization product **28**.

The pyridinium salt **23** can be prepared by refluxing a mixture of 2-chloroacetamide and pyridine (1.16 equiv) in

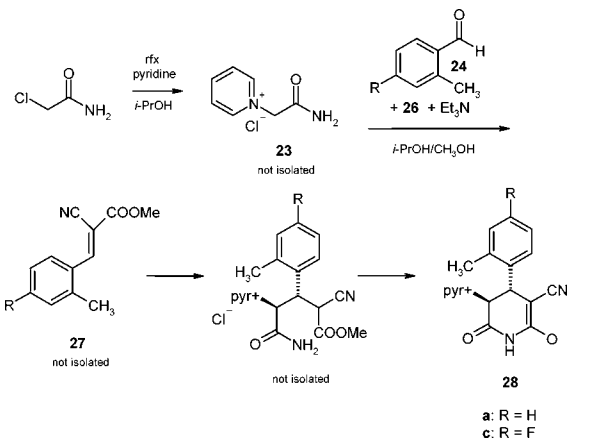
(4) Roch, J.; Müller, E.; Narr, B.; Nickl, J.; Haarmann, W. US4182887 (1/8/80).

(5) (a) Shestopalov, A. M.; Litvinov, V. P.; Rodinovskaya, L. A.; Sharanin, Yu. A. *Synthesis* **1991**, 402. (b) Shestopalov, A. M.; Sharanin, Yu. A.; Litvinov, V. P. *Khim. Geterotsikl. Soedin.* **1990**, 363. (c) Litvinov, V. P.; Shestopalov, A. M. *Zh. Org. Khim.* **1997**, *33*, 975.

Scheme 3. **Route from Shestopalov pyridinium inner salts 28 to 2, 3, and 4**



Scheme 4. **Shestopalov synthesis of bipyridinium inner salt 28**



n-butyl acetate. The salt is isolated by cooling the suspension, filtering, and washing the solid with hexane (92% yield) (Method A). Alternatively, refluxing 2-chloroacetamide and pyridine (1.02 equiv) in isopropanol affords a suspension of pyridinium salt **23** suitable for use in the pyridine ring construction (Method B). We prefer to avoid the salt isolation by using Method B. A near-optimal procedure for the ring construction involves preparation of pyridinium salt **23** in isopropanol, addition of 1 equiv of methyl cyanoacetate **26**, 1 equiv of aldehyde **24**, and methanol, and then dropwise addition of 1.1 equiv of triethylamine. After 24 h, analytically pure **28** is isolated by filtration and washing with methanol (89−93%).

Dichloropyridine 29. By returning to the route presented in Scheme 3, conversion of the inner salt **28a** to the dichloropyridine **29a** (82−87% yield) was demonstrated using 0.64 mL, 1.25 mL, 2.5 mL, and 5 mL of phosphorus oxychloride per g of **28a** at 105−150 °C. While the mixture becomes homogeneous and the reaction goes to completion at 135 °C using just 0.64 mL of phosphorus oxychloride per g of **28a**, a greater excess of phosphorus oxychloride is necessary to maintain a stirrable mixture during the phase/viscosity changes observed during heatup. The phase/viscosity changes observed in the RC-1 calorimeter during heatup using 5 mL of phosphorus oxychloride per g of **28a** are shown in Figure 2.

Regioselective Chlorine Displacement from the 3-Cyano-2,6-dichloropyridine 29 by Amine. Since 3-cyano-2,6-diaminopyridines are precursors of couplers for the preparation of azo dyes, the regioselective replacement of one chlorine of a 3-cyano-2,6-dichloropyridine is well documented. There are many examples of attack by nonhindered primary amines at the 2-position and by hindered primary amines and secondary amines at the 6-position.[6] Solvent polarity often plays a critical role, with attack at the 2-position favored by a decrease in solvent polarity. The regioselectivity in our reaction of 3-cyano-2,6-dichloropyridine **29a** with morpholine is presented in Table 1. The table shows a negligible influence of reaction temperature (in ethanol) and the expected strong influence of solvent polarity. We chose to use methanol as solvent: the regioselectivity in methanol at 25 °C is 10:1, and the desired regioisomer **30a** crystallizes from the reaction mixture (78% yield) while the amine hydrochloride byproduct remains in solution.

Table 1. **Regioselectivity in the reaction of 3-cyano-2,6-dichloro-4-(2-methylphenyl) pyridine 29a with morpholine[a]**

solvent	temp (°C)	product ratio[b] **30a**:regioisomer
MeOH	25	10:1
EtOH	25	12:1
EtOH	0	11:1
EtOH	−10	11:1
EtOH−acetone (1:1)	−10	14:1
acetone	−10	11:1
CH_3CN	−10	10:1
MTBE	−10	7:1
THF	−10	7:1
EtOAc	−10	5:1

[a] Conditions: 2.20 equiv of morpholine, 18−22 h. [b] Determined by 500 MHz ^{1}H NMR.

The reaction of 3-cyano-2,6-dichloropyridine **29a** with 1-methylpiperazine in methanol at 25 °C is also regioselective (10:1). After dilution of the methanol suspension with water, 2-chloro-3-cyano-4-(2-methylphenyl)-6-(4-methylpiperazinyl)pyridine **30b** is isolated in 77% yield. The reaction of 3-cyano-2,6-dichloropyridine **29c** with thiomorpholine in methanol at 25 °C is also regioselective (10:1). Considerably less 2-chloro-3-cyano-4-(4-fluoro-2-methylphenyl)-6-(4-thiomorpholinyl)pyridine **30c** is lost to the methanol crystallization liquors (88% yield).

Hydrogenolysis and Hydrolysis. Many pyridine ring construction methods produce 2- or 4-hydroxypyridines. Replacement of the hydroxyl group by hydrogen via conversion to the chloropyridine and hydrogenolysis is well documented. Since the hydrogen chloride produced can poison the catalyst, the hydrogenolysis is often carried out in the presence of a base. Hydrogenolyses of our 6-amino-2-chloro-

(6) (a) Fleckenstein, E.; Heinrich, E.; Mohr, R. US4061642 (12/6/77). (b) Lamm, G.; Dehnert, J. US 3853895 (12/10/74).

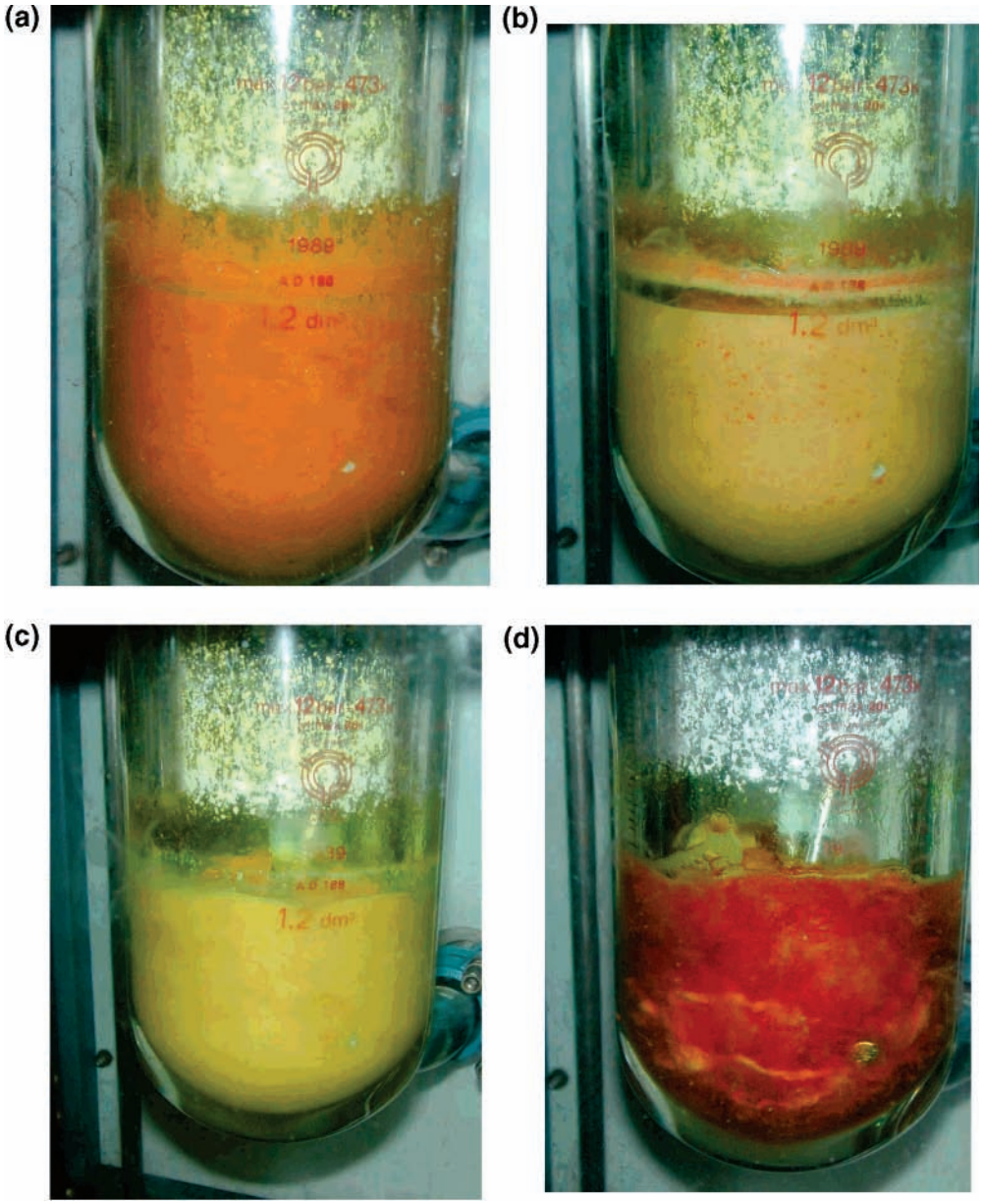
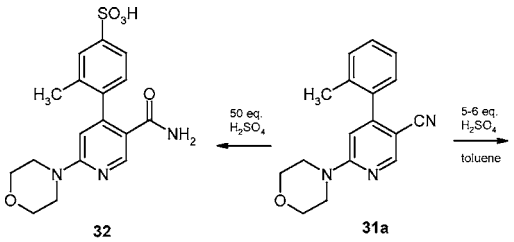


Figure 2. **Phase changes during heatup of the salt (28a)-phosphorus oxychloride mixture at (a) 66, (b) 75, (c) 90, and (d) 120 °C.**

3-cyanopyridines **30** were accomplished using triethylamine and palladium hydroxide on carbon in methanol at 25 °C (93−96%). Side products resulting from overhydrogenation can be removed after the hydrogenation by an acid wash or after the nitrile hydrolysis by adsorption on silica.

A nicotinonitrile can be converted to a nicotinamide with sulfuric acid,[7] aqueous hydroxide,[8] basic hydrogen peroxide,[9] or potassium trimethylsilanolate.[10] We observed that stoichiometry and the presence of a sacrificial solvent are critical factors in an efficient process using sulfuric acid. To illustrate, reaction of nitrile **31a** with ∼50 equiv of 98% sulfuric acid at 50 °C for 3 h followed by an aqueous quench results in nitrile hydrolysis and ring sulfonation (eq 3). Nearly

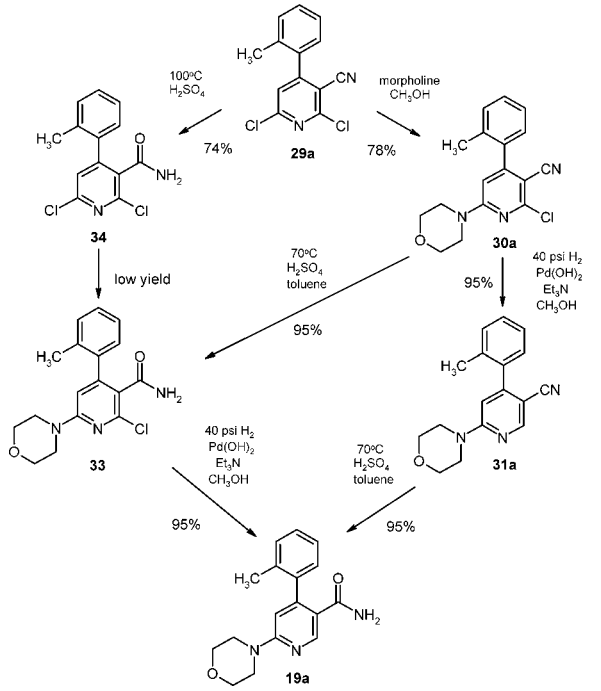


(3)

complete conversion to **19a** with minimal ring sulfonation is observed in the reaction of nitrile **31a** with 5 to 6 equiv

(7) Miyamoto, T.; Egawa, H.; Shibamori, K.-i.; Matsumoto, J.-i. *J. Heterocycl. Chem.* **1987**, *24*, 1333.
(8) Salem, M. A. I.; Madkour, H. M. F.; Soliman, E.-S. A.; Mahmoud, N. F. H. *Heterocycles* **2000**, *53*, 1129.
(9) Humphries, M. J.; Ramsden, C. A. *Synthesis* **1999**, 985.
(10) Merchant, K. J. *Tetrahedron Lett.* **2000**, *41*, 3747.

Scheme 5. **Three alternative sequences from 29a to 19a**



of sulfuric acid in toluene at 70 °C after 2 h. We did observe some toluene sulfonation but did not determine the quantity of toluenesulfonic acid produced.

Alternative Sequences from 29a to 19a. 3-Cyano-2,6-dichloropyridine **29a** is converted to 6-morpholino-3-pyridinecarboxamide **19a** in overall 70% yield by three reactions: a chlorine displacement by morpholine, a chlorine hydrogenolysis, and a nitrile hydrolysis. These transformations could potentially be run in a different order (Scheme 5). With the understanding that there is no precedent for the efficient hydrogenolysis of one chlorine of a 2,6-dichloropyridine, the two possible alternative sequences are displacement−hydrolysis−hydrogenolysis (via intermediates **30a** and **33**) and hydrolysis−displacement−hydrogenolysis (via intermediates **34** and **33**).

The displacement−hydrolysis−hydrogenolysis sequence via intermediates **30a** and **33** also affords 6-morpholinylpyridine-3-carboxamide **19a** in overall 70% yield. However, the nitrile hydrolysis to the 2-chloropyridine-3-carboxamide **33** is much slower (5 to 6 equiv of sulfuric acid in toluene at 70 °C for 120 h) than the nitrile hydrolysis to the pyridine-3-carboxamide **19a** (5 to 6 equiv of sulfuric acid in toluene at 70 °C for 12 h).

The alternative hydrolysis−displacement−hydrogenolysis sequence via intermediates **34** and **33** is not competitive. The hydrolysis to the 2,6-dichloropyridine-3-carboxamide **34** is very slow using 5 to 6 equiv of sulfuric acid in toluene at 70 °C. We produced amide **34** (75% yield) using neat sulfuric acid at 100 °C. The displacement reaction with morpholine (2.1 equiv) in methanol at 25 °C is also slower than the displacement reaction of the 3-cyano-2,6-dichloropyridine **29a**. Reaction of **34** with excess morpholine (10 equiv) in methanol at reflux does result in complete conversion but produces a mixture of regioisomers *favoring the wrong isomer*.

Conclusion

One of the most difficult challenges we face in pharmaceutical process research and development is to meet all the short-term clinical supply demands while still pursuing process improvements for subsequent campaigns at larger scales. Rapidly approaching clinical supply deadlines for delivery of 1−10 kg often drive the development of the Discovery Chemistry route. Subsequent supply deadlines 1−2 years out for delivery of tens to hundreds of kilograms drive the development of a scaleable and robust Process Chemistry route. Supply planning for 5−10 years out is driven by still other priorities: Are the starting materials readily available in bulk from several suppliers? What will be the environmental impact of the process reagents, solvents, and aqueous waste streams? In this report, we described our efforts to address some long-term supply priorities for the nicotinamide precursors of several Roche NK-1 receptor antagonists.

Reaction of a Shestopalov salt **28** with phosphorus oxychloride is the key step in a new synthesis of the nicotinamide precursors by pyridine ring construction. The 3-cyano-2,6-dichloropyridines **29** produced are efficiently converted to the nicotinamide precursors **19** by regioselective displacement of one chlorine by an amine, hydrogenolysis of the remaining chlorine, and nitrile hydrolysis. While our objective was process development for antagonists **2**−**4**, the versatile ring construction strategy we developed can provide other nicotinamides with substitution patterns not accessible when the 4-aryl substituent is derived from an arylboronic acid or arylmagnesium halide.

Experimental Section

o-Tolualdehyde **24a** is commercially available. Aldehyde **24c** has been produced from 3-fluorotoluene by direct formylation[11] and from 2-bromo-5-fluorotoluene by metal−halogen exchange and aryllithium addition to DMF.[12]

4-Fluoro-2-methylbenzaldehyde (**24c**). 2-Bromo-5-fluorotoluene (37.5 mL, 56.1 g, 297 mmol) is dissolved in 500 mL of dry THF, and the solution is cooled to −78 °C under dry N_2. Butyllithium in hexanes (2.5 M) (119 mL, 297 mmol, 1.0 equiv) is added at −75 to −78 °C over 35 min, and the suspension is stirred at −78 °C for 20 min. Dry *N*,*N*-dimethylformamide (27.6 mL, 26.0 g, 356 mmol, 1.2 equiv) is added over 26 min at −75 to −78 °C. The resulting solution is stirred at −78 °C for 60 min and then allowed to warm to 15 °C over 2 h.

Ammonium chloride (100 g of 15.9% aqueous) is added over 5 min at 15−20 °C. The solution is concentrated by fractional distillation (10” 24/40 Vigreux column)(597 mL collected at 50−61 °C). The distillation pot layers are separated. The aqueous layer is extracted with 25 mL of MTBE 3 times. The combined organic layers are washed with 50 mL of brine and then dried ($MgSO_4$), filtered, and fractionally distilled (10” 14/20 Vigreux column) (bp 54−62 °C) to leave 59.3 g of yellow oil. The oil is fractionally distilled (10” 14/20 Vigreux column) at 60−62 °C (bath 80−

(11) Anderson, J. D. O.; Scrivens, W. A. US6300525 (10/9/01).
(12) Robl, J. A. EP044533 (9/4/91).

100 °C) and 1.6−2.0 mmHg to afford 28.041 g (68.4%) of **24c** as a colorless oil.

Methyl 2-Cyano-3-(2-methylphenyl)-2-propenoate 27a. A 100 mL one-necked round-bottom flask (with a magnetic stirbar and dry N_2 adapter) is charged with 11.6 mL (12.0 g, 100 mmol) of *o*-tolualdehyde **24a**, 8.8 mL (9.9 g, 100 mmol) of methyl cyanoacetate **26**, and 50 mL of isopropanol. Morpholine (0.50 mL, 0.55 g, 6.3 mmol, 6.3 mol %) is added, and the mixture was stirred at 20−33 °C for 60 min. The suspension is diluted with 25 mL of isopropanol. The precipitate is suction filtered, washed with 10 mL of isopropanol, and dried in vacuo (17 h at 25 °C and 1 mmHg) to afford 17.37 g (86.3%) of **27a** as a colorless solid.

1-(2-Amino-2-oxoethyl)pyridinium Chloride 23 (Method A). A 3000 mL four-necked round-bottom flask (with a reflux condenser/dry N_2 adapter, perforated Teflon paddle stirrer with a glass shaft, septum with a Teflon-coated thermocouple, and Teflon stopper) is charged with 190.76 g (2.04 mol) of 2-chloroacetamide, 2.0 L of *n*-butyl acetate, and 192 mL (187.8 g, 2.37 mol) of dry pyridine. The resulting suspension is refluxed (bath 137 °C, pot 119 °C) at 150 rpm for 24 h. The suspension is cooled to 25 °C. The precipitate is suction filtered, washed with 500 mL of *n*-butyl acetate, washed with 500 mL of hexanes twice, and then dried in vacuo (17 h at 25 °C and 15 in Hg) to afford 324.05 g (92.0%) of **23** as a beige solid.

1-(2-Amino-2-oxoethyl)pyridinium Chloride 23 (Method B). A 2000 mL pressure bottle with a paddle stirrer is charged with 93.51 g (1.00 mol) of 2-chloroacetamide, 300 mL of isopropanol, and 82.4 mL (80.7 g, 1.02 mol) of pyridine. The resulting suspension is heated at 110 °C and 150 rpm for 18 h. The suspension is cooled to 25 °C, and the bottle is vented.

5′-Cyano-1′,2′,3′,4′-tetrahydro-6′-hydroxy-4′-(2-methylphenyl)-2′-oxo-1,3′-bipyridinium, Inner Salt 28a (Method A). A 100 mL two-necked round-bottom flask (with septum and reflux condenser with dry N_2 adapter) is charged with 1.726 g (10.0 mmol) of the pyridinium salt **23**, 2.012 g (10.0 mmol) of propenoate **27a**, and 20 mL of methanol. Triethylamine (1.55 mL, 1.11 g, 11.0 mmol, 1.10 equiv) is added. The mixture is refluxed for 1 min and then allowed to cool to 25 °C and stir for 66 h. The precipitate is suction filtered, washed with 10 mL of methanol, 10 mL of toluene, and 10 mL of hexanes, and then air-dried for 1 h to afford 2.734 g (89.5%) of **28a** as a bright yellow solid.

5′-Cyano-1′,2′,3′,4′-tetrahydro-6′-hydroxy-4′-(2-methylphenyl)-2′-oxo-1,3′-bipyridinium, inner salt 28a (Method B). A 3000 mL four-necked flask (with a 250 mL pressure equilibrating addition funnel/dry N_2 adapter, septum with a Teflon-coated thermocouple, Teflon paddle stirrer/glass shaft, and stopper) is charged with 115.6 mL (120.15 g, 1.0 mol) of *o*-tolualdehyde **24a**, 87.9 mL (99.09 g, 1.0 mol) of methyl cyanoacetate **26**, 172.61 g (1.0 mol) of the pyridinium salt **23**, and 2.0 L of methanol. The addition funnel is charged with 153.3 mL (111.3 g, 1.1 mol) of triethylamine. The amine is added over 20 min at 170 rpm and 20−25 °C (intermittent ice−water bath). The resulting mixture is stirred at 25−30 °C for 24 h. The precipitate is suction filtered, washed with 500 mL of 25 °C methanol, 500 mL of 25 °C toluene, and 500 mL of 25 °C hexanes, and then air-dried 6 h at 25 °C to afford 285.10 g (93.4%) of **28a** as a bright yellow solid.

5′-Cyano-1′,2′,3′,4′-tetrahydro-6′-hydroxy-4′-(2-methylphenyl)-2′-oxo-1,3′-bipyridinium, Inner Salt 28a (Method C). A 3000 mL four-necked flask (with a 250 mL pressure equilibrating addition funnel/dry N_2 adapter, septum with a Teflon-coated thermocouple, Teflon paddle stirrer/glass shaft, and stopper) is charged with 115.6 mL (120.15 g, 1.0 mol) of *o*-tolualdehyde **24a**, 87.9 mL (99.09 g, 1.0 mol) of methyl cyanoacetate **26**, the suspension of 172.61 g (1.0 mol) of pyridinium salt **23** in 300 mL of isopropanol (from pyridinium salt Method B), and 1.7 L of methanol. The addition funnel is charged with 153.3 mL (111.3 g, 1.1 mol) of triethylamine. The amine is added over 24 min at 170 rpm and 20−25 °C (intermittent ice−water bath). The resulting mixture is stirred at 25−30 °C for 24 h.

The precipitate is suction filtered, washed with 500 mL of 25 °C methanol, 500 mL of 25 °C toluene, and 500 mL of 25 °C hexanes, and then air-dried 18 h at 25 °C to afford 284.69 g (93.2%) of **28a** as a bright yellow solid, mp 232−233 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.82 (s, 1H), 8.98 (d, 2H), 8.50 (t, 1H), 8.04 (t, 2H), 7.45 (br, 1H), 7.12 (t, J = 7.0 Hz, 1H), 6.99 (t, J = 7.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 13 Hz, 1H), 6.13 (d, J = 13 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.4, 163.8, 147.3, 145.8, 137.2, 137.0, 128.3, 128.1, 127.5, 126.9, 126.0, 75.3, 53.6, 19.8; IR (KBr) 3625−3300, 3162, 3135, 3045, 2956, 2929, 2168, 1701, 1634, 1600 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_2O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.66; H, 5.10; N, 13.80.

5′-Cyano-1′,2′,3′,4′-tetrahydro-6′-hydroxy-4′-(2-methyl-4-fluorophenyl)-2′-oxo-1,3′-bipyridinium, Inner Salt 28c. A 1000 mL four-necked flask (with a 50 mL pressure equilibrating addition funnel/dry N_2 adapter, septum with a Teflon-coated thermocouple, Teflon paddle stirrer/glass shaft, and stopper) is charged with 28.01 g (203 mmol) of 4-fluoro-2-methylbenzaldehyde **24c**, 17.8 mL (20.1 g, 203 mmol) of methyl cyanoacetate **26**, 35.00 g (203 mmol) of pyridinium salt **23**, and 400 mL of methanol. The addition funnel is charged with 31.1 mL (22.6 g, 223 mmol) of triethylamine. The amine is added over 11 min at 170 rpm and 20−25 °C (intermittent ice−water bath). The resulting mixture is stirred at 25−30 °C for 24 h.

The precipitate is suction filtered using a 600 mL coarse sintered glass funnel. The precipitate is washed with 100 mL of 25 °C methanol, 100 mL of 25 °C toluene, and 100 mL of 25 °C hexanes, and then air-dried 3.5 h at 25 °C to afford 60.69 g (92.6%) of **28c** as a bright yellow solid, mp 236−237 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.84 (s, 1H), 8.98 (d, J = 6.0 Hz, 2H), 8.52 (t, J = 7.5 Hz, 1H), 8.07 (dd, 2H), 7.50 (br, 1H), 6.97 (br t, 7.0 Hz, 1H), 6.80 (dd, J = 1.5 Hz, J = 10 Hz, 1H), 6.26 (d, J = 13 Hz, 1H), 4.81 (d, J = 13 Hz, 1H), 2.08 (br, 3H); ^{13}C NMR (DMSO-d_6) δ 166.3, 163.7, 161.2 (d, J = 241.9 Hz), 147.4, 145.8, 139.9, 133.4, 130.3, 128.5, 126.0, 117.4, 113.7, 75.2, 53.6, 31.4, 19.7; IR (KBr) 3170, 3130, 3045, 2168, 1703, 1633, 1602, 1577 cm^{-1}. Elem. Anal. Calcd for $C_{18}H_{14}FN_3O_2$: C, 66.87; H, 4.36; F,

5.88; N, 13.00. Found: C, 66.31; H, 4.29; F, 6.05; N, 12.72.

3-Cyano-2,6-dichloro-4-(2-methylphenyl)pyridine 29a. A mixture of 40.00 g (131.0 mmol) of the pyridinium inner salt **28a** and 50.0 mL (82.3 g, 536 mmol) of phosphorus oxychloride was heated in a 300 mL Parr bottle at 135 °C for 10 h.

The syrup was cooled to 25 °C, and the bottle was vented. Methylene chloride (75 mL) was added. The solution was transferred onto 350 g of ice. Methylene chloride (25 mL) was used to complete the transfer. During the subsequent stir time (<1 h), the ice melted, the mixture refluxed briefly, and the temperature began to drop. The layers were separated. The aqueous layer was extracted with 25 mL of methylene chloride twice and then with 50 mL of toluene twice. The combined extracts were dried (5.0 g Na_2SO_4) and then filtered through 15 g of Filtrol on a 60 mL coarse sintered glass funnel. The flask and cake were washed with 50 mL of fresh toluene. The combined mother liquors were concentrated in vacuo (rotary evaporator at 35 °C and 100−20 mmHg and then vacuum pump at 25 °C and 1 mmHg for 3 h) to afford 28.70 g (83.3%) of **29a** as a near colorless solid (LC assay 100.7 wt %).

An analytical sample was prepared by recrystallization from isopropanol, mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 7.43 (dt, J = 1.5 Hz, J = 7 Hz, 1H), 7.37−7.31 (m, 2H), 7.33 (s, 1H), 7.18 (dd, J = 1.5 Hz, J = 8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.1, 153.9, 153.3, 135.3, 134.1, 131.3, 130.7, 128.8, 126.7, 124.5, 113.7, 110.3, 20.0; IR (KBr) 3087, 2227, 1603, 1569, 1520, 1340 cm^{-1}. Anal. Calcd for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65; Cl, 26.95. Found: C, 59.00; H, 3.05; N, 10.64; Cl, 27.76.

3-Cyano-2,6-dichloro-4-(4-fluoro-2-methylphenyl)pyridine 29c. A mixture of 55.00 g (170.1 mmol) of the pyridinium inner salt **28c** and 65 mL (106.9 g, 697 mmol, 4.1 equiv) of phosphorus oxychloride was heated in a 300 mL Parr bottle at 135 °C for 12 h.

The syrup was cooled to 25 °C, and the bottle was vented. Methylene chloride (200 mL) was added. The solution was transferred onto 450 g of ice, and stirring continued until the ice melted. Methylene chloride (25 mL) was used to complete the transfer. The layers were separated. The aqueous layer was extracted with 25 mL of methylene chloride twice. The aqueous layer was extracted with 125 mL of toluene twice. The combined extracts were filtered through 15 g of Filtrol on a 60 mL coarse sintered glass funnel. The flask and cake were washed with 100 mL of fresh toluene. The combined mother liquors were concentrated in vacuo (rotary evaporator at 35 °C and 200−20 mmHg and then vacuum pump at 25 °C and 1 mmHg for 17 h) to afford 39.70 g (83.0%) of **29c** as a near colorless solid.

An analytical sample was prepared by recrystallization from isopropanol, mp 161.5−162.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1H), 7.18 (dd, J = 5.5 Hz, J = 8.5 Hz, 1H), 7.08 (dd, J = 2.5 Hz, J = 9.5 Hz, 1H), 7.04 (dt, J = 2.5 Hz, J = 8−8.5 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.9 (d, J = 250 Hz), 158.0, 154.0, 153.4, 138.4 (d, J = 8.4 Hz), 130.8 (d, J = 8.8 Hz), 130.1 (d, J = 3.6 Hz), 124.6, 118.2 (d, J = 21.6 Hz), 114.0 (d, J = 21.6 Hz), 113.6, 110.4, 20.2 (d, J = 1.6 Hz); IR (KBr) 3100, 2920, 2230, 1590, 1578, 1566, 1521, 1496 cm^{-1}. Anal. Calcd for $C_{13}H_7Cl_2FN_2$: C, 55.54; H, 2.51; F, 6.76; N, 9.97. Found: C, 55.32; H, 2.55; F, 7.02; N, 9.78.

2-Chloro-3-cyano-4-(2-methylphenyl)-6-(4-morpholinyl)-pyridine 30a. The crude dichloride **29a** (194.8 g, 0.740 mol) and 1100 mL of methanol were added to a 2000 mL three-necked flask (with a 125 mL pressure-equilibrating addition funnel/dry N_2 adapter, septum with a Teflon-coated thermocouple, and Teflon paddle stirrer/glass shaft). The suspension was cooled to 18 °C (at 200 rpm) using an ice−water bath. Morpholine (132.3 mL, 132.2 g, 1.52 mol) was charged to the addition funnel and then added dropwise to the suspension at 18−22 °C over 45 min. The resulting suspension was stirred at 20−25 °C for 18 h.

The precipitate was suction filtered, washed with 150 mL of 25 °C methanol and then with 1000 mL of water, air-dried for 90 min at 25 °C, and then dried in vacuo (vacuum oven at 53−57 °C and ~15 in Hg for 67 h) to afford 182.04 g (78.4%) of **30a** as a colorless solid.

An analytical sample was prepared by recrystallization from isopropanol, mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (dt, J = 1.5 Hz, J = 7.5 Hz, 1H), 7.31−7.28 (m, 1H), 7.26 (dd, J = 1.5 Hz, J = 7.5 Hz, 1H), 6.37 (s, 1H), 3.81−3.79 (m, 4H), 3.68−3.66 (m, 4H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 156.9, 153.0, 136.4, 135.1, 130.6, 129.5, 128.4, 126.1, 115.8, 104.7, 97.8, 66.4, 44.8, 19.7; IR (KBr) 2966−2843, 2216, 1597, 1490 cm^{-1}. Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39; Cl, 11.30. Found: C, 65.38; H, 5.28; N, 13.36; Cl, 11.65.

2-Chloro-3-cyano-4-(2-methylphenyl)-6-(4-methylpiperazinyl)pyridine 30b. Crude dichloride **29a** (78.00 g, 0.296 mol) and 330 mL of methanol were added to a 1000 mL three-necked flask (with a 125 mL pressure-equilibrating addition funnel/dry N_2 adapter, septum with a Teflon-coated thermocouple, and Teflon paddle stirrer/glass shaft), and the suspension was cooled to 18 °C (at 150 rpm) using an ice−water bath. 1-Methylpiperazine (67.3 mL, 60.78 g, 0.607 mol) was charged to the addition funnel and then added dropwise to the suspension at 18−22 °C over 15 min. Seed crystals of **30b** were added after 2 h, and the suspension was stirred at 20−25 °C for an additional 18 h.

Water (165 mL) was added dropwise over 1 h, and the resulting suspension was stirred at 25 °C for 3 h. The precipitate was suction filtered, washed with 90 mL of 25 °C 2:1 methanol−H_2O and then with 100 mL of water, air-dried for 78 min at 25 °C, and then dried in vacuo (vacuum oven at 53−57 °C and ~15 in Hg for 69 h) to afford 74.19 g (76.6%) of **30b** as a beige solid.

An analytical sample was prepared by recrystallization from isopropanol, mp 116−123 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (dt, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.3−7.25 (m, 2H), 7.14 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 6.37 (s, 1H), 3.71 (br m, 4H), 2.49 (br t, 4H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.4, 156.9, 153.2, 136.8, 135.4, 130.9, 129.6, 128.7, 126.3, 116.2, 105.0, 97.3, 54.7, 46.3, 44.8, 20.0; IR (KBr) 2966, 2936, 2846, 2797, 2215, 1592, 1498 cm^{-1}. Anal.

Calcd for $C_{18}H_{19}ClN_4$: C, 66.15; H, 5.86; N, 17.14; Cl, 10.85. Found: C, 66.04; H, 6.04; N, 17.11; Cl, 10.94.

2-Chloro-3-cyano-4-(4-fluoro-2-methylphenyl)-6-(thiomorpholino)pyridine 30d. Crude dichloride **29c** (32.44 g, 115.4 mmol) and 300 mL of methanol were added to a 500 mL three-necked flask (with a 25 mL pressure-equilibrating addition funnel/dry N_2 adapter, septum with a Teflon-coated thermocouple, and Teflon paddle stirrer/glass shaft). Thiomorpholine (23.0 mL, 25.0 g, 242 mmol, 2.10 equiv) was added dropwise over 22 min, and the resulting suspension was stirred at 20−25 °C for 18 h. The precipitate was suction filtered, washed with 30 mL of methanol, and then dried in vacuo (vacuum pump at 25 °C and 1 mmHg for 24 h) to afford 35.47 g (88.4%) of **30d** as a beige solid.

An analytical sample was prepared by recrystallization from ethanol, mp 195.3−197.3 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (dd, J = 5.5 Hz, J = 8.5 Hz, 1H), 7.01 (dd, J = 3.0 Hz, J = 10 Hz, 1H), 6.97 (dt, J = 3.0 Hz, J = 8.5 Hz, 1H), 6.33 (s, 1H), 4.04 (br, 4H), 2.70 (br t, J = 5.0 Hz, 4H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.3 (d, J = 247 Hz), 157.7, 156.2, 153.4, 138.3 (d, J = 8.5 Hz), 132.7 (d, J = 3.1 Hz), 130.5 (d, J = 8.5 Hz), 117.7 (d, J = 21.3 Hz), 116.0, 113.4 (d, J = 21.6 Hz), 105.3, 97.5, 48.1, 27.0, 20.2 (d, J = 1.6 Hz); IR (KBr) 2219, 1594, 1581, 1502, 1489, 1448, 1432 cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClFN_3S$: C, 58.70; H, 4.35; N, 12.08. Found: C, 58.76; H, 4.43; N, 12.04.

2-Chloro-3-cyano-4-(4-fluoro-2-methylphenyl)-6-(1,1-dioxo-thiomorpholin-4-yl)pyridine 30c. Oxone (56.18 g, 91.4 mmol) was added to a solution of 26.54 g (76.3 mmol) of the sulfide **30d** in 200 mL of NMP in a 1000 mL three-necked flask (with a Teflon paddle stirrer, septum with a Teflon-coated thermocouple, and dry N_2 adapter). The suspension was stirred at 25 °C for 20 h (cool H_2O bath). Water (800 mL) was added, and the suspension was stirred at 25 °C for 30 min. The precipitate was suction filtered using a 350 mL coarse sintered glass funnel, slurry-washed several times with H_2O on the funnel, and air-dried 24 h at 25 °C to afford 29.30 g (101.1%) of **30c** as a colorless solid.

An analytical sample was prepared by recrystallization from acetonitrile, mp 264−267 °C ^{1}H NMR (DMSO-d_6) δ 7.30 (dd, J = 5.5−6 Hz, J = 8.8 Hz, 1 H), 7.26 (dd, J = 2.5 Hz, J = 10 Hz, 1H), 7.17 (dd, J = 2.5 Hz, J = 8.5−9.0 Hz, 1H), 7.07 (s, 1H), 4.15 (m, 4H), 3.22 (br, 4H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.1 (d, J = 244 Hz), 158.2, 155.8, 152.1, 139.1 (d, J = 8.4 Hz), 133.3 (d, J = 2.9 Hz), 131.6 (d, J = 8.8 Hz), 117.6 (d, J = 21.3 Hz), 116.4, 113.6 (d, J = 21.3 Hz), 107.9, 97.5, 51.2, 44.1, 20.1; IR (KBr) 2930, 2223, 1588, 1522, 1500, 1494, 1474, 1429, 1125 cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClFN_3O_2S$: C, 53.76; H, 3.98; N, 11.06. Found: C, 53.76; H, 3.94; N, 11.06.

5-Cyano-4-(2-methylphenyl)-2-(4-morpholinyl)pyridine 31a. A mixture of 20.00 g (63.74 mmol) of the chloropyridine **30a**, 9.77 mL (7.10 g, 70.11 mmol, 1.1 equiv) of triethylamine, 33.9 mg of $Pd(OH)_2$ or 249 mg (0.242 mmol, 0.379 mol %) of 20% palladium hydroxide on carbon [Pearlman's catalyst, 32.2% LOD], and 80 mL of methanol was stirred in a 300 mL Parr bottle at 25 °C and 48.0−41.3 psi hydrogen for 21 h.

The pressure was vented, and the mixture diluted with 40 mL of H_2O. The suspension was transferred to a round-bottom flask using 40 mL of methanol. Methanol was removed on a rotary evaporator at 35 °C and 60−30 mmHg (collected 107.5 mL). The resulting suspension was diluted with 80 mL of toluene and then suction filtered through 2.0 g of celllulose powder on a coarse sintered glass funnel. The catalyst−celite cake was washed with 10 mL of fresh toluene 3 times. A solution of 2.80 g (70.1 mmol) of sodium hydroxide in 5 g of H_2O was added to the combined mother liquors. The layers were separated, and the aqueous (pH = 13−14) layer was extracted with 20 mL of toluene 3 times. The combined organic layers were concentrated in vacuo (rotary evaporator at 35 °C and 30 mmHg, trituration with hexanes, and then vacuum pump at 25 °C and ∼1 mmHg for 22 h) to afford 17.95 g of **31a** as a colorless solid (LC assay 91.8−93.9 wt %) (yield 92.6−94.7%).

An analytical sample was prepared by radial chromatography on silica gel followed by recrystallization from isopropanol, mp 128.5−129.7 °C; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.35 (dt, J = 1.5 Hz, J = 7.5 Hz, 1H), 7.31−7.29 (m, 1H), 7.28−7.26 (m, 1H), 7.16 (dd, J = 1.5 Hz, J = 7.5 Hz, 1H), 6.48, (d, 1H), 3.82−3.80 (m, 4H), 3.68−3.66 (m, 4H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 154.0, 153.1, 136.8, 135.2, 130.6, 129.2, 128.7, 126.0, 117.9, 106.3, 98.4, 66.5, 44.8, 19.7; IR (KBr) 2967, 2892, 2853, 2210, 1593, 1503, 1444 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.40; H, 6.18; N, 15.03.

5-Cyano-4-(2-methylphenyl)-2-(4-methylpiperazinyl)-pyridine 31b. A mixture of 20.00 g (61.19 mmol) of the chloropyridine **30b**, 9.38 mL (6.81 g, 67.3 mmol, 1.1 equiv) of triethylamine, 25.8 mg of $Pd(OH)_2$ or 190 mg (0.184 mmol, 0.300 mol %) of 20% palladium hydroxide on carbon [Pearlman's catalyst, 32.2% LOD], and 80 mL of methanol was stirred in a 300 mL Parr bottle at 25 °C and 48.3−43.0 psi hydrogen for 10 h.

The pressure was vented, and the mixture was diluted with 40 mL of H_2O. The suspension was transferred to a round-bottom flask using 40 mL of methanol. Volatiles were removed on a rotary evaporator at 35 °C and 60−30 mmHg. The resulting suspension was diluted with 80 mL of toluene and then suction filtered through 2.0 g of cellulose powder on a coarse sintered glass funnel. The catalyst−celite cake was washed with 10 mL of fresh toluene 3 times. A solution of 2.80 g (70.1 mmol) of sodium hydroxide in 5 g of H_2O was added to the combined mother liquors. The layers were separated, and the aqueous (pH = 13−14) layer was extracted with 20 mL of toluene 3 times. The combined organic layers were concentrated in vacuo (rotary evaporator at 35 °C and 30 mmHg). The residual yellow syrup was taken up in 100 mL of toluene, washed with dilute HCl (20.5 mL, 20 mL of H_2O with 0.5 mL of 12 N HCl), washed with 20 mL of H_2O, and then concentrated in vacuo (rotary evaporator at 35 °C and 30 mmHg, trituration with hexanes, and then vacuum pump at 25 °C and ∼1 mmHg for 21 h) to afford 16.85 g (94.2%) of **31b** as a near-colorless solid.

An analytical sample was prepared by recrystallization from isopropanol, mp 109.5−110.4 °C; ^{1}H NMR ($CDCl_3$)

δ 8.46 (s, 1H), 7.34 (t, J = 7 Hz, 1H), 7.30 (d, J = 7 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.16 (dd, J = 7.5 Hz, 1H), 6.49 (s, 1H), 3.72 (br t, 4H), 2.50 (t, J = 5 Hz, 4H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.7, 154.0, 153.4, 137.2, 135.5, 130.8, 129.3, 128.9, 126.2, 118.3, 106.6, 98.0, 54.9, 46.4, 44.7, 20.0; IR (KBr) 3019, 2936, 2884, 2848, 2793, 2210, 1607, 1590, 1504 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_4$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.04; H, 7.03; N, 18.98.

5-Cyano-4-(4-fluoro-2-methylphenyl)-2-(1,1-dioxo-thiomorpholin-4-yl)pyridine 31c. A 300 mL Parr bottle was charged with 19.86 g (52.29 mmol) of the crude chloropyridine **30c**, 10.9 mL (7.94 g, 78.4 mmol, 1.50 equiv) of triethylamine, 220 mg of $Pd(OH)_2$ or 1.62 g (1.57 mmol, 3.0 mol %) of 20% palladium hydroxide on carbon [Pearlman's catalyst, 32.2% LOD], and 100 mL of dry DMF. The suspension was stirred at 25 °C and 48.9−43.2 psi hydrogen for 25.5 h.

The pressure was vented. The suspension was suction filtered through 5.0 g of cellulose on a coarse sintered glass funnel. The catalyst−cellulose cake was washed with 10 mL of fresh DMF. Water (400 mL) was added to the mother liquors, and the resulting suspension was stirred at 25 °C for 30 min. The precipitate was suction filtered, washed several times with H_2O, and air-dried for 3 h at 25 °C to afford 17.52 g (97.0%) of **31c** as a slightly gray solid (97% conversion).

A 300 mL Parr bottle was charged with 17.31 g of the crude **31c**, 7.3 mL (5.30 g, 52.4 mmol) of triethylamine, 148 mg of $Pd(OH)_2$ or 1.09 g (1.05 mmol) of 20% palladium hydroxide on carbon [Pearlman's catalyst, 32.2% LOD], and 100 mL of dry DMF. The suspension was stirred at 25 °C and 42.5−28.2 psi hydrogen for 23 h.

The pressure was vented. The suspension was suction filtered through 5.0 g of cellulose on a coarse sintered glass funnel. The catalyst−cellulose cake was washed with 10 mL of fresh DMF. Water (400 mL) was added to the mother liquors, and the resulting suspension was stirred at 25 °C for 30 min. The precipitate was suction filtered, washed several times with H_2O, and air-dried 5 h at 25 °C to afford 17.04 g (95.5%) of **31c** as a colorless solid (100% conversion).

An analytical sample was prepared by recrystallization from acetonitrile, mp 219.5−220.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 1 Hz, 1H), 7.14 (dd, J = 5.5 Hz, J = 8.5 Hz, 1H), 7.04 (dd, J = 2.5 Hz, J = 9.5 Hz, 1H), 7.00 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H), 6.61 (d, J = 1 Hz, 1H), 4.27 (br t, 4H), 3.10 (br t, 4H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.4 (d, J = 248 Hz), 157.9, 154.4, 153.6, 138.2 (d, J = 8.0 Hz), 132.5 (d, J = 3.3 Hz), 130.7 (d, J = 8.8 Hz), 117.8 (d, J = 21.6 Hz), 117.2, 113.5 (d, J = 21.6 Hz), 107.2, 100.6, 51.6, 43.8, 20.2; IR (KBr) 2930, 2217, 1599, 1531, 1494, 1432, 1123, 1117 cm^{-1}. Anal. Calcd for $C_{17}H_{16}FN_3O_2S$: C, 59.12; H, 4.67; N, 12.17. Found: C, 59.19; H, 4.69; N, 12.17.

4-(2-Methylphenyl)-6-(4-morpholinyl)-3-pyridinecarboxamide 19a (Method A). A suspension of 17.71 g of the crude nitrile **31a** (LC assay 91.8−93.9 wt %), 18 mL of toluene, and 17.0 mL (33.1 g, 319 mmol) of concentrated sulfuric acid was heated at 70 °C for 12 h. The suspension was cooled and then quenched by addition of 100 mL of cold H_2O. Ethyl acetate (100 mL) was added followed by a solution of 25.5 g (638 mmol) of sodium hydroxide in 50 g of H_2O at 25−30 °C. The layers were separated. The aqueous layer was extracted 3 times with 50 mL of ethyl acetate. The combined organic layers were concentrated in vacuo (rotary evaporator at 35 °C and 70−50 mmHg, trituration with 25 °C hexanes, and then vacuum pump at 25 °C and 1 mmHg for 17 h) to afford 19.14 g of **19a** as a colorless solid (LC assay 87.7 wt %)(yield 94.9−97%).

An analytical sample was prepared by filtration through a plug of silica gel and recrystallization from ethyl acetate, mp 144−145.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1H), 7.36 (dt, J = 1.5 Hz, J = 7.5 Hz, 1H), 7.32−7.29 (m, 2H), 7.21−7.20 (m, 1H), 6.30 (s, 1H), 5.6 (br, 1H), 5.1 (br, 1H), 3.82−3.80 (m, 4H), 3.64−3.62 (m, 4H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.0, 160.1, 151.8, 149.5, 139.0, 135.8, 130.7, 129.0, 128.2, 126.5, 117.6, 106.2, 66.6, 45.0, 19.8; IR (KBr) 3462, 3300−3000, 2959, 2854, 1660, 1584, 1491, 1391 cm^{-1}. Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.78; H, 6.48; N, 14.11.

4-(2-Methylphenyl)-6-(4-morpholinyl)-3-pyridinecarboxamide 19a (Method B). A mixture of 5.00 g (15.1 mmol) of the 2-chloropyridine-3-carboxamide **33**, 2.31 mL (1.68 g, 16.5 mmol, 1.1 equiv) of triethylamine, 6.4 mg of $Pd(OH)_2$ or 47 mg (0.0453 mmol, 0.30 mol %) of 20% palladium hydroxide on carbon [Pearlman's catalyst, 32.2% LOD], and 50 mL of methanol was stirred in a 300 mL Parr bottle at 25 °C and 40.2−31.2 psi hydrogen for 21 h.

The pressure was vented. The suspension was then suction filtered through 2.0 g of cellulose powder on a coarse sintered glass funnel. The catalyst−celite cake was washed with 10 mL of methanol twice. Methanol was removed on a rotary evaporator at 35 °C and 60 mmHg. The residue was taken up in 25 mL of toluene and 10 mL of H_2O. A solution of 660 mg (16.5 mmol) of sodium hydroxide in 2 g of H_2O was added. The layers were separated, and the aqueous layer was extracted with 10 mL of toluene 3 times. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo (rotary evaporator at 35 °C and 30 mmHg, trituration with hexanes, and then vacuum pump at 25 °C and ~1 mmHg for 15 h) to afford 4.24 g (94.6%) of **19a** as a colorless solid.

4-(2-Methylphenyl)-6-(4-methylpiperazinyl)-3-pyridinecarboxamide 19b. A suspension of the crude nitrile **31b** (16.85 g, 57.6 mmol), 18 mL of toluene, and 27 mL (49.7 g, 507 mmol) of concentrated sulfuric acid was heated at 70 °C for 12 h. The suspension was cooled and then quenched by addition of 200 mL of cold H_2O. Ethyl acetate was added followed by a solution of 45.6 g (1.14 mol) of sodium hydroxide in 200 g of H_2O at 20−25 °C. Water (200 mL) was added to dissolve the precipitated salt. The layers were separated. The aqueous layer was extracted with 100 mL of ethyl acetate several times. The combined organic layers were concentrated in vacuo (rotary evaporator at 35 °C and 75 mmHg, trituration with 25 °C hexanes, and then vacuum pump at 25 °C and 1 mmHg for 17 h) to afford 17.55 g

(98.1%) of **19b** as a colorless solid.

An analytical sample was prepared by recrystallization from isopropanol and final recrystallization from toluene−hexanes, mp 127.5−128.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1H), 7.35 (m, J = 1.5 Hz, J = 7−8 Hz, 1H), 7.31−7.28 (m, 2H), 7.21 (m, 1H), 6.31 (s, 1H), 3.68 (br t, J = 5 Hz, 4H), 2.51 (t, J = 5 Hz, 4H), 2.35 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 160.2, 152.1, 149.7, 139.4, 136.0, 130.9, 129.2, 128.4, 126.7, 117.3, 106.5, 55.0, 46.4, 44.8, 20.0; IR (KBr) 3459, 3324, 3273, 3168, 2967, 2935, 2849, 2795, 1665, 1581 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.76; H, 7.33; N, 17.92.

4-(4-Fluoro-2-methylphenyl)-6-(1,1-dioxo-thiomorpholin-4-yl)pyridine-3-carboxamide 19c. A mixture of 14.80 g (42.85 mmol) of nitrile **31c**, 15 mL of toluene, and 15 mL (27.6 g, 281 mmol) of concentrated sulfuric acid was heated in a 500 mL flask (with dry N_2 adapter and Teflon stirbar) at 70 °C for 12 h.

The suspension was cooled and quenched by the addition of 150 mL of cold H_2O. A solution of 22.8 g (570 mmol) of sodium hydroxide in 200 mL of H_2O was added dropwise at 25−30 °C over 15 min. The precipitate was suction filtered, washed with H_2O, and air-dried for 21 h at 25 °C to afford 15.68 g (100.7%) of **19c** as a colorless solid (2 wt % toluene remains).

An analytical sample was prepared by recrystallization from acetonitrile, m.p.235−236 °C; ^{1}H NMR (DMSO-d_6) δ 8.38 (s, 1H), 7.36 (br, 1H), 7.13 (dd, J = 6 Hz, J = 8.5 Hz, 1H), 7.09−7.07 (m, 2H), 7.02 (dt, J = 2.5 Hz, J = 8.5 Hz, 1H), 6.78 (s, 1H), 4.11 (br, 4H), 3.11 (br, 4H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.9, 160.3 (d, J = 241 Hz), 155.8, 148.2, 146.3, 136.7 (d, J = 8.0 Hz), 134.6 (d, J = 2.8 Hz), 129.1 (d, J = 8.4 Hz), 121.3, 114.8 (d, J = 20.8 Hz), 110.8 (d, J = 20.8 Hz), 107.2, 49.3, 42.1, 18.7; IR (KBr) 3446, 3324, 3147, 1663, 1608, 1575, 1496, 1399, 1372, 1121 cm^{-1}. Anal. Calcd for $C_{17}H_{18}FN_3O_3S$: C, 56.19; H, 4.99; N, 11.56. Found: C, 56.14; H, 4.99; N, 11.88.

2-Chloro-4-(2-methylphenyl)-6-(4-morpholinyl)-3-pyridinecarboxamide 33. A suspension of 16.80 g (53.5 mmol) of nitrile **30a**, 15 mL of toluene, and 14.3 mL (26.2 g, 268 mmol) of concentrated sulfuric acid was heated at 70 °C for 120 h. The suspension was cooled and then quenched by addition of 160 mL of cold H_2O. Isopropyl acetate (150 mL) was added followed by a solution of 24.46 g (612 mmol) of sodium hydroxide in 120 g of H_2O at 20−25 °C. The precipitate was suction filtered. The filtered precipitate was dried in vacuo (vacuum pump at 25 °C and 1 mmHg for 17 h) to afford 16.83 g (94.8%) of **33** as a colorless solid.

An analytical sample was prepared by recrystallization from toluene to afford shiny colorless needles, mp 217−219 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.19 (dd, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.32 (s, 1H), 5.72 (br, 1H), 5.43 (br, 1H), 3.79 (m, 4H), 3.55 (m, 4H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.9, 158.2, 152.4, 146.6, 138.0, 135.5, 130.6, 128.8, 128.5, 125.8, 120.8, 105.7, 66.7, 45.3, 20.3; IR (KBr) 3393, 3197, 2970, 2920, 2900, 2861, 1666, 1607, 1594, 1525 cm^{-1}. Elem. Anal. Calcd for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.65; H, 5.44; N, 12.56.

2,6-Dichloro-4-(2-methylphenyl)-3-pyridinecarboxamide 34. A mixture of 15.00 g (57.0 mmol) of the nitrile **29a** and 15 mL of concentrated sulfuric acid was heated at 100 °C for 3 h. The mixture was cooled and quenched by the addition of 150 mL of H_2O. The suspension was extracted with ethyl acetate 3 times. The combined organic layers were washed with 50 mL of H_2O twice, dried ($MgSO_4$), filtered, and concentrated in vacuo (rotary evaporator at 35 °C and 80 mmHg, hexanes trituration, and then vacuum pump at 25 °C and 1 mmHg for 17 h) to afford 11.99 g (74.8%) of **34** as a near-colorless solid.

An analytical sample was prepared by recrystallization from toluene, mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (dt, J = 1.5 Hz, J = 7.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.20 (s, 1H), 7.12 (dd, J = 1 Hz, J = 7.5 Hz, 1H), 5.76 (br, 1H), 5.53 (br, 1H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 153.4, 150.6, 147.4, 135.4, 135.3, 130.9, 129.7, 128.5, 126.1, 124.5, 95.0, 20.4; IR (KBr) 3391, 3303, 3167, 2360, 2350−2340, 1685, 1565, 1525 cm^{-1}. Elem. Anal. Calcd for $C_{13}H_{10}Cl_2N_2O$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.51; H, 3.57; N, 9.81.

Supporting Information Available

A detailed description of the HPLC method. This material is available free of charge via the Internet at http://pubs.acs.org.

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