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Development of an Efficient and Scalable Process of a Respiratory Syncytial Virus Inhibitor

David P. Provencal,* Kirsten D. Gesenberg, Hua Wang, Carlos Escobar, Henry Wong, Matthew A. Brown, Andrew J. Staab, and Yadagiri R. Pendri*

Process Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut 06492, U.S.A.

Abstract:

An improved process has been developed for compound 1, a respiratory syncytial virus (RSV) inhibitor. This improved process is convergent, safe, efficient, and useful to prepare compound 1 in kilogram quantities.

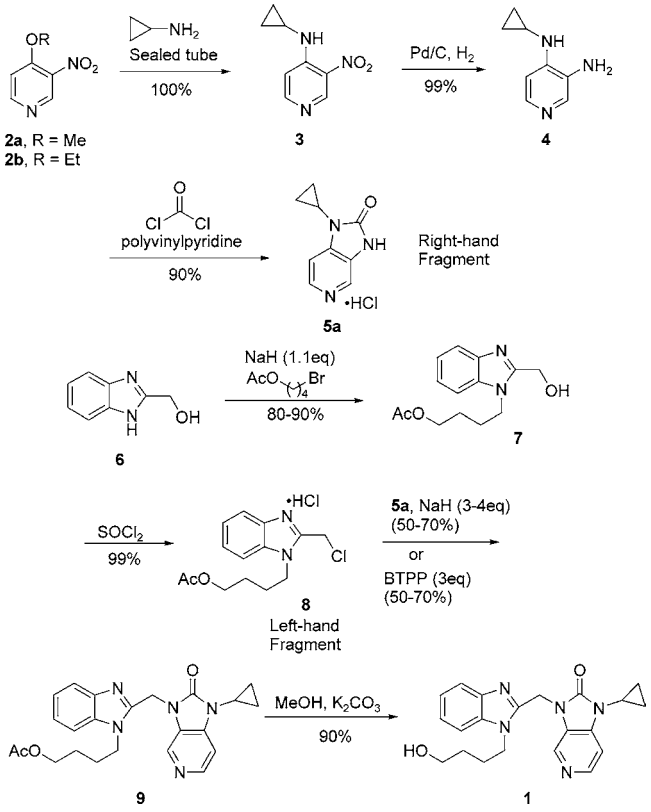
Introduction

Respiratory syncytial virus (RSV) has been shown to be the principal cause of lower respiratory tract infections in the elderly, infants, and the immunocompromised population.[1] The incidence of RSV infection in children younger than two years is high, and in a recent study RSV was identified as the most common viral cause of death in children under five years of age.[2] At present there is a great need for the development of small-molecule drugs to treat this disease. Current treatments for RSV infection utilize expensive protein-based biologicals such as Synagis, RespiGam, and one small-molecule nucleoside (Ribavirin). The discovery and antiviral activity of a new structural class of RSV inhibitors, the azabenzimidazolone derivative, **1**, has been described recently.[3] Preclinical investigations have demonstrated that compound **1** is a potent inhibitor of RSV in animal models[4] and has excellent bioavailability. This class of compounds appears to act by preventing the fusion of virus and host membranes. An investigation was undertaken to develop an efficient, scalable, and robust process to prepare kilogram quantities to support clinical studies.

Results and Discussion

Original Route. To prepare the relatively small amounts of material necessary for biological studies compound **1** was initially synthesized using the route shown (Scheme 1). While this route readily provided a sufficient quantity of **1** for initial preclinical evaluation, it soon became necessary to design a more practical route to generate kilogram quantities for the following reasons: (a) the S_NAr reaction involving cyclopropylamine and the expensive 4-methoxy-3-nitropyridine **2a** was carried out in a sealed tube at 100 °C; (b) the use of phosgene to prepare the azabenzimidazolone **5a** posed a serious safety concern, as does the use of sodium hydride during the synthesis of chloromethyl derivative **8** and in its subsequent reaction with **5a**; (c) an alternative to thionyl chloride was desirable as was a telescoped procedure to avoid the isolation and handling of **8** due to a positive Ames test for mutagenicity. Furthermore, we planned to reduce the cost of goods for **1** by eliminating chromatographic purification of intermediates **3**, **7**, and **9**, as well as the expense associated with the synthesis of **3** and the use of the phosphazene base BTPP.

Scheme 1



Synthesis of the Right-Hand Fragment 5a. An inexpensive alternative route to **3** was developed (Scheme 2). 4-Hydroxypyridine **10** was nitrated using potassium nitrate

* To whom correspondence should be addressed. Telephone: 203-677-7104. E-mail: yadagiri.pendri@bms.com.

(1) (a) Meanwell, N. A.; M. Krystal, M. *Drug Discovery Today* **2000**, *5*, 241. (b) Ottolini M. G.; Hemming, V. G. *Drugs* **1997**, *54*, 867. (c) Wyde, P. R. *Antiviral Res.* **1998**, *39*, 63. (d) Halstead, D. C.; Jenkins, S. G. *South. Med. J.* **1998**, *91*, 433.

(2) Thompson, W. W.; Shay, D. K.; Weintraub, E.; Brammer, L.; Cox, N.; Anderson, L. J.; Fukuda, K. *J. Am. Med. Assoc.* **2003**, *289*, 179.

(3) Cianci, C.; Yu, K.-L.; Combrink, K.; Sin, N.; Pearce, B.; Wang, A.; Civiello, R.; Voss, S.; Luo, G.; Kadow, K.; Genovesi, E.; Venables, B.; Gulgeze, H.; Trehan, A.; James, J.; Lamb, L.; Medina, I.; Roach, J.; Yang, Z.; Zadjura, L.; Colonno, R.; Clark J.; Meanwell, N.; Krystal. M. *Antimicrob. Agents Chemother*. **2004**, *48*, 413−422.

(4) Yu, K.-L.; Yi, Z.; Civiello, R.; Kadow, K.; Cianci, C.; Krystal, M.; Meanwell, N. *Bioorg. Med.Chem. Lett.* **2003**, *13*, 2141−2144.

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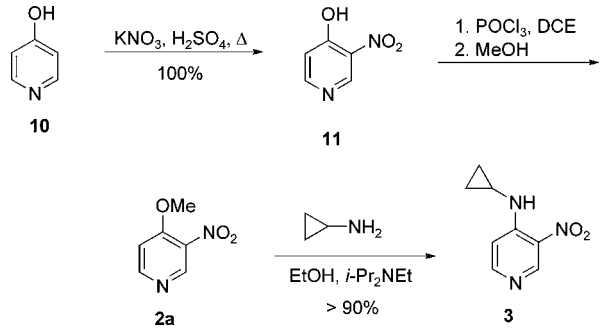
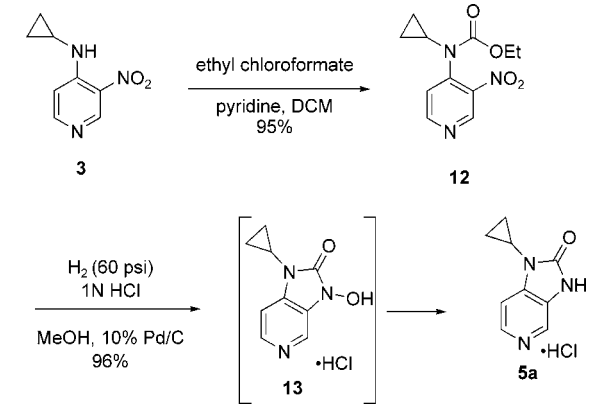
Scheme 2



Scheme 3



in sulfuric acid.[5] This reaction is highly exothermic, and the addition rate of solid KNO_3 to the reaction mixture was carefully controlled to avoid an uncontrolled exotherm and vigorous off-gassing of nitrogen oxides. The resulting nitrophenol **11** was isolated by salting it out with ammonium chloride. This compound was then converted to the intermediate methyl ether **2a** via the corresponding chloride.[6] S_NAr reaction of **2a** with cyclopropylamine and Hünig's base in refluxing ethanol resulted in displacement of the −OMe group by cyclopropylamine to provide cyclopropylamino nitropyridine **3** in >90% overall yield after crystallization.

The first approach to circumvent the use of phosgene involved treatment of a solution of compound **3** with pyridine and ethyl chloroformate (ECF) to give carbamate **12** in 95% yield (Scheme 3). Hydrogenation of nitropyridine **12** gave the desired azabenzimidazolone **5a** in 96% yield. However, there were several drawbacks to this method. Although nearly quantitative yields were obtained after aqueous workup, 8.0 equiv of ECF and 10.0 equiv of pyridine were required to complete the reaction. The hydrogenation leading to compound **5a** was very slow (>2 days) and difficult to drive to completion on larger scale. Without sufficient water in the reaction mixture, the reaction stopped at intermediate **13**, which is insoluble in methanol. Therefore, the reaction had to be carried out in a 1:1 mixture of methanol and aqueous 1N HCl.

The ECF reaction was investigated in greater detail in a design of experiment (DOE) study for optimization of

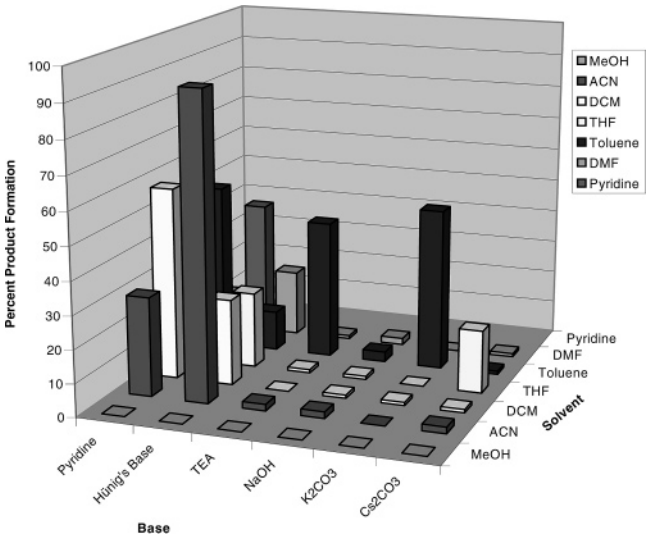
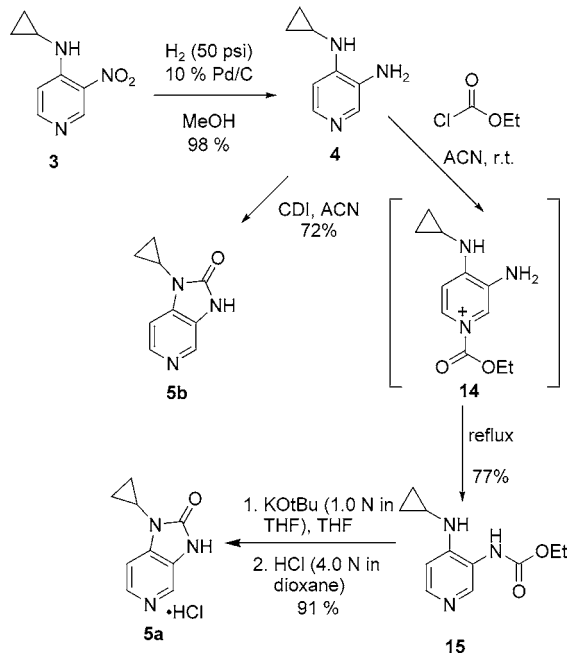


Figure 1. **DOE of ethylchloroformate addition using 4.0 equiv of ECF and 5.0 equiv of base**

Scheme 4



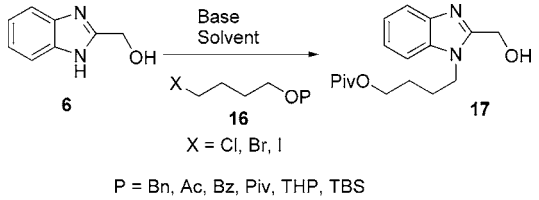
conditions with base and solvent as class variables[7] for the transformation of **3** to **12** (Figure 1).

Even though it is possible to obtain an 82% conversion using acetonitrile and Hunig's base (Figure 1), formation of a byproduct (up to 10%), derived from reaction of acetonitrile with ECF, became an issue. In addition, the need to use methanol and aqueous HCl for hydrogenation discouraged further pursuit of this route. Furthermore, it was felt that phosgene equivalents that are not acid chlorides might be advantageous in handling the chemistry on a large scale.

An alternate route involved reversing the steps of the synthesis (Scheme 4): first hydrogenation of **3** to form the diamine **4** and then cyclization to produce **5a**. Facile reduction of the nitro group of **3** in methanol at 50 psi gave

(5) Dodd, R. H.; Doisy, X.; Potier, P. *Heterocycles* **1989**, *28*, 1101−1113.
(6) Campbell, J.; Greene, J.; Lavagnino, E.; Gardner, D.; Pike, A.; Snoddy, J. *J. Heterocycl.Chem.* **1986**, *23*, 669−672.
(7) Lendrem, D.; Owen, M.; Godbert, S. *Org. Process Res. Dev.* **2001**, *5*, 324−327.

Scheme 5



diamine **4** in 98% yield. Since the pyridine moiety in **4** can serve as an acylation catalyst, refluxing **4** with ECF in acetonitrile gave carbamate **15** in 77% yield. The best reaction conditions for conversion of **15** to **5a** were found to be potassium *tert*-butoxide in THF at ambient temperature followed by an aqueous HCl workup. Although the overall yield of the final cyclization step was high (91%), the workup and isolation was tedious due to the water solubility of **5a**. Also, during the subsequent coupling studies (vide infra) it was determined that free base **5b** was preferred to the salt **5a**. However, isolation of the free base **5b** obtained via this route was difficult, and exploration of additional routes became necessary.

The direct conversion of **4** to **5b** was attempted using CDI in DMF (Scheme 4). The reaction was complete in 1 h at room temperature, but separation of the desired product from imidazole proved difficult in DMF. Reaction in acetonitrile was also complete within 1 h at room temperature, and **5b** precipitated out in 72% yield with no trace of imidazole. This yield was comparable with that from the overall two-step procedure using ECF and potassium *tert*-butoxide, and the process has many advantages in terms of procedural simplicity. The CDI process was thus used to prepare ∼3 kg of target molecule **5b** in a single batch.

Synthesis of the Left-Hand Fragment. For purposes of early development, commercially available 2-(hydroxymethyl)benzimidazole **6** was used as the starting material. Previous work had detailed the synthesis of **6** from inexpensive starting materials, phenylenediamine and glycolic acid.[8] These conditions were used as the starting point for the synthesis of the left-hand fragment of **1**.

Several hydroxyl-protecting groups were investigated (Scheme 5). The benzyl group performed well during subsequent chemistry, but there was concern over the use of palladium for its removal at such a late stage in the synthesis. Both acetate and benzoate proved to be too labile under the alkylation and coupling conditions (vide infra), as extensive protecting-group migration was observed. Both the TBS and THP analogues suffered from a lack of crystallinity. Fortunately, the pivaloyl protecting group provided an acceptable balance between stability, ease of removal, and crystallinity of intermediates.

The leaving group at the other end of the side chain also affected the outcome of the alkylation reaction (Scheme 5). In general, chlorides proved to be unreactive, even in the presence of sodium iodide. Both bromides and iodides gave the desired product. The iodide[9] was chosen over the bromide due to processing issues related to the synthesis of **16**. Specifically, during the workup of **16**, it was found that the volatility of the pivaloate-protected bromide complicated the isolation step.

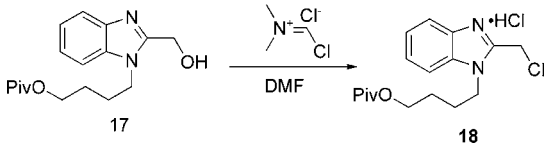
(8) Phillips, M. *J. Chem. Soc.* **1928**, 2395.

(9) The side chain was synthesized by opening THF with pivaloyl chloride and sodium iodide. Similar procedures have been reported in the literature. Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681−684.

Table 1. **DOE results for alkylation of 6 to give 17 (% yield)**

	Cs_2CO_3	K_2CO_3	KOH	$KOH_{(aq)}$
acetone	77	24	77	69
ACN	67	28	74	78
EtOAc	28	4	6	7
IPA	57	14	58	51
THF	35	6	54	63

Scheme 6

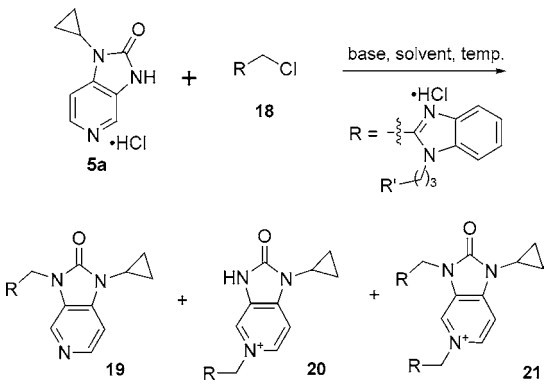


With the protecting and leaving groups finalized, work was focused on the elimination of sodium hydride from the alkylation reaction. A DOE study comparing bases and solvents for the alkylation reaction was conducted (Table 1). The less expensive aqueous KOH in acetone gave results comparable to those using cesium carbonate, without the stirring problems associated with the cesium salts. These conditions were used to prepare 3 kg of **17** in ∼69% isolated yield.

Coupling/Deprotection Protocol. The original approach to the coupling reaction required conversion of **7** to its corresponding chloride using thionyl chloride (Scheme 1). The chloride was isolated as its HCl salt and then coupled to **5a** using sodium hydride or BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane). These coupling procedures were not amenable to scale-up due to safety and cost considerations. In addition, both steps gave variable yields (50−70%) with a high amount of pyridine alkylation as a side reaction in the coupling step. Our studies revealed that the Vilsmeier reagent (either commercial or prepared in situ from oxalyl chloride/DMF in THF) produced the desired chloride as the HCl salt (**18**), which was isolated by filtration directly from the reaction mixture in greater than 95% yield. (Scheme 6).

Next, for the coupling of **5a** with **18**, it was found that cesium carbonate in DMF or DMA gave superior results compared to those from either of the previously employed conditions (Table 2). On small scale, yields ranged from 75 to 87%, and the product could be isolated by addition of water followed by filtration of the precipitated product. However, batches >10 g gave inconsistent results. As we had previously observed in the conversion of **6** to **17** using cesium carbonate, adequate stirring of the reaction mixture was problematic. Reaction times were considerably longer (30 h vs 3 h on a small scale), and a significant amount of pyridine alkylation impurity **20** was produced. These results prompted an investigation of other bases for the coupling reaction. Cesium hydroxide gave incomplete reaction, while potassium *tert*-butoxide gave better selectivity between compounds **19** and **20** but in lower yield. The use of

Table 2. **Optimization of the coupling of 5a and 18**

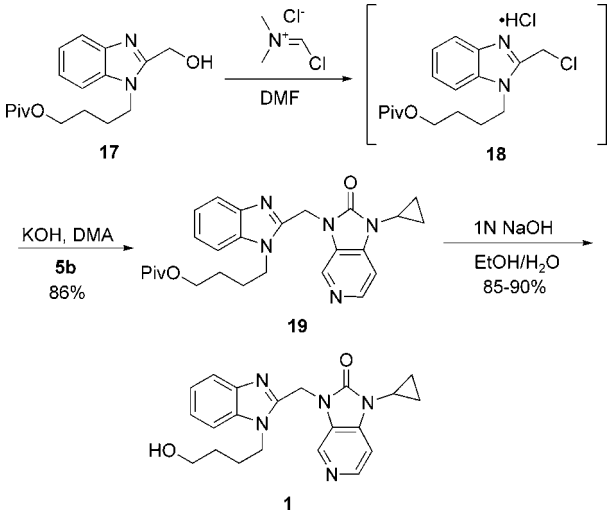


entry	solvent	base	rxn concen (M)	temp	product ratio 19:20:21:18	isolated yield (%)
1	DMF	K_2CO_3	0.12	rt	12:1:1:0	78
2	DMF	K_2CO_3	0.12	reflux	1:60:15:0	
3	DMF	Cs_2CO_3	0.12	rt	16:1:0:0	80
4	DMF	Cs_2CO_3	0.24	rt	4:1:0:0	
5	DMA	Cs_2CO_3	0.18	rt	14:1:0:0	71
6	DMA	Cs_2CO_3	0.24	rt	7:1:0:0	79
7	DMF	CsOH	0.24	rt	11:1:0:2.7	
8	DMA	KOtBu	0.16	rt	60:1:0:1	63
9	DMA	KOH (12.7M)	0.16	rt	25:1:0:0	77
10	DMA	KOH (8.0M)	0.24	rt	18:1:2:2	68
11	DMA	KOH (9.5M)	0.24	rt	10:0:1:0	71
12	DMA	KOH (11.0M)	0.24	rt	15:0:1:0.5	73
13	DMA	KOH (12.7M)	0.24	rt	16:1:0:0	77
14	CH_3CN	KOH (12.7M)	0.16	rt	2:1:0:0	
15	acetone	KOH (12.7M)	0.16	rt	2:1:0:0	
16	THF	KOH (12.7M)	0.16	rt	0.5:1:0.3:0	
17	iPrOH	KOH (12.7M)	0.16	rt	1:1:0:0	

potassium hydroxide gave the best combination of selectivity and yield. Several solvents and base concentrations were examined (Table 2). While the selectivity was lower with KOH than with potassium *tert*-butoxide (entry 9 vs 8), the higher isolated yield was a distinct advantage. It was also found that using more concentrated base increased the yield (entries 9−12). Finally, solvent screening indicated DMA to be the preferred solvent for the coupling (entries 13−17). The best conditions are shown in entry 9.

To avoid exposure to mutagenic compounds such as **8** and **18** during manufacture, a telescoped procedure was developed (Scheme 7). Earlier work on similar compounds demonstrated that use of the free base **5b** gave 10−15% higher isolated yields compared to those with the HCl salt **5a**. Therefore, the free base **5b** was chosen for all subsequent development work. For the two-step process, the Vilsmeier-mediated chloride formation was performed in THF, which allowed the product to directly precipitate from the reaction mixture. However, for the purpose of the telescoped route,

Scheme 7



DMF gave an easily transferable solution allowing the facile addition of the chloride into a stirred mixture of **5b** and KOH in DMA. Early attempts at this transformation on small scale gave ∼86% isolated yield (75−80% on larger scales) of the desired compound **19**. During these initial studies it became necessary to closely monitor the reaction to avoid undesired removal of the pivaloate group due to the presence of excess base. To minimize the premature loss of this protecting group, urea **5b** was preequilibrated with a reduced amount of KOH (2.7 equiv) for about 30 min, and the reaction temperature was kept to ≤35 °C.

Interestingly it was found that addition of a 2.8 M solution of ammonium chloride followed by seeding with **19** (0.002 mol %) resulted in smooth crystallization of the desired product over 12−15 h. Analysis of the final product indicated the absence of mutagenic intermediate **18**. The pivaloate deprotection was studied using sodium hydroxide in three alcoholic solvents (MeOH, EtOH, and *i*-PrOH). 2-Propanol produced small particles upon crystallization, resulting in an extremely slow filtration. Methanol and ethanol gave similar particles, although more rapid filtration times were observed. Ethanol was chosen as the reaction solvent due the slightly improved filtration times and a better safety profile. Further optimization of the reaction found that 2.0 equiv of base gave a clean and fast reaction (2−3 h). Decreasing the base to 1.5 and 1.2 equiv resulted in longer reaction times, 6, and 8 h, respectively.

Conclusions

In conclusion, a practical and highly convergent synthesis of **1** has been developed and demonstrated on scale. Efficient routes to azabenzimidazolone **5b** and benzimidazole **17** have been developed. Several expensive and hazardous reagents as well as all chromatographic purifications were eliminated during the optimization of this route. Coupling of **5b** and **17** was accomplished with a telescoped procedure using the Vilsmeier reagent and potassium hydroxide to replace thionyl chloride and NaH/BTPP and avoid handling of mutagenic intermediate **18**. Both penultimate intermediate and API were isolated by filtration from the reaction mixture in high purity.

Experimental Section

General Procedures. Proton and carbon NMR spectra were recorded at 500 and 125 MHz, respectively, unless otherwise noted. Chemical shifts are reported in ppm downfield from TMS and coupling constants in Hertz using residual protonated solvent as the reference. Unless otherwise noted, infrared spectra were taken as KBr pellets. All reagents were obtained from a commercial supplier and were used without further purification. Unless otherwise stated, all reactions were run under nitrogen, and products were dried in a vacuum oven. When applicable, all solvents were removed under vacuum using a rotary evaporator.

4-Hydroxy-3-nitropyridine (11). A round-bottomed flask was charged with H_2SO_4 (155 mL) and cooled to 0 °C. 4-Hydroxypyridine (**10**, 25.0 g, 0.263 mol) was added in portions followed by *SLOW* addition of KNO_3 (53.0 g, 0.526 mol) via a solid addition funnel.[10] The resulting mixture was heated to 100 °C for 1 h and then cooled to 0 °C and poured onto ice water (100 mL). The mixture was neutralized (pH = 6.5) with NH_4OH (220 mL) at 0 °C. The precipitate was filtered and dried in vacuo to provide **11** (36.0 g, 98%). ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 1H), 7.77 (d, J = 7, 1H), 6.47 (d, J = 7, 1H).

4-Methoxy-3-nitropyridine (2a). A three-necked flask (equipped with mechanical stirrer) was charged with 4-hydroxy-3-nitropyridine (**11**, 100.0 g, 0.714 mol) and 1,2-dichloroethane (571 mL) and heated to 80 °C. $POCl_3$ (80.0 mL, 0.856 mol) was added dropwise at such a rate to maintain the temperature around 80 °C. Upon completion of addition, the reaction was heated at 85 °C for 4 h and cooled to 0 °C, and then MeOH (396 mL) was added dropwise. The mixture was heated at 65 °C for 1 h and then cooled to 0 °C. The precipitate was filtered and dried in vacuo to provide **2a** (104 g, 76%). ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 1H), 8.78 (d, J = 6, 1H), 7.59 (d, J = 6, 1H), 4.07 (s, 3H).

***N*-Cyclopropyl-3-nitropyridin-4-amine (3).** A round-bottomed flask was charged with 3-nitro-4-ethoxypyridine hydrochloride (**2b**, 70.6 g, and 0.345 mol), absolute EtOH (250 mL), *i*-Pr_2NEt (125 mL, 0.718 mol) and cyclopropylamine (50.0 g, 0.876 mol). The resulting solution was refluxed for 3 h. The reaction was cooled to 0 °C, and the solid was collected by filtration. The filter cake was washed with cold ethanol (absolute, 2 × 30 mL) to give **3** (52.4 g, 85%). The mother liquor was concentrated and partitioned between water (200 mL) and ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated to give a second crop of product (10.7 g, 15% (slightly impure)). ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1H), 8.34 (d, J = 6, 1H), 8.19 (broad singlet, 1H), 7.15 (d, J = 6, 1H), 2.62 (m, 1H), 0.99 (m, 2H), 0.71 (m, 2H).

***N*^{4}-Cyclopropylpyridine-3,4-diamine (4).** A suspension of 4-(*N*-cyclopropyl)amino-3-nitropyridine (**2**, 120 g, 0.670 mol) and 10% Pd/C (50% water; 24 g) in EtOH (1 L) was hydrogenated at 50 psi H_2 for 4 h. The suspension was filtered through Celite and concentrated. The residue was dried in vacuo to provide **4** (97.4 g, 97%). ^{1}H NMR (DMSO-d_6) δ 7.61 (s, 1H), 7.61 (d, J = 5, 1H), 6.64 (d, J = 5, 1H), 5.76 (s, 1H), 4.51 (s, 2H), 2.36, (m, 1H), 0.72 (m, 2H), 0.40 (m, 2H).

Ethyl 4-(cyclopropylamino)pyridin-3-ylcarbamate(15). To a solution of **4** (36.0 g, 0.240 mol) in CH_3CN (480 mL) was added ethyl chloroformate (46.0 mL, 0.480 mol) dropwise at room temperature. The resulting mixture was heated at 75 °C for 15h. The mixture was cooled to room temperature, filtered, and dried in vacuo to provide **15** (47.8 g, 77%). ^{1}H NMR (DMSO-d_6) δ 9.32 (broad singlet, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 8.23 (d, J = 7, 1H), 7.20 (d, J = 7, 1H), 4.13 (q, J_1 = 7, J_2 = 14, 2H), 2.68 (m, 1H), 1.23 (t, J = 7, 3H), 0.89 (m, 2H),0.64 (m, 2H).

1-Cyclopropyl-1,3-dihydroimidazo[4,5-*c*]pyridin-2-one Hydrochloride (5a). KOtBu (1.0 N in THF, 730 mL, 0.730 mol) was added dropwise to a suspension of **15** (47.0 g, 0.182 mol) in THF (365 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 15 h, and then cooled to 0 °C. HCl (4.0 N in 1,4-dioxane, 180 mL, 0.720 mol) was added dropwise. The precipitate was collected by filtration and redissolved in MeOH (1.8 L) at 50 °C. The solution was cooled to room temperature and the insoluble salts were removed by filtration. The mother liquor was concentrated and the residue was triturated with MeOH (700 mL). The solid was filtered and dried in vacuo to provide **5a** (34.9 g, 91%). ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 8.47 (s, 1H), 7.65 (d, J = 7, 1H), 3.02 (m, 1H), 1.08 (m, 2H), 0.92 (m, 2H).

1-Cyclopropyl-1,3-dihydroimidazo[4,5-*c*]pyridin-2-one (5b). To a solution of **4** (20.0 g, 0.134 mol) in CH_3CN (268 mL) at 0 °C was added CDI (22.8 mL, 0.141 mol), and the resulting mixture was warmed to room temperature over 1 h. The precipitate was collected by filtration and dried in vacuo to give **5b** (16.9 g, 72%). ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 8.17 (d, J = 5, 1H), 8.15 (singlet, 1H), 7.17 (d, J = 5, 1H), 2.88 (m, 1H), 1.00 (m, 2H), 0.85 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 154.15, 142.12, 137.38, 129.24, 125.76, 103.88, 22.27, 5.60. Anal. Calcd for $C_9H_9N_3O$: C 61.70, H 5.18, N 23.99; found: C 61.51, H 5.10, N 23.94. KF < 0.1%

2,2-Dimethylpropionic Acid, 4-Iodobutyl Ester (16). A suspension of sodium iodide (61.7 g, 0.412 mol) in CH_3CN (100 mL) was cooled to ~2 °C, and THF (28.6 mL, 0.352 mol) was added, followed by the addition of a solution of trimethylacetyl chloride (42.8 mL, 0.348 mol) in CH_3CN (60 mL) at a rate to keep the internal temperature below 10 °C. The mixture was stirred at 10 °C for 2 h and then warmed to room temperature and stirred for 15 h. *tert*-Butyl methyl ether (450 mL) was added followed by 1 N sodium thiosulfate (275 mL). After 30 min the layers were separated, and the organic layer was washed with water (325 mL) and half-saturated aqueous brine (275 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield **16** (93.5 g, 94%). IR (KBr) 1725 (C═O) (cm^{-1}); ^{1}H NMR (DMSO-d_6) δ 4.03 (t, J = 6, 2H), 3.31 (t, J = 7, 2H), 1.81 (m, 2H), 1.66 (m, 2H), 1.14 (s, 9).

(10) Rapid addition of KNO_3 results in a dangerous exotherm and severe off-gassing.

2,2-Dimethyl-propionic Acid, 4-(2-Hydroxymethyl-benzoimidazol-1-yl)butyl Ester (17). A suspension of **6** (40.0 g, 0.270 mol), KOH (18.7 g, 0.284 mol) and acetone (360 mL was heated to 50 °C. To this mixture, a solution of **16** (88.2 g, 0.311 mol) in acetone (180 mL) was added at a rate to keep the temperature below reflux. The reaction mixture was held at 50 °C for 2.5 h and then cooled to room temperature. The insoluble solids were removed by filtration, and the mother liquor was concentrated. The residue was dissolved in EtOAc (355 mL) and heated to 65 °C. The insoluble material was removed by filtration and washed with EtOAc (80 mL). The combined organic layers were heated to 60 °C, and heptane (400 mL) was added at a rate to maintain the temperature at 60 °C. The suspension was cooled to room temperature and the product collected by filtration. The filter cake was washed with heptanes (150 mL), H_2O (4 × 250 mL), and heptanes (250 mL). The solid was dried in vacuo to afford **17** (56.5 g, 69%). A second crop (slightly less pure) was also recovered from the mother liquor upon concentration, filtration, washing, and drying. ^{1}H NMR (DMSO-d_6) δ 7.59 (d, J = 8, 1H), 7.55 (d, J = 8, 1H), 7.22 (t, J = 7, 1H), 7.17 (t, J = 7, 1H), 5.60 (t, J = 6, 1H), 4.71 (d, J = 6, 2H), 4.31 (t, J = 7, 2H), 4.04 (t, J = 6, 2H), 1.84 (m, 2H) 1.63 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 177.27, 153.55, 141.89, 135.21, 121.99, 121.26, 118.97, 110.06, 63.23, 56.49, 42.78, 38.07, 26.77, 25.89, 25.55. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C 67.08, H 7.95, N 9.20; found: C 66.19, H 7.53, N 9.11. KF < 0.1%

2,2-Dimethyl-propionic Acid, 4-[2-(1-Cyclopropyl-2-oxo-1,2-dihydroimidazo[4,5-*c*]pyridin-3-ylmethyl)-benzoimidazol-1-yl]butyl Ester (19). A solution of **17** (1.54 kg, 5.06 mol) in DMF (6.1 L) was added over 30 min to a suspension of the Vilsmeier reagent (741 g, 5.80 mol) in DMF (1.3 L). After 1 h, additional Vilsmeier reagent (17.0 g, 0.l33 mol) was added. The resulting mixture was stirred for 20 min to give a solution of **18**. In a separate vessel, 12.7 N KOH (980 mL, 12.4 mol) was added to a suspension of **5b** (795 g, 4.54 mol) in DMA (6.58 L). After 15 min, the solution of **18** from above was added over 10 min at a rate to keep the internal temperature below 35 °C with external cooling. The original reactor for **18** was rinsed with DMF (300 mL). The resulting mixture was stirred vigorously for 2 h at room temperature. The salt precipitate was removed by filtration, and the filter cake was washed with fresh DMA (900 mL). The organic layer was cooled in a 15−20 °C bath, and a solution of NH_4Cl (2.8 M, 7.2 L) was added at such a rate to keep the internal temperature below 25 °C. The solution was cooled to 18 °C and seeded with **19** (5.34 g, 11.6 mmol). The mixture was stirred for 16 h at room temperature followed by addition of H_2O (20 L). The suspension was cooled to 10 °C over 2 h and stirred for an additional 2 h. The solid was collected by filtration, washed with H_2O (18.6 L) and heptane (16.8 L), and dried in vacuo (38 °C) to provide **19** (1.63 kg, 78%). ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 8.25 (d, J = 5.2, 1H), 7.58 (t, J = 7.0, 2H), 7.28 (d, J = 5.2, 1H), 7.24 (t, J = 7.6, 1H), 7.18 (t, J = 7.6, 1H), 5.38 (s, 2H), 4.37 (t, J = 7.4, 2H), 4.02 (t, J = 6.3, 2H), 2.99 (m, 1H), 1.71 (m, 2H), 1.61 (m, 2H) 1.10 (s, 9H), 1.07 (m, 2H), 0.91 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 177.25, 152.82, 148.71, 142.62, 141.86, 136.09, 135.06, 129.36, 126.19, 122.38, 121.66, 119.04, 110.35, 104.00, 63.08, 42.78, 38.06, 37.64, 26.76, 25.87, 25.44, 22.62, 5.47; Anal. Calcd for $C_{26}H_{31}N_5O_3$: C 67.66, H 6.77, N 15.17; found: C 67.17, H 7.32, N 14.94. KF = 0.47%

1-Cyclopropyl-3-[1-(4-hydroxybutyl)-1H-benzoimidazol-2-ylmethyl]-1,3-dihydroimidazo[4,5-*c*]pyridin-2-one (1). Compound **19** (138.5 g, 0.300 mol) was charged to a 5-L, three-necked, round-bottomed flask equipped with a condenser and mechanical stirrer. EtOH (95%, 990 mL) was added, followed by slow addition of H_2O (660 mL) with stirring to form a clear solution. Aqueous NaOH (4.0 N, 150 mL) solution was added to the reaction solution and heated at 70 °C. After the reaction was complete (typically in 2−3 h, monitored by HPLC), H_2O (1320 mL) was added slowly to the reaction mixture. The mixture was stirred at 70 °C for 2 h, and then slowly cooled to room temperature overnight. The solid crystalline product was collected by filtration and washed with 1:2 EtOH (95%)/H_2O (1000 mL) and H_2O (4 × 1000 mL). The product was dried at 55 °C under reduced pressure overnight to afford **1** as an off-white crystalline solid (100.8 g, 89.0%). ^{1}H NMR (CD_3OD) δ 8.30 (s, 1H, Ar), 8.25 (d, 1H, J = 5.4 Hz), 7.58 (d, 1H, J = 8.1 Hz), 7.54 (d, 1H, J = 8.1 Hz), 7.39 (d, 1H, J = 5.4 Hz), 7.31 (t, 1H, J = 7.2 Hz), 7.24 (t, 1H, J = 7.2 Hz), 5.47 (s, 2H), 4.40 (t, 2H, J = 7.6 Hz), 3.56 (t, 2H, J = 6.2 Hz), 3.05−3.02 (m, 1H), 1.82−1.77 (m, 2H), 1.62−1.58 (m, 2H), 1.18−1.14 (m, 2H), 1.07−1.03 (m, 2H); ^{13}C NMR: (DMSO-d_6) δ 152.79, 148.68, 142.64, 141.84, 136.08, 135.15, 129.37, 126.16, 122.37, 121.60, 119.00, 110.42, 103.98, 60.18, 43.13, 37.69, 29.44, 26.23, 22.61, 5.47; Anal. Calcd for $C_{21}H_{23}N_5O_2$: C 66.83, H 6.14, N 18.55; found: C 67.06, H 6.03, N 18.67.

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