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Synthesis and Purification of 6-Ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic Acid Benzylamide

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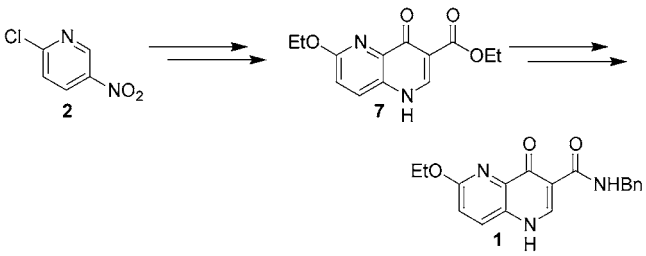
Abstract:

The synthesis of 6-ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid benzylamide (1) on multikilogram scale is described. The major challenge for the synthesis of this quinolone GABA partial agonist was in the isolation of product of acceptable purity for clinical studies due to the insolubility of this compound. Also described are efforts to circumvent a high-temperature cyclization required for the synthesis of the quinolone ring system.

Introduction

6-Ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid benzylamide (**1**) is a subtype-selective GABA-A receptor inverse agonist[1] and was recently of interest for clinical evaluation as an agent for the treatment of cognition disorders such as Alzheimer's disease. The pharmacological selectivity of subtype-selective GABA-A receptor modulators such as **1** is anticipated to provide an efficacious agent with limited side effects.



The synthesis of **1**[2] is depicted in Scheme 1.[3] Although the chemistry to make the drug candidate is high yielding and relatively simple, the insolubility of the quinolones makes them quite difficult to purify. As a result, it was necessary for the synthesis to produce material of high enough purity that a rework would not be necessary or alternatively needed to identify methods of purification for the intermediates and product.

The synthesis of ester **7** has been previously reported and is depicted in Scheme 1. The published synthesis, with minor improvements, was used to prepare material for the regulatory synthesis. 2-Chloro-5-nitropyridine **2** was treated with KOH in EtOH to provide ethyl ether **3**. After an aqueous workup, the organic (CH_2Cl_2) layer is concentrated to give a yellow solid in 66% yield. Pyridine **3** is then taken back in EtOH and reduced using 8 equiv of iron and 0.5 equiv of $CaCl_2$ for completion. The resulting product (**4**) is an oil that slowly decomposes on standing.

To streamline the process, a one-pot single-solvent procedure was devised to transform **2** into **4** which is isolated as a stable phosphate salt (Scheme 2). NaOEt was used in place of KOH in EtOH. Upon reaction completion, the nitro group was reduced with 1.2 equiv of BH_3-NMe_3 complex using 3% loading of Pearlman's catalyst.[4] The spent catalyst and NaCl were removed by filtration, and H_3PO_4 was added to deliver the corresponding phosphate salt of **4** in 93% yield.

The coupling of aminopyridine **4** with malonate derivative **5** was shown to proceed as either the phosphate salt or free base in refluxing CH_2Cl_2 (83 °C), toluene (100 °C), or trifluorotoluene (102 °C). The high-temperature cyclization of diester **6** was successfully scaled, but the reaction was difficult to run. Rapid heating and cooling as well as fairly precise control over reaction time were required to minimize the formation of impurities in this step.

A number of alternative methods for the production of this material without the high temperatures needed for the cyclization were investigated (Scheme 3) so that the process could be run in a general-purpose manufacturing plant if desired. Efforts to facilitate cyclization using Lewis acids or bases to lower the temperature at which acylketene formation would occur resulted in no reaction or decomposition. Protection of the NH with a benzyl group inhibited the cyclization. Synthesis of a 2-bromopyridine and attempted metal−halogen exchange followed by cyclization also failed to provide desired product (e.g., **10** → **7**). Heck coupling of bromide **9** with methyl β-methoxyacrylate did provide the cyclization product **11** in modest yield (28%). However, the desired C−C bond formation is almost certainly occurring in an intramolecular fashion, as all attempts to effect an intermolecular Heck coupling with an *N*-blocked substrate

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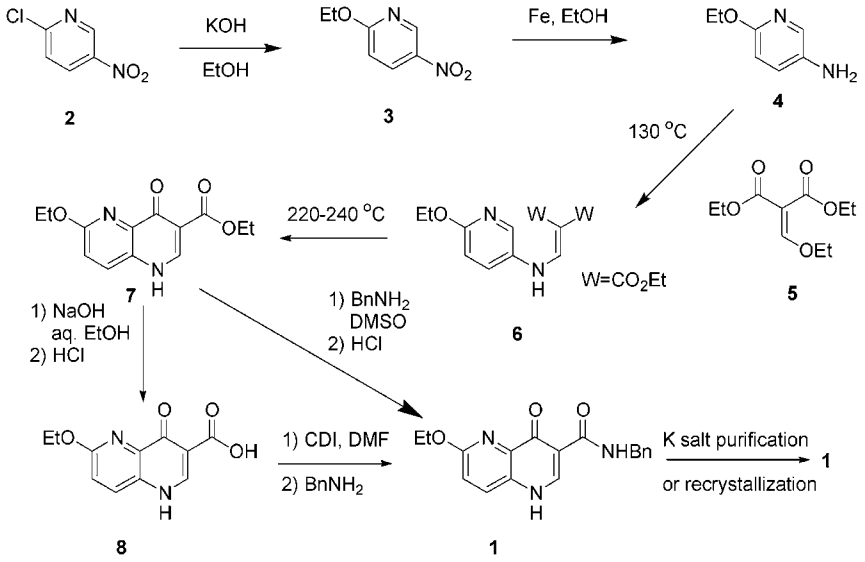
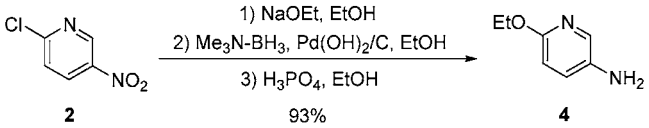
Scheme 1



Scheme 2



(e.g., the formamide or sulfonamide derived from **9** or formamidine **12**) were unsuccessful. Since an intramolecular Heck cyclization delivers a product with C-2 in the wrong oxidation state (e.g., **11**), this approach was not pursued further. Attempted Baylis−Hillman cyclization of nitrile or the corresponding ester (**14**−**7**) also failed to deliver the desired product.

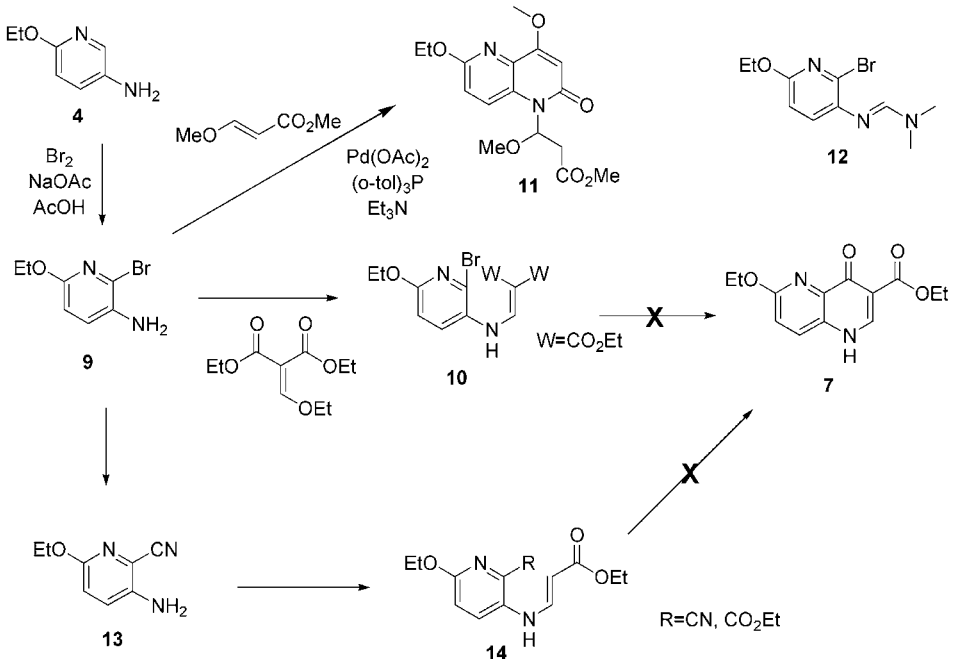
As alternate methods for the preparation of ester **7** were not identified and using the high-temperature route could obtain large quantities of material (several hundred kilograms were prepared), the decision was made to stay with the original synthesis and investigate the advantages of a high-temperature flow reactor as an alternative should the program progress further.

Ethyl ester **7** has a very low solubility in most solvents. While it could be recrystallized from DMF, high dilutions and temperatures were required for the purification. Because of the difficulty in controlling the impurity profile at this intermediate, carboxylic acid **8** was defined as the regulatory starting material for the synthesis. The ethyl ester (**7**) could be hydrolyzed to the carboxylic acid using NaOH in EtOH and H_2O. The resulting sodium salt solution was acidified using concentrated HCl to precipitate the free acid (**8**). In the first few campaigns, the filtration of this acid intermediate proved to be the most troublesome operation in the synthesis, with the filtration of 34 kg on a 33-in. diameter Nutsche filter routinely taking 3−5 days. Aging the solids at elevated temperature (85 °C for 4 h) resulted in a faster-filtering slurry; however, during this process an impurity (8%) was formed. This impurity was identified as the ethyl ether cleavage product by HPLC/MS. To exploit the faster filtration without the impurity issue, the stability of acid **8** was determined at a range of pH under the reaction conditions. It was found that the solids could be successfully aged at reflux provided that the pH of the solution was above 1.0. The pK_a of the carboxylic acid in the reaction mixture was determined by titration to be between 4.5 and 6. A pH target range of 2−2.5 was selected for the bulk run. As the pH range proved difficult to hit while acidifying the reaction mixture, it was determined that using 50% NaOH to back-adjust the pH provided equivalent results. Under these conditions, pilot experiments involving heating at reflux for 48 h showed minimal formation of the previously observed impurity. These solids filtered much more quickly and required only 1 day to filter 155 kg in four centrifuge loads on a 40-in. diameter centrifuge basket. The final bulk saponification afforded a 94% yield of acceptable carboxylic acid **8** with 4% of fine solids passing through the centrifuge bag.

The formation of **1** is best accomplished using CDI in DMF, followed by the addition of $BnNH_2$. Depending on the relative amount of CDI used, one of two impurities is observed, either unreacted acid **8** or dibenzylurea. As dibenzylurea proved easier to purge (vide infra), an excess of CDI is preferable in this step. In practice, 1.1 equiv of CDI and 1.1 equiv of benzylamine are employed in the transformation. The initial stage of the reaction, wherein the acylimidazole is formed, is a very thick slurry and at least 4 L/kg of DMF is required to maintain stirring in a pilot plant reactor. This stage of the reaction is assayed by derivatization of a sample to the API with $BnNH_2$. After formation of the acylimidazole, $BnNH_2$ is added. Upon reaction completion, H_2O is added, and the product is isolated by filtration. The intermediate acylimidazole has sufficient stability for an alternate procedure wherein the excess CDI can be quenched by the addition of H_2O prior to addition of $BnNH_2$. This procedure (1.5 equiv of CDI, followed by H_2O, then $BnNH_2$), yielded no dibenzylurea, and free-acid **8** is observed at a level of <1.0%. Because of the relative ease of purging the dibenzylurea, this procedure was not adopted on scale.

As a result of the low solubility of **1**, low exposure of the drug candidate was observed in the toxicology studies.

Scheme 3



Therefore, several kilograms of the more soluble potassium salt were required for the toxicology program in which higher drug exposure was desired. The potassium salt could be generated in THF using KO*t*-Bu with a small amount of H_2O.[5] In the course of developing this salt formation prior to scaling, it was noted that the potassium salt was soluble enough to be recrystallized. This recrystallization proved to be a very effective purification, especially with regard to any dibenzylurea formed in the previous step of the synthesis. The ratio of H_2O to THF in this crystallization was critical to the recovery. In addition, the solution of the potassium salt provided an ideal point for a 1 micron filtration prior to isolation of the API.[6] As a result, this salt formation was adopted as a purification step in the synthesis of **1** as the free acid as well. In practice, the potassium salt was generated (KO*t*-Bu, THF, 9 equiv H_2O), filtered through a 1 micron filter at 45 °C, then cooled to 15 °C, granulated for 12 h, and filtered to provide the potassium salt.[7] When the free acid was the final target, the potassium salt wet cake was resuspended in H_2O (15 L/kg) and acidified with HCl (1 equiv). The solids were slurried and isolated by filtration in 68% yield for the salt formation and break. Although the product was routinely isolated in very high purity (>99.5%), this procedure suffered from the resultant slurries being foamy and giving slow-filtering, clay-like solids, which required 2 H_2O slurries or washes to reduce the residue on ignition (ROI) content to acceptable levels. Alternatively, a cheaper potassium salt purification was developed in the lab, which consisted of adding 1.4 equiv of 50% aqueous KOH solution to **1** in 7 L/kg THF with 1 vol of *i*-PrOH and heating to 50 °C. The resultant solution was filtered, and the salt crystallized upon cooling to 5 °C. The isolated salt was dissolved in 12 L/kg of H_2O and converted to final product **1** using HCl in an 80% overall yield.

A second alternative for production of acceptably pure API is to isolate the acylimidazole intermediate during the amide formation. The acylimidazole precipitates from triethylamine and can be isolated by filtration. Conversion of this to the final product by addition of $BnNH_2$ produced high-purity product in pilot experiments.

The simplest way to produce acceptably pure API is to add acetone and H_2O to the slurry at the conclusion of the amide formation reaction. The addition of 7 L/kg of acetone and H_2O results in a faster filtration and also proved effective for the purge of the dibenzylurea byproduct in the lab, giving clinical-grade API in good yields (>87%) and purities (>98.5%) for the amide formation.

Compound **1** is highly insoluble in most solvents but can be recrystallized from either aqueous DMF or HOAc. DMF was not a preferred final crystallization solvent. Dissolution in 10 L/kg of HOAc and subsequent dilution with 2 L/kg of H_2O proved very effective at purifying the API, giving a fast-filtering solid, which was easily washed with H_2O. The purification typically afforded an 86% recovery of **1** (>98.5%) with residual HOAc levels and residue on ignition analyses lower than 0.1%.

Ester **7** could be converted directly to amide **1** by treatment with $BnNH_2$ in DMF and DMSO at high temperature. The DMSO reactions afforded superior yields over the DMF reactions, with the reaction rate greatly enhanced by the quantity of $BnNH_2$ used. Reaction of 3 equiv of $BnNH_2$ with **7** in 5 L/kg DMSO at 110 °C afforded a 96% yield of crude **1** (88%). Recrystallization with aqueous HOAc afforded a 69% recovery of pure **1** (>98.0%).

(5) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918−920.
(6) All materials going into the final drug substance crystallization are filtered in solution or neat through a 1 micron filter prior to crystallization per an internal operating procedure.
(7) The isolated yield of the potassium salt was 77% in a campaign where the solid salt was dried.

Experimental Section

All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by HPLC. HPLC analyses were performed using a YMC basic column (15 cm × 4.6 mm, 3 μm) and a mobile phase of 72/28 (v/v) (0.1% H_3PO_4, 10 mM SDS in H_2O)/acetonitrile. ^{1}H-spectroscopy was performed at 300, 400, and 500 MHz on Bruker-Spectrospin Avance instruments. The LOD (loss on drying) was determined by concentrating a weighed sample from the bulk material.

5-Amino-2-ethoxy-pyridine (4).[3] To a strirred slurry of 2-chloro-5-nitro-pyridine (76.1 g, 480 mmol) in EtOH (500 mL) was added a solution of sodium ethoxide (21% in EtOH, 196 mL, 576 mmol) over 20 min. After 6 h of additional stirring at room temperature, EtOH (150 mL), borane trimethylamine (43.3 g, 576 mmol), and palladium hydroxide (2.16 g, 50% wet) were successively added, and the resulting suspension was heated to reflux for 2 h. Upon cooling to room temperature, the mixture was filtered over Celite, and the filtrate was concentrated under vacuum to a final volume of 300 mL. The concentrate was diluted with additional EtOH (1.50 L), and phosphoric acid (56.5 g, 576 mmol) was added dropwise. The resulting slurry was filtered, and the solid material was washed with EtOH (225 mL) and dried to yield the title compound as a pale yellow crystalline solid (106 g, 93%).

6-Ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid (8). To a clean 1000-gal, glass-lined reactor was charged 185 kg of ethyl 6-ethoxy-4-oxo-1,4-dihydro-[1,5]-naphthyridine-3-carboxylic acid, ethyl ester (**7**), 1480 L of H_2O, and 437 kg of 2-B EtOH.[8] To the slurry was added 150 kg of 50% NaOH solution and 185 L of H_2O at temperatures below 40 °C. The reaction was heated to reflux and held for 2 h. The solution was cooled to 45 °C and transferred through a preheated polish filter to a second clean 1000-gal, glass-lined reactor. The empty reactor and polish filter were rinsed with 110 L of H_2O. At 25 °C, the reaction filtrate was adjusted to a pH of 2−4 with filtered concentrated HCl and 50% NaOH. The slurry was heated to reflux and held for 1 h. The slurry was stirred for 1 h at 22 °C and then filtered on a 240-L centrifuge in four loads. Each load was washed with 95 L of filtered H_2O and dried together in a vacuum tray dryer at 66 °C until the H_2O content (KF) was 0.2%. This procedure afforded a 94% yield (155 kg) of spec-free **8**. mp 260−268 °C. Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.30; H, 3.96; N, 11.93. ^{1}H NMR (400 MHz, DMSO): δ 8.85 (s, 1H), 8.12 (d, J = 9.2, 1H), 7.33 (d, J = 9.2, 1H), 4.44 (q, J = 7.2, 2H), 1.38 (t, J = 7.2, 3H). ^{13}C NMR (125 MHz, DMSO): δ 176.6, 166.5, 160.8, 142.8, 137.2, 133.1, 132.0, 118.9, 110.7, 62.1, 14.2.

6-Ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic Acid Benzylamide (1). To a clean and dry nitrogen-purged 500-gal, glass-lined reactor was charged 29 kg of 6-ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid (**8**), 31 gal of DMF, and 22 kg of CDI. The mixture was heated to 90 °C and held for 2 h with gas evolution. The crude mixture was cooled to 35 °C and sampled.[9] Once the reaction was observed to be complete, 14.6 kg of $BnNH_2$ was added, and the mixture was stirred at 35 °C for 2 h. The reaction was sampled for reaction completion and then diluted with 192 gal of process H_2O. The slurry was allowed to granulate for 4 h, and then the product was isolated via filtration. The product was allowed to dry for 24 h at 45 °C until the KF was 0.5%, yielding 38.9 kg, 97%.

To a clean and dry 500-gal, glass-lined reactor was charged 38 kg of 6-ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid benzylamide (**1**), 80 gal of THF, 13.5 kg of KO*t*-Bu, and 19 L of USP H_2O. The slurry was heated to reflux and held for 1 h. The solution was then filtered via a jacketed sparkler filter at a temperature just below[10] reflux to a clean 300-gal, glass-lined reactor. The filter and lines were rinsed with 10 gal of 55 °C THF. To the batch was added an additional 80 gal of THF, and the batch was concentrated atmospherically to 55 gal. The reaction mixture was allowed to cool and granulate for 16 h. The desired salt (27.4 kg, wet cake, first crop) was isolated and used in the next step without drying. The mother liquor from the first crop was diluted with 55 gal of THF and concentrated atmospherically to a final volume of 15 gal. The reaction mixture was allowed to cool and granulate for 16 h. A second crop of the desired salt was isolated by filtration (17.4 kg, wet cake). mp 208 °C. ^{1}H NMR (400 MHz, DMSO): δ 8.72 (s, 1H), 8.03 (d, J = 9.2, 1H), 7.34−7.23 (m, 5H), 7.21 (d, J = 9.2, 1H), 4.54 (d, J = 5.2, 2H), 4.39 (q, J = 7.2, 2H), 1.33 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, DMSO): δ 172.8, 168.8, 159.2, 150.9, 143.2, 141.2, 141.1, 140.3, 129.0, 127.9, 127.2, 114.8, 112.8, 61.5, 42.4, 15.2.

To a 300-gal reactor was charged 120 gal of USP H_2O and 27.4 kg of 6-ethoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid benzylamide potassium salt (**1**) (THF-wet). The slurry was stirred at 19 °C, and 6 L of 37% HCl was added. The pH was measured to be 2.4, and the slurry was allowed to granulate for 4 h at 20 °C. The product was isolated via filtration and was then washed with 2 × 10 gal of 40 °C H_2O.[11] The product was dried under vacuum at 45−50 °C for 48 h under a nitrogen bleed. The desired product was isolated in 42% yield (16.2 kg). mp 199 °C. Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.69; H, 5.18; N, 12.91. ^{1}H NMR (500 MHz, DMSO): δ 12.73 (br s, 1H), 10.61 (br t, J = 5.6, 1H), 8.73 (s, 1H), 8.05 (d, J = 9.0, 1H), 7.35 (d, J = 4.4, 2H), 7.27 (dd, J = 4.4, 8.6, 2H), 7.22 (d, J = 9.0, 1H), 4.56 (d, J = 5.8, 2H), 4.42 (q, J = 7.0, 2H), 1.35 (t, J = 7.1, 3H). ^{13}C

(8) Toluene-denatured ethanol.
(9) Assay was accomplished by derivatization of the acylimidazole to the desired product with $BnNH_2$ and analyzing by HPLC.
(10) All transfer equipment must be preheated to ensure that the potassium salt remains in solution during the sparkle step.
(11) This filtration took under 1 h including the wash, which was necessary to reduce ash levels.

NMR (125 MHz, DMSO): δ 174.5, 164.5, 160.1, 141.6, 139.3, 138.6, 132.1, 131.5, 128.4, 127.3, 126.9, 117.5, 113.6, 61.7, 42.1, 14.3.

3-Amino-2-bromo-6-ethoxypyridine (9).[12] A solution of 2-ethoxy-5-aminopyridine **4** (3.00 g, 21.7 mmol) was dissolved in AcOH (18 mL) at room temperature. NaOAc (1.73 g, 21.1 mmol) was added in a single portion, followed by bromine (1.04 mL, 1.36 g, 20.2 mmol), added dropwise over 10 min. The thick reaction mixture was stirred for 60 min and then quenched by portionwise addition to an ice-cold 10% aq NaOH solution (120 mL). This mixture was extracted with two 150 mL portions of EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide 4.9 g of a reddish-orange oil. ^{1}H NMR analysis showed the desired product, contaminated with AcOH and some unreacted starting material. The material was redissolved in EtOAc (150 mL) and washed with H_2O, 10% aq NaOH, H_2O, and brine. After drying over Na_2SO_4, filtering, and evaporation, the desired product was obtained as an orange oil (4.16 g, 19.2 mmol, 88% yield), which solidified upon storage at 0 °C. MS (EI) *m*/*z*: 218, 216 (M, 30). ^{1}H NMR ($CDCl_3$): δ 7.03 (d, J = 8, 1H), 6.55 (d, J = 8, 1H), 4.25 (q, J = 7, 2H), 1.35 (t, J = 7, 3H).

2-[(2-Bromo-6-ethoxy-pyridin-3-ylamino)-methylene]-malonic Acid Diethyl Ester (10). A neat solution of 2-bromo-6-ethoxy-pyridin-3-ylamine (2.20 g, 10.1 mmol) and 2-ethoxymethylene-malonic acid diethyl ester (2.05 mL, 2.18 g, 10.1 mmol) were heated to 50 °C for 8 h to form a moist, blackened solid. The solid was recrystallized from a minimum of isopropyl ether. The solid was filtered and washed with 0 °C ethyl ether to yield opaque, light pink, needlelike crystals (3.45 g, 88%). mp 166 °C. R_f = 0.23 (10% EtOAc−hexane). Anal. Calcd for $C_{15}H_{19}BrN_2O_5$: C, 46.53; H, 4.95; N, 7.23. Found: C, 46.45; H, 4.88; N, 7.09. ^{1}H NMR (400 MHz, CD_3OD): δ 11.17 (bd, J = 11.4, 1H), 8.33 (d, J = 13.3, 1H), 7.50 (d, J = 8.7, 1H), 6.75 (d, J = 8.7, 1H), 4.35 (q, J = 6.2, 4H), 4.24 (q, J = 7.3, 2H), 1.38 (t, J = 7.1, 6H), 1.32 (t, J = 7.3, 3H). ^{13}C NMR (300 MHz, CD_3OD): δ 168.7, 165.9, 159.9, 151.1, 150.9, 129.8, 129.2, 127.6, 112.7, 111.1, 95.4, 63.3, 60.9, 60.6, 14.6.

3-(6-Ethoxy-4-methoxy-2-oxo-2*H*-[1,5]naphthyridin-1-yl)-3-methoxy-propionic Acid Methyl Ester (11). Bromide **9** (1.0 g, 4.6 mmol), methyl β-methoxyacrylate (1.0 mL, 1.08 g, 9.2 mmol), $Pd(OAc)_2$ (53 mg, 0.23 mmol, 5 mol %), and tri-(*o*-tolyl)phosphine (578 mg, 1.84 mmol, 40 mol %) were combined in a dry, N_2-purged flask equipped with a reflux condenser. Triethylamine (2.3 mL, 1.67 g, 16.5 mmol) was added, and the flask was placed in a 100 °C oil bath for 5 days. The reaction mixture was cooled to room temperature and diluted with ca. 50 mL of 1:1 hexanes−EtOAc. The solution was filtered through Celite and then washed with two 20-mL portions each of H_2O, aq $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated to provide 700 mg of a dark-brown solid. Chromatography on 50 g of silica gel, eluting with 40:10:1 hexanes−EtOAc−Et_3N provided Heck product **11** (R_f = 0.16 in 2:1 hexanes−EtOAc) as a dark-green oil which solidified upon storage at 0 °C (434 mg, 1.29 mmol, 28% yield). MS (CI) *m*/*z*: 337 (M + H, 100). ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H), 7.80 (d, J = 9, 1H), 6.68 (d, J = 9, 1H), 5.70 (t, J = 6, 1H), 4.51 (q, J = 7, 2H), 3.91 (s, 3H), 3.63 (s, 3H), 3.20 (s, 3H), 3.15 (dd, J = 16, 7, 1H), 2.93 (dd, J = 16, 6, 1H), 1.42 (t, J = 7, 3H).

***N′*-(2-Bromo-6-ethoxypyridin-3-yl)-*N*,*N*-dimethylformamidine (12).** Bromide **9** (300 mg, 1.38 mmol) and *N*,*N*-dimethylformamide-dimethylacetal (0.22 mL, 0.20 g, 1.66 mmol) were combined in 8 mL of toluene and placed in a 50 °C oil bath for 3 days. GC/MS indicated incomplete conversion; therefore, another portion of dimethylacetal (0.055 mL, 0.049 g, 0.41 mmol) was added. After warming to 50 °C for another 20 h, the reaction mixture was cooled to room temperature and concentrated to provide a dark red oil. The crude product was purified by chromatography on 15 g of silica gel, eluting with 40:10:1 hexanes−EtOAc−Et_3N. The product-containing fractions were combined and concentrated to provide amidine **12** as a red solid (295 mg, 1.08 mmol, 78% yield). MS (CI) *m*/*z*: 274, 272 (M + H, 100).; ^{1}H NMR ($CDCl_3$): δ 7.44 (s, 1H), 7.22 (d, J = 8, 1H), 6.60 (d, J = 8, 1H), 4.30 (q, J = 7, 2H), 3.14 (br s, 3H), 3.07 (br s, 3H), 1.35 (t, J = 7, 3H).

3-Amino-6-ethoxy-pyridine-2-carbonitrile (13). To a stirring solution of 2-bromo-6-ethoxy-pyridin-3-ylamine (23.0 g, 106 mmol) in DMF (500 mL) was added $Zn(CN)_2$ (18.7 g, 159 mmol), followed by $Pd(PPh_3)_4$ (12.20 g, 11 mmol). The mixture was heated to 80 °C for 3 h and then cooled to 25 °C. The solids were filtered, and the filtrate was diluted with EtOAc (1.0 L) and washed with 1.0 N HCl (1.0 L) and H_2O (3 × 1.0 L). The organic phase was collected and dried over $MgSO_4$. The solvent was removed via rotary evaporator, and the resulting solid recrystallized from 20:1 hexane−EtOAc (800 mL) to yield small, rust-colored crystals (12.1 g, 70.0%). mp 104−105 °C. R_f = 0.65 (10% CH_3OH/CH_2Cl_2). Anal. Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.72; H, 5.25; N, 25.44. ^{1}H NMR (400 MHz, CD_3OD): δ 7.08 (d, J = 9.2, 1H), 6.77 (d, J = 9.2, 1H), 4.25 (q, J = 7.1, 2H), 3.96 (bs, 2H), 1.33 (t, J = 7.1, 3H). ^{13}C NMR (300 MHz, CD_3OD): δ 156.9, 142.7, 128.3, 118.2, 116.8, 111.5, 62.3, 14.7.

3-(2-Cyano-6-ethoxy-pyridin-3-ylamino)-acrylic Acid Ethyl Ester (14). To a stirring solution of 3-amino-6-ethoxy-pyridine-2-carbonitrile (2.0 g, 12.3 mmol) and 3-ethoxy-acrylic acid ethyl ester (1.95 mL, 1.95 g, 13.5 mmol) in THF (25 mL) at −78 °C was added NaHMDS (1.0 M in THF, 14.8 mL, 14.8 mmol) dropwise over 20 min. The solution was allowed to warm to 25 °C and was stirred for 1 h. The crude reaction mixture was concentrated via rotary evaporator, and the crude residue was purified on a silica gel column, 4:1 hexane−EtOAc. Two major UV active products were visible. The less-polar UV active product was collected and concentrated to yield a light-yellow, flaky solid (1.68 g, 52.2%). mp 140−141 °C. R_f = 0.15 (10% EtOAc−hexane).

(12) den Hertog, J. *Recl. Trav. Chim. Pays-Bas* **1953**, *72*, 125−131.

Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.69; H, 5.64; N, 15.94. ^{1}H NMR (400 MHz, CD_3OD): δ 10.44 (bd, J = 11.6, 1H), 7.42 (d, J = 9.1, 1H), 7.10 (dd, J = 11.8, 8.3, 1H), 5.02 (d, J = 8.5, 1H), 4.32 (q, J = 7.1, 2H), 4.24 (q, J = 7.1, 2H), 1.37 (t, J = 7.3, 3H), 1.31 (t, J = 7.1, 3H). ^{13}C NMR (300 MHz, CD_3OD): δ 169.9, 159.1, 141.0, 137.0, 126.0, 117.9, 116.2, 115.6, 112.5, 92.0, 62.9, 60.2, 14.6.

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