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Regioselective Synthesis of an Imidazo[4,5-*c*]pyridine through Selective Acylation of 3,4-Diaminopyridine: Synthesis of CP-885,316

Stéphane Caron,* Nga M. Do, Ruth E. McDermott, and S. Bahmanyar†

Chemical R&D, Pfizer Global R&D, MS-8118D/4002, Groton, Connecticut 06340, U.S.A.

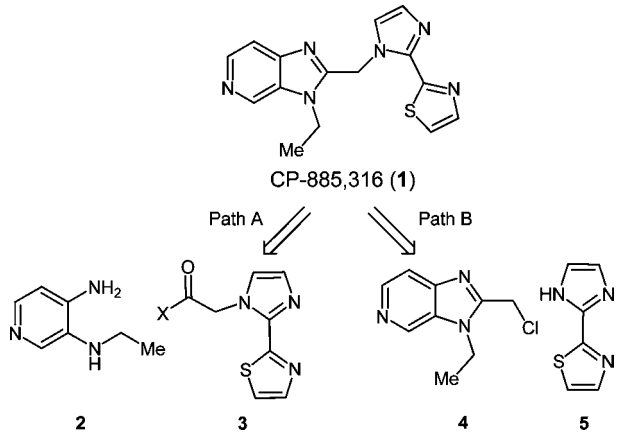
Abstract:

CP-885,316 (1), an imidazo[4,5-*c*]pyridine, 4, was prepared from 3,4-diaminopyridine (9). Two routes were demonstrated using the regioselective introduction of either an acetamide at the 3-position or a *tert*-butylcarbamate at the 4-position.

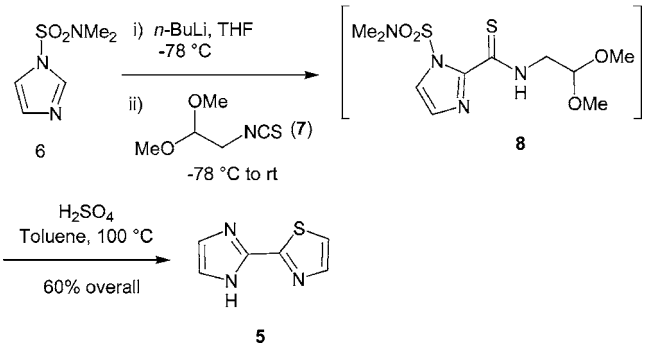
The benzimidazole[1–3] and imidazopyridine[4–6] moieties are important pharmacophores which have proven to be useful for a number of biologically relevant targets. The preparation of these compounds is usually straightforward, and a number of synthetic methods are already available.[7–11] We were recently asked to identify an efficient synthesis of imidazo-[4,5-*c*]pyridine (**1**) which would be amenable to its preparation on a multikilogram scale. Two retrosyntheses for the final assembly of **1** involve either the reaction of the diaminopyridine **2** with a carboxylic acid derivative **3** (Path A) or the alkylation of imidazo[4,5-*c*]pyridine, **4**, with a thiazoloimidazole **5** (Path B) as depicted in Scheme 1. The latter was selected as our last bond-forming step since it allowed the use of two key intermediates with anticipated superior stability and handling properties.

Herein, we report our efforts in the identification of a scalable route for the preparation of CP-885,316 (**1**) which led to the discovery of an unanticipated reversal in the regioselectivity in the acylation of 3,4-diamino-pyridine (**9**) with either acetyl chloride or di-*tert*-butyl-dicarbonate.

Scheme 1. **Potential retrosynthesis of 1**



Scheme 2. **Synthesis of thiazoloimidazole 5**



Discussion

The synthesis of thiazoloimidazole **5** was accomplished readily by a simple modification of a procedure recently identified by Liras and co-workers.[12] Lithiation at the 2-position of the sulfonamide-protected imidazole **6**[13] and reaction with thioisocyanate **7** led to formation of thioamide **8** which was not isolated and was cyclized using sulfuric acid in toluene to afford the desired product in 60% overall yield (Scheme 2).

The preparation of imidazo[4,5-*c*]pyridine, **4**, proved to be a more difficult task. While the obvious starting material, 3,4-diaminopyridine (**9**), is commercially available,[14,15] conditions for the regioselective introduction of the ethyl side

* To whom correspondence should be addressed. E-mail: stephane.caron@pfizer.com.

† Chemical R&D, Pfizer Global R&D-La Jolla, 10578 Science Center Drive, San Diego, California 92121.

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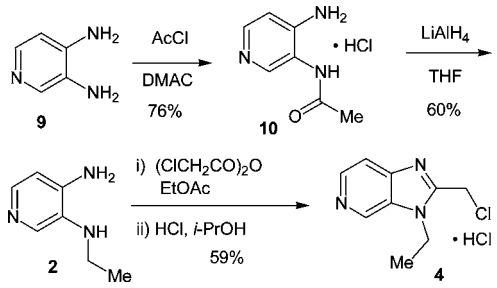
Scheme 3. **Synthesis of imidazo[4,5-*c*]pyridine, 4, by selective acylation at the 3-position**



chain at the 3-position needed to be identified. Reductive amination with acetaldehyde was first attempted but led to a complex mixture of several products. The second strategy evaluated was the selective acylation of the 3-amino position. We reasoned that the 4-position of the pyridine should be deactivated, thus leaving the 3-position more nucleophilic.[16,17] Furthermore, HBTU-mediated coupling of a carboxylic acid with **9** as been reported.[18] Upon treatment of **9** with one equivalent of acetyl chloride in dimethylacetamide (DMAC), the hydrochloride salt of the 3-acetylated pyridine **10** was generated and precipitated from the reaction mixture in 76% yield. This result is in contrast with what has been reported with a substoichiometric amount of an acid chloride[19] as well as a benzoyl chloride derivative.[20] The choice of solvent for this reaction proved to be a key contributing factor since it precipitated the desired product and kept small amounts of the 4-acetylated and 3,4-diacetylated products in solution. Amide **10** was reduced to its ethyl derivative **2** with $LiAlH_4$ in THF to provide a 60% yield after crystallization from toluene.[21] Finally, the imidazole was generated in a two-step process by treatment of dianiline **2** with chloroacetic anhydride in EtOAc followed by reaction with HCl in 2-propanol to complete the dehydration and salt formation. Imidazo[4,5-*c*]pyridine, **4**, was isolated in 59% yield as its hydrochloride salt after crystallization from 2-propanol as shown in Scheme 3.

An alternative approach was identified when **9** was reacted with *tert*-butyl dicarbonate in CH_2Cl_2. Unexpectedly, the carbamate was regioselectively introduced at the 4-position of the pyridine in 78% yield after crystallization from MTBE/hexanes.[22,23] The reversal of the regiochemical outcome certainly came as a surprise to us. Frontier molecular orbital

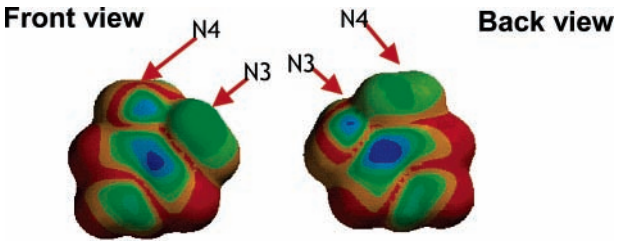
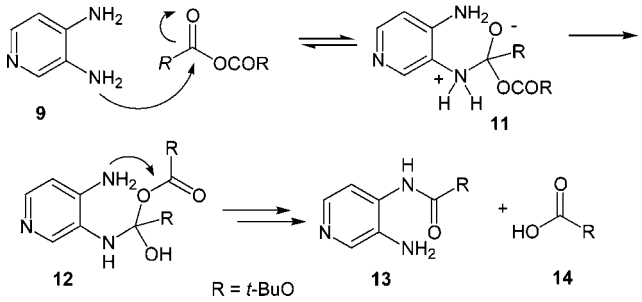


Figure 1. **HOMO maps generated for 3,4-diaminopyridine. The darker the blue contour, the larger the HOMO coefficient at that site.**

Scheme 4. **Proposed mechanism for the selective acylation at the 4-position with *tert*-butyl dicarbonate**



analysis[24] confirmed that the N-3 nitrogen would be expected to be more nucleophilic as shown in Figure 1.[25]

It is clear that the different regioselectivity obtained from Boc_2O is not the outcome of kinetic reactivity at the N-4 center but rather the outcome of a change in reaction mechanism between the acid chloride and the dicarbonate. One potential mechanism is depicted in Scheme 4. It is probable that the acylation still proceeds at the 3-position to provide intermediate **11**. Zwitterion **12** could be generated after deprotonation of the 4-amino position. The anilide can then add to the carbonate to provide carbamate **13** and *tert*-butylcarbonic acid which decomposes to CO_2 and *t*-BuOH. Alternatively, proton transfer could occur at the 3-position which could be followed by nucleophilic attack by the amine at the 4-position. When the reaction is conducted with an anhydride such as acetic anhydride, acylation at the 3-position was observed. This could be resulting from the fact that the intermediate analogous to **11** contains an acetate which is a better leaving group than a carbonate. Additionally, the 3-ethyl carbamate was prepared by reaction of **13** with ethyl chloroformate and deprotection of the *tert*-butyl carbamate. We have not observed migration of the ethyl carbamate to the 4-position.

With the 4-protected aminopyridine **13** in hand, introduction of the ethyl side chain at the 3-position through reductive amination was now possible (Scheme 5). Indeed, the imine was generated in ethanol with acetaldehyde and reduced with $NaBH_4$ at 0 °C to ethyl aniline **15**. The crude solid thus obtained could be converted directly to the desired imidazo-[4,5-*c*]pyridine, **4**, by condensation with chloroacetic anhydride in the presence of a catalytic amount of TFA followed

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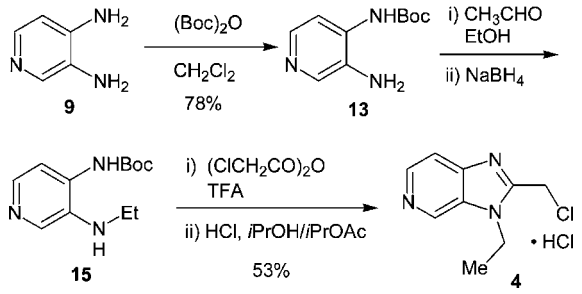
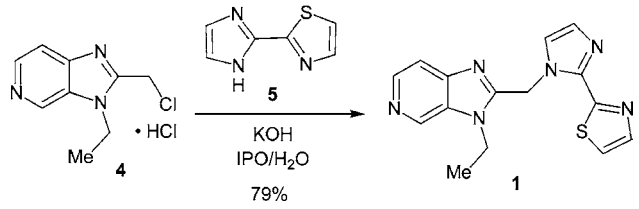
(25) HOMO maps were generated using *Spartan*, V2.0; Wavefunction, Inc: Irvine, CA 92612. Details of the calculations can be found in Supporting Information.

Scheme 5. **Synthesis of Imidazo[4,5-*c*]pyridine, 4, by selective carbamate formation at the 4-position**



Scheme 6. **Completion of the Synthesis of CP-885,316 (1)**



by cyclization with hydrochloric acid in a mixture of *i*-PrOH and *i*-PrOAc. This sequence provided **4** in 53% overall yield from carbamate **13**.

As shown in Scheme 6, completion of the synthesis was achieved by alkylation of the HCl salt **4** with thiazoloimidazole **5** in a *i*-PrOH/H_2O mixture using KOH as the base to afford **1** in 78% yield.

In conclusion, an efficient, convergent synthesis of CP-885,316 (**1**) was exemplified. Two routes to the key imidazo-[4,5-*c*]pyridine, **4**, were discovered, and conditions for the selective acylation of either the 3- or 4-position of 3,4-diaminopyridine were identified. While both synthetic routes proved to be acceptable for scale-up, the second route presented is preferable because of the higher throughput, the avoidance of cryogenic conditions, and a more practical reducing agent in $NaBH_4$. Further evaluation of the reaction mechanism which led to such regioselectivity is underway.

Experimental Details

Experimental Section. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Reactions were performed under a dry N_2 atmosphere and monitored using HPLC. Melting points were measured in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured in $CDCl_3$ unless otherwise indicated. IR spectra were recorded as thin films on NaCl plates unless otherwise indicated.

2-(1*H*-Imidazol-2-yl)thiazole (5). To a solution of imidazole-1-sulfonic acid dimethylamide (**6**) (8.45 g, 48.2 mmol) in THF (80 mL) at −78 °C under N_2 was added *n*-BuLi (21.2 mL of a 2.5 M solution in hexanes, 53.0 mmol) slowly, while maintaining internal temperature below −65 °C. The resulting reaction mixture was stirred at −78 °C for 1 h before 2-isothiocyanato-1,1-dimethoxy-ethane (**7**) (6.50 mL, 48.2 mmol) was added, while maintaining internal temperature below −65 °C. The resulting reaction mixture was stirred at −78 °C for 2 h, allowed to warm to room temperature, and stirred overnight. The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (50 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 1-dimethylsulfamoyl-1*H*-imidazole-2-carbothioic acid (2,2-dimethoxy-ethyl)amide (**8**) as a dark-brown oil. The crude material (15.55 g) was dissolved in toluene (70 mL), and H_2SO_4 (20 mL) was added. The resulting reaction mixture was heated to 100 °C and stirred overnight. H_2O (100 mL) was added, and the reaction mixture was then cooled to room temperature. (Note: If reaction was cooled prior to addition of H_2O, the reaction mixture solidified.) The layers were separated, and the aqueous phase was basified with NH_4OH (to pH 9). The basified aq layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a brown, soft solid. The material was triturated with MTBE (50 mL) and filtered to afford isolated brown crystals of 2-(1*H*-imidazol-2-yl)thiazole (**5**) (4.34 g, 60%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.05 (s, 1), 7.27 (s, 1), 7.72 (d, 1, J = 3.3 Hz), 7.89 (d, 1, J = 3.3 Hz), 13.09 (br s, 1). ^{13}C NMR (100 MHz, d_6-DMSO) δ 119.71, 120.88, 130.40, 141.71, 143.88, 159.68. IR 3112, 1572, 1492, 1353, 1289, 1107, 937, 776, 731, 617 cm^{-1}. Anal. calcd for $C_6H_5N_3S$: C, 47.66; H, 3.33; N, 27.79. Found: C, 47.72; H, 3.02; N, 27.38.

***N*-(4-Amino-pyridin-3-yl)acetamide Hydrochloride (10).** To a solution of the 3,4-diaminopyridine (**9**) (10.53 g) in dimethyl acetamide (100 mL) was slowly added acetyl chloride (6.9 mL), keeping the temperature below 22 °C. The reaction was stirred at room temperature for 16 h upon which time cream solids had precipitated. The solids were filtered, washed with CH_2Cl_2 (2 × 50 mL), and dried under vacuum to give *N*-(4-amino-pyridin-3-yl)acetamide hydrochloride (**10**) (13.803 g, 76%). Mp = 232−234 °C dec. ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.11 (s, 3), 6.9 (d, 1, J = 6.6 Hz), 7.99 (d, 2, J = 6.6 Hz), 8.52 (s, 1), 10.05 (s, 1), 13.56 (s, 1). ^{13}C NMR (100 MHz, d_6-DMSO) δ 24.01, 109.88, 120.83, 134.53, 137.09, 154.26. IR 3353, 3187, 2950, 2836, 1651, 1563, 1507, 1372, 1268, 1029, 817, 668, 577 cm^{-1}. Anal. calcd for $C_7H_{10}ClN_3O$: C, 44.81; H, 5.37; N, 22.40. Found: C, 44.80; H, 5.35; N, 22.18.

***N*-3-Ethyl-pyridine-3,4-diamine (2).** To a slurry of *N*-(4-amino-pyridin-3-yl)acetamide hydrochloride (**10**) (16.27 g) in THF (165 mL) under N_2 was added slowly, via an addition funnel, a 1.0 M solution of $LiAlH_4$ in THF (260 mL) while maintaining an internal temperature below 25 °C. The resulting reaction mixture was stirred at room temperature for 16 h. The resulting reaction mixture was cooled to 0 °C and was quenched by addition of solid Na_2SO_4·10H_2O (50 g). The resulting mixture was warmed to room temperature and stirred for 2.5 h. The reaction mixture was filtered through Celite and washed with EtOAc (2 × 50 mL). The filtrate was concentrated in vacuo and crystallized from toluene to give *N*-3-ethyl-pyridine-3,4-diamine (**2**) (7.10 g, 60%). MP = 119−121 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.16 (t, 3, J = 7.0 Hz), 3.01 (qd, 2, J = 7.0 Hz, 5.4 Hz),

3.34 (s, 1), 4.34 (t, 1, $J = 5.2$), 5.38 (s, 1), 6.37 (d, 1, $J = 5.0$), 7.49 (d, 2, $J = 5.0$). ^{13}C NMR (100 MHz, d_6-DMSO) δ 15.16, 38.42, 108.41, 131.54, 135.96, 139.98, 142.28. IR 3358, 3243, 2971, 1588, 1519, 1427, 1333, 821, 740 cm^{-1}. Anal. calcd for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63. Found: C, 60.99; H, 8.05; N, 30.84.

2-Chloromethyl-3-ethyl-3*H*-imidazo[4,5-*c*]pyridine Hydrochloride (4). To a solution of chloroacetic anhydride (10.30 g) in EtOAc (40 mL) was added in one portion *N*-3-ethyl-pyridine-3,4-diamine (**2**) (2.01 g). After approximately 10 min, bright yellow solids had precipitated. The slurry was stirred at room temperature under N_2 for 16 h. The reaction slurry was poured into 6 *N* NaOH (40 mL). The layers were separated and the organic layer was washed again with 1 *N* NaOH. The combined aqueous layers were back extracted with additional EtOAc (20 mL). The combined organic phases were then washed with brine, dried over Na_2SO_4, and filtered. Concentrated HCl (2 mL) was added and the filtrate was diluted with *i*-PrOH (30 mL). All solvents were removed in vacuo. The resulting yellow soft solid was recrystallized from *i*-PrOH to give 2-chloromethyl-3-ethyl-3*H*-imidazo[4,5-*c*]pyridine (**4**) (2.02 g, 59%). MP = 218−220 °C decomp. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.41 (t, 3, $J = 7.2$), 4.56 (q, 2, $J = 7.2$), 5.24 (s, 1), 8.21 (d, 1, $J = 6.6$), 8.59 (d, 1, $J = 6.6$), 9.64 (s, 1). ^{13}C NMR (100 MHz, d_6-DMSO) δ 15.84, 36.34, 41.01, 117.36, 129.58, 133.20, 133.89, 151.66, 160.25. IR 3046, 2966, 2511, 1640, 1461, 1318, 848 cm^{-1}. Anal. calcd for $C_9H_{11}Cl_2N_3$: C, 46.57; H, 4.77; N, 18.10. Found: C, 46.79; H, 4.71; N, 17.93.

(3-Amino-pyridin-4-yl)-carbamic acid *tert*-butyl ester (13). To a suspension of 3,4-diaminopyridine (**9**) (8.35 g, 75 mmol) in CH_2Cl_2 (75 mL) was added dropwise di-*tert*-butyl dicarbonate (16.73 g, 75 mmol) in CH_2Cl_2. The reaction was allowed to stir at room temperature overnight. 1N HCl (86.2 mL) was added dropwise and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (75 mL) and the organic extracts were discarded. To the aqueous layer was added CH_2Cl_2 (75 mL). The mixture was stirred and K_2CO_3 (8.25 g) was added. The resulting pH of the aqueous layer was 8−9. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. The product was crystallized from MTBE and hexanes at 0 °C to provide (3-amino-pyridin-4-yl)-carbamic acid *tert*-butyl ester (**13**) as a light-yellow solid (12.24 g, 78%). Mp = 124−126 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.46 (s, 9), 5.08 (bs, 2), 7.50 (d, 1, $J = 5.2$), 7.68 (d, 1, $J = 5.4$), 7.91 (s, 1), 8.61 (s, 1). ^{13}C NMR (100 MHz, d_6-DMSO) δ 28.70, 80.47, 115.21, 131.28, 135.27, 138.41, 138.88, 153.37. IR 2978, 1716, 1588, 1515, 1249, 1154 cm^{-1}. Anal. calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.50; H, 7.29; N, 20.06.

(3-Ethylamino-pyridin-4-yl)carbamic Acid *tert*-Butyl Ester (15). To a solution of (3-amino-pyridin-4-yl)carbamic acid *tert*-butyl ester (**13**) (5 g, 23.89 mmol) in EtOH (119 mL) at 0 °C was added dropwise acetaldehyde (3.35 mL, 58.72 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The mixture was cooled to 0 °C, and $NaBH_4$ (2.26 g, 59.74 mmol) was added in three portions, keeping the temperature below 5 °C. The reaction was allowed to warm to room temperature and was stirred for 10 h. The mixture was cooled to 0 °C, and H_2O (∼140 mL) was added dropwise, keeping the temperature below 5 °C. CH_2Cl_2 (100 mL) was added to the mixture followed by a dropwise addition of a 10% aqueous citric acid until the pH was neutral. The mixture was stirred for an additional 30 min, and CH_2Cl_2 (100 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give (3-(ethylamino)pyridin-4-yl)carbamic acid *tert*-butyl ester (**15**) (5.94 g of crude material, 89% purity, 93% yield). A small portion of the material was purified by silica gel chromatography (25% MeOH/MTBE) for characterization purposes. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.20 (t, 3, $J = 7.1$), 1.46 (s, 9), 3.04−3.11 (m, 2), 5.15 (t, 1, $J = 4.5$), 7.54 (d, 1, $J = 5.2$), 7.76 (d, 1, $J = 5.2$), 7.83 (s, 1), 8.67 (s, 1). ^{13}C NMR (100 MHz, d_6-DMSO) δ 14.89, 28.69, 38.30, 80.55, 115.04, 131.71, 133.53, 135.27, 138.84, 153.42. IR 2976, 1734, 1591, 1512, 1242, 1156 cm^{-1}. Anal. calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.85; H, 7.95; N, 17.61.

2-Chloromethyl-3-ethyl-3*H*-imidazo[4,5-*c*]pyridine Hydrochloride (4). To a solution of chloroacetic anhydride (9.80 g, 57.3 mmol) in CH_2Cl_2 (44 mL) was added (3-(ethylamino)pyridin-4-yl)carbamic acid *tert*-butyl ester (**15**) as a crude solid from the previous step (3.39 g, 14.3 mmol). To the clear, bright-yellow solution was added TFA (0.21 mL, 2.7 mmol). The reaction was stirred at 30 °C for 3 days, poured into a separatory funnel, and washed with 5 N NaOH (32.5 mL). The layers were separated, and the organic extract was washed with 1 N NaOH (22.5 mL) and brine (22.5 mL). The organic extract was diluted with *i*-PrOH (22 mL) and *i*-PrOAc (74 mL), and concentrated HCl (2.2 mL) was added. The mixture was concentrated to an orange solid under reduced pressure, and the product was crystallized from *i*-PrOH to afford 2-chloromethyl-3-ethyl-3*H*-imidazo[4,5-*c*]-pyridine hydrochloride (**4**) (1.78 g, 53%). This product was identical by ^{1}H NMR to the product prepared by the acetyl chloride approach.

3-Ethyl-2-(2-thiazol-2-yl-imidazol-1-ylmethyl)-3*H*-imidazo[4,5-*c*]pyridine (CP-885,316) (1). To a solution of 2-(1*H*-imidazol-2-yl)-thiazole (**5**) (3.70 kg, 24.4 mol) in *i*-PrOH (22 L) was added KOH (3337 g of 85% grade, 50.55 mol) in H_2O (28 L). To the mixture was added 2-chloromethyl-3-ethyl-3*H*-imidazo[4,5-*c*]pyridine hydrochloride (**4**)-(4.88 kg, 21.0 mol) in H_2O (15.5 L); the reaction mixture was stirred at room temperature for 16 h, cooled to 0 °C, filtered, and washed with H_2O (4 × 10 L). The solids were dried in vacuo to give CP-885,316 (**1**) (5.16 kg, 79%). ^{1}H NMR (400 MHz, CD_3OD) δ 1.41 (t, 3, $J = 7.5$), 4.55 (q, 1, $J = 7.5$), 6.28 (s, 1), 7.19 (d, 1, $J = 1.2$), 7.44 (d, 1, $J = 1.2$), 7.54 (d, 1, $J = 3.3$), 7.55 (d, 1, $J = 1.6$), 7.73 (d, 1, $J = 3.3$), 8.29 (d, 1, $J = 5.4$), 8.91 (s, 1). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 15.50, 39.99, 44.22, 114.91, 120.49, 124.06,

130.40, 133.49, 133.96, 140.64, 142.53, 143.57, 148.13, 152.67, 160.67. IR 3123, 3065, 2976, 1605, 1579, 1497, 1468, 1355, 1280, 1056, 994, 913, 816, 619 cm^{-1}. Anal. calcd for $C_{15}H_{14}N_6S$: C, 58.05; H, 4.55; N, 27.08; S, 10.33. Found: C, 58.07; H, 4.51; N, 27.03; S, 10.13.

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Supporting Information Available

Cartesian coordinates and details about the calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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