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Synthesis of 3-Aminopyrazinone Mediated by 2-Pyridylthioimidate−$ZnCl_2$ Complexes. Development of an Efficient Route to a Thrombin Inhibitor

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A six-step preparation of thrombin inhibitor drug candidate **1** from pyrazinone **7** in 47% overall yield is described. The problem of low reactivity between weak amine nucleophile **4** and poor electrophile 3-bromopyrazinone **17** was overcome with the use of pyridinylthioimidate **27** in the presence of $ZnCl_2$ to afford adduct **3** in high yield. Several zinc complexes were characterized by solution and solid-state NMR and X-ray crystallographic analyses, and provided insight into the reaction mechanism. Preparation of pyridine *N*-oxide amine **4** was accomplished via a selective oxidation of the corresponding pyridinylamine **6**. Pyridinylthioimidate **27** was prepared from pyrazinone **7** via a two-step one-pot process in near quantitative yield. Chlorination of the pyrazinone ring in **3** followed by hydrolysis and amide coupling completed the synthesis of **1**. This chromatography-free synthesis was used successfully to prepare multikilogram quantities of the drug with reproducibility and high purity.

Introduction

Compound **1** is a potent, orally active thrombin inhibitor potentially useful for the prevention and treatment of venous and cardiogenic thromboembolism.[1] The compound is a rapid-binding, reversible competitive inhibitor of thrombin with high selectivity versus other protease targets. The compound has good oral bioavailability and shows efficacy against thrombosis in the rat ferric chloride and the African Green Monkey models. In addition to a clean profile in the in vitro assays, the compound exhibited minimum side effects in a Rhesus model. To further study this molecule and its biological activity, an efficient synthesis was required.

Compound **2a**, a related thrombin inhibitor analogue reported previously,[1] differs from **1** by only a *N*-oxide-free pyridine and a different arylmethylamine (Scheme 1). Our initial synthetic efforts were predicated on the expectation that a late intermediate common to compound **2a** could be easily oxidized to a pyridine *N*-oxide. However, **2a**−**d** rapidly degraded in the presence of oxidants via fragmentation of the pyrazinone ring based on LC/MS analyses. Therefore, the pyridine *N*-oxide functionality required construction prior to appending to the pyrazinone. Scheme 1 illustrates the three necessary building blocks: 2,2-difluoro-2-(1-oxido-2-pyridinyl)ethylamine (**4**), pyrazinone **7**, and 2-fluorobenzylamine. Compound **4** could be derived from a selective oxidation of pyridine amine **6**, which in turn would be made from 2-bromopyridine. The preparation of pyrazinone **7** has been described previously from oxalate, glycine ester, and glycinal acetal,[1] and 2-fluorobenzylamine is commercially available. We expected to join **4** and **7** via halogenated imidate **5**.[1] However, this coupling reaction suffered due to the weak nucleophilicity of amine **4** and the poor reactivities of halo-imidates **5**. This paper reports our solution to this coupling problem via activation by 2-pyridylthioimidate and $ZnCl_2$, which significantly improved the coupling efficiency. In addition, we detail the characterization of several $ZnCl_2$ complexes in an effort to gain further insight into the mechanism of the reaction. We also describe a selective oxidation of pyridine amine **4**, an efficient preparation of **27**, and the final construction to **1**.

Results and Discussion

Pyridine *N*-Oxide Amine 4. A seven-step route[1] to **4** (Scheme 2, route A) was previously reported from these laboratories involving condensation of 2-lithiopyridine

† Department of Analytical Research.

(1) (a) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Nantermet, P. G.; Selnick, H. G.; Isaacs, R. C. A.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Singh, R.; Miller-Stein, C.; White, R. B.; Wong, B.; Lyle, E. A.; Stranieri, M. T.; Cook, J. J.; McMasters, D. R.; Pellicore, J. M.; Pal, S.; Wallace, A. A.; Clayton, F. C.; Bohn, D.; Welsh, D. C.; Lynch, J. J., Jr.; Yan, Y.; Chen, Z.; Kuo, L.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1353−1357. (b) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Sanderson, P. E. J.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Singh, R.; Miller-Stein, C.; White, R. B.; Wong, B.; Lyle, E. A.; Williams, P. D.; Coburn, C. A.; Dorsey, B. D.; Barrow, J. C.; Stranieri, M. T.; Holahan, M. A.; Sitko, G. R.; Cook, J. J.; McMasters, D. R.; McDonough, C. M.; Sanders, W. M.; Wallace, A. A.; Clayton, F. C.; Bohn, D.; Leonard, Y. M.; Detwiler, T. J., Jr.; Lynch, J. J., Jr.; Yan, Y.; Chen, Z.; Kuo, L.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. *J. Med. Chem.* **2003**, *46*, 461−473. (c) Dolling, U. H.; Alabaster, R. J.; Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Davies, A. J. PCT Int. Appl. WO 0246160, 2002. (d) Cowden, C.; Cooper, V. B.; Rush, D. J.; Frech, P. PCT Int. Appl. WO 0192234, 2001. (e) Burgey, C.; Isaacs, R. C.; Dorsey, B. D.; Robinson, K. A.; Staas, D.; Sanderson, P. E.; Barrow, J. PCT Int. Appl. WO 0138323, 2001. (f) Burgey, C. S.; Robinson, K. A.; Williams, P. D.; Coburn, C. A.; Lyle, T. A.; Sanderson, P. E. PCT Int. Appl. WO 0075134, 2000.

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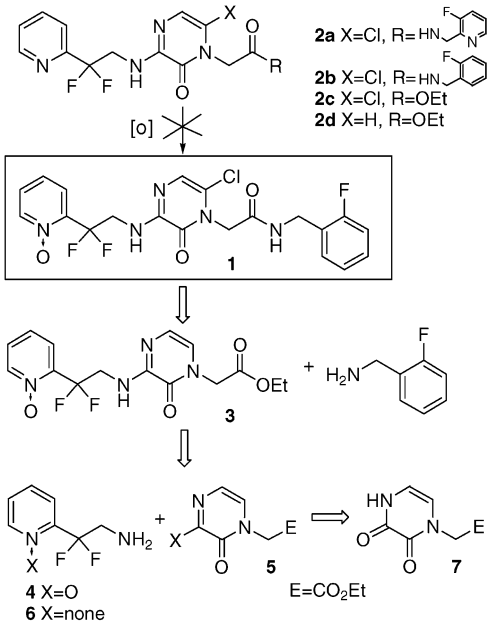
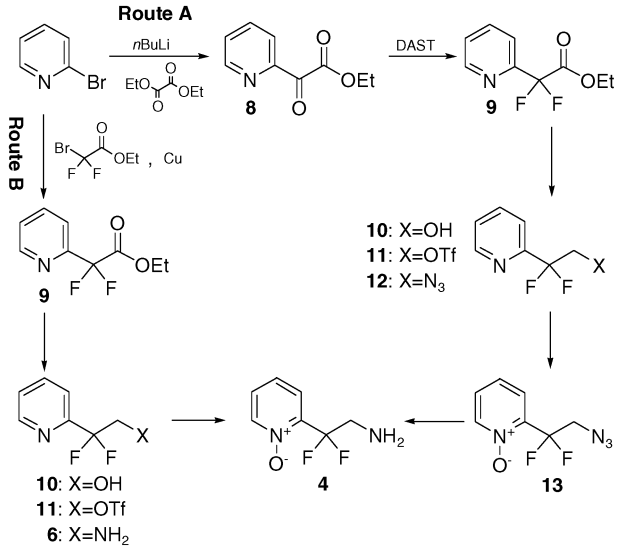
SCHEME 1. Retrosynthetic Analysis of 1

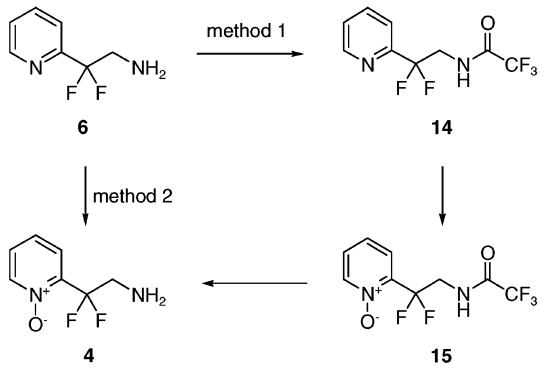


SCHEME 2. Synthesis of 4

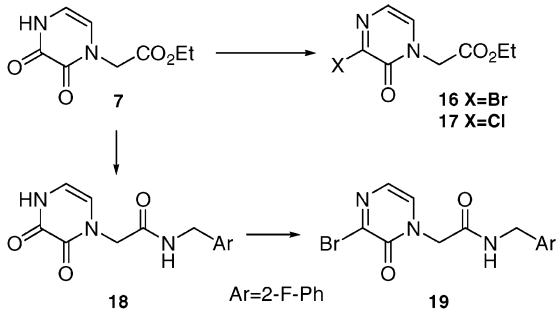


and diethyl oxalate followed by DAST difluorination, $NaBH_4$ reduction, triflate formation, and azide displacement to afford 2,2-difluoro-2-(2-pyridyl)ethyl azide (**12**, 34% overall yield). Subsequent MCPBA *N*-oxidation, followed by triphenylphosphine reduction of azide **13** afforded amine **4**. A more efficient synthesis of **4** was later devised based on Kobayashi et al.'s copper-mediated coupling of 2-bromopyridine and iododifluoroacetate (route B).[2] Several modifications were made to make this reaction more amenable for large-scale synthesis. The more readily available ethyl bromodifluoroacetate replaced ethyl iododifluoroacetate.[3] DMF replaced DMSO due to safety concerns with Cu-DMSO exotherms at high

SCHEME 3. Pyridine *N*-Oxidation of 6



SCHEME 4. Preparation of Bromopyrazinones 16 and 19



temperatures. In addition, the conversion of alcohol **10** to amine **6** was accomplished by directly treating the corresponding triflate with ammonium hydroxide. Pure amine **6** was isolated as the benzenesulfonate salt (BSA).[1]

Two methods were developed for the conversion of pyridine amine **6** to pyridine *N*-oxide **4** (Scheme 3) based on Caron et al.'s trifluoroacetic anhydride (TFAA)/urea hydrogen peroxide (UHP) procedure:[4] (1) protection of the primary amine as a trifluoroacetamide **14**, pyridine *N*-oxidation with TFAA/UHP to give crystalline derivative **15**, solvolysis with ammonium hydroxide, and isolation of **4** as the trifluoroacetic acid salt; or (2) direct oxidation of the trifluoroacetic or the benzenesulfonic salt of **6**. We used the later route for the large-scale preparation due to its simplicity.

Trifluoroperacetic acid (TFPAA) was generated by the addition of TFAA to a slurry of excess UHP at −20 °C.[5] Pyridine amine **6**·BSA was then added to the peracid at <0 °C and amine **4** was eventual isolated as the crystalline amine **4**·HCl salt. Formation of the free base produced pyridine *N*-oxide **4** in isolated yields of 80% on both the gram and the kilogram scale.

First Generation Coupling Reactions. Initially, we examined the coupling of pyridine *N*-oxide amine **4** with two bromopyrazinone derivatives, bromoester **16** and bromoamide **19** (Schemes 4 and 5). Bromoester **16** was prepared from pyrazinone **7** with use of $POBr_3$ in aceto-

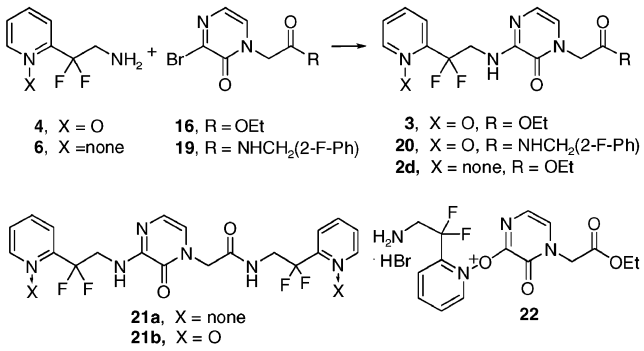
(2) (a) Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103−6106. (b) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Chem. Lett.* **1989**, 389−392.

(3) Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Wallace, D. J.; Davies, A. J.; Kennedy, D. J.; Dolling, U. H. *Tetrahedron Lett.* **2002**, *43*, 9271−9273.

(4) Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299−2302.

(5) Early oxidation efforts with TFPAA, produced by the addition of TFAA to UHP under acidic conditions in the presence of 1.2 equiv of TFA or BSA to protect the primary amine, gave a selective oxidaton of the pyridine ring in good yields, but the reaction mixture contained about 30% of the trifluoroamide **15**. Although an aqueous NaOH workup cleaved the trifluoroacetamide, isolation via extraction of very water soluble pyridine *N*-oxide **4** proved to be difficult.

SCHEME 5. Coupling with Bromopyrazinones 16 and 19

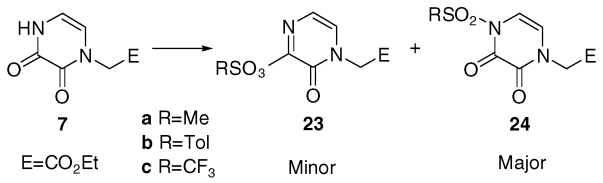


nitrile at 50−65 °C in 92−97% assay yield and 82−89% isolated yields as a crystalline solid.[1,6] Bromoamide **19** was prepared in two steps by heating pyrazinone **7** with 2-fluorobenzylamine in propionitrile to give hydroxy amide **18**, which was precipitated from the reaction by the addition of water, followed by reaction with $POBr_3$ in acetonitrile.

The coupling reactions of pyridine *N*-oxide **4** with bromoester **16** to form **3** only reached 50% conversion after refluxing in acetonitrile or toluene for 80 h. The coupling reaction of **4** with bromo-amide **19** was further complicated by the poor solubility in these solvents. Polar solvents, such as DMSO or DMPU at 120 °C, gave significant decomposition. In contrast, the coupling of pyridine amine **6** with **16** to make **2d** proceeded three times faster under the same conditions.[1,7] We speculated that the pyridine *N*-oxide functionality in **4** further contributes to the electron deficiency of the primary amine relative to **6**, and accounts for the decreased nucleophilicity (calculated pK_a values for **6** and **4** are 6.3 and 5.9, respectively). The poor nucleophilicity of amine **4** is also supported by the fact that the formation of bis-adduct **21b** is negligible relative to bis-adduct **21a** formed as a significant byproduct from the reaction with amine **6**.

In addition to decreased basicity, the pyridine *N*-oxide oxygen may be acting as a competing nucleophile. Pyridine *N*-oxides are known to add to imidoyl chlorides at or below room temperatures.[8] To amplify this side reaction, we performed the coupling reaction between pyridine *N*-oxide amine **4** and bromide **16** in refluxing anhydrous ethanol without base. The reaction reached 97% consumption of bromide **16** after 72 h**,** but gave only 50% assay yield of product, and upon workup significant amounts of pyrazinone **7** (**7**:**3** = 42:57 relative LCAP at 330 nm) were found. The reaction profile of this coupling showed that after production of **3** plateaus at about 50%, the formation of pyrazinone **7** predominated. It appeared that at 50% conversion, the remaining unreacted amine **4** was completely protonated as the HBr salt, and the addition of pyridine *N*-oxide oxygen to bromide **16** became the major manifold. The resulting adduct **22** hydrolyzed to **7** upon aqueous workup.

SCHEME 6. Sulfonylation of Pyrazinone 7



Solvents and bases were screened for the coupling reaction of **4** and **16** and the best condition achieved was toluene/EtOH (3:1; 1.5 M), 1.1 equiv of pyridine *N*-oxide amine, 1.3 equiv of Hunig's base (or 2.3 equiv with TFA salts) at ∼100 °C. The reaction remained slow, requiring 5 days to reach 90% conversion, to give assay yields of 75−80% and isolated yields of 70−75%. Due to safety concerns,[6] the reaction temperature in the kilogram scale coupling reactions was limited to 85 °C, which then required 7 days to achieve 85% conversions and 78% reaction yield.

The use of the HCl salt of amine **4** in the coupling reaction was deleterious, resulting in the conversion of bromopyrazinone **16** to chloropyrazinone **17**,[1] which reacted significantly slower than bromide **16** and led to poor coupling yields (50% vs 75%). In the presence of 2 equiv of NaI, the reaction proceeded through the intermediary iodoimidate, but gave only 46% conversion after 4 days. Other approaches, such as Pd-catalyzed amination conditions[9] ($CsCO_3$, $Pd_2(dba)_3$, BINAP, toluene), gave only ∼25% yields of product. Attempted coupling between trifluoroamide **15** and bromide **16** with NaH, KOtBu, or Mitsunobu conditions between **15** and **7** failed to give the desired product. Several attempts to prepare the fluoro analogue of **5** also failed.

Coupling of Pyridine *N*-Oxide Amine and Thioimidate. Despite the ability of the above coupling reaction to produce kilogram quantities of **3**, the long reaction time required was not practical. Although there are few known approaches to enhance the nucleophilicity of primary amines,[10] we searched for alternatives for bromopyrazinone **16** due to its instability and potential shock sensitivity safety problems.[6] We briefly examined activation of **7** via *O*-sulfonyl imidates **23**. However, reaction of **7** with mesyl chloride,[11] tosyl chloride,[12] and triflic anhydride[13] provided predominantly *N*-sulfonylated products **24**, which did not react with **4** (Scheme 6).

We were attracted to 2-mercaptopyridine as an activation group based on its successful application in the areas

(6) **CAUTION!** Solid bromopyrazinone **16** is thermally unstable with an exothermic initiation at ∼50 °C, potentially shock sensitive (1 out of 6 positive drop weight tests), and gradually decomposes at room temperature.

(7) Fleitz, F. J.; Lyle, T. A.; Zheng, N.; Armstrong, J. D., III; Volante, R. P. *Synth. Commun.* **2000**, *30*, 7171−3180.

(8) (a) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127−3129 and references therein. (b) Pyridine *N*-oxide addition to imidoyl chloride: Tachikawa, R.; Wachi, K.; Sato, S.; Terada, A. *Chem. Pharm. Bull.* **1981**, *29*, 3529−3535.

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(11) Holan, G.; Virgona, C. T.; Watson, K. G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 77−80.

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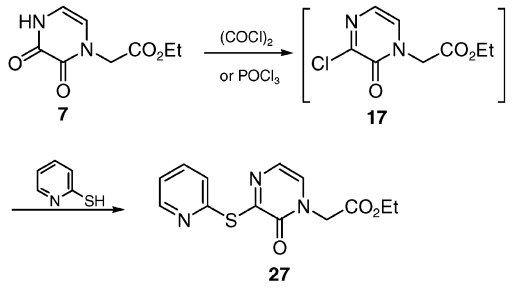
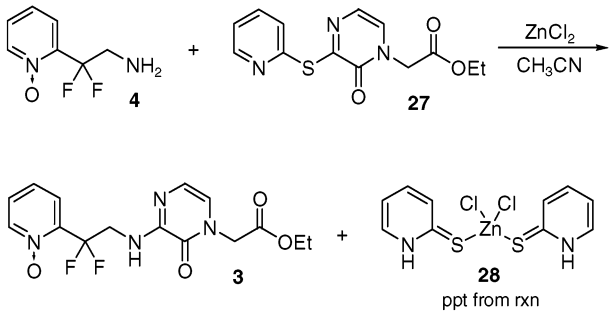
SCHEME 7. Preparation of Pyridylthiopyrazinone 27

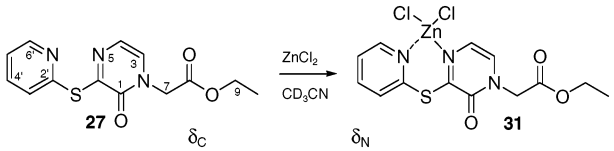


SCHEME 8. Coupling with Pyridylthiopyrazinone 27



of macrolide formation, peptide coupling, and glycoside syntheses.[14−16] Its ability to provide a template effect in the presence of a metal should enhance reactivity. The preparation of thioimidate **27** was accomplished by the addition of 2-mercaptopyridine to chloroimidate **17**, which was generated in situ from pyrazinone **7** with oxalyl chloride in acetonitrile/DMF (Scheme 7).[17] Addition of base (TEA) was unnecessary and undesirable due to a marked slowing of the reaction of chloroimidate with 2-mercaptopyridine. Upon completion of reaction, addition of brine to the reaction mixture at pH 5−6 precipitated thioimidate **27** in 95% yield and 98 wt % assay purity. Control of the aqueous quench at pH <7 and <30 °C was important to avoid ester hydrolysis.

With thioimidate **27** in hand, we proceeded to study its coupling reaction with pyridine *N*-oxide amine **4**. Initially, the reaction carried out in refluxing *i*-PrOAc without any additive was very slow with generation of a new impurity, which appeared to be the product derived from attack on the pyridine carbon bearing sulfur. With the use of $ZnCl_2$, we observed significant rate enhancement. The reaction of thioimidate **27** and amine **4** in the presence of 1 equiv of $ZnCl_2$ in THF (0.5 M) at 82 °C in a sealed tube afforded a 92% assay yield of adduct **3** after 24 h with only 4% of **27** remaining (Scheme 8). Other Lewis acids such as $CuBr_2$ and $MgCl_2$, and protic acid (HCl) were inferior to $ZnCl_2$. The coupling reaction between amine **4** and chloroimidate **17** with catalytic amounts of 2-mercaptopyridine (20%) and $ZnCl_2$ (15%)



C#	27	31	N#	27	31
1	154.5	154.8	2	~161	~166
3	128.0	132.4	5	~316	~277
6	158.5	156.9	1′	~322	~260
8	168.0	167.3			
2′	153.8	152.8			
4′	138.3	142.7			
6′	151.4	151.5			

FIGURE 1. Solution NMR data for **31**.

proceeded slowly and resulted in only a 46% conversion after 2 days but with a very clean purity profile.

The rate of the coupling of **27**/**4**/$ZnCl_2$ was slower at lower temperatures, as noted by the reaction carried out in refluxing THF, taking 4 days to reach completion at 67 °C compared to 1 day at 88 °C. Other higher boiling solvents were screened, with acetonitrile, dioxane, dimethoxyethane, and dichloroethane providing better yields and better solubility, whereas aromatic solvents such as toluene, chlorobenzene, and trifluorotoluene did not offer enough solubility and the reaction mixtures tended to form gelatinous mixtures. At a concentration of 1 M in dioxane with 1 equiv of $ZnCl_2$, the reaction proceeded to 84% yield after 4.5 h at 88 °C, and 94% after 20 h. Reactions in acetonitrile (83 °C) or 1,2-dichloroethane (83 °C) gave similar rates and yields.

$ZnCl_2$ Complexes. During the coupling reaction of **27**/**4**/$ZnCl_2$ in acetonitrile a precipitate formed, which was found to be a 1:2 $ZnCl_2$/2-thiopyridone complex (**28**). The structure was confirmed by single-crystal X-ray analysis (recrystallized from EtOH). Interestingly, in the solid state, the zinc was coordinated to the sulfurs, but in DMSO-d_6 solution, the NMR evidence (see the Supporting Information) was consistent with nitrogen coordination.[18]

To gain further insight into the mechanism of the zinc(II)-mediated coupling, we studied the complexation of $ZnCl_2$ with each of the starting materials, pyridine *N*-oxide **4** and thioimidate **27**, by solution (^{1}H, ^{13}C, ^{15}N) and solid-state NMR and X-ray diffraction. In both cases, solid complexes were formed upon mixing in acetonitrile and were isolated by filtration. Solution NMR of complexed thioimidate **27** provided evidence that the zinc was coordinated to both N-1′ and N-5 as in **31** (Figure 1). Specifically, N-1′ and N-5 were shifted upfield from ∼322 and ∼316 ppm, respectively, in **27** to ∼260 and 277 ppm, respectively, for the complexed species **31**. Also, there were several diagnostic ^{13}C shift changes: (1) both C-3 and C-4′ shifted downfield from 128.0 and 138.3 ppm, respectively, in **27** to 132.4 and 142.7 ppm in **31**; (2) both C-2′ and C-6 shifted upfield from 153.8 and 158.5 ppm, respectively, in **27** to 152.8 and 156.9 ppm in **31**; and (3)

(14) (a) Schmidt, U.; Gleich, P. *Angew. Chem.* **1985**, *97*, 606−607. (b) Lloyd, K.; Young, G. T. *J. Chem. Soc. (C)* **1971**, 2890−6.

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(16) Zhou, X.-X.; Welch, C. J.; Chattopadhyaya, J. *Acta Chem. Scand.* **1986**, *B40*, 806−816.

(17) Early effort with $POCl_3$ for the preparation of **16** gave a slower reaction and lower yield, and coprecipitation of inorganic phosphate salts with isolated product **27** after workup.

(18) (a) Moran, D.; Sukcharoenphon, K.; Puchta, R.; Schaefer, H. F.; Schleyer, P. v. R.; Hoff, C. D. *J. Org. Chem.* **2002**, *67*, 9061−9069. (b) Stoyanov, S.; Petkov, I.; Antonov, L.; Stoyanove, T. *Can. J. Chem.* **1990**, *68*, 1482−1489. (c) Shunmugam, R.; Sathyanarayana, D. N. *J. Coord. Chem.* **1985**, *14*, 27−30. (d) Kennedy, B. P.; Lever, A. B. P. *Can. J. Chem.* **1972**, *50*, 3488−3507. (e) Penfold, B. R. *Acta Crystallogr.* **1953**, *6*, 707−713.

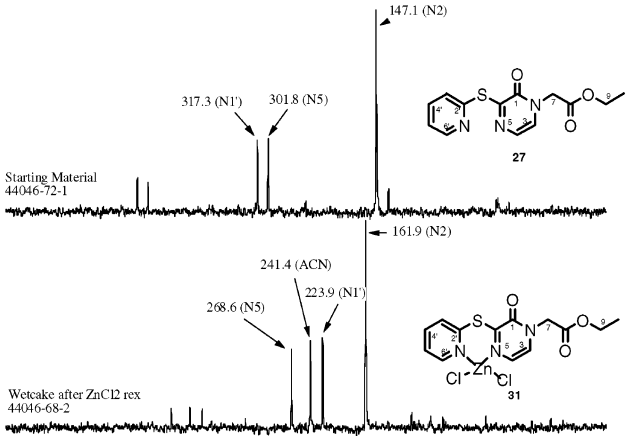
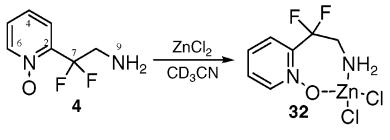


FIGURE 2. Solid-state ^{15}N NMR for **27** and **31**.



	δ_C			δ_H			δ_N	
C#	4	32	H#	4	32	N#	4	32
2	144.1	143.5	3	7.66	7.81	1	~291	~281
4	126.2	130.7	4	7.38	7.66	9	~7	~13
6	142.1	142.8	5	7.43	7.61			
7	120.9	118.6	6	8.18	8.42			
8	45.3	46.3	8	3.63	3.80			

FIGURE 3. Solution NMR data for **4** and **32**.

no significant change in the ^{13}C shift of C-1 was observed, 154.5 ppm in **27** versus 154.8 ppm in **31**.

As a complement to the solution NMR work, solid-state ^{15}N CP/MAS NMR was also performed to gain insight into zinc coordination. Akin to the solution results, **31** displayed three nitrogen sites representing the three unique nitrogen environments in the molecule (Figure 2). The ^{15}N spectrum of the undried precipitate after $ZnCl_2$ reaction displayed an upfield shift of the N-1′and N-5 sites in **27**, as well as a minimal downfield shift for the N-2 species. These ^{15}N shift values are consistent with the solution spectra and suggest zinc coordination to both N-1′ and N-5 in **31**. Additionally, it is clear that the undried precipitate is an acetonitrile solvate as the peak representing incorporated acetonitrile is present in the spectrum at 241.4 ppm. Solvation is also confirmed by ^{13}C solid-state NMR work (not displayed). Finally, the structure of **31** as the acetonitrile solvate was confirmed by single-crystal X-ray.

For pyridine *N*-oxide **4**, the zinc complex appears to be **32** by (^1H, ^{13}C, ^{15}N) solution NMR (Figure 3). This structure is based upon the upfield ^{15}N shift for N-1 from ~291 ppm in **4** to ~281 ppm in **32** and the downfield shift for NH N-9 from ~7 ppm in **4** to ~13 ppm in **32**. In addition, there were changes in the ^{13}C and ^1H shifts: (1) C-4 and C-8 shifted downfield from 126.2 and 45.3 ppm, respectively, in **4** to 130.7 and 46.3 ppm in **32**. (2) H-4, H-6, and H-8 were all shifted downfield from 7.38, 8.18, and 3.63 ppm, respectively, in **1** to 7.66, 8.42, and 3.80 ppm in **4**.

Amine **4**−$ZnCl_2$ complex was shown by solid-state NMR to be an amorphous solid, therefore not much information could be extracted. However, elemental analysis data confirmed a 1:1 composition of **4** to $ZnCl_2$.

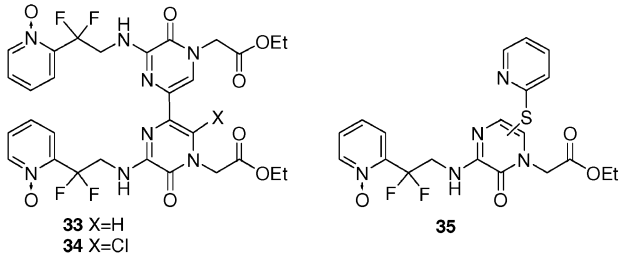


FIGURE 4. Chlorination reaction impurities.

A competitive complexation study with a 1:1:1 mixture of **4**, **27**, and $ZnCl_2$ was examined via NMR in CD_3CN. The NMR signals observed were intermediate values between that of complexed and noncomplexed species, indicating that there is rapid equilibrium between all the species, and no one particular species predominates. This is very likely the reason $ZnCl_2$ is the optimum Lewis acid.

Optimization of $ZnCl_2$ Stoichiometry. In theory, the reaction requires only 0.5 equiv of $ZnCl_2$ to form the 2:1 complex **28**. We screened 0.25, 0.6, 0.75, and 1.0 equiv of $ZnCl_2$ in the coupling reaction, and the yields for all these runs fell within the 80−94% range. The fact that sub-stoichiometric 0.25 equiv of $ZnCl_2$ still gives a reasonable yield suggests that the 2-thiopyridone−$ZnCl_2$ complexes must be an active catalyst or these complexes could easily disproportionate to liberate free $ZnCl_2$. Indeed, when complex **28** was used in place of $ZnCl_2$ in the coupling reaction, a 75−80% assay yield was obtained after 24 h.

The optimized coupling condition uses 0.75 equiv of $ZnCl_2$, 1.1 equiv of amine **4,** and 1.0 equiv of thioimidate **27** at a concentration of 1 M in acetonitrile at reflux (82−84 °C) for 24 h. This was successfully demonstrated on 2−10 kg scales and achieved >98% conversion and 90−95% reaction yield in 24 h. Product isolation involved filtering the reaction mixture to remove the insoluble zinc salts and crystallization from ethanol to afford amidine **3** in 87% isolated yield and ≥95 wt % purity.

Use of this material in the subsequent chlorination step gave 10−15% lower yields than expected. It was determined that residual zinc salts present in **3** were the cause for the lower yield and high impurity levels. This was confirmed by spiking $ZnCl_2$ or Zn salt **28** into a reaction mixture starting with Zn-free starting materials. Some of the impurities generated were identified to be dimers **33**, **34**, and thiopyridine adducts **35**, presumably arising from radical reactions (Figure 4). Indeed, $ZnCl_2$ is known to act as an NCS radical promoter.[19] This problem was resolved by EDTA treatment of amidine **3** in an aqueous acetonitrile solution. Subsequent removal of acetonitrile by vacuum distillation resulted in the crystallization of amidine **3** from water. In this manner, the Zn content in amidine **3** was consistently reduced to <10 ppm with >95% recovery of product.

Other Thioimidate Analogues. Three other thioimidate analogues were also prepared and evaluated in the coupling reaction with amine **4**. In all three cases,

(19) Ko, M.; Sato, T.; Otsu, T. *J. Macromol. Sci., Chem.* **1975**, *A9*, 199−210.

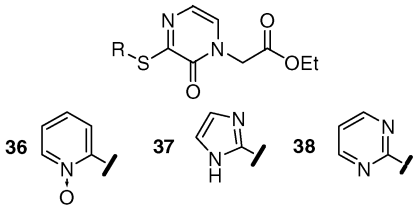
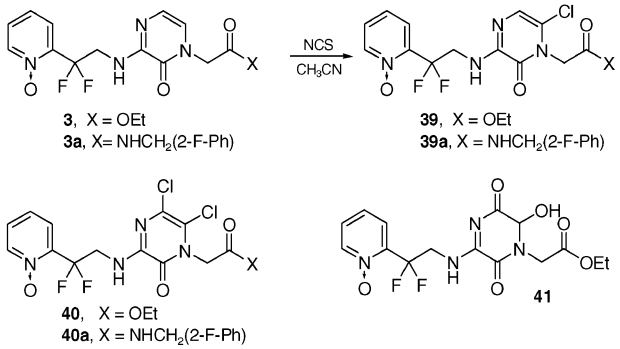


FIGURE 5. Other thioimidates.

SCHEME 9. Chlorination of Pyrazinone 3



3, X = OEt
3a, X= $NHCH_2$(2-F-Ph)
39, X = OEt
39a, X = $NHCH_2$(2-F-Ph)
40, X = OEt
40a, X = $NHCH_2$(2-F-Ph)
41

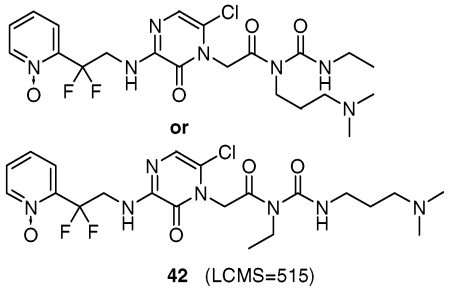
36, **37**, and **38** (Figure 5), the yields of their preparation and subsequent coupling reactions were significantly inferior relative to those of pyridine thioimidate **27**, confirming that bidendate chelation as in **31** is important for rate-enhanced, high-yielding reactions.

Chlorination of Pyrazinone 3. With ester **3** in hand, chlorination was attempted on amide **3a**, which was prepared from ester **3** via hydrolysis followed by EDC coupling with 2-fluorobenzylamine (Scheme 9). Amide **3a** turned out to be poorly soluble in acetonitrile and gave very little reaction with NCS even at 65 °C. Complete dissolution was achieved at 80 °C, but the reaction produced large amounts of bis-chlorination byproduct **40a**. On the other hand, ester **3** was completely soluble in acetonitrile at 55−65 °C, and slow addition of NCS at these temperatures produced chloropyrazinone **39** in >90% yield.

A slight excess of NCS was necessary to ensure complete chlorination, but formation of bis-chloro pyrazinone **40** became competitive. Because ester **3** is easier to reject by crystallization than dichloro **40**, it is important to limit the amount of excess NCS to achieve acceptable levels of **40** in the final isolation of **1**.

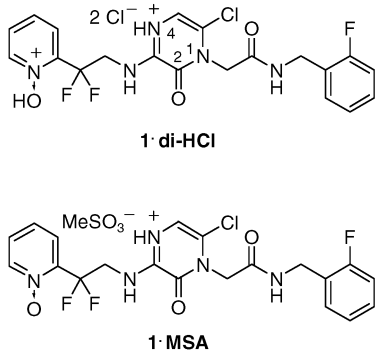
We found that small amounts of water in the reaction mixture led to the formation of an unstable impurity identified as hydroxy dione **41**. This material rapidly decomposes to amine **4** and an unknown byproduct. It was therefore important to control the water content of the reaction (<100 μg/mL) to maintain high yield. After the chlorination was completed, addition of the acetonitrile reaction mixture to a 10% aq NaCl solution precipitated chloropyrazinone **39** in 85−90% isolated yield. Other chlorinating agents, such as dichloro dimethylhydantoin, gave messy reactions, using various solvents and temperatures. In most cases, the formation of hydantoin adducts predominated.

Formation of Compound 1. The formation of **1** was accomplished as a one-pot hydrolysis of ester **39** and coupling with 2-fluorobenzylamine, using EDC and HOBt. The rate of the coupling reaction was pH dependent. At pH 11 coupling required 2 days at 67 °C and gave an isolated yield of 74%. At pH 6, the coupling reaction completed in less than 3 h at 22 °C and the isolated yield of **1** was 90%. In initial experiments we observed formation of acyl urea **42** based on LCMS (515) (Figure 6), which varied from a few percent to upward of 20% in reactions. To control this impurity, we changed the order of the reagent addition after the hydrolysis reaction to adding 2-fluorobenzylamine first, followed by pH adjustment, then adding HOBt and EDC-HCl. This modification resulted in a reproducible and discernible yield improvement (>92% isolated yield with <1 area % **42**). Compound **1** could also be isolated as the bis-HCl salt or the mesylate salt (Figure 7).



42 (LCMS=515)

FIGURE 6. Acyl urea impurity.



1·**di-HCl**

1·**MSA**

FIGURE 7. Bis-HCl and mesylate salts of compound **1**.

In summary, we have developed a practical synthesis of **1** in high yield and high purity, suitable for large-scale preparation. The utilization of thioimidate/$ZnCl_2$ leaving group/activation in the key coupling step overcame the problem of weak amine nucleophile coupling with a poor electrophile, and provided the coupling rate acceleration through a template effect. In addition, we have gained some mechanistic understanding through the characterization of several $ZnCl_2$ complexes by NMR and X-ray diffraction studies.

Experimental Section

2,2-Difluoro-2-(1-oxido-2-pyridinyl)ethylamine (4). To a slurry of urea hydroperoxide (UHP, 114.8 mmol, 10.8 g) in acetonitrile (30 mL) cooled to −10 °C was added a solution of trifluoroacetic anhydride (TFAA, 99.5 mmol, 20.9 g) in acetonitrile (7 mL) over 75 min while maintaining the temperature at <0 °C. The mixture was stirred 30 min at −5 °C to give a near homogeneous solution, then cooled to −10 °C. To the solution was added solid **6**-benzenesulfonate salt[1] (18.1 g, 90 wt %, 50.0 mmol assay) over 30 min, maintaining the temperature at <0 °C. The reaction remained completely homogeneous during the addition of the first ~20% of pyridine **6**,

then benzenesulfonic acid (BSA) precipitated. The slurry was maintained at −5 °C, and stirred ∼30 min until the reaction reached completion (<0.1 LC area % @ 210 nm of **6** vs **4**). The slurry was cooled to −10 °C. The mixture was filtered, and the solids washed with cold (−10 °C) acetonitrile (20 mL). The filtrate was maintained at −5 °C and concentrated aq HCl (6.6 mL) was added over 20 min to produce a thick white precipitate. The slurry was stirred at −5 °C for 1 h and filtered, and the solids were washed with cold (−5 °C) acetonitrile (20 mL) and dried with vacuum/N_2 at 20 °C until a constant weight (13.5 g). The assay of isolated solid was 69.2 wt % as **4**−HCl, 83.4 LC area % with 16.6 LC area % BSA. The solid was added to a mixture of ethyl acetate (40 mL) and triethylamine (13 mL) at 20 °C. The resulting slurry was stirred for 19 h, diluted with isopropyl acetate (6 L), and filtered. The solids were washed with isopropyl acetate (35 mL). The solution was concentrated in vacuo at <35 °C to an oil. The oil was diluted with acetonitrile (2 L) and re-concentrated. The dilution and concentration was repeated twice to obtain an oil (7.7 g, 91 wt % as **4**) for an overall isolated yield of 80%. After this preparation, safety studies restricted the concentration of **4** to <17 wt % in either ethyl acetate, isopropyl acetate, or acetonitrile. HPLC assay: column, Luna C18, 4.6 × 250 mm; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 1% to 50% over 20 min; flow rate, 1.0 mL/min; wavelength, 205 nm; t_R for **4**, 2.7 min, for **14**, 4.7 min, for BSA, 11.6 min. Free base **4**: mp 38−40 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (br s, NH_2), 3.74 (t, J = 15.2 Hz, 2H), 7.34 (m, 2H), 7.67 (m, 1H), 8.24 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 143.6, 141.1, 127.2, 125.4, 125.3, 119.1, 44.8. ^{1}H NMR (499.87 MHz, CD_3CN) δ 8.18 (br d, J = 6.4 Hz, 1H), 7.66 (dd, J = 8.0, 2.0 Hz, 1H), 7.44 (ddd, J = 8.0, 6.4, 2.0 Hz, 1H), 7.38 (td, J = 8.0, 1.2 Hz, 1H), 3.63 (t, J_{HF} = 15.1 Hz, 2H); ^{13}C NMR (125.69 MHz, CD_3CN) δ 144.1 (t, J_{CF} = 30.1 Hz, C-2), 142.1 (C-6), 128.9 (C-5), 126.6 (t, J_{CF} = 7.4 Hz, C-3), 126.2 (C-4), 120.9 (t, J_{CF} = 242.7 Hz, C-7), 45.3 (t, J_{CF} = 27.4 Hz, C-8); ^{15}N NMR (50.66 MHz, CD_3CN, reference to external NH_3, shifts were measured from 2D ^{1}H−^{15}N HMBC) δ ∼291 (N-1), ∼7 (N-9). Anal. Calcd for $C_7H_8F_2N_2O\cdot{}^1/_5H_2O$: C, 47.30; H, 4.76; N, 15.76; F, 21.38. Found: C, 47.33; H, 4.70; N, 15.87; F, 21.22. **4**·HCl salt: mp 230−240 °C dec. ^{1}H NMR (400.25 MHz, D_2O) δ 8.39 (d, J = 6.2 Hz, 1H), 7.92 (m, 1H), 7.79 (br t, J = 7.9 Hz, 1H), 7.70 (M, 1H), 4.68 (OH, 3H), 4.12 (br t, J = 15.1 Hz, 2H). ^{13}C NMR (100.65 MHz, D_2O) δ 141.3, 140.7 (t, J = 28.6 Hz), 131.7, 129.7, 125.8 (t, J = 7.2 Hz), 115.4 (t, J = 246.1 Hz), 42.2 (t, J = 26.2 Hz). ^{19}F NMR (376.61 MHz, D_2O) δ −104.79. Anal. Calcd for $C_7H_9ClF_2N_2O$: C, 39.92; H, 4.31; N, 13.30; F, 18.04; Cl, 16.83. Found: C, 39.84; H, 4.10; N, 13.18; F, 18.32; Cl, 16.67.

Bromoimidate 16. This material was prepared by using a published procedure except 1,2-dichloroethane was replaced by acetonitrile.[1f,6]

Ethyl [2-Oxo-3-(pyridin-2-ylthio)pyrazin-1(2*H*)-yl]acetate (27). To a round-bottom flask equipped with a condenser, HCl trap, and nitrogen inlet was charged acetonitrile (350 mL), DMF (6.5 mL), and pyrazinone **7** (48.0 g, 99.5%, 0.24 mol). Oxalyl chloride (23.0 mL, 0.26 mol) was added to the slurry mixture over 2.5 h at 20−25 °C. The resulting yellow solution was heated at 40 °C for 1−2 h, or until pyrazinone **7** was <0.5% relative to chloropyrazinone **17**[1] by HPLC assay (relative area % at 215 nm). An analytical sample of **17** was obtained by aqueous workup and extraction with IPAC: ^{1}HNMR ($CDCl_3$) δ 7.14 (d, J = 4.4 Hz, 1H), 7.12 (d, J = 4.4 Hz, 1H), 4.64 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ 161.1, 152.7, 148.7, 139.8, 129.1, 121.6, 62.6, 50.9, 14.1. The resulting brown solution was cooled to 20 °C, and 2-mercaptopyridine (29.4 g, 0.26 mol) was added in three equal portions at 20-min intervals. The mixture was stirred at 22 °C until chloropyrazinone **17** was ≤0.5 LC area % relative to **27** (3−20 h). More 2-mercaptopyridine (3−5 mol %) was added to complete the reaction if required. The resulting dark green solution was quenched into a solution of water (800 mL) and NaCl (80 g) at <20 °C. The resulting burgundy solution (pH 0) was adjusted to pH 5−6 with solid $NaHCO_3$ (∼42 g), during which time two clear layers of liquid formed. The mixture was seeded with several milligrams of product and concentrated under reduced pressure (30−50 mmHg, 24 °C) to about 850 mL, during which time the product crystallized. The resulting mixture (pH 6.8) was adjusted to pH 6 with 1.4 mL of 1 N HCl and then stirred overnight at 21 °C. The mixture was stirred at 0−5 °C for 1−2 h, filtered, and washed with 0−5 °C water (3 × 100 mL). The wet cake was vacuum dried at 22 °C with a nitrogen sweep overnight. Yield = 66.6 g of **27** as a light beige solid. LCAP @ 215 nm = 99.5 area %; LCWP = 99.8% (66.5 g, 95.1% yield); no impurity >0.11 area %. Product loss to combined ML/washes was 2.5% (2.2 g). HPLC conditions: column, Luna C18, 5 μm; 4.6 × 250 mm; mobile phase, CH_3CN/0.1% aqueous H_3PO_4, 20% to 80% over 20 min; flow rate, 1.0 mL min^{-1}; UV detection, 215 nm; column temperature, 25 °C; t_R for DMF, 3.10 min, for dione **7**, 4.00 min, for 2-mercaptopyridine, 3.61 min, for 2-pyridylsulfide, 8.50 min, for chloropyrazinone **17**, 9.23 min, for thiopyrazinone **27**, 9.43 min. **27**: mp 97−99 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (m, 1H), 7.72 (m, 2H), 7.29 (m, 1H), 7.10 (d, J = 4.4 Hz, 1H), 6.87 (d, J = 4.4 Hz, 1H), 4.62 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 166.4, 159.1, 153.5, 152.7, 150.6, 137.1, 130.4, 125.2, 123.3, 123.2, 62.3, 50.0, 14.1. ^{1}H NMR (499.87 MHz, CD_3CN) δ 8.58 (ddd, J = 4.8, 2.0, 1.0 Hz, 1H), 7.79 (td, J = 7.8, 2.0 Hz, 1H), 7.73 (dt, J = 8.0, 1.2 Hz, 1H), 7.35 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.13 (d, J = 4.4 Hz, 1H), 7.06 (d, J = 4.4 Hz, 1H), 4.61 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2, 3H); ^{13}C NMR (125.69 MHz, CD_3CN) δ 168.0 (C-8), 158.5 (C-6), 154.5 (C-1), 153.8 (C-2′), 151.4 (C-6′), 138.3 (C-4′), 131.3 (C-3′), 128.0 (C-3), 124.5 (C-5′), 123.6 (C-4), 62.9 (C-9), 51.3 (C-7), 14.5 (C-10); ^{15}N NMR (50.66 MHz, CD_3CN, reference to external NH_3, shifts were measured from 2D ^{1}H−^{15}N HMBC) δ ∼322 (N-1′), ∼316 (N-5), ∼161 (N-2). Anal. Calcd for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.49; H, 4.44; N, 14.33; S, 11.09.

{3-[2,2-Difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-2-oxo-2*H*-pyrazin-1-yl}-acetic Acid Ethyl Ester (3). Method A. Coupling via Bromoimidate 16. To a round-bottom flask equipped with a condenser, a thermometer, and nitrogen inlet/outlet was charged 3:1 toluene/ethanol (4.8 L), amine **4** (1104 g, 6.34 mol), bromopyrazinone ester **16** (1530 g, 5.76 mol), and *N*,*N*-diisopropylethylamine (1.305 L, 7.36 mol). The mixture was stirred and heated to reflux at 85−88 °C under a nitrogen atmosphere for 7 days. The reaction mixture (85% conversion by LC assay) was cooled to 22 °C, diluted with 1/4 of a solution of H_2O (21.7 L) and NaCl (2.17 kg), and concentrated under reduced pressure at 25−30 °C. After most of the organic solvents were removed, the rest of the brine solution was added and the mixture was stirred at ambient for 2−4 h. The slurry was filtered and washed with NaCl solution (10.9 L of H_2O + 1.09 kg of NaCl) and H_2O (5.4 L). The wet cake was vacuum dried at 22 °C under nitrogen overnight. Yield = 1.63 kg of **3** as a beige solid; 82% yield. LCAP @ 330 nm = 96.8 area %; LCWP = 96.9%; 2.5 area % bis-adduct **21b**; 0.7 area % (0.53 wt %) bromo pyrazinone 16; 0.03 wt % ionic Br^-. HPLC conditions: column, Discovery RP Amide C16, 4.6 × 250 mm; mobile phase, CH_3CN/0.1% aqueous H_3PO_4 15/85; flow rate, 1.0 mL min^{-1}; UV detection, 203 and 330 nm; column temperature, 35 °C; t_R for 2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamine **4**, 2.43 min, for ionic bromide, 3.85 min, for bis-adduct **21b**, 5.21 min, for coupled product **3**, 9.55 min, for bromo pyrazinone **16**, 11.9 min.

Method B. Coupling via Thioimidate 27. To a round-bottom flask equipped with a condenser, a thermometer, and nitrogen inlet was charged amine **4** oil (1510 g, 91.0%, 7.89 mol), acetonitrile (7 L), and thiopyrazinone ester **27** (2410 g, 86.7%, 7.17 mol) at 20 °C. The mixing was endothermic, which brought down the temperature to 11 °C. The mixture was warmed to 20 °C, then zinc chloride (748 g, 98%, 5.38 mol) was added. The mixture exothermed to ∼40 °C and was heated to reflux at 82−84 °C under a N_2 atmosphere for 24 h. The

reaction mixture was cooled to 22 °C, diluted with acetonitrile (65.6 L), and stirred for 1 h at 22 °C. The mixture was filtered through a silica plug (6.6 kg, wetted with acetonitrile with 3.3 kg of sand on top), and the filter cake was washed with 72 L of acetonitrile. The filtrate was concentrated to 3.5−4 L, flushed with ethanol (4 × 4 L) until ≤0.1% acetonitrile. Ethanol was added to give a final concentration of ∼10 mL of ethanol/g of product (∼24 L total). The slurry was heated at reflux (for 1 h) to give a clear yellow solution, and then cooled slowly to crystallize the product. The mixture was concentrated to half of the original volume (∼12 L) and then stirred at 0 °C for 1 h. The slurry was filtered and washed with ice cold ethanol (7.2 L) and the wet cake was vacuum dried at +22 °C under nitrogen overnight. Yield = 2.32 kg of **3** as a light beige solid. LCAP @ 215 nm = 99.2 area %; LCWP = 94.4% (2.19 kg, 86% yield); 0.8 area % 2-thiolpyridine; 7700 ppm Zn. Product loss to ML and washes was 1.6% (41 g). HPLC conditions: column, Luna C18, 5 um; 4.6 × 250 mm; mobile phase, CH_3CN/0.1% aqueous H_3PO_4 20% to 80% over 20 min; flow rate, 1.0 mL min^{-1}; UV detection, 215 nm; column temperature, 25 °C; t_R for 2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamine **4**, 1.90 min, for 2-thiolpyridine, 3.61 min, for bis-adduct **21b**, 4.24 min, for coupled product **3**, 7.25 min, for thiopyrazinone **27**, 9.43 min.

To a round-bottom flask equipped with a thermometer and nitrogen inlet/outlet was charged water (240 mL), EDTA·4Na·$3.6H_2O$ (2.4 g, 5.39 mmol) and NaCl (9.7 g). The resulting pH 10.3 solution was adjusted to pH 7.4 with 12 N HCl (0.48 mL). To this solution was added crude **3** (20 g, 94.8 wt %, 53.5 mmol, containing 7800 ppm Zn) and acetonitrile (300 mL) to give a homogeneous solution. The solution was concentrated under reduced pressure (50−70 Torr, 27 °C water bath) to about 230 mL with acetonitrile content at ≤5 vol %. The resulting slurry was filtered and washed with water (3 × 40 mL). The wet cake was vacuum dried at 22 °C under nitrogen to afford 18.2 g of **3** as an off-white solid. The purity was 99.9 area % and 99.3 wt % (18.1 g, 95% yield) by HPLC. The zinc content was 4 ppm by elemental analysis. 2-Thiolpyridine was not detected. **3**: mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 6.4 Hz, 1H), 7.60 (dd, J = 7.6, 2.1 Hz, 1H), 7.33 (m, 1H), 7.26 (m, 1H), 6.76, (d, J = 4.7 Hz, 1H), 6.41 (br t, J = 6.9 Hz, NH), 6.37 (d, J = 4.7 Hz, 1H), 4.65 (dt, J = 13.8, 6.9 Hz, 2H), 4.52 (s, 2H), 4.22 (q, J = 7.2 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 166.8, 151.4, 151.1, 143.3, 141.0, 127.4, 125.3, 125.2, 122.0, 117.5, 117.4, 62.0, 49.6, 42.9, 14.0. Anal. Calcd for $C_{15}H_{16}F_2N_4O_4$: C, 50.85; H, 4.55; N, 15.81; F, 10.72. Found: C, 50.69; H, 4.31; N, 15.81; F, 10.81.

Ethyl 3-(2,2-Difluoro-2-(2-pyridyl-*N*-oxide)ethylamino)-6-chloropyrazin-2-one-1-acetate (39). To a 50-L vessel, equipped with mechanical stirrer, thermocouple, and condenser with nitrogen inlet, was charged acetonitrile (6.5 L, KF ≤ 100 μg) and amidine **3** (1973 g, 5.57 mol). The slurry was heated to 55 °C and *N*-chlorosuccinimide (751.3 g, 5.63 mol) in acetonitrile (4.3 L, KF ≤ 100 μg) was added over 5 min. The slurry was heated to 60 °C to dissolve, then cooled to 50 °C. The clear solution was stirred at 50 °C for 20 min, then cooled to 35−40 °C and stirred at this temperature for 1 h. When dichloropyrazinone **40** was between <0.4 and 0.25 HPLC area % relative to product (about 0.5−1 h), the reaction mixture was cooled to 27 °C, and cold 10% aqueous NaCl solution (24 L) was added. The mixture was cooled to 0 °C, and more cold 10% aqueous NaCl solution (52.8 L) was added. After the mixture was stirred for 2 h at 0 °C, the slurry was filtered. The wet cake was washed with cold water (2 × 13 L) and dried by drawing nitrogen through the cake with a vacuum to afford 2070 g of chloropyrazinone **39**. The purity was 90.8 wt % and the corrected yield was 86.8%. HPLC conditions: column, Waters Symmetry Shield RP18, 4.6 × 150 mm, 3.5 μm; mobile phase, CH_3CN/0.1% aqueous H_3PO_4 20% to 28% over 3 min, hold 2 min, to 70% over 8 min, hold 2 min; flow rate, 1.0 mL/min; UV detection, 210 and 330 nm; temperature, 35 °C; t_R for hydroxy dione **41**, 3.1 min, for amidine **3**, 4.27 min, for dimer **33**, 8.84 min, for thio adduct **35**, 9.86 min, for Cl-dimer **34**, 10.17 min, for di-Cl pyrazinone **40**, 11.18 min, for des-oxide **2c**, 12.92 min. **39**: mp 162−164 °C; ^{1}H NMR (DMSO-d_6) δ 8.34 (d, J = 6.4 Hz, 1H), 7.65−7.50 (m, 2H + NH), 7.38 (t, J = 7.7 Hz, 1H), 6.82 (s, 1H), 4.85 (s, 2H), 4.45 (dt, J = 13.4, 6.7 Hz), 4.16 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 167.4, 151.4, 149.7, 142.4 (t, J = 28.5 Hz), 141.3, 128.7, 125.7, 125.3 (t, J = 6.7 Hz), 119.9, 117.9 (t, J = 245.7 Hz), 117.6, 62.0, 46.7, 42.0 (t, J = 28.0 Hz), 14.4. Anal. Calcd for $C_{15}H_{15}ClF_2N_4O_4$: C, 46.34; H, 3.89; Cl, 9.12; F, 9.77; N, 14.41. Found: C, 46.34; H, 4.04; Cl, 9.14; F, 9.77; N, 14.38.

2-Fluorobenzyl 3-(2,2-Difluoro-2-(2-pyridyl-*N*-oxide)-ethylamino)-6-chloropyrazin-2-one-1-acetamide (1). To a 100-L vessel, equipped with mechanical stirrer, thermocouple, addition funnel, and nitrogen inlet was charged sequentially THF (23 L), chloropyrazinone **39** (1965 g, 90.8 wt %, 4.59 mol), and 1 M KOH (11.5 L). The slurry was stirred at 20 °C and it became a clear solution. The progress of the reaction was monitored by HPLC. When the starting material was <1 area % relative to product (about 1 h), 2-fluorobenzylamine (776 g, 6.2 mol) was added. The solution was adjusted to pH 5−6 with 2 N HCl (∼5 L). Then, HOBt hydrate (250 g, 1.85 mol) and finally EDC-HCl (1364 g, 7.12 mol) were added. The reaction mixture was stirred at 18−22 °C. HPLC conditions: column, Waters Symmetry Shield RP18, 4.6 × 150 mm, 3.5 μm; mobile phase, CH3CN/0.1% aqueous H_3PO_4 20% to 28% over 3 min, hold 2 min, to 70% over 8 min, hold 2 min; flow rate, 1.0 mL/min; UV detection, 210 and 330 nm; temperature, 35 °C; t_R for hydroxy dione **41**, 3.1 min, for amidine **3**, 4.27 min, for dimer **33**, 8.84 min, for thio adduct **35**, 9.86 min, for Cl-dimer **34**, 10.17 min, for di-Cl pyrazinone **40**, 11.18 min, for des-oxide **2c**, 12.92 min. When the starting material was <1 area % relative to product (2−3 h), 7 wt % aqueous $NaHCO_3$ (46 L) was added and the solution was stirred for 1 h and filtered. The wet cake was washed with water (38.5 L) and cold EtOH (8 L) and vacuum-dried under nitrogen to afford 2164 g of compound **1**. The purity was 95.4 area % and 93.7 wt % by HPLC and the corrected yield was 94%. HPLC conditions: column, Waters Symmetry Shield RP18, 4.6 × 150 mm, 3.5 μm; mobile phase, CH_3CN/0.1% aqueous H_3PO_4 20% to 28% over 3 min, hold 8 min, to 70% over 15 min; flow rate, 1.0 mL/min; UV detection, 210 and 330 nm; temperature, 35 °C; t_R for des-Cl **3a**, 4.27 min, for des-F of **1**, 12.6 min, for **1**, 14.15 min, for; di-Cl **40a**, 22.04 min, for mono-Cl dimmer **34**, 22.49 min, for des-oxide **2b**, 25.1 min.

Compound **1** was further purified by crystallization as the di-HCl salt: Compound **1** (2084 kg, 93.7 wt %, 4.17 mol) in glacial acetic acid (9.2 L) was warmed to 60−70 °C under nitrogen to give a homogeneous solution. To this was added 1 N HCl in acetic acid (9.0 L, 9.0 mol) over 15 min, which produced a crystalline precipitate. The slurry was cooled to 20 °C and filtered, washed with glacial acetic acid (2 × 4 L), washed with isopropyl acetate (4 × 4 L), then dried with a flow of nitrogen through the filter cake at 20 °C overnight to give 2340 g of **1**·di-HCl salt. The dried cake (2310 g) was added to water (50 L) and stirred for 12−20 h, during which time the pH dropped to 1, and the slurry became thicker. The slurry was filtered and washed with water (3 × 20 L) to give a filtrate with pH >4. The solids were dried via nitrogen drawn through the cake with vacuum to a constant weight at 20 °C to give compound **1** free base (1960 g, 97 wt %, 97.4% recovery). Compound **1** (1930 g) was combined with dry DMF (9.5 L) and heated to 75 °C to dissolve. The solution was filtered (5 μm) and cooled slowly. Methanol (21 L) was added after crystals appeared at about 30 °C. After further cooling to 23 °C, water (9.5 L) was added. The slurry was stirred at 18−23 °C overnight, then filtered. The wet cake was washed with water (40 L) and dried by drawing nitrogen through the cake with a vacuum. The recovery yield of compound **1** free base was 96.5% (1840 g, 98.5 wt %). **1**: mp 224−225 °C; ^{1}H NMR (DMSO-d_6) δ 8.75 (t, J = 5.6 Hz, NH), 8.34 (d, J = 6.4 Hz, 1H), 7.60 (dd,

J = 7.8, 1.8 Hz, 1H), 7.57−7.50 (m, 1H + NH), 7.39 (t, J = 7.8 Hz, 1H), 7.31 (m, 2H), 7.16 (m, 2H), 6.79 (s, 1H), 4.73 (s, 2H), 4.46 (dt, J = 13.4, 6.7 Hz, 2H), 4.33 (d, J = 5.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 166.0, 160.5 (d, J = 244.1 Hz), 151.7, 149.9, 142.5 (t, J = 28.5 Hz), 141.3, 129.9 (d, J = 4.0 Hz), 129.5 (d, J = 8.0 Hz), 128.6, 125.9 (d, J = 14.5 Hz), 125.8, 125.3 (t, J = 6.7 Hz), 124.8 (d, J = 3.6 Hz), 119.6, 118.3, 118.0 (t, J = 244.9 Hz), 115.5 (d, J = 20.9 Hz), 47.7, 42.1 (t, J = 28.0 Hz), 36.6 (d, J = 4.5 Hz). Anal. Calcd for $C_{20}H_{17}ClF_3N_5O_3$: C, 51.35; H, 3.66; Cl, 7.58; F, 12.18; N, 14.97. Found: C, 51.25; H, 3.40; Cl, 7.57; F, 12.24; N, 14.87.

Compound 1 Methanesulfonate Salt. To a slurry of compound **1** (475 g, 98.5 wt %, 1.0 mol) in glacial acetic acid (3.61 L) was added methanesulfonic acid (78 mL, 1.2 mol). After being stirred at 20 °C for 5 min, the mixture became a homogeneous solution. The solution was heated to 80−85 °C, then isopropyl acetate (7.22 L) was added over 1 h, while keeping the internal temperature >70 °C. After cooling to 67 °C, the solution was seeded with **1**·MSA salt (0.6 g) and cooled slowly to 20 °C over 6 h. After stirring overnight, isopropyl acetate (7.22 L) was added to the slurry, stirred for additional 4 h, and then filtered. The wet cake was washed with isopropyl acetate (7.22 L) and vacuum dried under nitrogen to afford pure **1**·MSA salt (549 g, 96.5% yield): mp 192−194 °C; both ^{1}H NMR and ^{13}C NMR are essentially identical with those of the free base in DMSO, except for the methanesulfonic acid signals at δ 2.46 (s, 3H) and 39.7. Anal. Calcd for $C_{21}H_{21}ClF_3N_5O_6S$: C, 44.73; H, 3.75; Cl, 6.29; F, 10.11; N, 12.42; S, 5.69. Found: C, 44.59; H, 3.78; Cl, 6.37; F, 10.15; N, 12.42; S, 5.77.

Bis-2(1H)-Pyridinethione Zinc Dichloride Complex (28 or 30). Filtration of the reaction slurry of the coupling reaction by method B, followed by washing with acetonitrile and vacuum drying afforded **28** as a beige solid. Complex **28** was also prepared by combining 2-mercaptopyridine with $ZnCl_2$ (2:1) in ethanol. Mp 241−243 °C; ^{1}H NMR (DMSO-d_6) δ 13.50, (br s, 1H), 7.70 (m, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 6.80 (m, 1H); ^{13}NMR (DMSO-d_6) δ 176.7, 138.6, 138.5, 133.2, 113.9; see text for ^{15}N NMR. Anal. Calcd for $C_{10}H_{10}Cl_2N_2S_2Zn$: C, 33.49; H, 2.81; Cl, 19.77; N, 7.81; S, 17.88; Zn, 18.23. Found: C, 33.51; H, 2.75; Cl, 19.51; N, 7.80; S, 17.66; Zn, 18.02.

Ethyl [2-Oxo-3-(pyridin-2-ylthio)pyrazin-1(2*H*)-yl]acetate Zinc Dichloride Complex (31). Combined thioimidate **27** (1.2 g, 4.0 mmol), $ZnCl_2$ (0.6 g, 4.3 mmol), and acetonitrile (7.2 m) were heated at 35 °C for 17 h. After the mixture was cooled to 22 °C over 3 h, the solid was filtered and washed with acetonitrile (5 mL). The wet cake was vacuum dried under nitrogen to afford 1.49 g (87%) of **31** as a crystalline solid suitable for single crystal X-ray. The acetonitrile solvate was gradually replaced by water upon exposure to air. Mp 180−182 °C; ^{1}H NMR (499.87 MHz, CD_3CN) δ 8.79 (ddd, J = 5.2, 2.0, 0.8 Hz, 1H), 8.10 (td, J = 8.0, 2.0 Hz, 1H), 7.89 (dt, J = 8.0, 1.2 Hz, 1H), 7.70 (ddd, J = 7.6, 5.2, 1.2 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.38 (d, J = 4.8 Hz, 1H), 4.68 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 1.96 (s, CH_3CN), 1.25 (t, J = 7.2, 3H); ^{13}C NMR (125.69 MHz, CD_3CN) δ 167.3 (C-8), 156.9 (C-6), 154.8 (C-1), 152.8 (C-2′), 151.5 (C-6′), 142.7 (C-4′), 132.4 (C-3), 130.8 (C-3′), 126.7 (C-5′), 122.2 (C-4), 63.2 (C-9), 51.9 (C-7), 14.4 (C-10); ^{15}N NMR (50.66 MHz, CD_3CN, reference to external NH_3, shifts were measured from 2D ^{1}H−^{15}N HMBC) δ ∼277 (N-5), ∼260 (N-1′), ∼166 (N-2). Anal. Calcd for $C_{13}H_{13}Cl_2N_3O_3SZn$·$K$$CH_3CN$·$J$$H_2O$: C, 37.35; H, 3.43; Cl, 15.38; N, 11.14; S, 6.96; Zn, 14.18. Found: C, 37.14; H, 3.42; Cl, 15.19; N, 11.03; S, 6.81; Zn, 14.42.

Preparation of Zinc Complex 32. To a solution of 2,2-difluoro-2-(1-oxido-2-pyridinyl)ethylamine (**4**) (7.8 g, 44.5 mmol) and dry CH_3CN (81 mL) was added $ZnCl_2$ (5.5 g, 30.4 mmol) in one portion without cooling. The temperature rose from 22 to 37 °C. After the mixture was stirred overnight at 22 °C, the slurry was filtered and washed with CH_3CN. The solid was vacuum dried under nitrogen: mp 223−225 °C dec; ^{1}H NMR (499.87 MHz, CD_3CN) δ 8.42 (br d, J = 6.4 Hz, 1H), 7.81 (dd, J = 8.0, 2.0 Hz, 1H), 7.66 (td, J = 6.4, 1.2 Hz, 1H), 7.61 (ddd, J = 8.0, 6.4, 2.0 Hz, 1H), 3.80 (t, J_{HF} = 14.5 Hz, 2H); ^{13}C NMR (125.69 MHz, CD_3CN) δ 143.5 (t, J_{CF} = 29.5 Hz, C-2), 142.8 (C-6), 130.7 (C-4), 129.9 (C-5), 126.8 (t, J_{CF} = 7.4 Hz, C-3), 118.6 (t, J_{CF} = 244.9 Hz, C-7), 46.3 (t, J_{CF} = 28.9 Hz, C-8); ^{15}N NMR (50.66 MHz, CD_3CN, reference to external NH_3, shifts measured were from 2D ^{1}H−^{15}N HMBC) δ ∼281 (N-1), ∼13 (N-9). Anal. Calcd for $C_7H_8Cl_2F_2N_2OZn$: C, 27.08; H, 2.60; Cl, 22.84; F, 12.24; N, 9.02; Zn, 21.06. Found: C, 27.44; H, 2.35; Cl, 22.61; F, 12.26; N, 9.16; Zn, 21.15.

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Supporting Information Available: Complete details supporting the X-ray crystallographic determination for **28** and **31** including the CIF files, NMR data for 2-mercaptopyridine and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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