Organic Process Research & Development

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Development of Scalable Syntheses of Selective PI3K inhibitors

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ABSTRACT: On the basis of a more practical and scalable route to an iodothiophene, an efficient and reliable synthesis has been developed for three selective PI3K inhibitors. From this advanced intermediate, the three title compounds were each prepared in five additional steps. Key learnings also include: high throughput experimentation (HTE) screening toward a more robust Suzuki coupling, a more efficient triazole synthesis, and an acid/base cleanup developed to purify the final compounds. The final enabled synthesis required no column chromatography.

INTRODUCTION

Inhibition of the PI3K receptor may result in an effective therapeutic intervention for the treatment of some types of cancer.[1] Our early research has identified compounds **1**, **2**, and **3** as highly promising candidates in our selective PI3K program (Figure 1).

The initial route for analogue generation in this PI3K triazole series is outlined in Scheme 1.[2] Unfortunately, there are several disadvantages associated with this route: (1) the aryl moiety, the point of diversity between the three compounds, is introduced in the first step, and as such they could not share a common intermediate; (2) while 2,4-dichloroacetophenone is a commercially available starting material,[3] we were required to synthesize 2-chloro-4-methoxyacetophenone and 4-cyano-2-fluoroacetophenone;[4] and (3) the original medicinal chemistry route is hampered by several steps which are not amenable for a large-scale synthesis. In addition, the initial halogenation step suffers from rapid bis-bromination, and the modified Gewald reaction (Step 4, with a messy three-component mixture)[5] is not a convenient step to the formation of tetra-substituted thiophenes.

To carry out further in vivo studies on these three compounds, gram amounts of each candidate were required. Therefore, a facile route was highly desired not only for serving as a more general and efficient route to access analogues of this series but also for the purpose of scale-up. In this work we describe a more efficient and scalable route to compounds **1**−**3**. While the syntheses for compounds **1** and **2** were improved significantly, the modified preparation of compound **3** contains improvements that would allow further scaling into a pilot-plant setting with minor changes.

Our retrosynthetic plan is outlined in Scheme 2. We envisioned that compounds **1**−**3** could be synthesized from amides **4a**, **4b**, and **4c**, respectively, followed by triazole formation. Amides **4a**−**4c** could be derived from esters **5a**−**5c** via aminolysis. Suzuki coupling of common intermediate **6** with the corresponding aryl boronic acids would generate esters **5a**−**5c**. On the basis of our previous experience in this series, we expected that this Suzuki reaction could potentially be a problematic step due to the steric bulkiness and the poor intrinsic reactivity of iodothiophenes. We found that intermediate **6** can be constructed rapidly over five steps from commercially available malononitrile. Alternatively, amide **7** could be utilized as a more

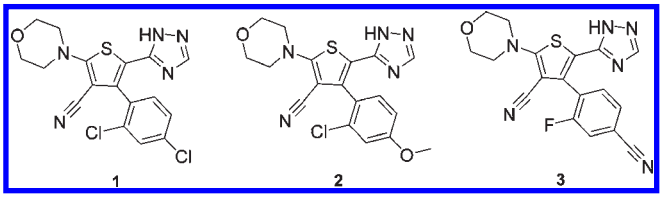
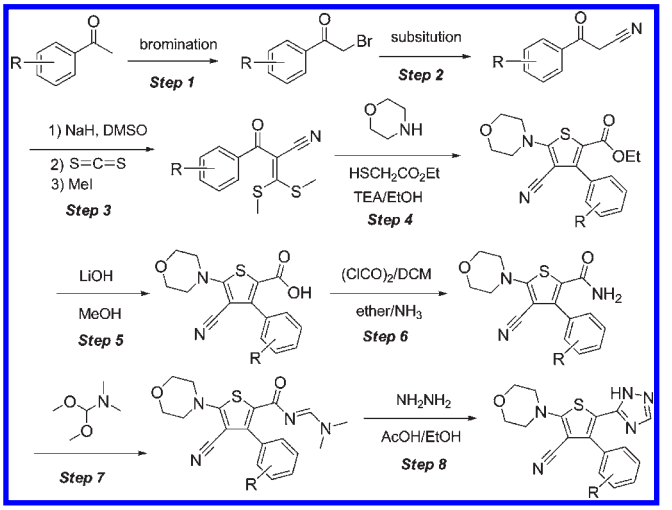


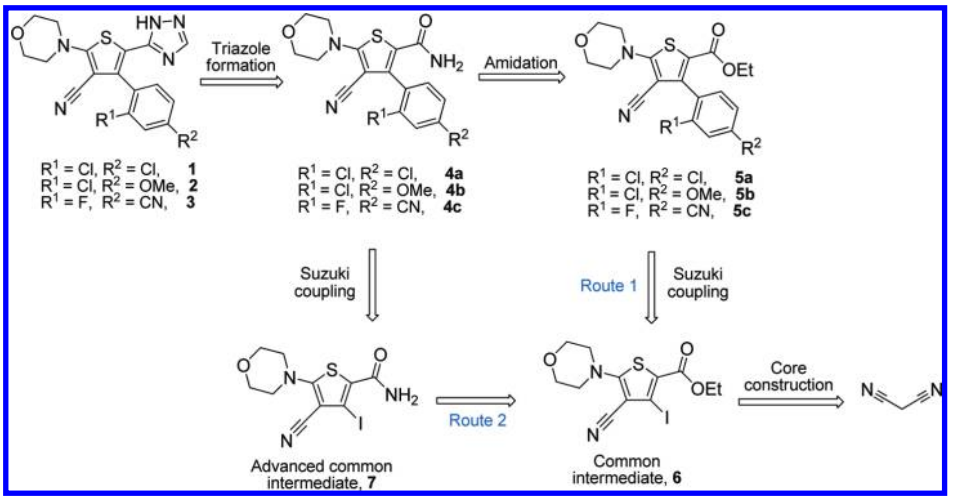
Figure 1. Potent selective PI3K inhibitors **1**, **2**, and **3**.

Scheme 1. Original route to triazole analogues for PI3K project

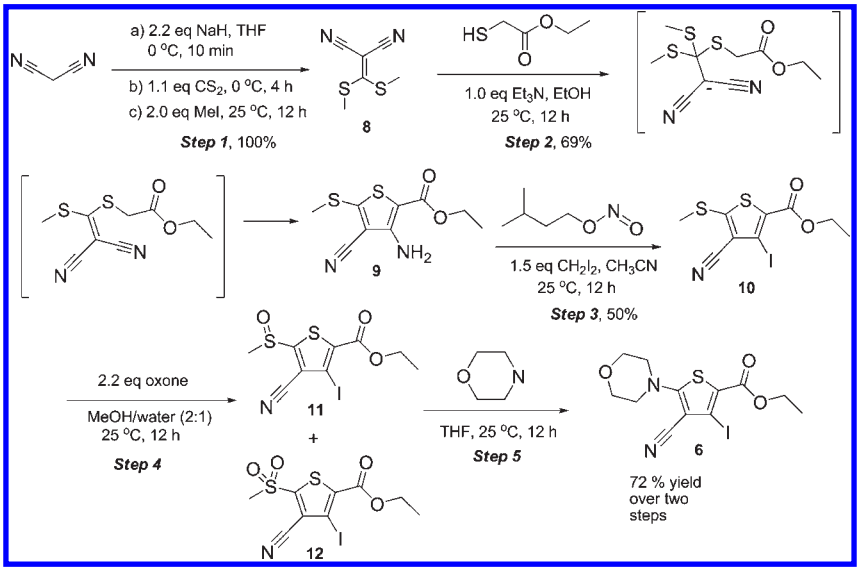


Received: October 25, 2010
Published: March 11, 2011

Scheme 2. Retrosynthetic analysis of compounds 1, 2 and 3



Scheme 3. Second-generation synthesis of iodothiophene 6



advanced common intermediate (route 2 in Scheme 2). The Suzuki couplings of both ester **6** and amide **7** have been examined, and the results are discussed herein.

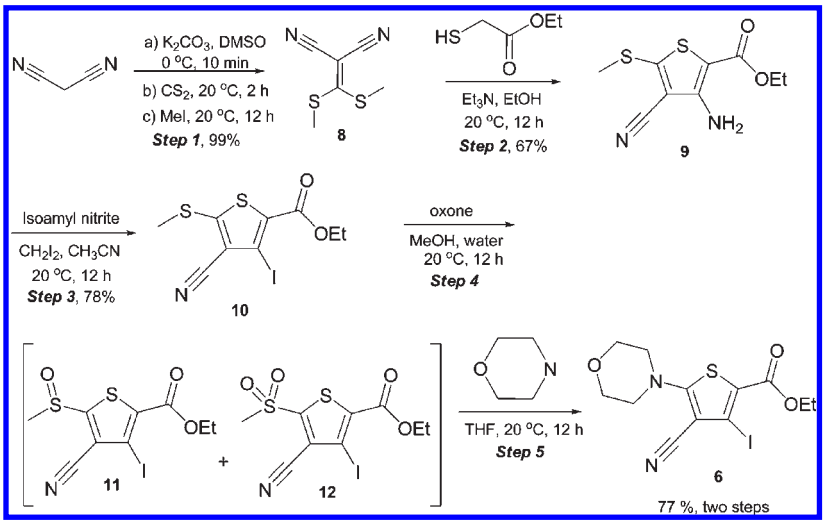
RESULTS AND DISCUSSION

In an attempt to develop a more direct second-generation synthesis, we found that iodothiophene **6** could be synthesized in five steps from commercially available malononitrile (Scheme 3).[3] Although the modified synthesis was relatively efficient, the process suffered from multiple nonscalable steps, relying on hazardous reagents such as NaH, CS_2, and MeI, as well as Sandmeyer chemistry. Treatment of malononitrile with NaH followed by CS_2 and MeI generated intermediate **8** in quantitative yield, which was isolated by water dilution. Condensation of compound **8** and ethyl thioacetate in the presence of Et_3N afforded aminothiophene **9** in 69% yield.[6] Subsequently, the Sandmeyer reaction of compound **9** using CH_2I_2 in CH_3CN gave iodothiophene **10** in 50% yield.[7] Thiophene **10** was quickly converted to sulfoxide **11** using Oxone in aqueous MeOH.[8] However, subsequent oxidation to the desired sulfone **12** was very sluggish even when a large excess of Oxone was employed. Fortunately, both sulfoxide **11** and sulfone **12** react smoothly with morpholine to afford the desired product. Therefore, a mixture of sulfoxide **11** and sulfone **12** (~1:1 ratio) was treated with morpholine in THF to afford the desired thiophene core **6**, which was precipitated out of the THF solution with water in good purity (>98%) and yield (72% over two steps).

Despite the use of these hazardous reagents, the second-generation synthesis afforded a convenient avenue to **6**, so we set out to further optimize the route to make it more process friendly (Scheme 4). Replacement of NaH with K_2CO_3 eliminated the primary risk associated with the step 1 condensation reaction,[9] and although the reaction still used MeI and CS_2, these reagents were charged in only near-stoichiometric quantities, reducing the risk of exposure and flammability. Replacement of THF with DMSO afforded a higher recovery of cleaner compound **8**, and we also observed that the yield of the Sandmeyer

dx.doi.org/10.1021/op100286g |*Org. Process Res. Dev.* 2011, 15, 556–564

Scheme 4. Modified second-generation synthesis of 6



reaction improved from 50% to 78% upon scale-up. Calorimetric examination allowed us to define the limits of the safe operation of these steps sufficiently to safely undertake a 1 kg preparation[10] of iodothiophene **6**.

With key intermediate **6** in hand, we screened for the optimal Suzuki coupling conditions,[11] but unfortunately these reactions typically generated significant amounts of des-iodo material and suffered from consistently low yields. Furthermore, the desired coupling products had poor solubility in organic solvents and displayed polarity similar to that of the unreacted starting materials, resulting in a problematic purification for a large-scale synthesis. Therefore, a high-throughput experimentation methodology (HTE) was initiated to identify optimal Suzuki conditions for this particular substrate−reactant combination.[12] A variety of catalysts [$Pd(P^tBu_3)_2$, $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$], bases (CsF, DIPEA, K_2CO_3, K_3PO_4), and solvents (toluene, dioxane, EtOH, water) were screened on 10 mg scale in varying stoichiometric ratios at 80 °C for 16 h. The results were processed and analyzed by Spotfire software and are illustrated in Scheme 5. In general, $Pd(P^tBu_3)_2$ was found to be superior to both $Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$, whilst bases CsF and DIPEA gave better coupling results than K_2CO_3 and K_3PO_4. Of the 200 screened reactions, three potential generic condition sets were identified for each set of coupling partners (Scheme 5). Unfortunately, a gram-scale test using Hunig's base resulted in much lower conversion and more des-iodo side products than in the corresponding screening reaction on 10 mg scale, possibly due to relatively easier Pd aggregation and precipitation in larger-scale reactions. Eventually, we found the following conditions to be effective for all substrates: 1.2 equiv boronic acid, 5 mol % $Pd(P^tBu_3)_2$, 1.2 equiv CsF, dioxane/water/toluene, 85 °C.[13] Remarkably, for both 2,4-dichlorophenylboronic acid and 2-chloro-4-methoxylphenylboronic acid, Suzuki coupling afforded over 98% conversion. On small scale, residual palladium was removed using Si-thiol resin[14] followed by aqueous extraction to obtain coupling products **5a** and **5b** as yellow solids with good purity. In the case of **5c**, extraction into toluene followed by cooling and crystallization resulted in isolation of the desired product in 90% yield in >98% purity on 250 g scale without the need for Si-thiol treatment.[15]

In addition, the Suzuki coupling of amide **7** with 2,4-dichlorophenylboronic acid and 2-chloro-4-methoxyphenylboronic acid was investigated (Scheme 6). Under various conditions examined (once again a high throughput screen of approximately 100 conditions was carried out), the coupling reaction of amide **7** always resulted in both low conversion with significant amounts of the des-iodo side product. We suspected that the poor solubility of amide **7** was the culprit for the unsatisfactory Suzuki coupling reactions. The desired coupling product from amide **7** also has poor solubility, and this caused difficulties with purification. Therefore, the ester **6**, rather than the amide **7**, was used for the Suzuki couplings to access **1**−**3**.

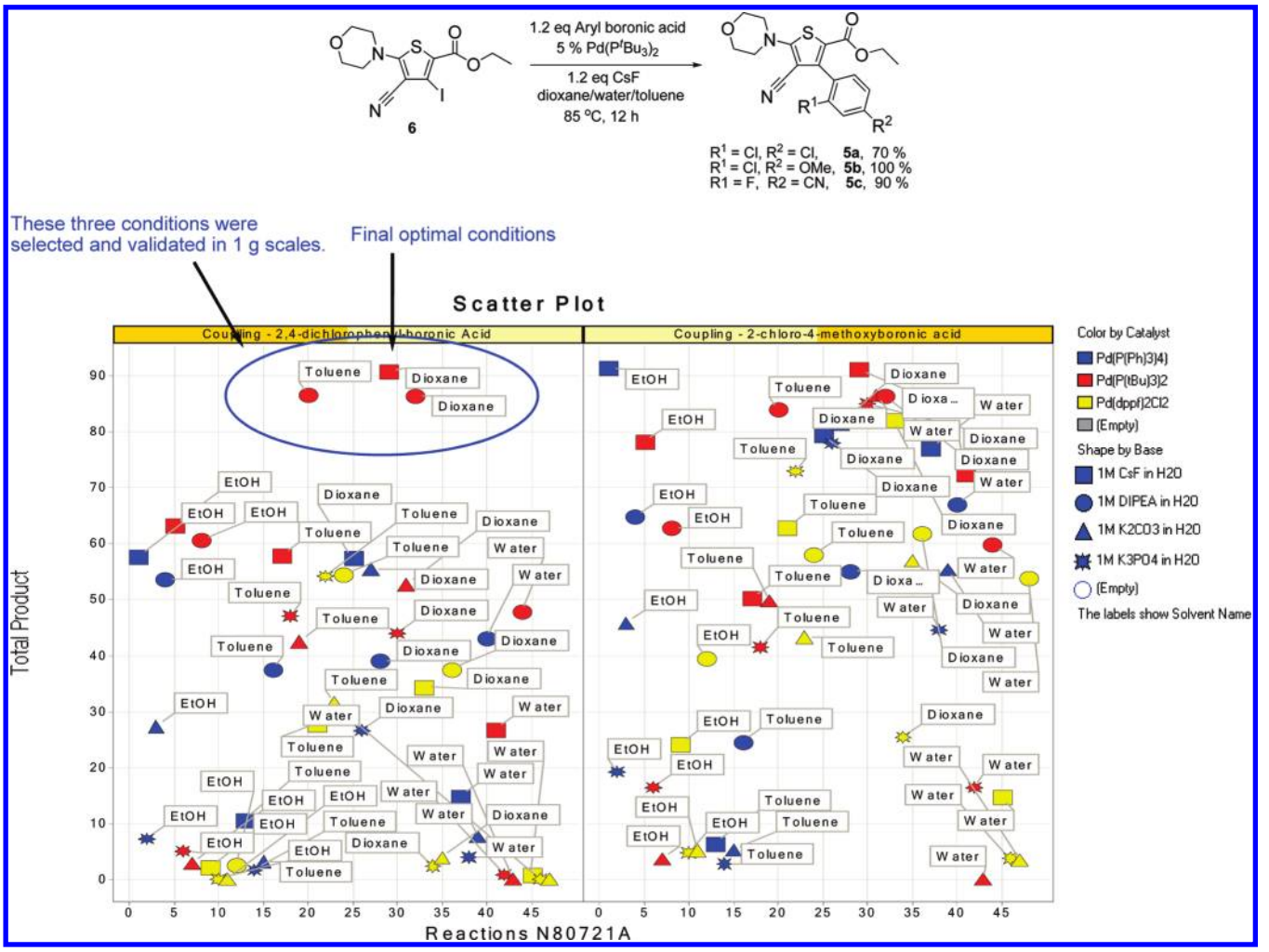
Esters **5a** and **5b** were converted to acids **13a** and **13b** via treatment with aqueous LiOH in water, and were readily precipitated out of solution after pH adjustment. However, the conversion of **5c** to **13c** did not work well under these conditions (<40% yield). After undergoing reaction screening, it was determined that saponification using aqueous NaOH in a mixture of EtOH and 2-MeTHF gave smooth conversion without decomposition of the sensitive aryl-fluoride group, but additional decomposition was observed upon pH adjustment with HCl. Inverse addition of the basic product solution into a mixture of aqueous HCl and NaCl solved this problem, allowing isolation of **13c** in 84% yield on 84 g scale (see Scheme 7).

The subsequent aminolysis reaction was carried out by first activating the acid with 2-chloro-4,6-dimethoxy-[1,3,5]triazine (CDMT) followed by treatment with gaseous ammonia to afford amides **4a**−**4c**.[16] The primary amides were purified by trituration with EtOAc and saturated aqueous $NaHCO_3$ in the case of **4a** and **4b**, and using a MeOH reslurry in the case of **4c**, each to afford product with over 95% purity. Compounds **4a**−**4c** were then treated with *N*,*N*-dimethylformamide dimethyl acetal (DMF−DMA) to afford **14a**−**14c**, which were purified via a MeOH reslurry.

When a solution of **14a**−**14c** in 5:1 EtOH/HOAc was treated in one portion with 10 equiv $NH_2NH_2 \cdot H_2O$, on small scale (~500 mg) at 60 °C, desired triazoles **1**−**3** were obtained in near quantitative yields (see Scheme 7). However, upon scaling up (5.0 g), the same process resulted in 50−70% of the desired triazole compounds along with 20−30% of the corresponding hydrolyzed amides (**4a**−**4c**). We hypothesize that, under these conditions, NH_2NH_2 was rapidly protonated to form an acetate salt, generating an exotherm[17] that might have led to decomposition

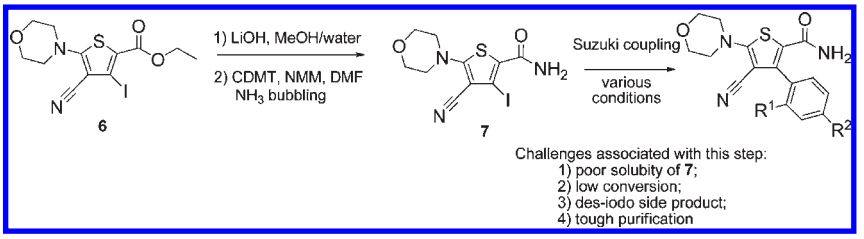
dx.doi.org/10.1021/op100286g |*Org. Process Res. Dev.* 2011, 15, 556–564

Scheme 5. Key Suzuki coupling to form esters 5a−5c[a]



[a] Screening conditions: **6** (10 mg, 0.025 mmol, 1.0 equiv), aryl boronic acid (0.030 mmol, 1.2 equiv), Pd catalyst (0.1 M in toluene, 25 μL, 0.1 equiv), base (1 M aqueous solution, 75 uL, 3.0 equiv), solvent (300 μL), reaction concentration 0.06 M, 80 °C, overnight.

Scheme 6. Attempted Suzuki coupling to form amide 7

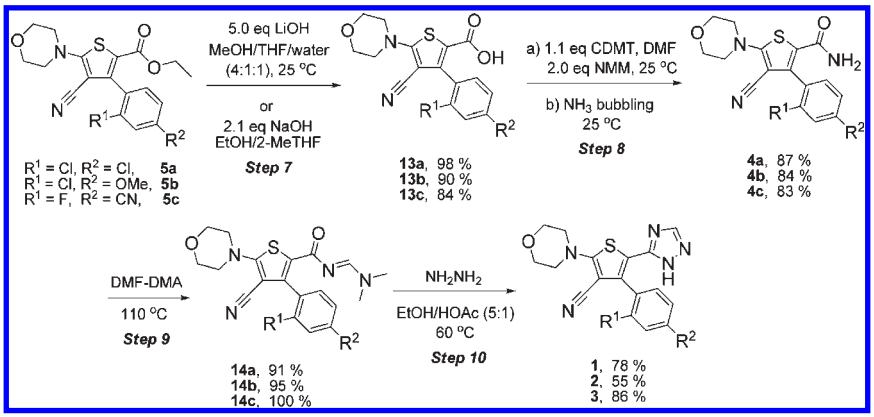


of **14a**−**14c** in aqueous EtOH. The problem was resolved by reversing the order of reagent addition and by carefully monitoring the heat of reaction during slow addition of the aqueous NH_2NH_2 solution. In the modified procedure, NH_2NH_2 was added dropwise into a solution of **14a**, **14b**, or **14c** in EtOH/AcOH whilst carefully maintaining the internal temperature at −10−0 °C. Heat generation was addition controlled, and as the NH_2NH_2 reacted quickly during the slow addition, formation of the corresponding amide impurity was virtually eliminated. Incorporation of this modified procedure enabled the synthesis of **3** in a more scalable manner, affording an 86% yield of high-purity **3** using only 5 equiv of NH_2NH_2.[18,19]

Early on we found it necessary to purify compounds **1**−**3** via silica gel chromatography. However, we later discovered that triazole products **1**−**3** could be purified by extraction into aqueous caustic, allowing removal of soluble organic impurities by extraction with EtOAc. The pH of the resulting aqueous solution was then adjusted to pH 4−5 with HOAc, and the desired products were extracted into the organic layer. Solvent removal afforded triazoles **1** and **2** with greater than 98% purity.

dx.doi.org/10.1021/op100286g |*Org. Process Res. Dev.* 2011, 15, 556–564

Scheme 7. Optimized synthesis of 1, 2, and 3



Compound **3** was isolated in a similar manner, although the basic product solution was reacidified to pH 5 with 1 N HCl[20] and filtered to afford **3** directly in 86% yield on 50-g scale.[21,22]

CONCLUSIONS

In conclusion, a general and scalable route has been successfully developed to synthesize PI3K inhibitors **1**, **2**, and **3** from inexpensive commercially available starting materials. A few key advantages and highlights associated with this route over the original medicinal chemistry route include: (1) employment of an advanced common intermediate strategy (i.e., **6**) to enable synthesis of multiple analogues on gram scale, (2) optimization of the key Suzuki coupling step using a high throughput experimentation approach, and (3) column chromatography was not needed. A scalable synthesis for this series was demonstrated in the synthesis of candidate **3**.[23]

EXPERIMENTAL SECTION

General. HPLC assays were performed on Agilent 1100 chromatographs equipped with PDA detectors. Routine reaction monitoring was done using a Phenomenex Prodigy ODS3 4.6 mm × 50 mm column or an equivalent C-18 column and a standard 8-min gradient program: 10:90 to 90:10 mixture of acetonitrile−water containing 0.02% of TFA with constant flow of 1 mL/min. LC/MS data were obtained on an Agilent 1100 LC system with an Agilent 1100 LC/MS detector. NMR spectra were recorded on a Bruker Avance DPX300 or a Bruker Avance DRX400 NMR spectrometer. HRMS data were gathered on an Agilent 1100 LC with MSD TOF (Agilent model G1969A) mass spec detectors running with electrospray spray ionization source. The purity of final APIs was determined by HPLC.

2-(Bis-methylsulfanyl-methylene)malononitrile (8). *Original Laboratory Procedure.* To a suspension of NaH (60% on mineral oil, 40 g, 989 mmol, 2.20 equiv) in THF (500 mL) at 0 °C was added malononitrile (30.0 g, 450 mmol, 1.0 equiv) at <5 °C. The resulting mixture was stirred at 0 °C for 10 min, followed by addition of CS_2 (30 mL, 495 mmol, 1.1 equiv) over 20 min. (Caution: significant effervescence observed.) The resulting deep-orange solution was allowed to warm to 25 °C for 4 h and was recooled to 0 °C. MeI (57 mL, 899 mmol, 2.0 equiv) was added (again significant effervescence) over 10 min, and the reaction mixture turned yellow. The resulting mixture was stirred at 25 °C for 12 h and was then poured into ice water (400 mL) to precipitate a yellow solid that was filtered, washed with water, and dried on the filter for 1 h. The crude product was triturated with MeOH (100 mL) to afford 77 g (100%) of **8** as a white solid with spectral properties identical to those previously reported.[9a]

Modified Laboratory Procedure. A suspension of K_2CO_3 (1.15 kg, 8.33 mol) in DMSO (5 L) at 20 °C was treated with malononitrile (0.5 kg, 7.57 mol) in one portion. The reactor was cooled to 0 °C, and CS_2 (0.50 L, 8.33 mol) was added over 30 min at 18−22 °C. The resulting yellow suspension was stirred at 20 °C for 2 h and then cooled to 0 °C over 20 min. MeI (0.77 L, 15.1 mol) was added over 30 min with pot temperature <5 °C. The reaction was warmed to 20 °C and stirred for 12 h. The resulting slurry was poured into ice water (12 L) to afford yellow solids that were collected by filtration, washed with water (2 × 1 L) and MeOH (500 mL), and dried to afford **8** (1.28 kg, 7.52 mol, 99%) as a white solid with spectral properties identical to those previously reported.[9a]

3-Amino-4-cyano-5-methylsulfanyl-thiophene-2-carboxylic Acid Ethyl Ester (9). A suspension of 2-(bis-methylsulfanyl-methylene)malononitrile (**8**) (2.58 kg, 15.1 mol) in EtOH (12 L) at 20 °C was treated with ethyl 2-mercaptoacetate (1.66 L, 15.1 mol) in one portion. The reactor was cooled with an ice bath, and Et_3N (2.11 L, 15.1 mol) was added via addition funnel over 45 min with pot temperature <20 °C. After being stirred at 20 °C for 12 h, the resulting slurry was filtered to afford yellow solids that were washed with EtOH (2 × 250 mL) and dried on the filter under vacuum for 12 h to afford **9** as a pale-yellow solid (2.47 kg, 10.1 mol, 67.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 1.34 (t, J = 7.05 Hz, 3 H) 2.65 (s, 3 H) 4.29 (q, J = 7.22 Hz, 2 H) 5.78 (br s, 2 H).

4-Cyano-3-iodo-5-methylsulfanyl-thiophene-2-carboxylic Acid Ethyl Ester (10). To a stirred suspension of 3-amino-4-cyano-5-methylsulfanyl-thiophene-2-carboxylic acid ethyl ester (**9**) (2.47 kg, 10.2 mol) in CH_3CN (10 L) was added CH_2I_2 (1.25 L, 15.3 mol) in one portion. The reaction was heated to 70 °C, and isoamyl nitrite (2.14 L, 15.3 mol) was added via addition funnel at a rate to maintain the pot temperature between 60 and 70 °C (50 mL was added rapidly to initiate the reaction, and the remainder was added over approx 120 min). After complete addition, the reaction mixture was cooled to 20 °C and stirred for 12 h, then cooled to 0 °C and stirred for 30 min. The resulting solids were collected by filtration, washed with cold CH_3CN (0 °C, 2 × 250 mL), and dried on the filter under vacuum for 12 h to afford **10** as a yellow solid (2.8 kg, 7.93 mol, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 1.34 (t, J = 7.18 Hz, 3 H) 2.64 (s, 3 H) 4.32 (q, J = 7.05 Hz, 2 H).

dx.doi.org/10.1021/op100286g |*Org. Process Res. Dev.* 2011, 15, 556–564

4-Cyano-3-iodo-5-methanesulfinyl-thiophene-2-carboxylic Acid Ethyl Ester (11) and 4-Cyano-3-iodo-5-methanesulfonyl-thiophene-2-carboxylic Acid Ethyl Ester (12). A suspension of 4-cyano-3-iodo-5-methylsulfanyl-thiophene-2-carboxylic acid ethyl ester (**10**) (900 g, 2.65 mol, 1.0 equiv) in MeOH (6 L) at 0 °C was treated with an aqueous solution of oxone (3.58 kg, 5.84 mol, 2.20 equiv in 8 L water) via addition funnel over 1 h with pot temperature <25 °C. The resulting mixture was stirred at 25 °C for 12 h and diluted with water (4 L). The resulting solids were collected by filtration, washed with water (2 × 1 L), and dried in vacuo at 40 °C for 12 h to afford 950 g of a crude mixture of products (sulfoxide **11** and sulfone **12**), that was carried into the next step without further purification.

4-Cyano-3-iodo-5-morpholin-4-yl-thiophene-2-carboxylic Acid Ethyl Ester (6). A solution of **11** and **12** (approx. 2.65 mol, crude from previous step) in THF (8 L) at 0 °C was treated with morpholine (1.21 L, 13.8 mol) via addition funnel over 10 min with the pot temperature <10 °C. The solution was stirred at 25 °C for 12 h. The resulting slurry was charged with water (6 L), cooled to 5 °C, and stirred for 30 min. The solids were collected by filtration, washed with water (2 × 500 mL), triturated with MeOH (500 mL), and dried under vacuum at 30 °C for 2 h to afford 0.8 kg (77% over 2 steps) of **6** as a white solid. MP 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (t, J = 7.18 Hz, 3 H) 3.55−3.70 (m, 4 H) 3.82−3.94 (m, 4 H) 4.34 (q, J = 7.22 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) 14.1, 50.0, 61.1, 65.0, 95.7, 96.1, 113.2, 117.1, 159.5, 168.5; IR (neat, cm^{-1}) 3055, 2984, 2211, 1709, 1494, 1265; HRMS Calcd for $C_{12}H_{13}IN_2O_3S$: 391.9692. Found: 391.9680.

Screening Procedure for Key Step Suzuki Coupling. Compound **6** and the corresponding boronic acid (1:1.2 molar ratio) were suspended in THF. An appropriate amount of suspension containing compound **6** (10 mg, 0.025 mmol, 1.0 equiv) and the corresponding boronic acid (0.030 mmol, 1.2 equiv) was transferred into 0.8 mL-capacity vials charged with small magnetic stir bars. The vials were placed in 96 vial plates, and all solvents were removed under vacuum overnight to afford neat dry solids. To the vials were added an appropriate solvent (300 μL), base (1 M aqueous solution, 75 μL, 3.0 equiv), and catalyst (0.1 M in toluene, 25 μL, 0.1 equiv). The resulting mixtures were stirred at 80 °C overnight. The screening plates were cooled to room temperature, and DMF (300 μL) was added to each vial. After being stirred at room temperature for 30 min, the mixtures were sonicated and analyzed directly by LC/MS. The resulting LC/MS data were processed and analyzed using Spotfire software.

4-Cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic Acid Ethyl Ester (5a). A suspension of 4-cyano-3-iodo-5-morpholin-4-yl-thiophene-2-carboxylic acid ethyl ester (**6**) (15 g, 38 mmol, 1.0 equiv), 2,4-dichlorophenylboronic acid (9.12 g, 45.9 mmol, 1.2 equiv), CsF (17.6 g, 115 mmol, 3.0 equiv), Pd(P^tBu_3)$_2$ (977 mg, 1.91 mmol, 0.05 equiv), dioxane (240 mL), toluene (15 mL), and water (60 mL) was flushed with N_2 and warmed up to 85 °C. After being stirred at 85 °C for 12 h, the reaction reached completion. To the reaction mixture was added Si-thiol (∼10 g), and the mixture was stirred at 25 °C for 3 h to remove Pd catalyst. The resulting mixture was then diluted with EtOAc and filtered through Celite. The filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 11.0 g of **5a** in 70% yield with over 85% purity as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 1.13 (t, J = 7.18 Hz, 3 H) 3.62−3.67 (m, 4 H) 3.85−3.91 (m, 4 H) 4.08−4.18 (m, 2 H) 7.21 (d, J = 8.06 Hz, 1H) 7.33 (dd, J = 8.31, 2.01 Hz, 1 H) 7.50 (d, J = 2.01 Hz, 1 H).

4-Cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic Acid (13a). To a slurry of 4-cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic acid ethyl ester (**5a**) (11.0 g, 8 mmol) in MeOH (120 mL) was added a solution of LiOH (3.2 g, 134 mmol, 5 equiv) in water (30 mL) at 25 °C. The resulting slurry was stirred at 25 °C for 3 h to reach completion. The volatiles were removed under reduced pressure. The aqueous solution solidified during concentration. This white slurry was diluted with water (150 mL) and adjusted to pH ∼3 with 2 N HCl. The solids were collected by filtration, washed with water and a minimal amount of MeOH, and dried under vacuum at 50 °C for 7 h to provide 10.5 g (98%) of **13a** as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 3.51−3.69 (m, 4 H) 3.72−3.85 (m, 3 H) 7.39 (d, J = 8.31 Hz, 1 H) 7.50 (dd, J = 8.31, 2.27 Hz, 1 H) 7.74 (d, J = 2.01 Hz, 1 H) 12.26−13.39 (m, 1 H).

4-Cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic acid amide (4a). To a solution of 4-cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic acid (**13a**) (15 g, 39 mmol, 1.0 equiv) in DMF (500 mL) was added CDMT (7.71 g, 43 mmol, 1.1 equiv) and *N*-methyl morpholine (NMM) (9.1 mL, 82.5 mmol, 2.0 equiv). The resulting mixture was stirred at 25 °C for 2 h. Ammonia gas was then bubbled through the suspension for 1 h, and the mixture was allowed to stir at 25 °C for 2 h to reach completion. To the reaction mixture was added 1.5 L water and solids precipitated out. The solid was collected by filtration and triturated with a mixture of EtOAc (50 mL) and saturated aq $NaHCO_3$ (50 mL). The resulting solids were filtered, washed with water and EtOAc, and dried under vacuum to afford 13 g (87%) of **4a** as a pale yellow solid. LC-MS (APCI, $M^+ + 1$) 382.2; ^{1}H NMR (400 MHz, DMSO-d_6) 3.48−3.58 (m, 4 H) 3.69−3.85 (m, 4 H) 7.43 (d, J = 8.31 Hz, 1 H) 7.50−7.60 (m, 1 H) 7.78 (d, J = 2.01 Hz, 1 H) 9.31 (s, 2 H).

4-Cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic Acid [2-Methyl-prop-(*E*)-ylidene]amide (14a). A brown slurry of 4-cyano-3-(2,4-dichloro-phenyl)-5-morpholin-4-yl-thiophene-2-carboxylic acid amide (**4a**) (11.5 g, 0.1 mmol) in 80 mL of DMF−DMA was heated to reflux at 110 °C for 1.5 h to form a yellow slurry. During the reaction, MeOH was generated. After cooling, the solvent was removed under reduced pressure. The sticky residue was triturated with MeOH and dried under vacuum to provide 12 g (91%) of **14a** as a white solid. LC−MS (APCI, $M^+ + 1$) 437.2; ^{1}H NMR (400 MHz, DMSO-d_6) 2.73 (s, 3 H) 3.07 (s, 3 H) 3.51−3.62 (m, 4 H) 3.73−3.81 (m, 4 H) 7.33 (d, J = 8.31 Hz, 1 H) 7.46 (dd, J = 8.18, 2.14 Hz, 1 H) 7.68 (d, J = 2.01 Hz, 1 H) 8.32 (s, 1 H).

4-(2,4-Dichlorophenyl)-2-morpholin-4-yl-5-(2*H*-[1,2,4]triazol-3-yl)thiophene-3-carbonitrile (1). To a slurry of 4-cyano-3-(2,4-dichlorophenyl)-5-morpholin-4-yl-thiophene-2-carboxylic acid [2-methyl-prop-(*E*)-ylidene]-amide (**14a**) (25 g, 57 mmol, 1.0 equiv) in glacial HOAc (40 mL) and EtOH (200 mL) was added dropwise $NH_2NH_2 \cdot H_2O$ (18.9 mL, 572 mmol, 10 equiv) whilst maintaining the inner reaction mixture temperature at −10−0 °C. Upon the completion of addition, the mixture was warmed to 60 °C and allowed to stir at this temperature for 1.5 h to reach completion. The resulting yellow slurry was cooled to 25 °C, diluted with water (1 L), and extracted with EtOAc (1 L). The separated organic layer was treated with 1.0 M NaOH (1 L) and the desired triazole product was taken into aqueous solution. The aqueous solution was separated and further washed with EtOAc (2 × 200 mL) to remove all other organic impurities. The

aqueous layer was then acidified by HOAc to pH = 4−5 to generate a slurry. The slurry was extracted with EtOAc (3 × 400 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to afford 18 g (78%) of **1** as a pale yellow solid. After being dried under vacuum overnight, ^{1}H NMR showed that the product was an acetate salt (0.8 equiv by NMR integration). LC−MS (APCI, $M^+ + 1$) 406.0; ^{1}H NMR (400 MHz, DMSO-d_6) of its HOAc salt: 1.91 (s, 3H from acetate salt), 3.49−3.58 (m, 4 H) 3.75−3.84 (m, 4 H) 7.37−7.44 (m, 1 H) 7.46−7.51 (m, 1 H) 7.72 (d, J = 2.01 Hz, 1 H) 8.42 (s, 1 H), triazole N−H protons were missing due to deuterium exchange; ^{13}C NMR (100 MHz, DMSO-d_6) 50.2, 65.2, 88.8, 115.9, 127.2, 128.8, 132.6, 133.0, 133.8, 134.2, 134.5, 144.0, 155.5, 165.1, one triazole carbon missing due to overlap; IR (neat, cm^{-1}) 3054, 2900, 2207, 1597, 1508; HRMS Calcd for $C_{17}H_{13}Cl_2N_5OS$: 405.0219. Found: 405.0218.

3-(2-Chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic Acid Ethyl Ester (5b). A mixture of 4-cyano-3-iodo-5-morpholin-4-yl-thiophene-2-carboxylic acid ethyl ester (**6**) (18 g, 46 mmol, 1.0 equiv), 2-chloro-4-methoxy phenylboronic acid (10.3 g, 55.1 mmol, 1.2 equiv), Pd(P^tBu_3)$_2$ (1.17 g, 2.3 mmol, 0.05 equiv), CsF (21.1 g, 138 mmol, 3.0 equiv), dioxane (200 mL), toluene (12 mL) and water (50 mL) was flushed with N_2 and stirred at 85 °C. After being stirred at 85 °C for 12 h, the reaction was judged complete by LC−MS. To the reaction mixture was added Si-thiol (15 g), and the mixture was stirred at 25 °C for 2 h to remove the Pd catalyst. The resulting mixture was then diluted with EtOAc and filtered through Celite. The filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford 19 g (100% yield) **5b** as a pale yellow solid with over 85% purity, which was used in the subsequent hydrolysis step without further purification. LC−MS (APCI, $M^+ + 1$) 407.0; ^{1}H NMR (400 MHz, DMSO-d_6) 0.99−1.05 (m, 3 H) 3.58−3.65 (m, 4 H) 3.75−3.81 (m, 4 H) 3.83 (s, 3 H) 3.98−4.08 (m, 2 H) 6.98 (dd, J = 8.56, 2.52 Hz, 1 H) 7.14 (d, J = 2.52 Hz, 1 H) 7.25 (d, J = 8.56 Hz, 1 H).

3-(2-Chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic Acid (13b). To a suspension of 3-(2-chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic acid ethyl ester (**5b**) (19.0 g, 47 mmol, 1.0 equiv) in MeOH (200 mL) and THF (50 mL) was added a solution of LiOH (5.59 g, 233 mmol, 5 equiv) in water (50 mL) at 25 °C. The resulting clear-orange solution was stirred at 25 °C for 12 h to reach completion. The volatiles were removed under reduced pressure. The remaining aqueous solution was solidified during concentration. This slurry was diluted with water and acidified to pH ≈ 3 with 2 N HCl. The resulting solids were filtered, washed with water and a minimal amount of MeOH, and dried under vacuum at 50 °C for 7 h to afford 16 g (90%) of **13b** as a pale-yellow solid. LC−MS (APCI, $M^+ + 1$) 379.0; ^{1}H NMR (400 MHz, DMSO-d_6) 3.54−3.63 (m, 4 H) 3.74−3.81 (m, 4 H) 3.83 (s, 3 H) 6.97 (dd, J = 8.56, 2.52 Hz, 1 H) 7.12 (d, J = 2.52 Hz, 1H) 7.25 (d, J = 8.56 Hz, 1 H).

3-(2-Chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic Acid Amide (4b). To a solution of 3-(2-chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic acid (**13b**) (15.0 g, 40 mmol, 1.0 equiv) in DMF (500 mL) was added CDMT (8.51 g, 47.5 mmol, 1.2 equiv) and NMM (9.2 mL, 83.4 mmol, 2.0 equiv). The resulting mixture was stirred at 25 °C for 1 h to form a transparent solution. Ammonia gas was bubbled through the mixture for 30 min, and the reaction was then allowed to stir at 25 °C for 2 h. To the reaction mixture was added 1.5 L water, and lots of solids were precipitated out. The solids were collected by filtration, triturated with a mixture of EOAc (50 mL) and saturated aq $NaHCO_3$ (50 mL), filtered, washed with water and EtOAc, and dried to afford 12.5 g (84%) of **4b** as a white solid. LC−MS (APCI, $M^+ + 1$) 378.0; ^{1}H NMR (400 MHz, DMSO-d_6) 3.47−3.59 (m, 4 H) 3.72−3.83 (m, 4 H) 3.85 (s, 3 H) 7.06 (dd, J = 8.56, 2.52 Hz, 1 H) 7.22 (d, J = 2.52 Hz, 1H) 7.36 (d, J = 8.56 Hz, 1 H).

3-(2-Chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic Acid [2-methyl-prop-(*E*)-ylidene]amide (14b). A brown slurry of 3-(2-chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic acid amide (**4b**) (12.5 g, 33.1 mmol) in 80 mL of DMF−DMA was heated to reflux at 110 °C for 1.5 h to form a yellow slurry. MeOH was generated as the reaction proceeded. After cooling, the solvent was removed under reduced pressure. The sticky residue was triturated with MeOH and dried under vacuum to afford 14.0 g (95%) of **14b** as a white solid. LC−MS (APCI, $M^+ + 1$) 433.0; ^{1}H NMR (400 MHz, DMSO-d_6) 2.75 (s, 3 H) 3.07 (s, 3 H) 3.51−3.60 (m, 4 H) 3.74−3.80 (m, 4 H) 3.81 (s, 3 H) 6.94 (dd, J = 8.56, 2.52 Hz,1 H) 7.08 (d, J = 2.52 Hz, 1 H) 7.19 (d, J = 8.31 Hz, 1 H) 8.31 (s, 1 H).

4-(2-Chloro-4-methoxy-phenyl)-2-morpholin-4-yl-5-(2H-[1,2,4]triazol-3-yl)-thiophene-3-carbonitrile (2). To a slurry of 3-(2-chloro-4-methoxy-phenyl)-4-cyano-5-morpholin-4-yl-thiophene-2-carboxylic acid [2-methyl-prop-(*E*)-ylidene]-amide (**14b**) (14 g, 32 mmol, 1.0 equiv) in HOAc (20 mL) and EtOH (100 mL) was added dropwise $NH_2NH_2 \cdot H_2O$ (10.7 mL, 323 mmol, 10 equiv) whilst maintaining the reaction mixture temperature at −10−0 °C with stirring. Upon the completion of addition, the reaction was slowly warmed to 60 °C and allowed to stir at this temperature for 1.5 h to reach completion. The resulting yellow slurry was cooled to 25 °C, diluted with water (500 mL), and extracted with EtOAc (500 mL). The separated organic layer was treated with 1.0 M NaOH (500 mL) and the desired triazole product was taken into aqueous solution. The aqueous solution was separated and further washed with EtOAc (2 × 200 mL) to remove all other organic impurities. The aqueous layer was then acidified by HOAc to pH = 4−5 to generate a slurry. The slurry was extracted with EtOAc (3 × 200 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to afford 8.0 g (55%) of **2** as a white solid. After being dried under vacuum overnight, the ^{1}H NMR showed that the product was an acetate salt (0.75 equiv). LC−MS (APCI, $M^+ + 1$) 402.0; ^{1}H NMR (400 MHz, DMSO-d_6) 1.91 (s, 3 H from HOAc salts) 3.49−3.56 (m, 4 H) 3.76−3.83 (m, 4 H) 3.84 (s, 3 H) 6.96 (dd, J = 8.69, 2.64 Hz, 1 H) 7.11 (d, J = 2.52 Hz, 1H) 7.27 (d, J = 8.56 Hz, 1 H) 8.41 (s, 1 H), triazole N−H protons were missing due to deuterium exchange; ^{13}C NMR (100 MHz, DMSO-d_6) 50.2, 55.3, 65.2, 88.9, 113.0, 114.3, 116.1, 125.3, 132.3, 133.7, 135.7, 144.0, 155.5, 160.8, 164.9, one triazole carbon missing due to overlap; IR (neat, cm^{-1}) 3239, 2902, 2205, 1606, 1503; HRMS Calcd for $C_{18}H_{16}ClN_5O_2S$: 401.0708. Found: 401.0713.

Ethyl 4-cyano-3-(4-cyano-2-fluorophenyl)-5-morpholinothiophene-2-carboxylate (5c). A slurry of ethyl 4-cyano-3-iodo-5-morpholinothiophene-2-carboxylate (**6**) (250.0 g, 637 mmol) and 4-cyano-2-fluorophenylboronic acid (126.2 g, 765 mmol, 1.2 equiv) in a mixture of toluene (188 mL) and 1,4-dioxane (3 L) was charged a with premade solution of CsF (290.5 g, 1.91 mol, 3 equiv) in water (750 mL) in a jacketed reactor. The resulting slurry was purged with N_2 for 20 min and charged with

$Pd(P^tBu_3)_2$ (5.0 g, 9.56 mmol, 1.5 mol %) in one portion. The reaction mixture was heated to reflux for 2 h until TLC analysis (3:1 heptane/EtOAc) indicated full conversion of iodide (0.3 R_f) to desired product (0.2 R_f). *Note: The jacket temperature was set to 65 °C and was adjusted as necessary to maintain the internal pot temperature between 55 and 65 °C during the remaining extractive workup steps to maintain solubility.* The reaction mixture was charged with toluene (1.0 L), stirred for 10 min, and separated. The lower aqueous layer was extracted with toluene (0.5 L) and discarded. The combined organic layer was extracted with aqueous NaCl (10 wt %, 2 × 1.5 L) followed by distillation under vacuum at 55−70 °C under a Dean−Stark apparatus until no more water was observed to collect. The resulting solution was distilled down to a final volume of 1.5 L and was cooled to 18 °C at a rate of 0.5 °C/min. The resulting slurry was filtered, rinsed with toluene (3 × 100 mL) followed by *n*-heptane (5 × 250 mL), and dried under vacuum at 50 °C for 12 h to afford 220 g (90%) of **5c** as a granular white solid.[24] LC−MS ($M^+ + 1$) 386.0; ^{1}H NMR (400 MHz, $CDCl_3$) 1.05 (t, J = 7.22 Hz, 3 H) 3.55−3.65 (m, 4 H) 3.70−3.80 (m, 4 H) 4.05−4.13 (m, 2 H) 7.62 (dd, J = 8.22, 1.99 Hz, 1 H) 7.81 (d, J = 7.98 Hz, 1H) 8.05 (d, J = 2.01 Hz, 1 H).

4-Cyano-3-(4-cyano-2-fluorophenyl)-5-morpholinothiophene-2-carboxylic Acid (13c). A slurry of ethyl 4-cyano-3-(4-cyano-2-fluorophenyl)-5-morpholinothiophene-2-carboxylate (**5c**) (80.0 g, 208 mmol) in EtOH (800 mL) and 2-MeTHF (320 mL) was charged with NaOH (50 wt %, 34.9 g, 436 mmol, 2.1 equiv) in one portion in a jacketed reactor. After being stirred at 55 °C for 0.5 h, TLC analysis (1:1 heptane/EtOAc) indicated full conversion of starting ester (0.4 R_f) to carboxylate (origin). The reaction mixture was charged with EtOAc (1.5 L) and transferred to a carboy. The reactor was charged with aqueous 1 N HCl (1.3 L) and saturated NaCl solution (500 mL), and the mixture was adjusted to 50 °C. The original reaction mixture was transferred back to the reactor over 10 min, stirred for 15 min, and the layers were separated. The organic layer was extracted with aqueous NaCl (10 wt %, 2 × 500 mL) and concentrated by rotary evaporation to ~250 mL total volume. The slurry was charged with *n*-heptane (150 mL) and stirred for 1 h at 18 °C. The resulting solids were collected by filtration, washed with *n*-heptane (2 × 100 mL), and dried on the filter under vacuum for 12 h to afford 62.4 g (84%) of **13c** as a pale-yellow solid. LC−MS ($M^+ + 1$) 358.0; ^{1}H NMR (400 MHz, DMSO-d_6) 3.55−3.64 (m, 4 H) 3.70−3.80 (m, 4 H) 7.63 (dd, J = 8.21, 2.49 Hz, 1 H) 7.80 (d, J = 2.42 Hz, 1H) 8.01 (d, J = 8.21 Hz, 1 H).

4-Cyano-3-(4-cyano-2-fluorophenyl)-5-morpholinothiophene-2-carboxamide (4c). A slurry of 4-cyano-3-(4-cyano-2-fluorophenyl)-5-morpholinothiophene-2-carboxylic acid (**13c**) (62.0 g, 173 mmol) in DMF (620 mL) was charged with CDMT (33.5 g, 191 mmol, 1.1 equiv) in one portion at 18 °C. NMM (35.1 g, 347 mmol, 2 equiv) was added via addition funnel over 5 min. The resulting slurry was stirred between 18 and 25 °C for 1 h. Ammonia gas was then bubbled through the suspension for 30 min, allowing the pot temperature to rise to 35 °C. Once the exotherm subsided, the ammonia source was removed, and the mixture was allowed to cool to 18 °C with stirring over 1 h. The reactor was charged with water (1 L) via addition funnel over 10 min. The resulting solids were collected by filtration, rinsed with water (3 × 150 mL), and dried on the filter for 30 min under vacuum. The resulting wet cake was reslurried in MeOH (100 mL), filtered, and dried under vacuum at 50 °C for 24 h to afford 51.5 g (83%) of **4c** as a white solid. LC−MS ($M^+ + 1$) 357.0; ^{1}H NMR (400 MHz, DMSO-d_6) 3.35−3.43 (m, 4 H) 3.55−3.63 (m, 4 H) 7.29 (dd, J = 8.40, 2.49 Hz, 1 H) 7.52 (d, J = 2.47 Hz, 1H) 7.79 (d, J = 8.39 Hz, 1 H).

(*Z*)-4-Cyano-3-(4-cyano-2-fluorophenyl)-*N*-((dimethylamino) methylene)-5-morpholinothiophene-2-carboxamide (14c). A slurry of 4-cyano-3-(4-cyano-2-fluorophenyl)-5-morpholinothiophene-2-carboxamide (**4c**) (105.0 g, 295 mmol) in DMF−DMA (1.2 L) was heated to reflux for 1.5 h in a jacketed reactor. The reaction mixture was cooled to 40 °C, and the resulting solids were collected by filtration, rinsed with MeOH (3 × 150 mL), and dried under vacuum at 50 °C for 24 h to afford 125.0 g (100%) of **14c** as a pale-tan solid. LC−MS ($M^+ + 1$) 412.0; ^{1}H NMR (400 MHz, DMSO-d_6) 2.75 (s, 3 H) 3.09 (s, 3 H) 3.55−3.61 (m, 4 H) 3.70−3.79 (m, 4 H) 7.55 (dd, J = 8.51, 2.49 Hz,1 H) 7.71 (d, J = 2.49 Hz, 1 H) 7.91 (d, J = 8.20 Hz, 1 H) 8.25 (s, 1 H).

4-(4-Cyano-2-fluorophenyl)-2-morpholino-5-(1*H*-1,2,4-triazol-5-yl)thiophene-3-carbonitrile (3). A slurry of (*Z*)-4-cyano-3-(4-cyano-2-fluorophenyl)-*N*-((dimethylamino)methylene)-5-morpholinothiophene-2-carboxamide (**14c**) (50.0 g, 122 mmol, 1.0 equiv) in EtOH (600 mL) and HOAc (120 mL) was charged with NH_2NH_2 (65 wt % in water, 30.0 g, 0.6 mol, 5.0 equiv) via addition funnel over 10 min with pot temperature <0 °C. The resulting solution was then warmed to maintain the pot temperature at 60 °C for 1 h, cooled to 18 °C, charged with water (1.25 L) via addition funnel over 5 min, and stirred for 1 h. The product solids were partitioned between isopropyl acetate (1 L) and aqueous sodium hydroxide (3 N, 1 L), and the organic layer was discarded. The product-containing aqueous layer was extracted with isopropyl acetate (2 × 200 mL), concentrated slightly on the rotary evaporator at 50 °C and 30 Torr to remove any residual organic solvents, and was treated with aqueous 1 N HCl to pH 5. The resulting solids were collected by vacuum filtration, rinsed on the filter with water (5 × 200 mL) followed by *n*-heptane (5 × 200 mL), and then dried under vacuum at 50 °C for 12 h to afford 40.0 g (86%) of **3** as a pale-yellow granular solid. LC−MS ($M^+ + 1$) 381.0; ^{1}H NMR (400 MHz, DMSO-d_6) 3.54−3.59 (m, 4 H) 3.71−3.80 (m, 4 H) 7.60−7.65 (m, 1 H) 7.75−7.79 (m, 1 H) 7.92−7.99 m, 1 H) 8.43 (s, 1 H), triazole N−H protons missing (deuterium exchange); ^{13}C NMR (100 MHz, DMSO-d_6) 50.9, 64.8, 89.2, 113.1, 116.5, 118.0, 119.9, 120.1, 128.3, 128.8, 130.5, 133.9, 158.1, 160.9, 166.3, one triazole carbon missing due to overlap; one triazole carbon missing due to overlap; IR (neat, cm^{-1}) 3230, 2910, 2230, 2208, 1618, 1499; HRMS Calcd for $C_{18}H_{13}FN_6OS$: 380.0856. Found: 380.0861.

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ACKNOWLEDGMENT

We thank Dr. Kevin Bunker, Michael Collins, Hayden Thomas, and Jared VanHaitsma for helpful discussions related to this work, and Jeffrey Raggon for outsourcing support. We are grateful to Xiukun Qin and Heping Wu from Chemizon Ltd. for preparing iodothiophene **6** on scale.

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(13) As the Pd catalysts (0.1 M in toluene) and bases (1.0 M aqueous solution) were prepared and utilized as solutions, identical amounts of water and toluene were incorporated for all the screening conditions. The screening reactions were carried out under highly dilute conditions; thus, the conditions were slightly modified on the concentration and ratio of solvents for 1 g condition validation and scale-up synthesis.

(14) For a reference describing the efficiency of use Si-thiol resin to remove palladium, see: Flahive, E. J.; Ewanicki, B. L.; Sach, N. W.; O'Neill-Slawecki, S. A.; Stankovic, N. S.; Yu, S.; Guinness, S. M.; Dunn, J. *Org. Process Res. Dev.* **2008**, *12*, 637–645.

(15) In the case of **5c**, Suzuki coupling of compound **6** with 4-cyano-2-fluorophenylboronic acid was carried out multiple times on 20- and 250-g scales, respectively. On 20-g scale, the optimal conditions indicated in the Scheme 5 were used, and on 250-g scale, the coupling conditions were slightly modified, in which 1.5 mol % of $Pd(P^tBu_3)_2$ and 3.0 equiv of CsF were used (also see Experimental Section for detail).

(16) The direct amination of esters **5a** and **5b** to amides **4a** and **4b** with NH_3 in various solvents has been briefly investigated. The reactions proceeded very slowly at elevated temperature using pressure vessels. However, longer reaction time and higher reaction temperatures led to decomposition of both the starting materials and products, while the reaction was difficult to achieve good conversion.

(17) We observed a ~ 25 °C exotherm on 5-g scale.

(18) While we were confident running this chemistry on 50 g scale (based on crude calorimetry data) with close monitoring of reaction internal temperature, it should be noted that additional process safety analysis would be required before attempting to scale NH_2NH_2 chemistry further. It is likely that the number of equivalents of hydrazine could be further reduced with additional studies.

(19) We did not investigate quenching excess NH_2NH_2 on this scale; unreacted NH_2NH_2 was purged in the aqueous sidestream.

(20) The acetate salt was avoided by using HCl with a direct-drop product isolation.

(21) The largest scales that this reaction was run are 25 g, 14 g, and 50 g for compounds **1**, **2** and **3**, respectively. No further scale-up was carried out because our PI3K project was held. The materials obtained from this method are pure enough for animal studies.

(22) As with any transformation, attempts to scale this chemistry further should be met with additional calorimetric scrutiny. DSC analysis of steps 7−10 indicated that all transformations except step 9 were carried out at more than 100 °C under any significant exothermic onset. DSC onsets for reaction mixtures of interest: step 7 saponification, 230 °C (120 J/g); step 8 amide formation, 244 °C (524 J/g); step 9 condensation, 179 °C [122 J/g, DMA-DMF has an onset of 255 °C (255 J/g)]; step 10 triazole formation, 169 °C [697 J/g, hydrazine hydrate has an onset of 180 °C (2334 J/g)].

(23) While several intermediates leading to compounds **1** and **2** were concentrated to dryness (see experimental description), workup and purification of intermediates **5c**, **13c**, **4c**, and **14c** were demonstrated in such a manner that we believe a successful plant campaign could be realized with minor additional process development work, such as solvent exchanges in place of concentrations to dryness.

(24) Determined by atomic absorption, the synthesized Suzuki product **5c** contained <50 ppm palladium.