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New conditions for the synthesis of thiophenes via the Knoevenagel/Gewald reaction sequence. Application to the synthesis of a multitargeted kinase inhibitor

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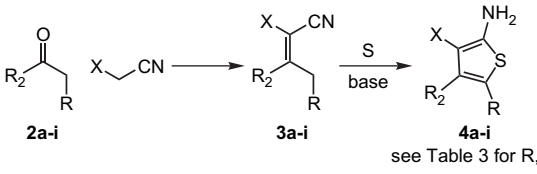
This paper is dedicated to Professor David MacMillan on the occasion of his receipt of the Tetrahedron *Young Investigator Award*

Abstract—Novel conditions have been developed for the preparation of substituted 2-aminothiophenes employing the Knoevenagel condensation followed by the Gewald reaction. The benefits of these conditions are their mildness, and the ease of product isolation. Thus, the Knoevenagel condensation is run in the presence of hexamethyldisilazane and acetic acid, which combine to perform the roles of desiccant, and catalyst. The Gewald reaction is performed with inorganic base in THF/water, which suppresses byproduct formation. This process has been employed in the total synthesis of a multitargeted kinase inhibitor.

1. Introduction

2-Aminothiophenes have demonstrated a broad spectrum of uses, including pharmaceuticals, dyes, and agrochemical applications.[1] Conceptually, the simplest and most convergent preparation of this class of compounds is the condensation of ketones with an activated nitrile and elemental sulfur, which was first described in 1960s by Gewald and co-workers.[2] Although a one-pot procedure is well-established, the two-step procedure in which an α,β-unsaturated nitrile is first prepared by Knoevenagel condensation of a ketone or aldehyde with an activated acetonitrile, followed by base-promoted reaction with sulfur, has generally been found to result in higher yields (Eq. 1).[1]



2a-i **3a-i** **4a-i**
see Table 3 for R, R_2

(1)

Thienopyrimidine **1** is a multitargeted receptor tyrosine kinase inhibitor, which demonstrates potent antitumor activity;[3] retrosynthetically, its heterocyclic core arises via condensation of 2-aminothiophene **4a** with formamide to form the pyrimidine ring (Scheme 1). Knoevenagel condensation of 4′-nitroacetophenone (**2a**) with malononitrile, followed by Gewald reaction with sulfur forms this aminothiophene in a concise fashion. Initial attempts to accomplish the synthesis of 2-aminothiophene **4a** employing standard literature conditions[1] provided poor yields for both the Knoevenagel and Gewald reactions and resulted in complicated mixtures that were difficult to purify. In this paper, we describe new conditions for both the Knoevenagel and Gewald reactions and their application in the synthesis of **1**. In addition, we describe the extension of these conditions to other substrates.

2. Results and discussion

2.1. Knoevenagel condensation

Literature preparation[4] of **3a** and similar ylidene compounds involves mixing of ketone, malononitrile, and a catalyst (e.g., ammonium acetate) in benzene or toluene (Eq. 2). The mixture is then warmed to reflux and water is removed via azeotropic distillation employing a Dean–Stark apparatus.

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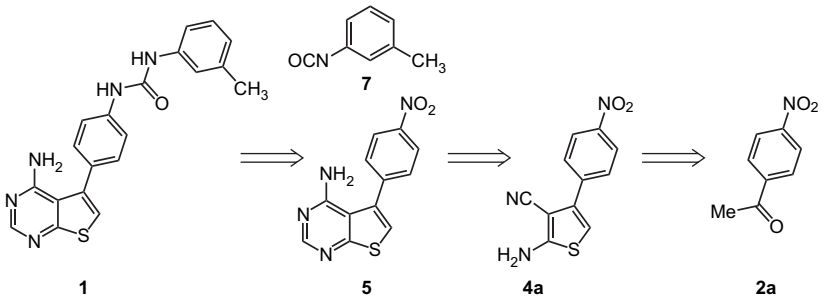
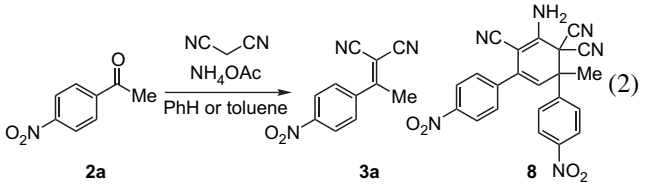


Scheme 1. Retrosynthesis of kinase inhibitor **1**.

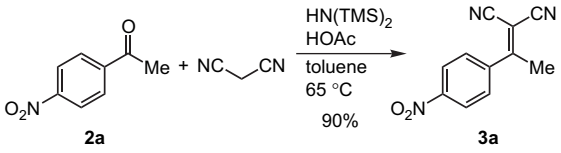


(2)

Ylidene **3a** is thermally unstable, hydrolytically sensitive, and decomposes in the presence of weak bases (i.e., sodium bicarbonate). This instability is most likely due to the combination of an unhindered enolizable methyl group and an electron withdrawing nitro-substituted aromatic ring. Analogous compounds derived from acetophenone or 4′-nitropropiophenone are much less prone to degradation. At the elevated temperatures required for azeotropic distillation, dimerization to form adduct **8** was significant; this dimerization resulted in highly variable yields of ylidene **3a** ranging from 10–70% (Eq. 2). Using lower boiling solvents such as THF or EtOAc resulted in even more ylidene dimerization. In addition, ylidene **3a** isolated by silica gel chromatography from these standard Knoevenagel reaction conditions was an unstable oil, which dimerized to **8** upon standing.

Lowering the reaction temperature to ~60 °C in toluene did show promise; however, the reaction stalled (~50% conversion); longer reaction times resulted only in significant dimerization. Isolated ylidene **3a** hydrolyzes to starting ketone **2a** under mild acidic conditions (LiH_2PO_4, THF/water) indicating that the condensation reaction is reversible, and that the removal of the water is necessary to drive the reaction to completion. Addition of inorganic desiccants ($MgSO_4$, Na_2SO_4, 4 Å molecular sieves) at 60 °C failed to improve the reaction. On the other hand, an organic desiccant, namely trimethylsilyl acetate (TMSOAc,[5] 1.5 equiv relative to ketone) afforded full conversion with only 5% dimerization in 6 h at 60 °C (toluene, NH_4OAc).

Aside from increasing the yield of the reaction, the significant decrease in ylidene dimerization under these conditions was surprising. Postulating that buffering of the reaction by acetic acid was responsible, the Knoevenagel reaction was attempted using acetic acid as solvent.[6] Without added TMSOAc the reaction stalled at around 80% conversion after 6 h at 65 °C, but the level of ylidene dimer **8** remained low (~2%). Addition of TMSOAc (Eq. 3) afforded 100% conversion in 6 h with ~1.5% dimer **8** at 65 °C. Hexamethyldisilazane (HMDS) could also be used to generate in situ not only the TMSOAc, but also the NH_4OAc promoter for the reaction (Eq. 3).[7] Thus simple premixing of HMDS (1.2 equiv relative to ketone) with acetic acid[8] prior to addition of 4′-nitroacetophenone (**2a**) and malononitrile (2.0 equiv), followed by warming to 65 °C affords 97% conversion in 5 h with ~1% dimer **8**. Following aqueous workup, crystallization from toluene/heptane afforded 90% yield of ylidene crystals, which were stable at ambient conditions for at least three months.



(3)

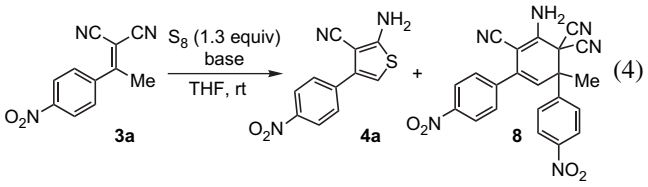
2.2. Gewald reaction

Classical conditions for the Gewald thiophene synthesis involve the reaction of ylidene and sulfur with an organic base (i.e., triethylamine, morpholine) in ethanol or dimethyl formamide (DMF). In the case of ylidene **3a** these conditions afforded mostly dimer **8** with thiophene **4a** as a minor component of the reaction mixture. A brief solvent screen (toluene, ethanol, tetrahydrofuran, DMF) for the reaction (using morpholine as base) identified tetrahydrofuran (THF) as showing the highest reactivity and selectivity toward product formation although the reaction still contained a significant amount of dimer **8** (30–40%).

A base screen in THF at ambient temperature next showed that inorganic bases are preferred to organic (Table 1). Aqueous sodium carbonate showed the highest reactivity and selectivity; in the absence of water, sodium carbonate provided almost no reaction. Careful monitoring of the sodium carbonate reaction showed that the reaction was mildly exothermic and complete upon mixing of the base. Continued exploration of inorganic bases highlighted aqueous $NaHCO_3$ as a superior base for the preparation of thiophene **4a**. In the optimized procedure, 1 equiv of $NaHCO_3$ in water is added to a stirring mixture of sulfur and ylidene in THF; the reaction is complete at the end of the addition. The reverse addition protocol did not offer any benefit to product purity and gave non-reproducible results.

The effect of temperature on the impurity profile of the reaction was also investigated. Four different reaction temperatures were investigated under otherwise identical conditions (Table 2). Cooling the reaction to 5 °C slowed the rate of product formation significantly while comparatively increasing the rate of ylidene dimerization. Increasing the reaction

Table 1. Gewald reaction base screen (Eq. 4)[a]

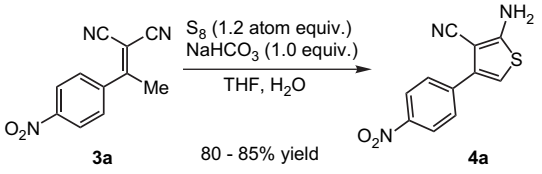


(4)

Base	HPLC PA%[b] **3a**	HPLC PA%[b] **4a**	HPLC PA%[b] **8**
Morpholine[c]	5.0	39.5	35.1
Pyridine[c]	71.8	0.5	1.7
i-Pr_2NH[c]	ND	64.4	14.7
Et_3N[c]	0.1	59.1	17.9
KOt-Bu[c]	1	35.1	6.1
Na_2CO_3[c]	88.5	3.2	2.1
Na_2CO_3 (aq)[d]	0.7	86.3	4.1
$NaHCO_3$ (aq)[d]	ND	91.2	1.6
K_2CO_3 (aq)[d]	0.6	69.5	2.6
K_3PO_4 (aq)[d]	0.5	80.7	2.1
NaOH (aq)[d]	0.5	66.2	2.5

[a] Base was added in one portion to sulfur and **3a** suspended in THF (10 mL/g **3a**). Reaction samples were analyzed by HPLC.
[b] Peak area percent of each component. ND=not detected.
[c] Monitored after 120 min.
[d] Monitored after 10 min.

temperature, while affording no appreciable increase in reaction rate, appeared to decrease the relative rate of dimer formation. At 60 °C there was no detectable formation of dimer **8**, however, the reaction generated new unidentified impurities. Therefore, the optimal reaction temperature was determined to be 35–40 °C. Following the reaction, the product was crystallized from a THF/EtOH/water mixture to provide aminothiophene **4a** in 80–85% isolated yield (Eq. 6).



(6)

Based upon the mechanism proposed by Gewald and others, the reaction should be catalytic in base.[1,9] Indeed, if substoichiometric $NaHCO_3$ (0.2 equiv) is employed the reaction goes to completion although with a slightly poorer purity profile. HPLC analysis of the reactions with stoichiometric versus catalytic $NaHCO_3$, showed that while dimer **8** is generated in both cases, prolonged stirring at 35 °C in the presence of 1.0 equiv of $NaHCO_3$ significantly degrades it to a secondary byproduct, which is easier to remove during the crystallization of desired product **4a**.

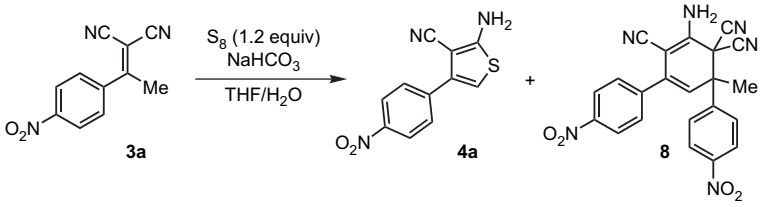
Using the optimized reaction conditions from the experiments described above, the thermochemical profile of the reaction was monitored with a MultiMax™ system (Fig. 1).[10] The initial endotherm arises from simple mixing of the sodium bicarbonate solution with THF. HPLC monitoring of the reaction mixture during the endotherm period showed that little reaction occurred (<10% PA **4a**). Most of the reaction occurs during the exotherm, with the majority of the reaction (>85% PA **4a**) complete once T_{max} is reached.

An interesting trend was observed in the temperature profile when the addition time was varied between 15 and 90 min. With the slower addition rates of 60 and 90 min, the initial endotherm (due to mixing) was followed by a return of internal temperature to the jacket temperature of 35 °C for a brief period of time, followed by the exotherm. As noted above, the reaction is complete prior to complete addition of the base solution. Samples of reaction mixtures pulled during the plateau period between endo- and exotherm events showed little reaction occurring. From these reactions we determined the amount of bicarbonate solution that had been added at the onset of the exotherm event to be 0.173 and 0.178 equiv of $NaHCO_3$, respectively. At this time, the underlying mechanism of this effect is not readily apparent, although a base-mediated reorganization of S_8 to a more reactive sulfur species may be implicated.[11]

2.3. Other substrates

This two-step procedure for the synthesis of 2-aminothiophenes was applied to other substrates.[12] As can be seen in Table 3, thiophenes with both electron rich (entries 2 and 7) and electron poor (entries 3–6) phenyl rings at the 4-position are prepared successfully. In addition, a 4-heterocycle-

Table 2. Temperature screen for the Gewald reaction (Eq. 5)[a]



(5)

Temperature,[b] °C	Assay yield%[c] **4a**	HPLC PA%[d] **8**
5	55	16
22	94	1.4
39	94	0.4
60	92	0

[a] Ylidene **3a** and sulfur (1.2 atom equiv) were suspended in THF at the specified temperature. $NaHCO_3$ solution was added over 30 s.
[b] Internal temperature at start of $NaHCO_3$ addition.
[c] Reaction yield determined by HPLC assay in relative to a standard.
[d] Peak area percent of each component.

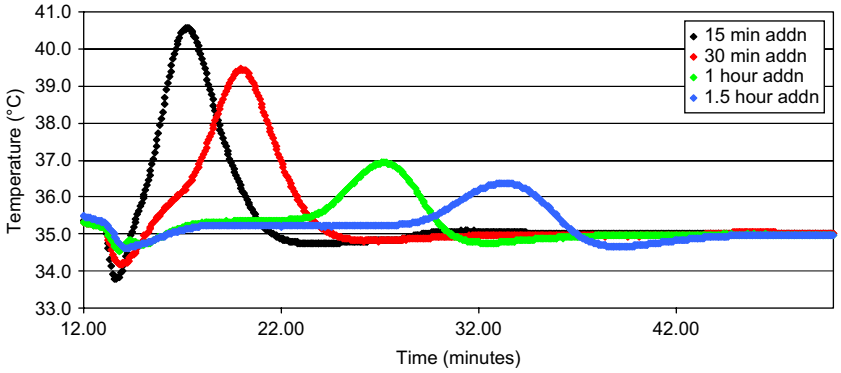
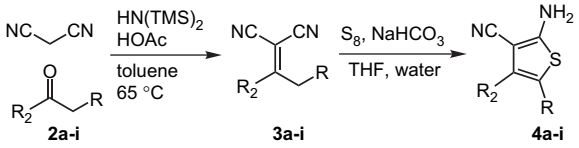


Figure 1. Temperature profiles of Gewald reaction at different $NaHCO_3$ addition rates.

Table 3. Application of the Knoevenagel and Gewald conditions to other substrates (Eq.7)



(7)

Entry	Ketone	R_2	R	Ylidene, yield%	Thiophene, yield%
1	**2a**	4-NO_2Ph	H	**3a**, 90	**4a**, 80
2	**2b**	Ph	H	**3b**, 82	**4b**, 40 (96)
3	**2c**	3-NO_2-Ph	H	**3c**, 83 (88)	**4c**, 81
4	**2d**	4-$MeSO_2$Ph	H	**3d**, 76	**4d**, 58 (96)
5	**2e**	4-BrPh	H	**3e**, 86	**4e**, 73 (96)
6	**2f**	2,6-F_2Ph	H	**3f**, 64 (73)	**4f**, 58 (98)
7	**2g**	4-MeOPh	H	**3g**, 82	**4g**, 80
8	**2h**	2-Thiophene	H	**3h**, 56	**4h**, 46 (100)
9	**2i**	Ph	Ph	**3i**, 80	**4i**, 78 (99)

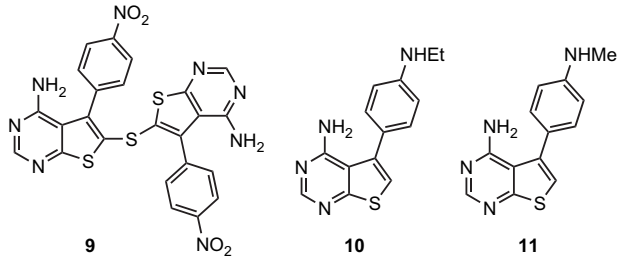
Numbers in parentheses represent assay yields prior to isolation.[13]

substituted derivative (entry 8) as well as a 5-substituted thiophene (entry 9) is accessible using this methodology.

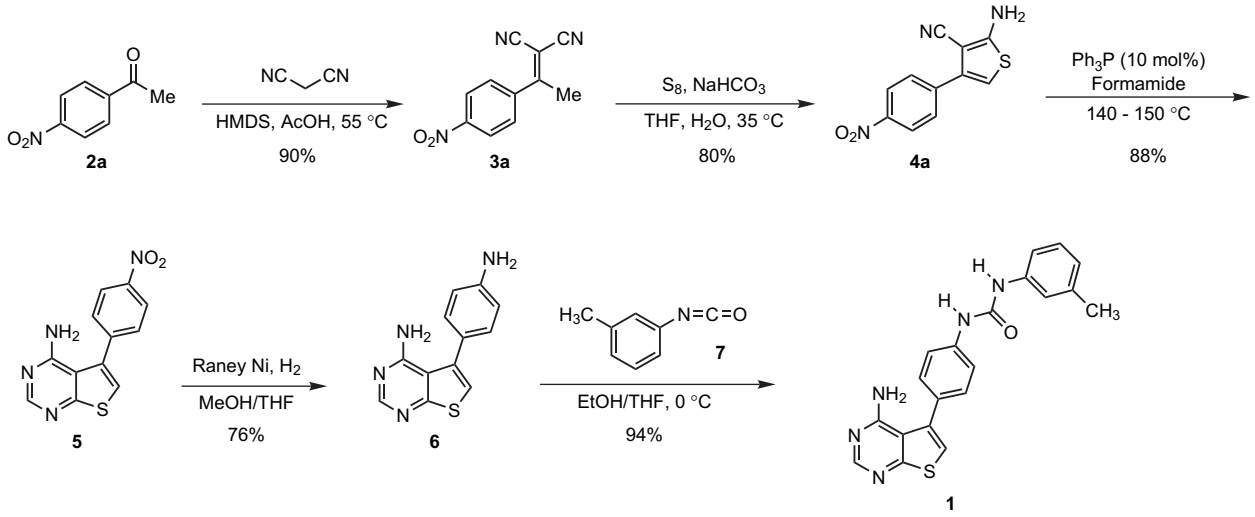
2.4. Synthesis of thienopyrimidine 1

The two-step synthesis of 2-aminothiophenes was employed in the context of a synthesis of thienopyrimidine **1** (Scheme 2). As discussed above, thiophene **4a** was prepared in 72% yield over two steps from 4′-nitroacetophenone. This set the stage for a highly convergent synthesis in which the isocyanate was added in the final step.

Condensation with formamide was accomplished at elevated temperatures to effect conversion to nitropyrimidine **5** in 88% yield.[14] In early experiments the sulfur-linked dimer **9** was observed in varying amounts. A small amount of triphenylphosphine (10 mol %) added to the reaction mixture was sufficient to scavenge residual sulfur from the Gewald reaction, providing an effective control of this impurity.



Previous reports have detailed the use of formamidine acetate as an effective reagent for the conversion of amino nitriles to pyrimidines.[15] While the use of this reagent (4 equiv) in formamide did permit the reaction to be run at lower temperatures (~125 °C), we observed evolution of CO and NH_3 during the course of the reaction. In the absence of



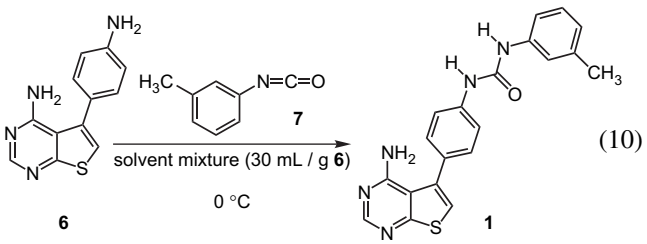
Scheme 2. Synthesis of thienopyrimidine **1**.

formamidine acetate, the thermal decomposition of formamide itself was not significant at <160 °C.

Hydrogenation of the nitro group to the corresponding aniline **6** was accomplished over Raney nickel in THF/MeOH, in 76% yield. The choice of methanol as the alcohol co-solvent was based on the formation of *N*-ethyl derivative **10** (1–2%) when EtOH was employed, presumably via an oxidation to acetaldehyde/reductive alkylation mechanism.[16] When methanol was employed, less than 0.5% of *N*-alkylated product **11** was observed.

The final step required acylation of aniline **6** with 3-tolylisocyanate **7**. There are two reactive amine sites, although the aniline (N_1) proved more reactive than the aminopyrimidine (N_2), overacylation to form bis-acyl **12** (Eq. 8) was observed. Under standard conditions (3:1 CH_2Cl_2/THF, 1.0 equiv isocyanate, 0 °C to rt),[3] from which the product precipitated early in the reaction, 3% of this impurity was formed at 99% conversion (HPLC peak area% levels at 265 nm). We expected that thienopyrimidine **1** reacted with residual isocyanate **7** at the end of the reaction and reasoned that an alternate, sacrificial nucleophile might be added to the mixture, which would not interfere with acylation of the aniline nitrogen, but would compete with overacylation of **1** (Eq. 8) to furnish an easily removable side-product (Eq. 9).

Table 4. Solvent effects in isocyanate acylation (Eq. 10)[a]

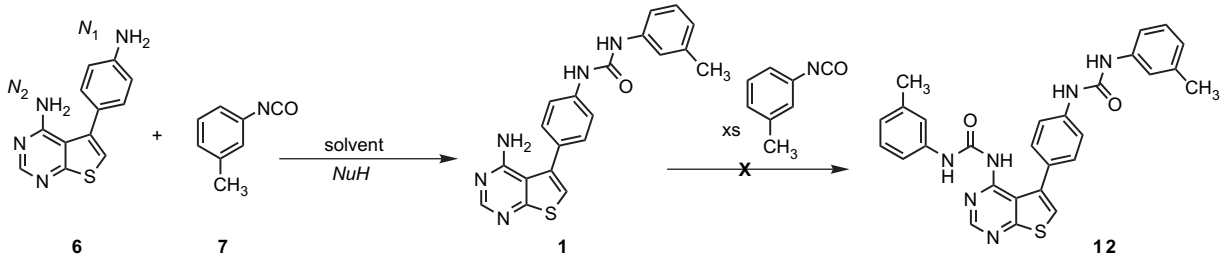


(10)

Entry	Solvent mixture	Isocyanate **7**, equiv	**6**, HPLC PA%[b]	**1**, HPLC PA%[b]	**12**, HPLC PA%[b]
1	THF/EtOH (2:1)	1.0	2.2	97.1	0.2
2	THF/EtOH (2:1)	1.25	0.2	98.7	0.4
3	THF/MeOH (2:1)	1.25	0.4	98.8	0.2
4	THF/MeOH (2:1)	1.5	0.1	98.4	0.4
5	CH_2Cl_2/THF (3:1)[c]	0.5	19.4	78.4	1.1
6	THF/EtOH (2:1)	0.625	13.9	85.6	0.08

[a] Isocyanate **7** was added dropwise to a mixture of **6** in the solvent mixture (30 mL/g **6**) over ~5 min, maintaining the temperature at <2 °C. Reactions were assayed after 2 h.
[b] Reactions were analyzed by HPLC at 265 nm.
[c] Reaction was run at 0 °C for 2 h, then warmed to rt for 2 h.

a sacrificial nucleophile of intermediate reactivity between that of the two amines of aniline **6**, so that excess isocyanate **7** is destroyed before it overacylates the product (even



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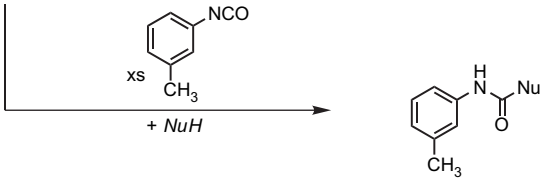

(9)

Alcohols react with isocyanates at a slower rate and possibly via a slightly different mechanism than do amines.[17] Due to the inherent low nucleophilicity of the aminopyrimidine, an alcohol might serve as an additive with the desired effect. When ethanol was added to a reaction in THF (2:1 THF/EtOH, 1.0 equiv isocyanate **7**, 0 °C), we observed good conversion to **1** (2.2% remaining **6**), with <0.2% overacylated impurity **12** (Table 4, entry 1). Both MeOH and EtOH in THF required extra isocyanate **7** to attain high levels of conversion (<0.4% remaining **6**), but a smaller excess was required with EtOH (1.25 equiv vs 1.5 equiv in MeOH for >99.8% conversion). Stirring overnight at ambient temperature did not significantly affect impurity levels. The product was crystallized from EtOH in 94% isolated yield.

Our results indicate that the alcohol co-solvent is playing two roles in the acylation reaction. First, it functions as with 1.25 equiv of isocyanate **7**, only 0.4% of **12** is formed). However, the lower levels of bis-acyl **12** even at incomplete conversion (entries 5 and 6) indicate that the alcohol is also affecting the relative reactivities of the two nitrogen atoms, perhaps by selective hydrogen bonding.[18]

In conclusion, we have described new reaction conditions for the Knoevenagel condensation and Gewald thiophene synthesis by which 4′-nitroacetophenone (**2a**) is converted to 2-aminothiophene **4a** in 72% yield via crystalline intermediates. This methodology has been extended to the use of other alkyl aryl and alkyl heterocyclic ketones, where it has also proven effective. Finally, we have applied this in the context of a synthesis of multitargeted kinase inhibitor **1**, which was prepared in 45% overall yield through five steps.

3. Experimental

3.1. Knoevenagel condensation

Hexamethyldisilazane (1.2 equiv) was added to acetic acid (0.67 mL/mmol ketone **2**) at a rate to maintain the internal temperature at or below 74 °C. (*Caution—this addition is very exothermic*!) The HMDS/acetic acid mixture is added to a solution of ketone **2** and malononitrile (2 equiv) in acetic acid (0.33 mL/mmol). After reaction completion, the mixture is cooled to ambient temperature with chilled toluene (1.67 mL/mmol, at 0 °C) and diluted with water (1.33 mL/mmol). The aqueous layer was separated and extracted with toluene (0.67 mL/mmol). The combined organic extracts were washed four times with water and dried over $MgSO_4$. The products **3** were isolated by crystallization or chromatography.

3.1.1. 2-[1-(4-Nitrophenyl)ethylidene]-malononitrile (3a). Reaction run using 4′-nitroacetophenone (10.00 g, 60.6 mmol). Crystallization with heptane (93 mL) provided 11.49 g (89.0%) of yellow crystalline **3a**. Mp=87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 7.69 (ddd, J=9.09, 2.40, 2.23 Hz, 2H), 8.36 (dt, J=9.16, 2.28 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 87.6, 111.5, 111.5, 124.1, 128.1, 141.2, 149.1, 172.3 ppm; MS (APCI+) m/z 212.0 (M−H); Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.69; H, 3.30; N, 19.74.

3.1.2. 2-[1-(Phenyl)ethylidene]-malononitrile (3b). Reaction run using acetophenone (9.7 mL, 83 mmol). Crystallization with heptane provided 11.48 g (82.3%) of white crystalline **3b**. Mp=94.5–95.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 7.31 (m, 5 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 84.6, 112.5, 112.5, 127.0, 128.8, 131.9, 135.5, 174.9 ppm; MS (APCI+) m/z 167.1 (M−H); Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.24; H, 4.47; N, 16.81.

3.1.3. 2-[1-(3-Nitrophenyl)ethylidene]-malononitrile (3c). Reaction run using 3′-nitroacetophenone (10.00 g, 60.6 mmol). Crystallization with heptane (93 mL) provided 10.76 g (83.4%) of yellow crystalline **3c**. Mp=99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 7.74 (t, J=8.03 Hz, 1H), 7.89 (ddd, J=7.75, 1.78, 1.03 Hz, 1H), 8.36 (t, J=1.85 Hz, 1H), 8.40 (ddd, J=8.23, 2.13, 1.03 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 87.4, 111.5, 111.6, 122.1, 126.1, 130.3, 132.6, 136.9, 148.0, 171.9 ppm; MS (APCI+) m/z 212.1 (M−H); Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.04; H, 3.10; N, 19.37.

3.1.4. 2-[1-(4-Methylsulfonylphenyl)ethylidene]-malononitrile (3d). Reaction run using 4′-methylsulfonylacetophenone (10.00 g, 50.5 mmol). The product crystallized during the reaction. After drying, the solids were stirred in ethanol (50 mL) and filtered. Drying in vacuo provided 9.47 g (76.2%) of crystalline **3d**. Mp=138.5–139.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.11 (s, 3H), 7.69 (d, J=8.37 Hz, 2H), 8.08 (d, J=8.37 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 44.5, 87.3, 111.6, 111.7, 128.0, 140.6, 143.1, 172.8 ppm; MS (APCI+) m/z 245.1 (M−H); Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.41; H, 3.78; N, 11.45.

3.1.5. 2-[1-(4-Bromophenyl)ethylidene]-malononitrile (3e). Reaction run using 4′-bromoacetophenone (10.00 g, 50.3 mmol). Crystallization with heptane (88 mL) provided 10.55 g (86.0%) of yellow crystalline **3e**. Mp=93.5–94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.23 (ddd, J=8.89, 2.47, 2.23 Hz, 2H), 7.46 (ddd, J=8.89, 2.47, 2.23 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 85.1, 112.2, 112.3, 126.8, 128.5, 132.1, 134.2, 173.3 ppm; MS (APCI+) m/z 247.0; Anal. Calcd for $C_{11}H_7BrN_2$: C, 53.47; H, 2.86; N, 11.34. Found: C, 53.26; H, 2.87; N, 11.19.

3.1.6. 2-[1-(2,6-Difluorophenyl)ethylidene]-malononitrile (3f). Reaction run using of 2′,6′-difluoroacetophenone (10.21 g, 65.4 mmol). Crystallization with heptane (100 mL) provided 8.48 g (63.5%) of yellow crystalline **3f**. Mp=80–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 3H), 7.22 (dd, J=8.51, 7.96 Hz, 2H), 7.65 (tt, J=8.51, 6.38 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 91.4, 110.9, 111.0, 112.1, 112.1, 112.1, 112.3, 112.3, 112.3, 113.3, 113.5, 113.7, 132.8, 132.9, 133.0, 156.7, 156.8, 159.2, 159.3, 165.3 ppm; MS (APCI+) m/z 203.0 (M−H); Anal. Calcd for $C_{11}H_6F_2N_2$: C, 64.71; H, 2.96; N, 13.72. Found: C, 64.47; H, 2.83; N, 13.78.

3.1.7. 2-[1-(4-Methoxyphenyl)ethylidene]-malononitrile (3g). Reaction run using 4′-methoxyacetophenone (2.89 g, 19.3 mmol). Crystallization with heptane (30 mL) provided 3.14 g (82.3%) of yellow crystalline **3g**. Mp=79.5–80.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3H), 4.15 (s, 3H), 7.26 (ddd, J=9.43, 3.16, 2.64 Hz, 2H), 7.88 (ddd, J=9.50, 3.09, 2.64 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 81.9, 113.1, 113.4, 114.2, 127.6, 129.5, 162.6, 173.4 ppm; MS (APCI+) m/z 197.1 (M−H); Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.38; H, 4.78; N, 14.07.

3.1.8. 2-[1-(2-Thiophene-yl)ethylidene]-malononitrile (3h). Reaction run using 2-acetylthiophene (8.5 mL, 78.9 mmol). At the end of the reaction, ethanol (60 mL) was added and the mixture was filtered. After drying the solids were stirred in ethanol (45 mL) and filtered. Drying in vacuo provided 7.67 g (56%) of crystalline **3h**. Mp=87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 7.24 (dd, J=4.87, 4.19 Hz, 1H), 7.77 (dd, J=4.94, 0.82 Hz, 1H), 8.04 (dd, J=4.05, 0.75 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 78.7, 113.3, 113.8, 128.8, 133.2, 134.1, 137.9, 162.1 ppm; MS (APCI+) m/z 173.0 (M−H); Anal. Calcd for $C_9H_6N_2S$: C, 62.05; H, 3.47; N, 16.08. Found: C, 60.66; H, 2.99; N, 15.84.

3.1.9. 2-[1-(Phenyl)benzylidene]-malononitrile (3i). Reaction run using deoxybenzoin (10.01 g, 51.0 mmol). Crystallization with heptane (100 mL) provided 9.98 g (80.0%) of white crystalline **3i**. Mp=78.7–79.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 2H), 7.10 (dd, J=7.20, 2.26 Hz, 2H), 7.28 (m, 3H), 7.49 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 85.4, 112.4, 112.6, 127.5, 128.7, 131.6, 133.9, 134.4, 176.9 ppm; Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.27; H, 4.78; N, 11.33.

3.2. Gewald reaction

Ylidene **3** and elemental sulfur (1.2 atom equiv) are suspended in tetrahydrofuran (10 mL/g **3**) and warmed to an

internal temperature of 35 °C. A solution of sodium bicarbonate (1.0 equiv in 5 mL of water/g **3**) is added over ~1 h. The mixture is stirred at 35 °C for approximately 30 min before the solution is transferred to a separatory funnel and washed with 12.5% aqueous NaCl and 25% aqueous NaCl. The products **4** were isolated by crystallization.

3.2.1. 2-Amino-4-phenyl-3-thiophenecarbonitrile (4b). Reaction run using 2-[1-(phenyl)ethylidene]-malononitrile (**3b**, 2 g, 11.9 mmol). HPLC assay following the reaction indicated a 96% yield. Crystallization from 15 mL of toluene yielded 0.93 g (40% yield) of the desired product as a white solid. Mp= 102.3–105.1 °C (lit.[19] 100–102 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48–7.56 (m, 2H), 7.38–7.44 (m, 2H), 7.30–7.36 (m, 1H), 7.23 (s, 2H), 6.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 137.9, 133.9, 128.1, 127.3, 126.4, 116.2, 104.7, 82.9 ppm. MS (ESI+) *m/z* 201 (M+H); Anal. Calcd for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found: C, 65.96; H, 3.84; N, 13.95.

3.2.2. 2-Amino-4-(3-nitrophenyl)-3-thiophenecarbonitrile (4c). Reaction run using 2-[1-(3-nitrophenyl)ethylidene]-malononitrile (**3c**, 2.51 g, 11.8 mmol). Crystallization from 25 mL of toluene yielded 2.34 g (81%) of the desired product. Mp=194–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (t, *J*=2.1 Hz, 1H), 8.19 (ddd, *J*=8.2, 2.3, 1.0 Hz, 1H), 7.99 (ddd, *J*=7.7, 1.8, 1.0 Hz, 1H), 7.72 (t, *J*=8.0 Hz, 1H), 7.38 (s, 2H), 6.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 147.4, 135.20, 135.17, 132.7, 129.8, 122.0, 120.7, 115.9, 106.9, 82.2 ppm; MS (ESI+) *m/z* 246 (M+H), 263 (M+NH$_4$), 268 (M+Na); Anal. Calcd for $C_{11}H_7N_3O_2S$: C, 53.87; H, 2.88; N, 17.13. Found: C, 53.85; H, 2.64; N, 17.03.

3.2.3. 2-Amino-4-(4-methanesulfonylphenyl)-3-thiophenecarbonitrile (4d). Reaction run using 2-[1-(4-methanesulfonylphenyl)ethylidene]-malononitrile (**3d**, 1.4 g, 5.7 mmol). HPLC assay following the reaction indicated a 96% yield. Crystallization from 22 mL of 2:1:1 water/EtOH/THF, followed by crystallization from 10 mL toluene yielded 0.91 g (58%) of the desired product. Mp=195–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, *J*=8.5 Hz, 2H), 7.78 (d, *J*=8.5 Hz, 2H), 7.36 (s, 2H), 6.73 (s, 1H), 3.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 139.2, 138.6, 136.1, 127.2, 126.9, 115.9, 107.2, 82.3, 43.4 ppm; MS (ESI+) *m/z* 279 (M+H), 296 (M+NH$_4$), 301 (M+Na); HRMS (ESI FTMS) Calcd for $C_{12}H_{11}N_2O_2S_2$ (M+H): 279.0256. Found: 279.0256.

3.2.4. 2-Amino-4-(4-bromophenyl)-3-thiophenecarbonitrile (4e). Reaction run using 2-[1-(4-bromophenyl)ethylidene]-malononitrile (**3e**, 1.98 g, 8.03 mmol). HPLC assay following the reaction indicated a 96% yield. Crystallization from 17 mL of 2:1:1 water/EtOH/THF, followed by crystallization from 17 mL toluene yielded 1.67 g (73%) of the desired product. Mp=190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, *J*=8.5 Hz, 2H), 7.47 (d, *J*=8.7 Hz, 2H), 7.28 (s, 2H), 6.58 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 136.5, 133.1, 131.1, 128.4, 120.6, 116.0, 105.3, 82.5 ppm; MS (APCI+) *m/z* 279, 281 (M+H); Anal. Calcd for $C_{11}H_7BrN_2S$: C, 47.33; H, 2.53; N, 10.04. Found: C, 47.02; H, 2.25; N, 9.78.

3.2.5. 2-Amino-4-(2,6-difluorophenyl)-3-thiophenecarbonitrile (4f). Reaction run using 2-[1-(2,6-difluorophenyl)ethylidene]-malononitrile (**3f**, 2.0 g, 9.8 mmol). HPLC assay following the reaction indicated a 98% yield. Crystallization from 32 mL of 2:1:1 water/EtOH/THF, followed by crystallization from 20 mL toluene yielded 1.35 g (58%) of the desired product. Mp=143.6–145.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (tt, *J*=8.4, 6.6 Hz, 1H), 7.27 (s, 2H), 7.19 (t, *J*=8.0 Hz, 2H), 6.56 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 160.1 (1/2 of doublet), 157.7 (1/2 of doublet), 130.2 (t), 124.5, 115.1, 111.6, 111.3, 109.7, 84.5 ppm; MS (ESI+) *m/z* 237 (M+H); HRMS (ESI FTMS) Calcd for $C_{11}H_7F_2N_2S$ (M+H): 237.0293. Found: 237.0289.

3.2.6. 2-Amino-4-(4-methoxyphenyl)-3-thiophenecarbonitrile (4g). Reaction run using 2-[1-(4-methoxyphenyl)-ethylidene]-malononitrile (**3g**, 1.98 g, 8.03 mmol). Crystallization from 28 mL of 2:1:1 water/EtOH/THF, followed by trituration in 15 mL toluene yielded 1.39 g (80%) of the desired product. Mp=164–166.5 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J*=8.9 Hz, 2H), 7.18 (s, 2H), 6.97 (d, *J*=8.9 Hz, 2H), 6.39 (s, 1H), 3.77 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 158.3, 137.6, 127.6, 126.5, 116.3, 113.6, 103.3, 83.1, 55.1 ppm; MS (APCI+) *m/z* 231 (M+H); Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.40; H, 4.29; N, 12.05.

3.2.7. 2-Amino-4-(2-thienyl)-3-thiophenecarbonitrile (4h). Reaction run using 2-[1-(2-thienyl)ethylidene]-malononitrile (**3h**, 2.00 g, 11.5 mmol). HPLC assay following the reaction indicated a 100% yield. Crystallization from 23 mL toluene yielded 1.09 g (46%) of the desired product. Mp=110–112 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, *J*=5.1, 1.2 Hz, 1H), 7.34 (dd, *J*=3.6, 1.2 Hz, 1H), 7.30 (s, 2H), 7.09 (dd, *J*=5.1, 3.6 Hz, 1H), 6.54 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 135.8, 130.5, 127.3, 124.9, 123.7, 116.0, 104.1, 82.2 ppm; MS (ESI+) *m/z* 207 (M+H); HRMS (ESI FTMS) Calcd for $C_9H_7N_2S_2$: 207.0045. Found: 207.0039; Anal. Calcd for $C_9H_6N_2S_2$: C, 52.40; H, 2.93; N, 13.58. Found: C, 51.45; H, 2.64; N, 13.20.

3.2.8. 2-Amino-4,5-diphenyl-3-thiophenecarbonitrile (4i). Reaction run using 2-[1-(phenyl)benzylidene]-malononitrile (**3i**, 1.20 g, 4.9 mmol). HPLC assay following the reaction indicated a 99% yield. Crystallization from 62 mL of 4:1:1 water/EtOH/THF, followed by trituration with 15 mL toluene yielded 1.06 g (78%) of the desired product. Mp=203–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (s, 2H), 7.29–7.38 (m, 2H), 7.10–7.26 (m, 6H), 7.02 (ddd, *J*=6.4, 1.7, 1.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 134.1, 133.7, 132.4, 128.8, 128.1, 127.6, 127.4, 126.4, 118.8, 115.7, 86.6 ppm; MS (ESI+) *m/z* 277 (M+H); Anal. Calcd for $C_{17}H_{12}N_2S$: C, 73.88; H, 4.38; N, 10.14. Found: C, 74.23; H, 4.25; N, 10.19.

3.3. Scale up of multitargeted kinase inhibitor 1

3.3.1. 2-[1-(4-Nitrophenyl)ethylidene]-malononitrile (3a). *Caution*: *malononitrile is highly toxic and readily absorbed through the skin*!

A round bottomed flask was charged with acetic acid (6 L), malononitrile [2.6 kg], and 4′-nitroacetophenone (3.0 kg).

To a separate flask was charged acetic acid (12 L) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (3.55 kg) was added at a rate to maintain the internal temperature at or below 45 °C. *Caution*: *the addition of HMDS to acetic acid is very exothermic*!

The contents of the first flask were transferred to the acetic acid/HMDS mixture and rinsed with acetic acid (300 mL). The contents were warmed to 55 °C±10 °C for 9 h 35 min, then the heat source was turned off. The reaction was rapidly cooled by charging pre-chilled toluene (30 L, chilled to 0 °C) to the flask. The reaction solution was then extracted with water (23.9 L). The aqueous layer was back-extracted with toluene (12 L). The combined organic layers were then repeatedly washed with water (4×24 L) to remove acetic acid and malononitrile. After drying over magnesium sulfate, the toluene solution was concentrated in vacuo to approximately four volumes (mL/g) and the mixture was seeded and the reaction was stirred for 15 min. Heptane (29.25 L) was added over 4.5 h and the slurry was stirred overnight. The slurry was then filtered and was washed with 6 L of heptane and the product was dried in a vacuum oven at room temperature for 8 h, to yield 3.486 kg (90.0% yield) of the desired product.

3.3.2. 2-Amino-4-(4-nitrophenyl)-3-thiophenecarbonitrile (4a). Ylidene **3a** (3300 g), sulfur (599.0 g), and tetrahydrofuran (29.4 kg) were charged to a flask. The reaction contents were warmed to an internal temperature of approximately 35 °C. The reaction mixture was charged with 7.0 kg of 7.3% aqueous $NaHCO_3$ over a period of approximately 50 min maintaining the reaction temperature below 65 °C. An additional 10.8 kg of the sodium bicarbonate solution was added to the reaction mixture at a rate, which maintained the reaction temperature above 30 °C. The reaction mixture was maintained at 35 °C for 30 min post addition time. The heat source was turned off and the reaction mixture was cooled to approximately 30 °C. NaCl solution (14.3 kg, 12.5%) was added in one portion to the reaction mixture, which was stirred for 10 min and then the layers were separated and the organics were washed with an additional 15.3 kg of the 12.5% NaCl solution. The layers were separated and the organics were washed with 25% NaCl solution (13.0 kg). The organics were concentrated in vacuo to a volume of approximately four volumes relative to theoretical yield of the product. At this point the mixture is warmed to an internal temperature of 60 °C and ethyl alcohol (14.5 L) added at such a rate to maintain internal temperature of 60 °C. After seeding, 23.2 L of water was added over approximately 5 h while maintaining 60 °C, then the slurry was cooled overnight. The slurry was filtered and the solids were dried in vacuo at 60 °C.

In order to remove sulfur, the solids product were removed from the vacuum oven and then charged into a flask. Toluene (28.6 kg) was charged and the slurry was stirred for approximately 1 h and then filtered. The filter cake was rinsed twice with toluene (5.7 kg) and then dried in vacuo at 60 °C to yield 3.04 kg (80.0% isolated yield) of the desired product **4a**. Mp=202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J=9.1 Hz, 2H), 7.80 (d, J=8.9 Hz), 7.40 (s, 2H), 6.82 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 146.0, 140.0, 135.5, 127.3, 123.5, 115.8, 108.0, 82.0 ppm; MS (APCI−) m/z 244 (M−H); HRMS (ESI FTMS) Calcd for $C_{11}H_8N_3O_2S$ (M+H): 246.0332. Found: 246.0327.

3.3.3. 4-Amino-5-(4-nitrophenyl)-thieno[2,3-*d*]pyrimidine (5). To a round bottomed flask were charged thiophene **4a** (2850 g, 11.62 mol), triphenylphosphine (243.8 g, 0.9296 mol), and formamide (48.6 kg). The reaction mixture was warmed to an internal temperature of 145–150 °C. *NOTE: This reaction has been shown to generate carbon monoxide and ammonia due to decomposition of formamide above 150 °C*. After 4 h 20 min the heating mantle was turned off and the reaction mixture allowed to cool to room temperature and stirred overnight. To the orange suspension was added 42.6 L of water and the reaction mixture stirred at room temperature for 1 h. The suspension was filtered and washed with water (3×14.3 L). The filter cake was then washed with acetone in portions until the filtrate was pale yellow (5×5.8 L). Thienopyrimidine **5** was dried in vacuo at 60–70 °C to yield 2.792 kg (88.2%) of an orange solid. Mp>225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.32 (d, J=8.9 Hz, 2H), 7.71 (d, J=8.9 Hz, 2H), 7.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.6, 153.3, 146.5, 141.4, 132.6, 129.5, 123.4, 122.4, 111.8 ppm; MS (ESI+) m/z 273 (M+H), 227 (M+H−NO_2); Anal. Calcd for $C_{12}H_8N_4O_2S$: C, 52.93; H, 2.96; N, 20.58. Found: C, 52.66; H, 2.57; N, 20.52.

3.3.4. 4-Amino-5-(4-aminophenyl)-thieno[2,3-*d*]pyrimidine (6). A slurry of nitrothienopyrimidine **5** (2.8 kg) in 32 kg of tetrahydrofuran and 29 kg of methanol was added to a mixture of Raney nickel (2.7 kg) and water (0.7 kg). The slurry was rinsed with 32 kg tetrahydrofuran then hydrogenated at 40 psi. After the reaction is complete, the reaction mixture is filtered the filter cake is rinsed with 13.5 kg of tetrahydrofuran. After distilling to about 12 L, 15 kg of EtOH is added and reconcentrated twice. Water (36 kg) is added over 1 h. The product was isolated by filtration, washed with 20.6 kg of water and dried in a vacuum oven at 55 °C to yield 1.894 kg (76%) of the desired aminothienopyrimidine **6**. Mp=185–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.25 (s, 1H), 7.09 (d, J=8.4 Hz, 2H), 6.66 (d, J=8.5 Hz, 2H), 5.37 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 157.8, 153.0, 148.4, 135.1, 129.1, 121.9, 118.5, 113.4, 113.0 ppm; MS (ESI+) m/z 243 (M+H); Anal. Calcd for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.12. Found: C, 59.60; H, 3.97; N, 22.96.

3.3.5. *N*-[4-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-phenyl]-*N*′-(3-methylphenyl)urea (1). To a solution of aniline **6** (45.7 g, 189 mmol) in 450 mL of ethyl alcohol and 900 mL of THF at 0 °C was added 3-methylphenylisocyanate (30 mL, 240 mmol) at such a rate to maintain the temperature ≤2 °C. The addition required 6 min. Following the addition, the reaction mixture was stirred in an ice/water bath for 2 h, then warmed to ambient for 2 h. The reaction mixture was concentrated, then washed twice with 200 mL EtOH to remove THF. The product was filtered and washed with 300 mL EtOH, then dried at 60 °C to yield 66.6 g (94% yield) of the product as a white solid. Mp=227–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.27 (s, 3H) 6.78 (d, J=7.27 Hz, 1H) 7.15 (t, J=7.75 Hz, 1H) 7.24 (d, J=8.65 Hz, 1H) 7.30 (s, 1H) 7.37 (d, J=8.51 Hz, 2H) 7.40 (s, 1H) 7.59

(d, J=8.65 Hz, 2H) 8.32 (s, 1H) 8.64 (s, 1H) 8.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 157.7, 153.1, 151.8, 139.4, 138.9, 137.4, 134.2, 128.9, 128.3, 128.1, 122.2, 119.7, 118.3, 117.8, 115.0, 112.7, 21.3 ppm; Anal. Calcd for $C_{20}H_{12}N_5OS$: C, 63.98; H, 4.56; N, 18.65. Found: C, 64.24; H, 4.35; N, 18.42.

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