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Development of a Scalable Synthesis of 4-Aminopyrimidin-5-ol, a Versatile Intermediate

Phuong T. Le,*[†] Paul F. Richardson,*[†] Neal W. Sach,[†] Shuibo Xin,[±] Shijian Ren,[±] Jiezhan Xiao,[±] and Liangliang Xue[±]

[†] Pfizer Worldwide Medicinal Chemistry, 10770 Science Center Drive, San Diego, California, 92121, United States, and [±]WuXi App Tec Co., Shanghai, China

Corresponding Author

*Phuong.Le@pfizer.com Phone: 858-638-6354

*Paul.F.Richardson@pfizer.com Phone: 858-526-4290

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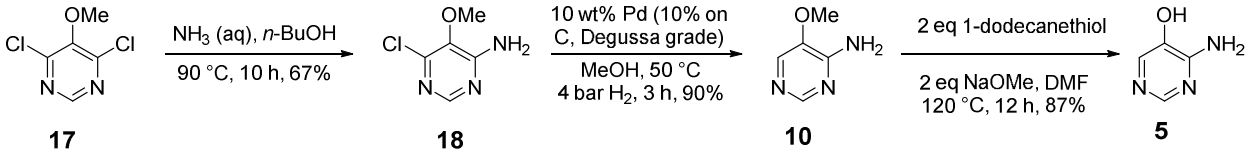


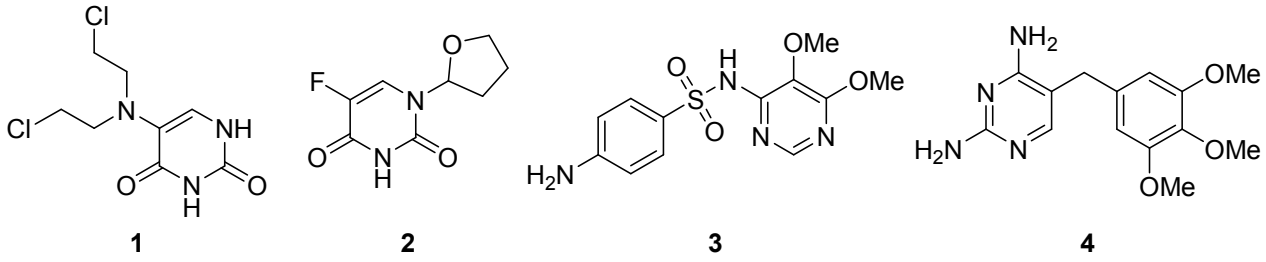
ABSTRACT. A robust process for the preparation of multigram quantities of 4-aminopyrimidin-5-ol (**5**) in good yield from an inexpensive and readily available pyrimidine starting material is described. An initial evaluation of the reported literature route for this material utilizing a *de novo* pyrimidine synthesis provided safety concerns over the scalability of several intermediates. In addition, a number of steps proceeded in mediocre yield, and involved chromatographic separations for the desired products. The newly developed route mitigates the safety concerns, reduces the number of steps from five to three, avoids column chromatography, leads to an 8-fold improvement in yield, and utilizes reagents, which are recognized to be more environmentally-benign.

Keywords: 4-Aminopyrimidin-5-ol, synthetic strategy, *O*-demethylation, scale-up

Introduction

Functionalized pyrimidines represent a popular motif in medicinal chemistry owing to their synthetic versatility based on their predictable reactivity patterns, and their ability to arrange the vectors connected to the heterocyclic core in a spatially defined fashion.[1] Examples of pyrimidine-containing drugs include Uramustine **1**, Tegafur **2**, Sulfadoxine **3**, and Trimethoprim **4** (Figure 1). As part of one of our current medicinal chemistry programs, we required a method to synthesize multigram quantities of 4-aminopyrimidin-5-ol (**5**), a versatile intermediate for preparation of novel kinase inhibitors.

Figure 1. Pyrimidine-containing Drugs



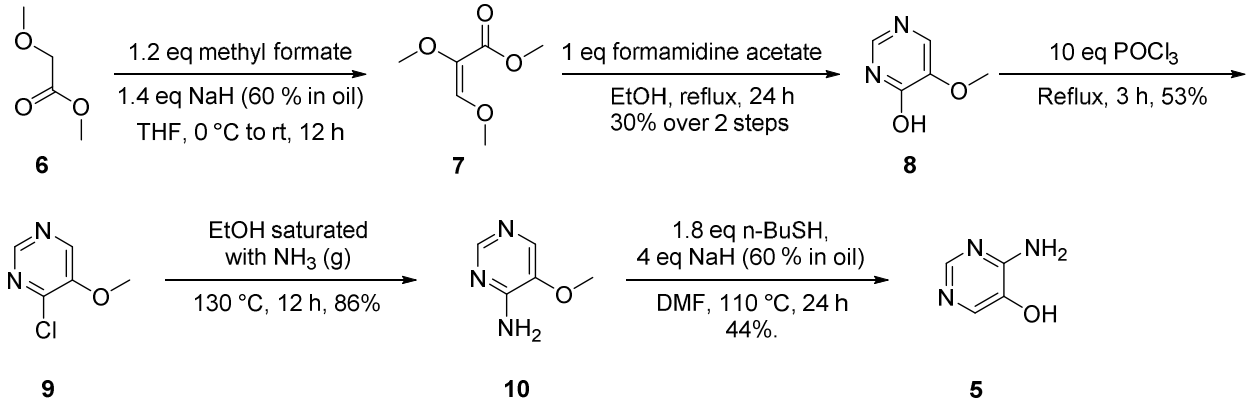
1 **2** **3** **4**

Results and Discussion

Given their popularity, there are numerous methods reported for the synthesis of functionalized pyrimidines.[2] These can be crudely broken down into those involving a *de novo* synthesis of the pyrimidine ring from suitably functionalized precursors, or those involving functional group manipulation of a readily available pyrimidine-based starting material. Koskinen has reported a

synthesis of **5**, which is shown in Scheme 1.[3] Initially, we chose to focus our attention on this route to see if it could be suitably developed to meet our compound needs.

Scheme 1. Literature Synthesis of **5**



Reaction of **6** with methyl formate in the presence of NaH as the base afforded **7**, which was isolated by filtration, and used directly in the Pinner-type condensation with formamidine acetate.[4] Scaling of these steps caused some initial concerns. Firstly, the use of NaH is not attractive, and as such screening for an alternative base to mediate this reaction would be required to evaluate more attractive options. Secondly, in the Pinner reaction on the laboratory scale, we observed sublimation of the formamidine acetate from the reaction mixture leading to build-up and clogging of the condenser. Finally, the overall yield of 30% over the 2 steps and the required chromatographic separation of **8** were a major obstacle to scale-up this compound.

The chlorination of heteroaromatic compounds with $POCl_3$ is a well-established procedure, which presents a number of challenges to develop on scale.[5] Typically in the research setting, a large excess of $POCl_3$ at reflux is employed to serve as both the reagent and the solvent leading to a hazardous exothermic quenching operation being required to neutralize the excess reagent in

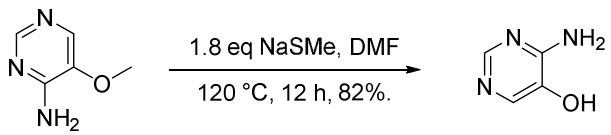
the presence of a potentially sensitive reaction product. Numerous studies have been published investigating this chlorination process, and it is known that the reaction only requires a slight excess of $POCl_3$ to proceed. However, the development of the optimal methodology to employ stoichiometric quantities of $POCl_3$ is both labor intensive, and is critically dependent on a number of key parameters such as reaction solvent, substrate solubility, use of additives, and the order of reagent addition.[6] In our initial studies on multigram scale, we utilized the Koskinen methodology, and removed the bulk of the excess $POCl_3$ through distillation under reduced pressure. This method somewhat mitigates the hazard in quenching a large excess of reagent. The issue now becomes carrying out the controlled quench on the residual gum. In addition, the $POCl_3$ distillate still needs to be suitably handled for disposal, and will lead to a large environmental burden from a waste perspective. While the current reaction proceeds in a moderate yield to provide **9**, development of a stoichiometric $POCl_3$-based methodology for **8** would be highly advantageous.

Introduction of the amino functionality in the conversion of **9** to **10** is achieved through direct displacement of the chloride utilizing a solution of ammonia. The reaction proceeds in high yield but requires extended heating in an autoclave at 130 °C, as well as an extractive work-up in the isolation of **10** as a solid. The final step in the sequence to form **5** is the *O*-demethylation of **10**. The literature conditions utilize an excess of *n*-BuSH with NaH as base at 110 °C and reproduction of these on scale presents issues. Firstly, there are concerns with handling *n*-BuSH based on its toxicity, flammability and the fact that it is a known irritant. In addition, this substance generates an extremely unpleasant odor with a low perception threshold. In human odor tests conducted on thiols, *n*-BuSH was ranked at 5 on a scale of 0 to 5 in which 5 represents the most malodorous and 0 refers to a thiol essentially possessing no detectable odor.[7] Secondly,

the use of DMF and NaH is known to present a thermal hazard on scale with the possibility of a runaway reaction at elevated temperature.[8] Finally, the demethylation reaction only provides a modest yield with a work-up, chromatographic separation and crystallization necessary to obtain the desired product in good purity. In considering sourcing options, this last step presented the greatest challenge with approximately a two-fold increase in both cost and lead-time being obtained for similar quantities of **10** and **5**.

With the problems associated with the final demethylation step, we evaluated whether an alternative reagent could be utilized to overcome the key issues of safety and odor associated with generation of the thiolate *in situ.* The possibility of utilizing a pre-formed thiolate reagent such as NaSMe was considered. As shown in scheme 2, the reaction proceeds in a significantly better yield on laboratory scale. However, this reagent is a flammable solid and also has significant toxicity concerns. In addition, it is typically available as a technical grade (> 90% purity), and still presents an odor issue due to the residual malodorous parent thiol utilized in its preparation. From a cost perspective, the preformed thiol reagent also presents an issue (as MeSH has been discontinued by Aldrich, the corresponding EtSH reagent was used as a comparator. This analysis demonstrated that roughly on a per gram basis, the technical grade of the thiolate was *ca*. 40 times more costly than the parent thiol).[9] Again, an aqueous work-up and chromatographic separation were utilized to obtain the desired pure compound.

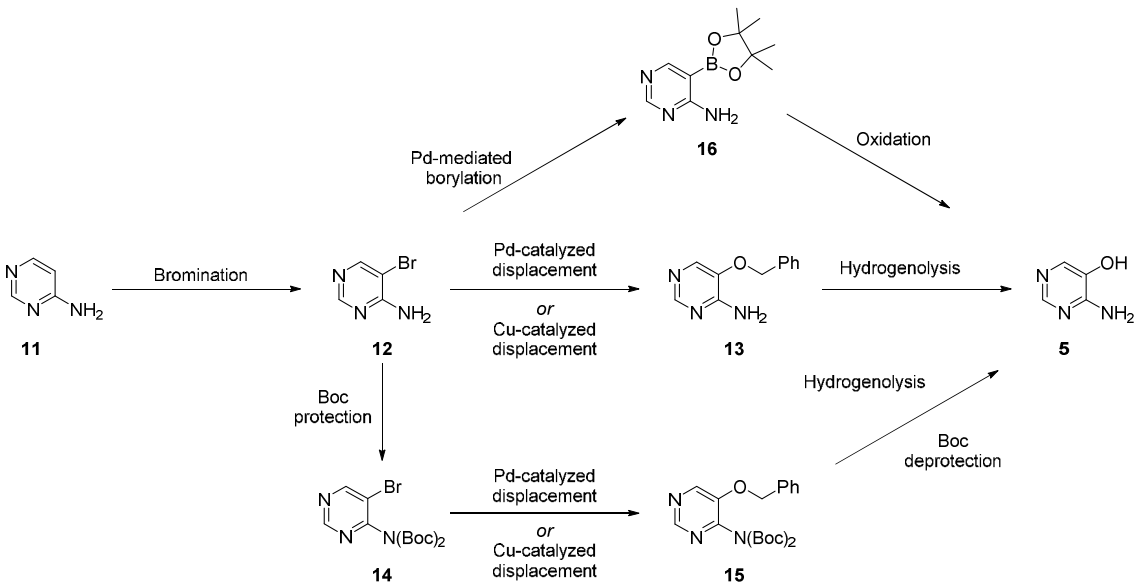
Scheme 2. Alternative conditions for the demethylation of **10**



10 **5**

Although the literature route was able to deliver gram quantities for our program, environmental, economic and safety concerns as well as the low yields and long lead time prompted us to consider alternative synthetic routes for the preparation of **5**. A central theme within our considerations was to investigate routes which did not involve construction of the pyrimidine ring. Instead we wanted to utilize a readily available and relatively inexpensive pyrimidine-based starting material, which through a simple set of functional group interconversions could lead to **5**. A range of possible starting materials can be envisioned to fit these criteria, and as such our feasibility studies focused not only on the availability/cost of the material but also on the precedence for, or rapid ability to evaluate the proposed chemistry. Our first consideration was the use of 4-aminopyrimidine (**11**), which is available from a wide range of suppliers. Despite being somewhat costly on gram scale, this material was also reported to be available in bulk. The proposed chemistry to evaluate this substrate as a potential starting material is illustrated in Figure 2.

Figure 2. Strategies to utilize **11** to access **5**



The bromination of **11** has been reported, and readily affords 4-amino-5-bromopyrimidine **12**, which is also commercially available.[10] From our perspective, this represents a versatile starting material with the correct regiochemistry already in place. We envisioned that a Buchwald or Ullmann type coupling would enable the installation of suitable oxygen protected functionality in the 5-position to access a precursor to **5**.[11,12] This chemistry also presents an additional element of versatility in being able to directly couple an alcohol into the pyrimidine, and thus potentially avoid a downstream alkylation step when constructing more complex molecular architectures within the projects chemical space. For the purposes of accessing multigram quantities of **5**, we utilized benzyl alcohol for our model studies with the view that this resulting ether product (**13**) would be easily deprotected *via* a simple hydrogenolysis, and thus avoid the problematic *O*-demethylation chemistry. A screen of both Pd- and Cu-mediated couplings using a range of ligands/catalysts were evaluated using our high throughput reaction screening platform.[13] However in none of these reactions could synthetically useful levels of the product be detected even under forcing conditions.[1] We hypothesized that perhaps the aminopyrimidine was inhibiting the desired reaction through competing complexation of the metal catalyst. With this as a working hypothesis, we evaluated the same series of reactions conditions on the *bis*-Boc protected precursor, **14**.[14] Across the series of reaction conditions evaluated, the desired product was readily observed; however, competing loss of one of the Boc protecting groups lead to both a complex analysis and the gradual retardation of the desired reaction over time. Synthetic designs employing a more robust amino protecting group were considered, but concerns over potential problems with its removal later in the synthesis prioritized execution on these.

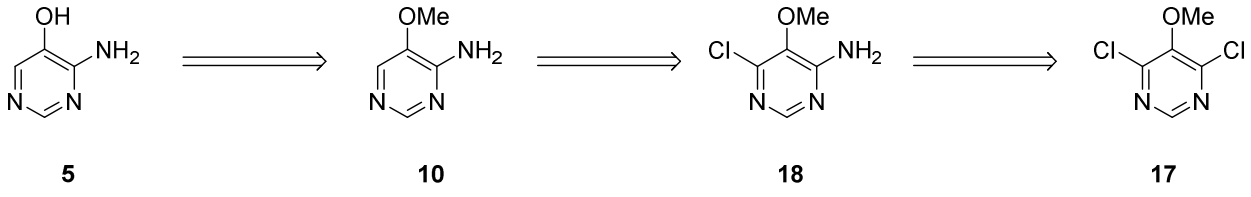
An alternative possibility using 5-bromo-4-aminopyrimidine (**12**) would be to carry out a Pd-mediated borylation with *bis*-pinacol ester to access the boronate ester (**16**), which could be

subjected to a range of mild oxidative conditions to access the desired phenol.[16] One advantage of this approach would be that this would enable direct access to the unprotected alcohol thus avoiding the problematic demethylation reaction encountered in the original synthesis. However, perhaps unsurprisingly based on the results from the screen of the Buchwald coupling described above, screening of a series of catalysts/bases/solvents for the proposed borylation failed to yield appreciable levels of the desired product, and as such further attempts on this approach were abandoned.[17]

At this time, we switched our attention to utilize 4,6-dichloro-5-methoxypyrimidine **17** as an alternative pyrimidine-based starting material. This compound is readily available in bulk quantities and inexpensive from a wide range of vendors.

From our perspective, we envisioned the following retrosynthetic approach in enabling **17** as a starting material to access our desired **5 as shown in Figure 3**. Initial displacement with ammonia or a suitable surrogate allows displacement of the initial chloride to afford **18**.[18] Halogen removal under reductive conditions from aromatic systems is also well precedented. The major drawback from our proposed sequence is that we would need to revisit the *O*-demethylation chemistry, which caused significant problems in the initial synthesis.

Figure 3. Proposed Retrosynthesis of **5** starting from **17**



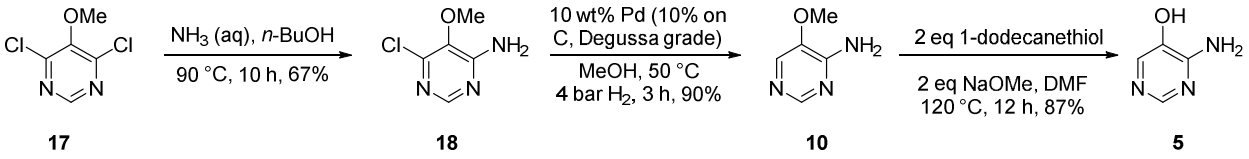
5 **10** **18** **17**

Investigating the aminolysis reaction, we found that heating **17** with 28% aqueous ammonia in *n*-butanol at 90 °C allowed for the clean formation of **18**. Although on scale, an autoclave was still used, a lower temperature was required from the initial synthesis. Additionally, the opportunity to utilize flow to further optimize this step exists.[19] On cooling the desired mono-substituted product precipitated from the reaction enabling direct isolation by filtration, thus obviating the need for chromatography. Whereas, using an ammonia surrogate such as benzylamine may allow milder conditions to be employed for this transformation, and could conceivably be cleaved during the hydrogenation step, employment of ammonia is the most atom-economical option for this transformation. Deschlorination of the intermediate **18** to afford the 4-amino-5-methoxypyrimidine was effected with hydrogenation using 10% Pd/C as the catalyst at 50 psi at 50 °C for 3 hours.[20] Hydrogenation also took place at ambient temperatures and pressure, but lead to longer reaction time. As such, the optimized conditions utilized mild heating. No base additive was required in the reaction. The work-up required simple filtration followed by addition of aqueous ammonia and solvent evaporation. The concentrate was then slurried in THF and CH_2Cl_2 resulting in the precipitation of the ammonium chloride and a second filtration. Concentration of the filtrate afforded the desired product **10** as a colorless solid in *ca*. 90% yield. The material was used directly in the next step.

Finally, we attempted to address the problems encountered in the *O*-demethylation step by systematically evaluating alternative reagents and conditions used on scale to alleviate the odor, safety and toxicity concerns. Initial tests using the classical demethylating reagent BBr_3 lead to both a sluggish reaction, and large excesses of reagent being required to obtain a decent conversion.[21] In addition, a complex work-up and the necessity for chromatography lead us to pursue alternative options. Methanesulfonic acid in combination with methionine has also been

reported as an effective combination to carry out *O*-demethylation on scale with advantages being a simple extractive work-up.[22] However, in our case, this combination failed to afford the desired product following the reported literature conditions. Reports suggest that alkanethiols with a chain length of 12 carbons or more are considered odorless.[23] For example, 1-dodecathiol has boiling point of 266-283 °C and is both inexpensive and available in large quantities. Its use has been reported for *O*-demethylation on scale.[24] Given our previous positive results with both sodium methanethiolate and butane-1-thiol in combination with NaH, we were confident that the use of 1-dodecanthiol and a suitable base would provide the desired product. Indeed switching NaH for NaOMe and reacting 5-methoxypyrimidin-4-amine **10** in the presence of 1-dodecanethiol in DMF at 120 °C for 12 h provided the desired product 4-aminopyrimidin-5-ol **5** as a gray white solid in 87% yield and 100% purity by HPLC with no column chromatography. The thiol by-products were removed by simple aqueous extractive work-up.

Scheme 3. Modified Synthesis of **5** from **17**



17 **18** **10** **5**

Conclusion

In summary, we have identified an alternative scalable 3 step synthesis to the literature reported route (5 steps, 6% overall yield in our hands) of 4-aminopyrimidin-5-ol (**5**) which proceeded in 52% yield from a known, commercially available, inexpensive starting material, 4,6-dichloro-5-methoxypyrimidine (**17**). On > 100 g scale, the new synthesis presented several advantages with no chromatography being required, and a number of safety concerns present in the original route

eliminated. The common step between the two routes involved the *O*-demethylation with the new route using 1-dodecanethiol as an odorless replacement to *n*-BuSH and NaOMe as the base. The newly developed route significant reduced the lead time to access 100g of the substrate by a factor of at least 4 (1-1.5 weeks) compared to the original route (6 -7 weeks).

Experimental

General. Starting materials and other reagents were purchased from commercial suppliers and were used without further purification unless otherwise noted. All reactions were performed under a positive pressure of nitrogen, argon, or with a drying tube, at ambient temperature (unless otherwise stated), and in anhydrous solvents, unless otherwise indicated. Analytical thin-layer chromatography was performed on glass-backed Silica Gel 60_F 254 plates (Analtech (0.4-0.5 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high-performance liquid chromatography (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV. ^{1}H NMR spectra were recorded on a Bruker instrument operating at 400 MHz unless otherwise indicated. ^{1}H NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions as indicated (reported in ppm), using DMSO-d_6 (2.50 ppm) or chloroform (7.25 ppm) as the reference standard. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants are reported in hertz. The mass spectra were obtained using liquid chromatography mass spectrometry (LC-MS) on an Agilent instrument using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI). High performance liquid chromatography (HPLC) conditions were as indicated.

Initial Route to 4-aminopyrimidin-5-ol (5).[3]

Preparation of methyl (*E*)-2,3-dimethoxyacrylate (7). This reaction was set up in two batches (2 x 83.2 g) with the batches being combined for work-up. To a mixture of compound methyl 2-methoxyacetate (**6**, 83.2 g, 0.8 mol) and methyl formate (57.6 g, 0.96 mol) in anhydrous THF (1.5 L) was added NaH (44.8 g, 1.12 mol, 60% in oil) in portions at 0 °C. The resulting mixture was stirred at room temperature for 12 h during which formation of a white solid was observed. MTBE (1 L) was added and the mixture was filtered. The filter cake (assume 100% yield ~1.6 mol) was dried under reduced pressure and then used without purification in the next step.

Preparation of 5-methoxypyrimidin-4-ol (8). This reaction was set up in two batches (2 x 0.8 mol) with the batches being combined for work-up and purification. The solid obtained from the previous step (~0.8 mol) was added to a solution of formamidine acetate (83.2 g, 0.8 mol) in EtOH (1.6 L). The resulting mixture was stirred at room temperature for 12 h, and then refluxed for a further 24 h. During the reflux period, a build-up of solids was observed in the condenser leading to a potential clogging issue. After being allowed to cool, water (400 mL) was added, and the mixture was acidified with AcOH (250 mL) to adjust the pH from 10 to ~ 5. The solution was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 50:1 to 10:1, R_f = 0.2 in CH_2Cl_2/MeOH = 10:1) to give 5-methoxypyrimidin-4-ol (**8**, 60 g, 30%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (br s, 1 H), 7.81 (s, 1 H), 7.52 (s, 1 H), 3.72 (s, 3 H).

Preparation of 4-chloro-5-methoxypyrimidine (9). A suspension of compound 5-methoxypyrimidin-4-ol (**5**, 57 g, 0.452 mol) in $POCl_3$ (751 g, 4.69 mol) was heated at reflux for

3 h. After being allowed to cool, the excess $POCl_3$ was removed under reduced pressure, and the remaining residue was poured into ice-water (~300 ml). The pH was then adjusted to ~ 7 with K_2CO_3 (*ca*. 250 g), and the mixture was extracted with EtOAc:MTBE (3:1, 4 x 250 mL). The organic layers were combined, washed with brine (100 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 4-chloro-5-methoxypyrimidine as a yellow solid (**9**, 35 g, 53%, R_f = 0.5 in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 8.33 (s, 1 H), 4.03 (s, 3 H).

Preparation of 5-methoxypyrimidin-4-amine (10). This reaction was set up in two batches (2 x 16 g) with the batches being combined for work-up and purification. A suspension of 4-chloro-5-methoxypyrimidine (**9**, 16 g, 0.109 mol) in EtOH (800 mL) saturated with ammonia gas was poured into an autoclave, which was heated to 130 °C with stirring for 12 h. After being allowed to cool, evaporation of the solution provided a tan residue, which was partitioned between CH_2Cl_2 (1 L) and brine (250 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (6 x 100 ml). The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 5-methoxypyrimidin-4-amine as a yellow solid (**10**, 24 g, 86%, R_f = 0.4 in CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1 H), 7.81 (s, 1 H), 6.72 (br s, 2 H), 3.81 (s, 3 H).

Preparation of 4-aminopyrimidin-5-ol (5). To a solution of compound 5-methoxypyrimidin-4-amine (**10**, 38 g, 0.3 mol) in anhydrous DMF (2 L) was added NaH (28.7 g, 1.2 mol, 60% in mineral oil pre-washed with hexanes) at room temperature. The resulting mixture was cooled using an ice bath to 0 °C before addition of *n*-BuSH (36.8 g, 0.405 mol). The resulting reaction mixture was stirred at 110 °C for 12 h. TLC (CH_2Cl_2/MeOH = 10:1, R_f = 0.1) indicated that compound **10** had been consumed and a new unknown spot was detected, which did not co-elute

with authentic **5**. A further charge of *n*-BuSH (12 g, 0.135 mol) was added to the reaction, which was then stirred at 110 °C for 12 h. TLC (CH_2Cl_2/MeOH = 10:1) indicated that the unknown spot was almost consumed. The mixture was concentrated *in vacuo* to dryness. AcOH (35 ml) and H_2O (200 mL) were added, and the reaction concentrated again. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 50:1 to 10:1), and then the product recrystallized from MeOH (100 mL) to give 4-aminopyrimidin-5-ol **(5)** as a yellow solid**.** (17 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (br s, 1 H), 7.91 (s, 1 H), 7.63 (s, 1 H), 6.42 (br s, 2 H). MS-ESI: *m/z* 112.6 $[M+H]^+$. HPLC: Column: YMC-pack ODS-A 150 x 4.6 mm, 5 μm. Retention Time: 3.418 min. Mobile phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B), holding at 0% (solvent B) for 4 minutes, and then using the elution gradient 0% - 30% over 6 min, and holding at 30% for 5 minutes at a flow rate of 1.0 ml/minutes showed 99.3% purity.

Preparation of di-tert-butyl (5-bromopyrimidin-4-yl)imidodicarbonate (14)

To a solution of compound 5-bromopyrimidin-4-amine 12 (800 mg, 4.60 mmol), (BOC)2 (3310 mg, 15.2 mmol) and DMAP (191 mg, 1.56 mmol) in anhydrous THF (6 mL) was added Et3N (2000 mg, 19.8 mmol). The mixture was stirred under N2 at RT for 16 h. LC-MS showed the reaction was completed. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in chloromethane (40 mL), and purified by Biotage (petroleum ether/ ethyl acetate=100/1 to 8/1) to give the desired product 14 as a white solid (810.4 mg, 47.1%). 1H NMR (400 MHz, DMSO-d_6): 9.23 (s, 1 H), 9.19 (s, 1 H), 1.37 (s 18 H). MS-ESI: m/z 397.9 $[M+23]^+$.

Modified preparation of 4-aminopyrimidin-5-ol (5). To a solution of compound 5-methoxypyrimidin-4-amine (**10**, 40 g, 0.32mol) in anhydrous DMF (2.5L) was added CH_3SNa (40.3 g, 575 mmol, 95% Aldrich, powdered solid) at room temperature. The resulting mixture

was heated at 120 °C for 12 h. TLC (CH_2Cl_2/MeOH = 10:1, R_f = 0.1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give a residue, to which was added AcOH (35 mL) and H_2O (100 mL). The mixture was again evaporated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 50:1 to 5:1) to give 4-aminopyrimidin-5-ol as a brown solid (**5**, 29 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (br s, 1 H), 7.91 (s, 1 H), 7.63 (s, 1 H), 6.42 (br s, 2 H).

Optimized Route to 4-aminopyrimidin-5-ol (5).

Preparation of 6-chloro-5-methoxypyrimidin-4-amine (18). A suspension of compound 4,6-dichloro-5-methoxypyrimidine (**17**, 550.00 g, 3070 mmol) in 28% aqueous ammonia (2 L) and *n*-butanol (1.5 L) was heated at 90 °C for 10 h in a 5 L autoclave. The mixture was cooled to room temperature. The precipitate, which had formed, was filtered, and the filter cake washed with EtOH (2 x 200 mL). The solid was collected and dried under high vacuum to give 6-chloro-5-methoxypyrimidin-4-amine as a white solid (**21**, 330 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1 H), 7.32 (br s, 2 H), 3.71 (s, 3 H). LC-MS: *m/z* $[M+H]^+$ 160.1. HPLC column: HPLC-BC (4-220) Ultimate XB-C18, 3.0 x 50mm, 3 μm. Retention Time: 2.37 min; Mobile phase: from 1 % MeCN in water (0.1% TFA) to 100 % MeCN in water (0.1% TFA) over 8 minutes Wavelength: 220 nm showed purity of 99.8%.

Preparation of 5-methoxypyrimidin-4-amine (10). To a suspension of 6-chloro-5-methoxypyrimidin-4-amine (**18**, 160 g, 10.03 mol) in methanol (1.6 L) was added Pd/C (32.0 g, 10% w/w Degussa grade containing ~50% H_2O). The mixture was degassed three times with N_2 and then placed under 50 psi of hydrogen pressure at 50 °C for 3 h. TLC (CH_2Cl_2/MeOH = 10/1) indicated the reaction was complete. The mixture was filtered through a pad of celite, and the

filter cake was washed with MeOH (3 x 100 mL). To the filtrate was added aqueous ammonia (25 mL), and the resulting mixture was concentrated *in vacuo*. The residue was dissolved in THF (1.0 L) and CH_2Cl_2 (1.0 L), and stirred for 1 h. The suspension was filtered, and the filtrate concentrated and dried under high vacuum to give 5-methoxypyrimidin-4-amine as a white solid**.** (**10**, 111.3 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1 H), 7.81 (s, 1 H), 6.71 (br s, 2 H), 3.81 (s, 3 H).

Preparation of 4-aminopyrimidin-5-ol (5). Sodium (25.7 g, 1.12 mol) was added in portions to anhydrous MeOH (700 mL) at room temperature, and the reaction stirred until the sodium had dissolved completely. The resulting solution was then concentrated under vacuum. To a suspension of 5-methoxypyrimidin-4-amine (**10**, 70.0 g, 559.4 mmol) and NaOMe (prepared as described above) in anhydrous DMF (1.3 L) was added 1-dodecanthiol (226 g, 1.12 mol). The suspension was heated to 120 °C to give initially a light yellow clear solution in which a white solid started to form after 30 min. The mixture was stirred at 120 °C for a further 12 h. TLC (CH_2Cl_2/MeOH = 10/1) showed the reaction was complete. The reaction mixture was concentrated to remove DMF. To the reaction mixture was added acetic acid (70 mL) and H_2O (150 mL) (pH = 5~6). The mixture was then concentrated under vacuum for over 10 minutes. EtOAc (400 mL) and H_2O (120 mL) were added to the reaction mixture. The majority of the supernatant from the organic layer (dodecanthiol and EtOAc) was decanted, the remaining suspension was filtered. The solid was washed with H_2O (2 x 30 mL), EtOAc (2 x 50 mL), and dried under high vacuum to give 4-aminopyrimidin-5-ol (**5**, 53.8 g, 87%) as a gray-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (br s, 1 H), 7.91 (s, 1H), 7.63 (s, 1 H), 6.44 (br s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155, 149, 137.6, 136. MS-ESI: m/z 112.1 $[M+H]^+$. HPLC column: Atlantis HILIC Silica 150 x 4.6mm, 5 μm; Mobile phase: 0.1% TFA in water (solvent

A) and 0.1% TFA in acetonitrile (solvent B), using the elution gradient 90% - 60% (solvent B) over 10 minutes and holding at 60% for 5 minutes at a flow rate of 1.0 mL/minute. Wavelength: 220 nm showed a purity of 100%.

AUTHOR INFORMATION

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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