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Convenient and Practical One-Pot Synthesis of 4-Chloropyrimidines via a Novel Chloroimidate Annulation

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ABSTRACT: Reaction of aromatic or heteroaromatic 2-acyl(amino)nitriles with phosphorus pentachloride triggers a novel chloroimidate cyclization, leading directly to the corresponding annullated 4-chloropyrimidines in good to excellent yields. The reaction lends itself to the telescoped one-pot construction of 4-functionalized pyrimidines from the corresponding (hetero)aromatic 2-aminonitriles. For a pyrazolopyrimidine development intermediate, this reaction was scaled up to multikilogram scale with excellent results. A total of 10 examples with different substrates are provided. This one-pot reaction provides an attractive and sustainable alternative to the commonly used multistep methodology for this transformation.

INTRODUCTION

Due to their excellent reactivity in aromatic nucleophilic (SN_{Ar}) substitutions and transition metal-catalyzed cross-coupling reactions, 4-halogenated pyrimidines[1−4] are widely used as activated building blocks for the construction of various pharmacophores. Traditional synthesis of 4-chloropyrimidines (**B**) involves reaction of the corresponding pyrimidin-4-one precursor (**A**) with an inorganic acid halide (e.g., phosphorus pentachloride, phosphorus oxychloride, or thionyl chloride)[5] (Scheme 1):

For annullated systems, the pyrimidin-4-ones **A** are usually obtained by cyclization of a (hetero)aromatic 2-acylamino carboxamide **C**, which in turn may be obtained via a variety of methods, including amidation of the corresponding carboxylic acid **D** or partial hydrolysis of a precursor nitrile **E** (Scheme 2).[5f]

In the context of one of our development programs, we assessed the preparation of the azolo-chloropyrimidine intermediate **4** via a three-step literature[6] sequence shown in Scheme 3.

From a process point of view, this stepwise hydrolysis/cyclization/chlorination protocol, although widely used for the assembly of highly substituted, annullated 4-chloropyrimidines (for examples, see refs 6−11), appeared tedious and fraught with both safety concerns (*heating alcoholic mixtures containing hydrogen peroxide*) and robustness issues (*basic hydroperoxide hydrolysis of the nitrile in presence of amide*). These led us to consider the direct transformation of **1** to **4**.

RESULTS AND DISCUSSION

We felt it was reasonable to assume intermediate imidoyl chlorophosphate formation from the secondary amide substructure and a phosphorus halide, in analogy to the first step in the Vilsmeier reaction of hydroxyheteroaromatics.[5] Hydrogen chloride addition to the nitrile group by one of the pathways shown below (**A** vs **B**) could follow. In this manner, a primary chloroimidate would be generated which might then attack either the imidoyl chlorophosphate (path B), or the secondary chloroimidate (path **A**) in a nucleophilic (*6-endotrig*) fashion, resulting in cyclization to the desired 4-chloropyrimidine (Scheme 4):[12]

This was indeed found to be the case. A variety of solvents were screened, with sulfolane providing the cleanest reactions and highest yields. Phosphorus pentachloride proved superior to phosphorus oxychloride (lower yields), whereas phosphorus trichloride and thionyl chloride led to decomposition. The desired azolo-(chloro)pyrimidine **4** (*vide supra*) was thus obtained in 90% yield on 200-g scale directly from the amide **1** (Scheme 5).

Investigation of the thermal safety data obtained by Thermal Screening Unit (TSu) testing (5 mL suspension of all starting materials mixed cold, with 2 equiv of PCl_5) showed a very shallow, small exotherm ranging from 70 to 170 °C and a second smaller exotherm from 170 to 250 °C. A residual pressure of 3 bar was observed (Figures 1 and 2). Additional ARSST (Advanced Reactive System Screening Tool, Fauske and Associates, LLC)[13] testing on a more concentrated sample, with 4 equiv of PCl_5, showed a small exotherm at 115 to 150 °C and a stronger exotherm ranging from 152 to 320 °C, whereas the isolated, crude compound **4** proved benign with regard to thermal safety (data not shown). On the basis of this initial safety testing result and the lack of internal and external scale-up experience with this new reaction type, the amount of PCl_5 for initial kilolab scale-up was limited to 2 equiv, the concentration was adjusted slightly towards higher dilution, and the batch was divided into three runs of approximately 2.8 kg each. Another concern was that on lab scale, under stronger nitrogen sweep flow rates, PCl_5 was sometimes observed to crystallize/accumulate in the condenser during the course of the reaction. This was addressed in the kilolab

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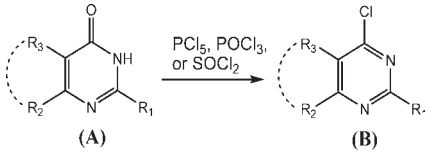
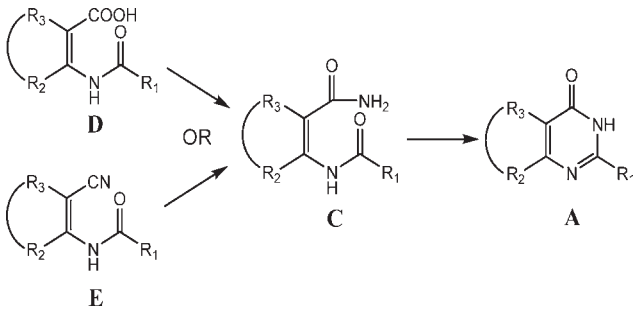
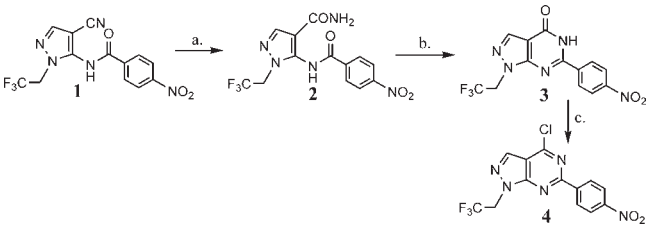
Scheme 1



Scheme 2



Scheme 3[a]



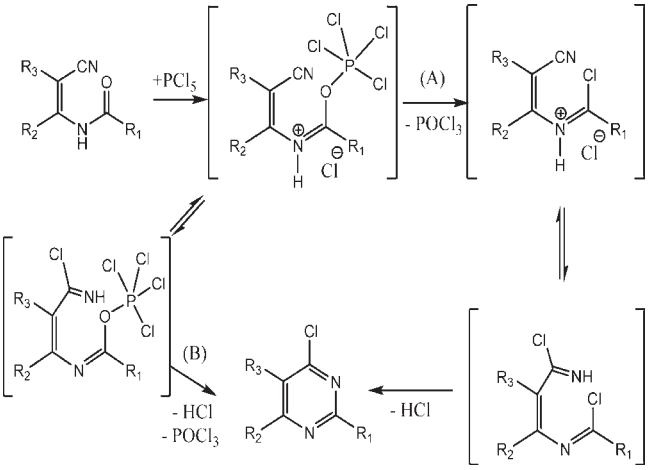
[a] Reagents and conditions: a) 30% H_2O_2, NaOH−EtOH. b) EtOH, reflux. c) $POCl_3$, cat. DMF.

scale-up through lower agitation rates and a minimized headspace nitrogen flow.

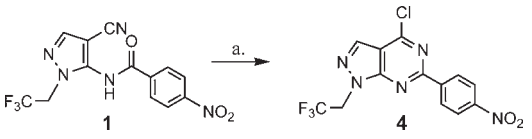
Each of the three ~2.8 kg kilolab runs gave a reproducible assay-corrected yield of ~85% and 99% HPLC-purity. On this scale, the two equivalents of PCl_5 used in the reaction gave 94% conversion after only 5 h reaction time, which was attributed to the minimal overhead nitrogen sweep applied and the reduced agitation rate (HCl flushout minimized). No exotherms or accumulation of PCl_5 in the condenser were observed under these conditions. To obtain a homogeneous batch, a crystallization step combining the three sublots in a DMF−water mixture was added, which also served to completely eliminate any residual sulfolane trapped in the product and resulted in an 81% assay corrected yield of ~7 kg of recrystallized **4** (99.9 A% HPLC purity).

Substrate scope was explored (Scheme 6), with good toleration of both a triazole (**5**) and a benzofuran (**7**) substrate on small scale using these conditions (*not optimized*). It was also found that both the acylation step from the amino-azole as well as the subsequent PCl_5-cyclization in sulfolane can be carried out in one pot, without workup or isolation of the intermediate amide (Scheme 6). At elevated temperatures, the acylation typically

Scheme 4



Scheme 5[a]



[a] Reagents and conditions: a) 4 equiv of PCl_5, sulfolane, 120 °C, 14 h, 90% yield (assay-corrected).

proceeds to ~90−95% completion in the absence of added base; therefore, we speculate that the neighboring cyano group may act as an internal base capturing the liberated hydrogen chloride and forming the chloroimidate to some extent already during the acylation step (this intermediate can be observed by HPLC in some cases).

This nucleophilic chloroimidate cyclization may be rather general, as demonstrated by synthesis of the chloro[benzo]-diazines **10**, **12**, and **14** shown below (Scheme 7); not only chloroquinazolines (**10**, **14**), but also pyrimido-chloropyrimidines (**12**) are readily accessible.

A telescoped process is also achievable in the case of the six-membered (hetero)aromatic aminonitriles. The aromatic β-amino nitriles were heated in sulfolane with an acid chloride in the absence of base and after completed acylation, phosphorus pentachloride was added, and heating was continued until the cyclization was complete (typically 8−12 h) (Scheme 8, compounds **16** and **18**). Additionally, acylated aminonitriles can be heated with phosphorus pentachloride and the reaction quenched directly with a nucleophile. For instance, 4-aminoquinazolines are readily accessible (Scheme 8, compound **20**). With a secondary amine as nucleophile, the sequence could even be telescoped over three steps with satisfactory overall yield (Scheme 8, compound **21**).

Mechanistically, pathway (A) in Scheme 4 appears more likely,[12] as an exploratory ^{13}C NMR experiment on 2-benzoylamino-benzonitrile showed the initial formation of a chlorophosphate imidate species ($^2J_{C,P} \approx 160$ Hz) upon PCl_5 addition which does *not* collapse directly to the product but instead goes through a mixture of non-phosphorus-containing intermediates before finally converging to the product spectrum. However,

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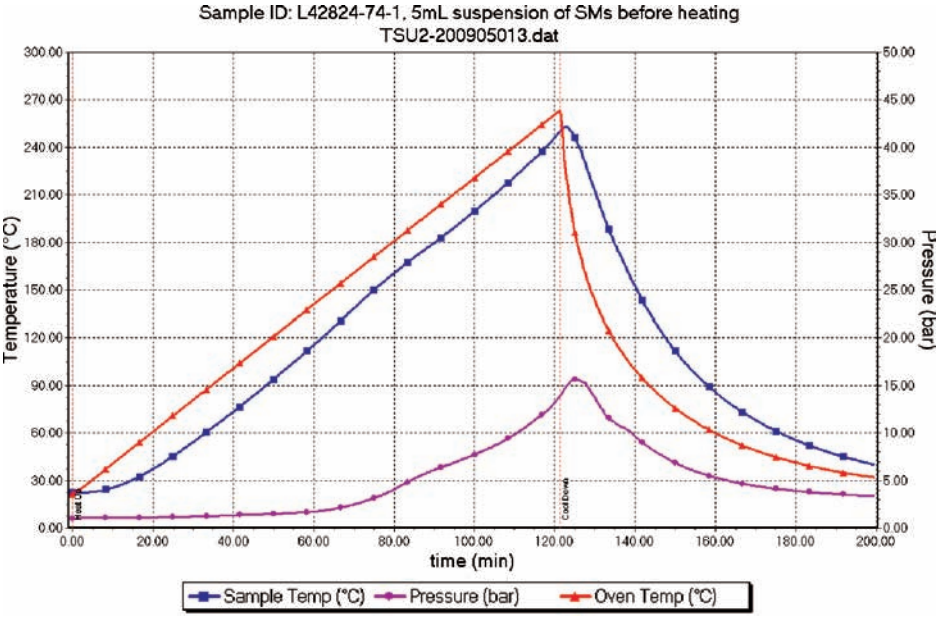

Figure 1. TSu safety data for reaction **1** → **4** *(starting materials mixed cold).*

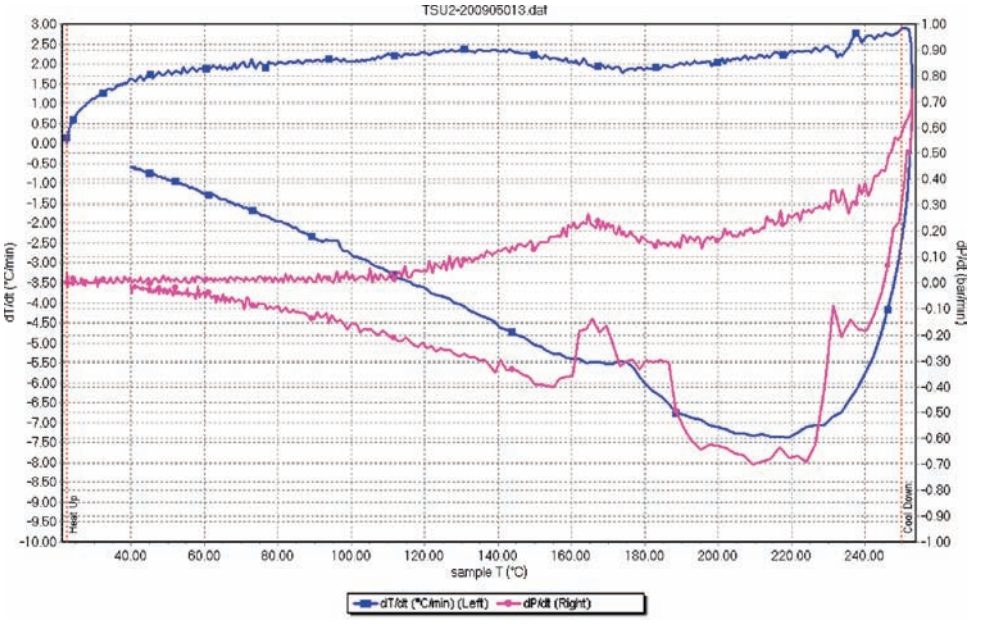

Figure 2. TSu safety data for reaction **1** → **4** *(starting materials mixed cold).*

since this experiment was carried out in CD_3CN (deuterated sulfolane was not available to us at the time), solvent participation in the mechanism cannot be excluded.

In conclusion, we have found and demonstrated scale-up viability for a novel and practical chloroimidate cyclization protocol, allowing rapid construction of annullated 4-chloropyrimidines from the corresponding (hetero)aromatic amino- or acylaminonitrile precursor in a straightforward fashion. The reaction lends itself to telescoped process variants. In most cases, the crude product isolated after aqueous workup is of good purity (typically ~95% HPLC). This one-pot reaction sequence represents significant progress over existing multistep methodology[6−11] developed for the same transformation, reducing waste and increasing sustainability.

EXPERIMENTAL SECTION

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. All the melting points are uncorrected and determined on a Büchi apparatus. ^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 125 MHz on a Bruker DRX-500 NMR instrument. Assignments were confirmed by the appropriate 2D-NMR experiments. IR spectra were measured on

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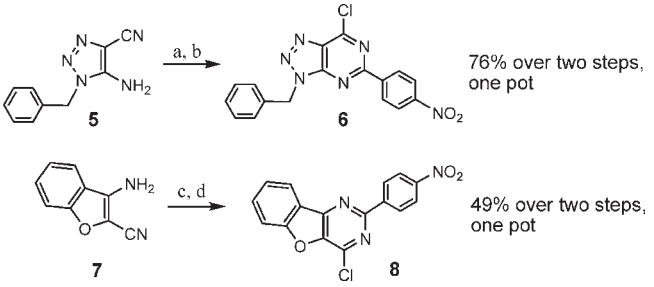
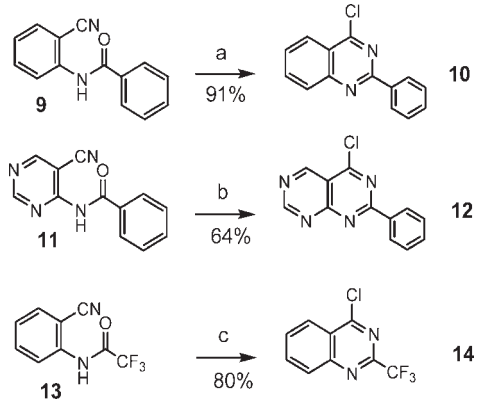
Scheme 6[a]



[a] Reagents and conditions: a) *p*-nitrobenzoyl chloride, sulfolane, 80 °C, 2 h. b) Add 2 equiv of PCl_5, 95 °C, 3 h. c) *p*-Nitrobenzoyl chloride, sulfolane, 30 °C, 2 h. d) Add 2 equiv of PCl_5, 95 °C, 2 h.

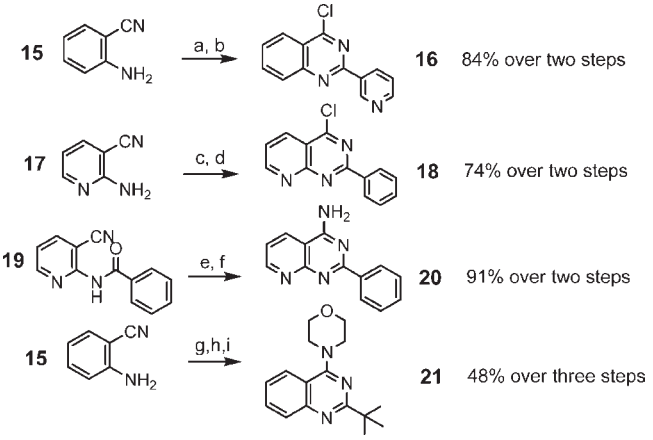
Scheme 7[a]



[a] Reagents and conditions: a) 1.75 equiv of PCl_5, sulfolane 110 °C, 16 h. b) 1.75 equiv of PCl_5, 100 °C, 3 h.) 1.75 equiv of PCl_5, 100 C, 16 h.

a Bruker IFS660 spectrometer. Exact mass determinations were performed on a ABI QSTARXL Q-ToF instrument (calibrated in positive ion mode with CsI and sex pheromone inhibitor iPD1 (Bachem)). Typical experimental procedures for the isolation of the chloropyrimidine products generally involved neutralization/precipitation with water, which usually gave material of sufficient (≥95% HPLC) purity. On small scale, some samples were purified by flash-chromatography (FC)[14] on SiO_2. HPLC Method (A): stationary phase: Sunfire C18, 3.5 μm, 4.6 mm × 150 mm, column oven temp: 35 °C; flow: 2.5 mL/min; Solvent A: 1900 mL of H_2O, 100 mL of CH_3CN, 1 mL of TFA; Solvent B: 1900 mL of CH_3CN, 100 mL of H_2O, 1 mL of TFA. Gradient: linear gradient 0 → 100% B over 4 min, then 100% B for 1 min. Method (B): stationary phase: SunFire C18, 3.5 μm, 4.6 mm × 150 mm, column oven temp: 35 °C; flow: 1.0 mL/min. Solvent A: 950 mL of H_2O, 50 mL of CH_3CN, 0.5 mL of H_3PO_4. Solvent B: 1000 mL of CH_3CN, 0.5 mL of H_3PO_4. Gradient: 70% A, 30% B for 5 min, then linear gradient 30% → 100% B over 5 min, then 100% B for 5 min. Detection: UV (λ = 220 nm, unless mentioned otherwise). Safety testing: (A) Thermal Screening Unit (HEL Ltd.): The sample is charged into a 9-mL (Hastelloy C unless otherwise indicated) test cell, which is then sealed into an oven. The oven temperature is ramped up to 250 °C at 2 °C/min, unless otherwise indicated. Sample temperature is monitored with a thermocouple immersed into the sample. Pressure and oven temperature are also monitored throughout the run. The containment volume—test

Scheme 8[a]



[a] Reagents and conditions: a) Nicotinoyl chloride, 100 °C, 12 h. b) PCl_5, sulfolane, 100 °C, 10th. c) Benzoyl chloride, 95 °C, 75 h. d) PCl_5, 100 °C, 12th. e) PCl_5, 100 °C, 19th. f) NH_3, H_2O−CH_3CN, rt → 50 °C, 1 h. g) Pivaloyl chloride, 75 °C, 48 h. h) PCl_5, 110 °C, 19 h. i) Morpholine−CH_3CH, rt, 1 h.

cell, pressure transducer, and piping—is approximately 10 mL. Advanced Reactive System Screening Tool (ARSST, Fauske and Associates, LLC.): The sample is charged into a 10-mL glass cell, which is then wrapped in a heating mantle and aluminum foil and fiberglass to minimize thermal losses. The cell is placed in a larger containment vessel (total containment is 310 mL). The containment vessel is pressurized with nitrogen gas to prevent solvent boiling. A thermocouple is immersed in the sample to measure sample temperature, and pressure is monitored throughout the run with a transducer. A small magnetic bar is used to induce sample stirring. The ARSST has an injection port, allowing for the charging of one of the reagents in situ during the run.

Experimental Procedures for 4-Chloropyrimidines (stepwise). *First Proof-of-Concept Experiment: 4-Chloro-2-phenylquinazoline (10).* To a solution of *N*-(2-cyanophenyl)-benzamide **9** (598 mg, 2.69 mmol) in sulfolane (12 mL) was added phosphorus pentachloride (1.04 g, 4.98 mmol) in one portion at 45 °C (yellow, clear solution). Solution was stirred at 110 °C in a 20-mL septum vial for 16 h, then cooled to 45 °C. HPLC showed 98 A% product (254 nm). Upon further cooling to to rt, water (1 mL) was slowly added, followed by Hünig's base (3.5 mL, 20 mmol), such that the temperature stayed below 30 °C. The pH was adjusted to 7 with AcOH, and the suspension was stirred in an ice bath for ∼30 min and then filtered over a medium porosity glass frit. The filter cake was washed with water (2 × 20 mL) and dried to constant weight at 40 °C (high vacuum). Obtained 588 mg (91%) assay-corrected {*using commercial AM-ex-OL (Aldrich) as ref standard*} yield of **10** as a white solid. HPLC (Method **A**): R_t 4.08 min, 98.8 A% (210 nm).

4-Chloro-2-phenylpyrimido[4,5-d]pyrimidine (12). To a solution of *N*-(2-cyanophenyl)-4-amino-5-cyanopyrimidine **11**[15] (800 mg, 3.56 mmol) in sulfolane (12 mL) was added phosphorus pentachloride (1.3 g, 6.24 mmol) in one portion at 45 °C (yellow, clear solution). Stirred at 100 °C in a 20-mL septum vial for 3 h, then cooled to 45 °C. HPLC showed 98 A% product (254 nm). Upon aq workup (as for (**10**)) and filtration, 1.3 g of a yellow solid was obtained (HPLC: 97 A% (254 nm)). The crude wetcake purity decreased to 85 A% after overnight drying at 45 °C in the vacuum oven (hydrolysis product detected). FC of

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this material (heptanes/EtOAc 3:1 → 2:1 gradient) provided 550 mg (64%) **12** as a slightly yellowish solid. HPLC (Method A): R_t 2.18 min, 98.2 A% (254 nm). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (m, 2H), 7.60 (m, 1H), 8.67 (d, 2H, J = 8.4 Hz), 9.65 (s, 1H), 9.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 114.9, 128.9, 130.1, 133.3, 135.0, 159.9, 162.5, 163.1, 163.3, 167.5. HR-MS: ionizes as [M + H_2O] (*hydrolysis under LC−MS conditions*): calculated for $C_{12}H_7ClN_4$ + H_2O: 260.0464; found: 260.0457.

4-Chloro-2-trifluoromethyl-quinazoline (14). To a solution of *N*-(2-cyanophenyl)-2,2,2-trifluoroacetamide **13** (1.15 g, 5.37 mmol) (HPLC) (Method A): R_t 2.36 min) in sulfolane (12 mL) was added phosphorus pentachloride (2.0 g, 9.4 mmol) in one portion at 45 °C (thin suspension). Stirred at 100 °C in a 20-mL septum vial overnight, then cooled to 40 °C. Reaction is slower than for **10** and **12**: HPLC showed 93% starting material conversion and 88.3A% (210 nm) product **14** after 15 h at 100 °C. Upon aq workup (as for (**10**)), filtration, and drying at 40 °C under high vacuum, 1.0 g (80%) of **14** was obtained as pale-yellow solid. HPLC (Method A): R_t 3.25 min, 99.4 A% (210 nm). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (dd, 1H, J = 6.8, 8.0 Hz), 8.11 (dd, 1H, J = 6.8, 8.4 Hz), 8.22 (d, 1H, J = 8.4 Hz), 8.37 (d, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 119.3 (q, CF_3, J = 275.7 Hz), 124.2, 126.0, 129.6, 131.1, 136.2, 150.4, 151.4, 164.2. ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ 69.95. HR-MS: calculated for $C_9H_4F_3ClN_2$: 232.0015; found: 232.0027.

One-Pot Telescoping Examples. *4-Chloro-2-(3-pyridyl)-quinazoline (16).* To a solution of 2-amino-benzonitrile **15** (240 mg, 2 mmol) in sulfolane (2 mL) was added nicotinoyl chloride hydrochloride (550 mg, 3 mmol). After stirring in a 4-mL septum vial at 100 °C overnight, HPLC showed full conversion of the aminonitrile (R_t 2.03 min) to an intermediate (R_t 1.66 min). Phosphorus pentachloride (730 mg, 3.5 mmol) was added in one portion, and stirring was continued at 100 °C until HPLC showed full conversion of the intermediate (∼10 h). After the usual workup (*vide supra*, **10**), and FC (heptane/EtOAc), 400 mg (83%) yield of **16** was obtained as a slightly tan solid. HPLC (Method A): R_t 2.45 min, 99.5A% (254 nm). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (dd, 1H, J = 4.8, 8.0 Hz), 7.69 (td, 1H, J = 1.2, 6.8, 8.4 Hz), 7.95 (td, 1H, J = 1.2, 6.8, 8.4 Hz), 8.09 (d, 1H, J = 8.4 Hz), 8.25 (d, 1H, J = 8.4 Hz), 8.74 (d, 1H, J = 4.8 Hz), 8.81 (dt, J = 1.2, 1.2, 8.0 Hz), 9.76 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 122.7, 123.4, 125.9, 128.8, 129.0, 132.3, 135.1, 135.9, 150.3, 151.65, 151.7, 158.2, 162.8. HR-MS: calculated for $C_{13}H_8ClN_3$: 241.0406; found: 241.0372.

4-Chloro-2-phenylpyrido[2,3-d]pyrimidine (18). To a solution of 2-amino-nicotine-nitrile **17** (500 mg, 4.19 mmol) in sulfolane (5 mL) was added benzoyl chloride (1.0 mL, 8.8 mmol). After stirring at 90−95 °C in a 20-mL septum vial for 72 h, LC−MS showed full conversion of the aminonitrile to an intermediate. The mixture was cooled to 45 °C before the volume was adjusted to 10 mL by addition of sulfolane. Phosphorus pentachloride (1.53 g, 7.53 mmol) was added in one portion, and stirring was continued at 100 °C until HPLC showed full conversion of the intermediate (∼12 h). After the usual workup (*vide supra*, **10**), the yellow wetcake obtained was dried overnight (vacuum oven, 45 °C), the crude product (1.2 g, >100%, HPLC: 80 A% [210 nm]) was purified by FC (heptane/EtOAc) to give 0.75 g (74%) of **18** as an off-white solid. HPLC (Method A): R_t 3.20 min, 98.8 A% (254 nm). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (m, 2H), 7.52 (m, 1H), 7.60 (dd, 1H, J = 4.4, 8.4 Hz), 8.57 (dd, 1H, J = 8.4, 2.0 Hz), 8.69 (m, 2H), 9.26 (dd, 1H, J = 2.0, 4.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 117.7, 123.6, 128.7, 129.4, 132.1, 135.3, 135.8, 158.7, 159.6, 163.1, 163.4. HR-MS: calculated for $C_{13}H_8ClN_3$: 241.0407; found: 241.0409.

2-Phenylpyrido[2,3-d]pyrimidin-4-amine (20). To a suspension of 2-benzoylamino-nicotine-nitrile **19** (1 g, 4.47 mmol, HPLC: R_t 2.12 min) in sulfolane (10 mL) was added phosphorus pentachloride (0.94 g, 4.47 mmol) in one portion, and the mixture was stirred overnight in a 20-mL septum vial at 100 °C. After 19 h, HPLC showed full conversion, clear-yellow solution, 96.7 A%, R_t 3.18 min (chloropyrimidine). This solution was cooled to 40 °C and added slowly under vigorous stirring into cold, aq conc. ammonia (20 equiv, open Erlenmeyer flask), such that the temperature stayed below 20 °C (ice cooling). After completed addition, the ice bath was removed, and the creamy suspension was warmed up to rt. Acetonitrile (10 mL) was added, and the suspension was stirred at 50 °C, until a reddish, clear solution formed (∼1 h). HPLC showed complete and clean conversion of the intermediate chloropyrimidine, 96.9 A%, R_t 1.79 min, LC−MS: [MH^+] = 223. The solution was cooled in an icebath, and the precipitated solid was filtered off and dried under vacuum to give **20** (0.9 g, 91%) as a slightly tan solid, HPLC (Method A): 98.3 A%, R_t 1.82 min [210 nm]. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.52 (dd, 1H, J = 4.4, 8.4 Hz), 7.54 (m, 3H), 8.19 (br s, 2H), 8.52 (m, 2H), 8.74 (dd, 1H, J = 8.4, 2.0 Hz), 9.03 (dd, 1H, J = 2.0, 4.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 107.9, 120.7, 128.1, 128.2, 130.5, 133.2, 138.2, 156.1, 159.4, 162.9, 163.4. HR-MS: calculated for $C_{13}H_9N_4$: 222.0906; found: 222.0902.

2-tert-Butyl-4-morpholinoquinazoline (21). To a suspension of 2-aminobenzonitrile **15** (1.54 g, 13.03 mmol, HPLC (Method A): R_t 2.0 min) in sulfolane (5 mL) was added pivaloyl chloride (1.92 mL, 15.64 mmol), and the mixture was stirred for 48 h at 75 °C in a 20-mL septum vial; HPLC showed 100% conversion at this point, mainly to the piv-amide (R_t 2.45 min), with some chloropyrimidine already present (R_t 4.0 min) also. The amber solution was cooled to room temperature and diluted with sulfolane (7 mL). Phosphorus pentachloride (4.1 g, 19.5 mmol) was added, and the suspension was stirred at 110 °C for 12 h, before more phosphorus pentachloride (0.54 g, 2.6 mmol) was added, and stirring was continued at 110 °C for 7 h. After cooling to room temp., HPLC showed 93% conversion of the intermediate amide; 78.6 A% chloropyrimidine (R_t 4.0 min). The yellow, clear solution was slowly added to an ice-cold solution of morpholine (20 equiv) in acetonitrile (25 mL), such that the temperature stayed below 10 °C (exothermic). After completed addition, the amber, creamy suspension was stirred at room temp. for 1 h. HPLC showed complete conversion of the chloropyrimidine, 67.3 A%, R_t 2.28 min (product **21**). After dilution with ice water and extraction with EtOAc, the organic phases were washed with pH 7 phosphate buffer and water. Drying of the combined organic phases over sodium sulfate, evaporation, and FC of the crude material (63.8 A%) on SiO_2 (heptane/EtOAc, 10:1) gave **21** as a slightly yellowish, crystalline solid (1.7 g, 48% over three steps). HPLC (Method A) 95.1 A% (210 nm) R_t 2.25 min. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.39 (s, 9H), 3.70 (t, 4H), 3.80 (t, 4H), 7.49 (m, 1H), 7.78 (m, 1H), 7.80 (d, 1H), 7.98 (d, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 29.4, 38.9, 49.8, 65.9, 114.0, 124.8, 124.9, 128.2, 132.4, 151.6, 163.7, 170.8. HR-MS: calculated for $C_{16}H_{21}N_3O$: 271.1685; found: 271.1682.

Experimental Procedures for Azolo-4-chloropyrimidines. *4-Chloro-6-(4-nitrophenyl)-1-(2,2,2-trifluoroethyl)-1,2,3-triazolo-[4,5-d]-pyrimidine (4)*

(a) Lab Scale. To a stirred slurry of *N*-[4-cyano-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-yl]-4-nitro-benzamide **1**[6] (200 g,

589.57 mmol) in sulfolane (1200 mL) was added phosphorus pentachloride (491.09 g, 2.36 mol, 4 equiv) at 30 °C (addition slightly exothermic) under nitrogen. The mixture was vigorously stirred at 120 °C under a nitrogen atmosphere for 14 h (HPLC indicated complete conversion). The mixture was cooled to 55 °C and slowly quenched into cold water while maintaining the temperature between 20−30 °C. The solution was basified by addition of triethylamine under ice cooling, such that the temperature stayed below 25 °C (*at temperatures above 45*°C, *hydrolysis to the hydroxypyrimidine accelerates*). After further cooling to 18−20 °C, the precipitated solid was filtered off, washed with water, and dried under vacuum at 50 °C. Product **4** was thus obtained as an off-white solid (193 g, 90% assay-corrected yield), HPLC (Method A) 96.3 A% (220 nm) R_t 3.85 min. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.59 (q, 2H, $^3J_{H-F}$ = 8.8 Hz), 8.36 (d, 2H, J = 8.8 Hz), 8.65 (d, 2H, J = 8.8 Hz), 8.67 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 47.5 (CH_2, J_{C-F} = 35.2 Hz), 112.3, 123.5 (CF_3, J_{C-F} = 280.7 Hz), 123.9, 129.6, 134.7, 141.0, 149.2, 154.5, 154.9, 159.0. HR-MS: calculated for $C_{13}H_8F_3ClN_5O_2$: 358.0313; found: 358.0346.

(b) Kilolab Scale-Up. A 50-L Hastelloy reactor was charged with sulfolane (23.8 kg). Amide **1** (2.71 kg, 7.99 mol) and phosphorus pentachloride (3.512 kg, 16.0 mol, 2.0 equiv) were charged to the solvent by means of a split butterfly valve. The mixture was heated to 122 °C and held under agitation for a period of 5 h. The batch was cooled to 55 °C and sampled for reaction completion by HPLC. The batch was cooled to 50 °C and quenched by addition of *N*-methyl-2-pyrrolidone (16.7 kg) over a period of 30 min while maintaining the batch temperature in the range 46−54 °C. The reaction solution was then cooled to 13−14 °C, and USP water (21.6 kg) was added over a 1-h period while keeping the batch temperature between 14−20 °C. The reaction suspension was then neutralized to pH 7.6 with triethylamine (4.4 kg, 43.5 mol) over a period of 2.3 h. The mixture was stirred at 23 °C overnight (11 h). The product was isolated by filtration on a 16-in diameter filter nutsche. The reactor and cake were rinsed with water (13.9 kg). The solid was dried on the filter under a nitrogen stream. The water content in the filter cake was followed by KF titration to <0.5%. Yield: 2.727 kg of **4**, 86.6 wt % assay, (83.1% assay-corrected yield), 99.7 A% HPLC purity [220 nm]. Two more similar sized batches were run that gave 2.85 kg (80.1% assay-corrected yield, 99.4 A% HPLC), and 3.27 kg (85.1% assay-corrected yield, 99.6 A % HPLC) crude product, respectively. The three crude lots were combined and recrystallized from DMF/water (3:1) to give an overall yield of 6.981 kg of **4** (81.4% overall assay corrected yield, 100.4 wt % by assay and 99.8 A% HPLC purity).

3-Benzyl-7-chloro-5-(4-nitro-phenyl)-3H-[1,2,3]triazolo[4,5-d] pyrimidine (6). A solution of 5-amino-1-benzyl-1*H*-[1,2,3] triazole-4-carbonitrile **5**[16] (0.78 g, 3.9 mmol) and *p*-nitrobenzoyl chloride (0.76 g, 4.1 mmol) in sulfolane (10 mL) was stirred at 80 °C in a 10-mL septum vial until HPLC showed complete acylation (~2 h). Phosphorus pentachloride (1.6 g, 7.8 mmol) was added, and temperature raised to 95 °C. After HPLC showed completion of the ring closure (~2−3 h), the reaction mixture was cooled and worked up as for **4** to afford crude product (1.8 g, assay corrected yield: 76% over two steps). HPLC (Method B) 97.9 A% (220 nm) R_t 10.64 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.95 (s, 2H), 7.36 (dd, 2H), 7.36 (m, 1H), 7.52 (d, 2H), 8.37 (d, 2H, J = 8.8 Hz), 8.74 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.6, 123.9, 128.6, 129.1, 129.5, 130.2, 133.3, 133.8, 141.1, 150.0, 150.7, 154.3, 160.4. HR-MS: calculated for $C_{17}H_{11}ClN_6O_2$: 366.063; found: 366.071.

4-Chloro-2-(4-nitrophenyl)benzo[4,5]furo[3,2-d]pyrimidine (8). A solution of 3-aminobenzofuran-2-carbonitrile **7**[17] (R_t 5.2 min) (0.64 g, 4.0 mmol) in sulfolane (15 mL) was treated with *p*-nitrobenzoyl chloride (0.82 g, 4.4 mmol) at ambient temperature (25−30 °C) resulting in formation of thick suspension. After disappearance of the starting material as judged by HPLC (amide, R_t 7.2 min), phosphorus pentachloride (1.7 g, 8.1 mmol) was added, and temperature raised to 95 °C. After stirring for 2 h, the reaction mixture was cooled and worked up as for **4** to afford crude product (0.64 g, assay-corrected yield: 49% over two steps). HPLC (Method B) 92.5 A% (220 nm) R_t 12.1 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (m, 1H, J = 1.2, 6.8, 7.8 Hz), 7.75 (dd, 1H, J = 1.2, 7.8 Hz), 7.78 (m, 1H, J = 1.2, 6.8, 7.8 Hz), 8.31 (dd, 1H, J = 1.2, 7.8 Hz), 8.35 (d, 2H, J = 9.0 Hz), 8.74 (d, 2H, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 113.2, 121.6, 122.9, 123.8, 125.0, 129.3, 132.8, 142.3, 142.8, 143.5, 149.2, 152.1, 157.8, 158.6. HR-MS: calculated for $C_{16}H_8ClN_3O_3$: 325.0254; found: 325.0252.

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DEDICATION

Dedicated to Dr. Michael Kolb, former Vice President Wyeth Research, Pearl River, NY, on the occasion of his 65th birthday.

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