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Solvent-Free or Low-Solvent Large-Scale Preparation of Chloropyrimidine and Analogues

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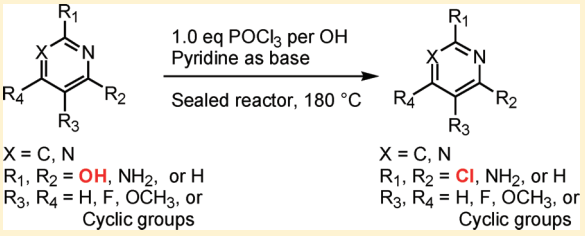
Supporting Information

ABSTRACT: Chloropyrimidine or other N-containing aromatic heterocyclic analogues can be efficiently prepared from the corresponding hydroxylated precursors under solvent-free or low-solvent conditions with equimolar or less chlorinating reagents. This high-yielding protocol allows successful preparations of multigram and kilogram batches of these important synthetic intermediates.



Pyrimidines are important functional groups in nature with their presence in nucleic acids and cofactors. It is not surprising that many pharmaceutical and agricultural chemicals contain pyrimidine moieties or analogous N-containing aromatic ring structures in order to mimic natural substances or act as inhibitors or promoters of biological processes. Therefore, chlorinated pyrimidine compounds are important synthetic intermediates (or starting materials) for the discovery and development of drugs, pesticides, and other biochemical reagents. Halogen substitution allows diverse further transformations such as reduction by catalytic hydrogenation, replacement with N-, O-, or S-containing nucleophiles, or C−C bond formations.

It has been known since the early 1900s that chloropyrimidines can be prepared from the corresponding hydroxyl precursors using $POCl_3$ or PCl_5 as the chlorinating reagents. These protocols used $POCl_3$ as solvent (i.e., in large excess to allow heating to maintain reflux) or with organic base such as the toxic *N*,*N*-dimethylaniline.[1,2] However, such a protocol is not environmentally ideal for large-scale production of chloropyrimidines. More recently, improvements in large-scale preparation of chloropyrimidines included the use of 0.1−2.0 equiv of trialkylamine hydrochloride and a reduced amount of $POCl_3$ (1:1.5 OH/$POCl_3$) or multiple steps of mixing reactants with 3.0 equiv of $POCl_3$ and 2.0 equiv of PCl_3.[3,4] The yields were over 80% in many cases. On other pyrimidine derivatives and nitrogen-containing aromatic moieties, analogous conversions of the hydroxyl precursors to chlorides are similarly achieved. Most of the transformations usually involve heating the hydroxyl compound in excess $POCl_3$. Therefore, they still suffer environmental drawbacks of dealing with excess reagents or solvents. In addition, some of the conversions have low yields of less than 50%[5−12] or occasionally less than 10%.[13] Selective examples related to this manuscript include the conversion of 2,4-dihydroxy-5-methoxypyrimidine,[14,15] 2-amino-4-hydroxypyrimidine,[16] 2,4-dihydroxy-5-fluoropyrimidine,[17,18] 2-hydroxypyridine,[5,19] xanthine,[6,7] 2,4-dihydroxyquinazoline,[20,21] and hydroxyl pyridopyrimidines[8−13,22,23] (for compounds with many references, only those reporting similar reaction scales to ours and reporting isolated yields are cited).

We sought to improve the transformation for large-scale preparation by developing a more environmentally friendly protocol that reduces or eliminates the use of solvent, either during the conversion or at the workup stage. We were encouraged by the fact that relatively low molar ratios of $POCl_3$ to OH were sufficient to produce desired pyrimidine products in good yields. We reasoned that the use of stoichiometric or substoichiometric amounts of $POCl_3$ would reduce waste, and at the same time the reaction conditions needed to be strong enough to promote high yielding conversion. We therefore decided to explore heating in a sealed environment so that we can use higher temperatures than those typically used for reflux conditions.

Our initial tests of conditions were conducted with 2,4-dihydroxypyrimidine, as shown in Table 1, at 10 mmol scale. The main variables in these tests were the ratio of chlorinating reagent to hydroxyl group and the base used in the reaction. All bases were used at 1 equiv per substrate (rather than per OH) partly because of the need to maintain mixing consistencies among different trials. The reagents were mixed in a Teflon-lined stainless steel reactor, sealed, stirred, and heated to 180 °C for 2 h. Because it was inconvenient to monitor reaction progress using traditional analytical methods that required opening of the reactor, we found that pressure change was a good indicator for us to follow, which also served as a safety indicator. The maximum pressure generated inside the reactor was generally

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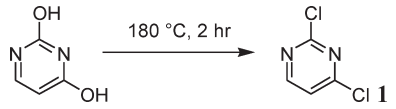
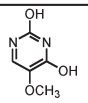
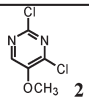
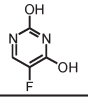
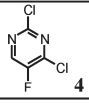
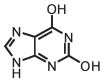
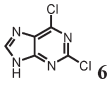
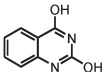
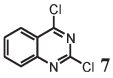
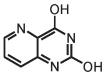
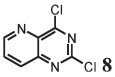
Table 1. Testing Conditions with 2,4-Dihydroxypyrimidine



1

entry	molar ratio of chlorinating reagents to OH	base used, at 1 equiv per substrate	yield (%)
1	$POCl_3$, 1 equiv	Et_3N	78
2	$POCl_3$, 1 equiv	pyridine	95
3	$POCl_3$, 1 equiv	3,5-lutidine	63
4	$POCl_3$, 0.5 equiv + PCl_5, 0.5 equiv	pyridine	83
5	PCl_5, 1 equiv	pyridine	32
6	$POCl_3$ 0.25 equiv + PCl_5 0.25 equiv	pyridine	75

Table 2. Expanding Application to Other Pyrimidine Analogues and N-Containing Aromatic Moieties[a]

Entry	Starting Material	Scale	Reagent ratio to OH	Product	Yield	Purity (HPLC)	Lit. Yield (scale) and conditions
1		180 g 1.3 mole	$POCl_3$ 1 eq	 **2**	92%	98%	90 – 95% (71 g) $POCl_3$ 2 – 5 eq[15]
2		180 g 1.3 mole	$POCl_3$ 0.5 eq + PCl_5 0.5 eq		78%	98%	
3		180 g 1.3 mole	$POCl_3$ 0.25 eq + PCl_5 0.25 eq		62%	98%	
4		12 Kg 84.5 mole	$POCl_3$ 1 eq		92%	97.5%	
5		33 g 0.3 mole	$POCl_3$ 1 eq	 **3**	95%	93.5%	70% (no scale given) $POCl_3$ as solvent[16] 92% (100 g) $POCl_3$ 2 eq, $ClSO_3H$ as solvent[24]
6		195 g 1.5 mole	$POCl_3$ 1 eq	 **4**	93%	99%	90% (104 g) $POCl_3$ as solvent[17] 95% (111 g) $POCl_3$ as solvent[18]
7		119 g 1.3 mole	$POCl_3$ 1 eq	 **5**	90%	96.8%	43% (using NCS, PPh_3, no scale given)[5] 64% (using PCl_5)[19]
8[b]		188 g 1.3 mole	$POCl_3$ 1 eq	 **6**	88%	94.5%	47 – 52% (6 g) $POCl_3$ at 10 eq as solvent[6] 43% (8 g) $POCl_3$ as solvent[7]
9[c]		203 g 1.3 mole	$POCl_3$ 1 eq	 **7**	94%	95%	88% (200 g) $POCl_3$ 1.2 eq, toluene as solvent[20]
10		49 g 0.3 mole	$POCl_3$ 1 eq	 **8**	94.5%	95%	58% (1 g) $POCl_3$ as solvent, PCl_5 4 eq[22]

[a] All reactions were carried out with 1 equiv of pyridine per substrate at 180 °C for 2 h in sealed reactors (100 mL and 1 L Teflon-lined stainless steel reactors or 50 L ceramic reactor depending on reaction scales). [b] Reaction time was 3 h. [c] Reaction was carried out at 150 °C for 2 h under nitrogen.

less than 0.15 MPa. The reaction time of 2 h was guided by the pressure inside the reactor, which dropped to ~0.02 MPa.

As listed in Table 1, it is gratifying to observe that with an equimolar amount of $POCl_3$ and pyridine as base, a 95% yield can be achieved (entry 2). Using 0.5 equiv of $POCl_3$ and 0.5 equiv of PCl_5 also produced respectable results (83%, entry 4). More interestingly, even with 0.25 equiv of $POCl_3$ and 0.25 equiv of PCl_5, a yield of 75% was achieved (entry 6), indicating that under these conditions, each molecule of $POCl_3$ or PCl_5 can efficiently utilize more than one chlorine atom for chlorination of hydroxypyrimidine. Encouraged by these initial test results, we ran the same transformation on a larger scale with 2.0 mol of 2,4-dihydroxypyrimidine (224 g), 4.0 mol of $POCl_3$, and 2.0 mol of pyridine in a 1 L Teflon-lined stainless steel reactor. 2,4-Dichloropyrimidine was isolated in 91% yield with 98.5% purity (by HPLC) after distillation under vacuum (85−88 °C/10 mmHg).

With the protocol successfully applied to the preparation of 2,4-dichloropyrimidine, we expanded the protocol for large-scale preparation of other pyrimidine analogues and N-containing

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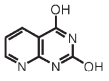
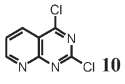
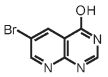
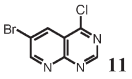
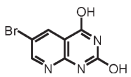
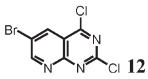
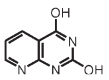
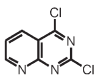
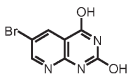
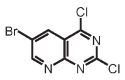
Table 3. Conversion of Hydroxypyrido[2,3-*d*]pyrimidines with Low Solvent Assistance[a]

Entry	Starting Material	Scale	Solvent and base per substrate	Reaction time	Product	Yield	Purity (HPLC)	Lit. Yield (scale)
1		187 g 1.3 mole	Toluene 95 mL (0.9 mole) Pyridine 1 eq	5 h	 **9**	73%	97.5%	17% (0.5 g)[8] 53% (10 g)[23] 7.6% (3 g)[13] 43.7% (20 g)[9]
2		207 g 1.3 mole	Toluene 180 mL (1.7 mole) Pyridine 1 eq	9 h	 **10**	75%	98%	40% (6.5 g)[10] 20% (no scale given)[11] 85.5% (20 g)[9] 35% (1 g)[12]
3		170 g 0.75 mole	Toluene 80 mL (0.75 mole) Pyridine 1 eq	2 h	 **11**	72%	96.5%	No report
4		182 g 0.75 mole	Toluene 90 mL (0.85 mole) Pyridine 1 eq	9 h	 **12**	76%	98%	No report
5		49 g 0.3 mole	Toluene 30 mL (0.3 mole) Et_3N 1 eq	2 h		25%[b]	Not analyzed	
6		73 g 0.3 mole	Toluene 30 mL (0.3 mole) Et_3N 1 eq	2 h		28%[b]	Not analyzed	

[a] All reactions were carried out at 180 °C in sealed reactors with 1 equiv of $POCl_3$ per OH. [b] Isolated yield after chromatography.

aromatic heterocycles. The results are summarized in Table 2 and compared to representative literature reported cases for which the reagents and reaction scales are as close to ours as possible.

As shown in Table 2, for pyrimidine starting materials (entries 1, 4−6), our procedure produced good yields at around 0.3−1.5 mol scale (33−195 g) with an equimolar ratio of $POCl_3$ per OH group. Extending beyond pyrimidines (entries 7−10), the procedure can be applied to pyridine, purine, quinazoline, and pyrido[3,2-*d*]pyrimidine rings. It is worth noting that while under these conditions chlorination worked well for 2-hydroxypyridine, it did not work for 4-hydroxypyridine for which a black tar was formed upon mixing reagents. In addition, using pressure as a guide, we were able to adjust reaction conditions to suit the individual substrate and obtain good results (entries 8 and 9). Because on a 100 g scale this procedure did not generate excessive pressure, we were able to adapt the protocol for a 12 kg scale preparation (entry 4). Again, only 0.12 MPa of pressure was reached during heating, and this was safely operated with a 50 L ceramic reactor and gave satisfactory results for conversion of 2,4-dihydroxy-5-methoxypyrimidine. Compared to literature reported results, overall in the pyrimidine analogues, our protocol produced comparable yields to methods that used excess $POCl_3$. For cases outside the pyrimidines, our methods showed significant improvements in yields with pyridine, xanthine, and pyrido[3,2-*d*]pyrimidine cases (Table 2, entries 7, 8, and 10).

While the above procedure worked well for pyrido[3,2-*d*]pyrimidine, direct adaptation of the solvent-free and equimolar $POCl_3$ protocol did not yield satisfactory results with pyrido[2,3-*d*]pyrimidine.[8−10,12,13,23] Instead, upon reaction completion (indicated by pressure drop to a constant level), multiple products were formed as revealed by TLC analysis. We reasoned that a small amount of stable and low vapor pressure solvent will dilute the mixed sample and may help maintain even mixing during the reaction. Therefore, we modified our protocol by adding 0.7−1.3 equiv of toluene per pyridopyrimidine substrate to facilitate sample mixing and dilution. In doing so, a longer reaction time was sometimes necessary to allow the pressure to drop to stable low levels for reaction completion. Overall, this modification allowed the preparation of chloropyrido[2,3-*d*]pyrimidines in ∼70% yields after quenching, filtration, and drying (Table 3, entries 1−4), which were improvements to literature-reported methods[8,10,12,13,23,24] except in one case compared to a 1955 report.[9] In addition, we investigated if pyridine was a better choice of base by comparing reactions with Et_3N (entries 5 and 6). In both cases with Et_3N, isolation of the desired chlorinated products required chromatography and was of low yield. At the same time, ^1H NMR and MS indicated a major byproduct with monodiethylamino substitution in each case. This was presumably due to nucleophilic substitution of one chlorine atom by Et_3N followed by elimination under the strong reaction conditions. As a consequence, the overall yield of the desired product was lower.

In summary, we developed a solvent-free or low-solvent protocol for chlorination of hydroxypyrimidines and other similar N-containing aromatic heterocycles. Reasonable to very good yields were obtained for many different kind of starting materials, at tens of grams to 12 kg scales. The workup and purification process also limited the use of solvents, therefore making this procedure more friendly to the environment and suitable for routine production of a variety of important chlorinated synthetic intermediates with pyrimidine and analogous moieties.

■ EXPERIMENTAL SECTION

HPLC was performed with a C_{18} reversed-phase column (5 μm, 4.6 by 250 mm) and monitored at 230 nm with aqueous TFA and CH_3CN gradients. NMR was recorded at 400 MHz for ^1H and 100 MHz for ^{13}C. Known compounds were positively identified with MS and satisfactory changes in ^1H or ^{13}C NMR from starting materials and compared to

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literature reports. New compounds were fully characterized with ^{1}H and ^{13}C NMR and MS.

Caution: The safety parameters of the reaction protocols were not systematically evaluated. Please exercise extreme caution and use proper protective gear when operating with sealed reactors at high temperature.

2,4-Dichloropyrimidine (1). To a 1 L Teflon-lined stainless steel reactor was added 161 mL of pyridine (2.0 mol) and 224 g of 2,4-dihydroxypyrimidine (2.0 mol). With stirring, 360 mL of $POCl_3$ (4.0 mol) was added. The reactor was sealed and heated to maintain at 180 °C for 2 h during which time the pressure inside rose to a maximum of 0.12 MPa and then dropped to 0.02 MPa. After being cooled to rt, the reaction mixture was poured into 600 mL of cold water (0−5 °C) with stirring. The resulting oil was extracted into 1 L of ethyl acetate, which was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resulting oil was distilled under vacuum (85−88 °C/10 mmHg) to give 272 g of desired product (91%): purity 98.5% (HPLC, 230 nm); MS (EI, *m*/*e*) 147.9 (100), 149.9 (64), 151.9 (10). Spectroscopic data matched literature reported data: ^{1}H NMR.[25]

2, 4-Dichloro-5-fluoropyrimidine (4): reaction scale 1.5 mol, product was obtained as oil after removal of extraction solvent; yield 233 g (93%); purity 99% (by HPLC, wavelength 230 nm); MS (EI, *m*/*e*) 165.7 (100), 167.8 (64). Spectroscopic data matched literature reported data: ^{1}H and ^{19}F NMR.[26]

Note: product extraction with organic solvent is not always required. After quenching, one could directly separate the oily organic phase from the aqueous phase and proceed to distillation after washing and drying. This no-extraction protocol was used in our preparation of 2-chloropyridine with good results (Table 2). **2-Chloropyridine (5):** reaction scale 1.3 mol; yield 127.5 g (90%, distillation 165 − 173 °C); purity 96.8% (by HPLC, wavelength 230 nm). Spectroscopic data matched literature reported data: ^{1}H NMR and MS.[27,28]

2,4-Dichloro-5-methoxypyrimidine (2). To a 50 L ceramic reactor was first added 6.8 L of pyridine (84.5 mol), followed by 12 kg (84.5 mol) of 2,4-dihydroxy-5-methoxypyrimidine. Then 16.5 L of $POCl_3$ (169 mol) was slowly added over 15−20 min with stirring, during which time the temperature of the mixture rose slightly from rt (from 25−30 °C to ∼35 °C). This small temperature rise may be partly due to water content of the 2,4-dihydroxy-5-methoxypyrimidine sample. At this stage, the reaction components were still a mixture of solid and liquid. The reactor was sealed and heated to reach an inside temperature of 180 °C in 30−40 min; at this time, the pressure inside the reactor reached its highest point of 0.12 MPa. After 30 min, the pressure inside dropped to 0.09 MPa. The reaction was maintained at 180 °C for 2 h, and the pressure dropped to 0.02 MPa. After cooling to rt, there was no excess pressure inside and the reactor was opened. The resulting reaction mixture existed as a slightly yellow liquid. It was poured into 20 L of cold water (0−5 °C) within 10 min with stirring. No significant heat release was observed during quenching. The resulting white crystalline solid was collected by filtration and washed with small amount (∼500 mL) of 1:1 petroleum ether:ethyl acetate. This afforded 13.9 kg (92%) of product after drying: purity 97.5% (by HPLC, wavelength 230 nm); mp 68−70 °C (lit.[15] mp 67−68 °C). Spectroscopic data matched literature reported data: ^{1}H NMR[29] and MS.[30]

2-Amino-4-chloropyrimidine (3): reaction scale 0.3 mol; yield 37 g (95%); purity 96.5% (by HPLC, wavelength 230 nm); mp 156−158 °C (lit.[31] mp 155−156 °C). Spectroscopic data matched literature reported data: ^{1}H NMR[31] and MS.[31]

2,6-Dichloro-9*H*-purine (6): reaction scale 1.3 mol, 3 h reaction; yield 206 g (88%); purity 94.5% (HPLC 230 nm); MS (EI, *m*/*e*) 187.9 (100), 189.9 (64), 191.9 (10); mp 176−178 °C (lit.[7] mp 181 °C dec). Spectroscopic data matched literature reported data: ^{1}H NMR.[32]

2,4-Dichloroquinazoline (7). The reaction was carried out at 150 °C for 2 h under nitrogen: reaction scale 1.3 mol; yield 232 g (94%); purity 95% (by HPLC, wavelength 230 nm); mp 118−120 °C (lit.[20] 118−120 °C); MS (EI, *m*/*e*) 197.9 (100), 199.9 (64). Spectroscopic data matched literature reported data: ^{1}H NMR.[33]

2,4-Dichloropyrido[3,2-*d*]pyrimidine (8): reaction scale 0.3 mol; yield 56.7 g (94.5%); purity 95% (HPLC 230 nm); mp 165−167 °C (lit.[22] 168−169 °C); MS (EI, *m*/*e*) 198.6 (100), 200.5 (64). Spectroscopic data (^{1}H and ^{13}C NMR in DMSO-d_6) matched literature reported data in DMSO-d_6[34] and $CDCl_3$.[22]

6-Bromo-4-chloropyrido[2,3-*d*]pyrimidine (11). To a 500 mL Teflon-lined stainless steel reactor was added 80 mL of toluene, followed by 60 mL of pyridine (0.75 mol) and 170 g of 6-bromo-pyrido[2,3-*d*]pyrimidin-4-ol (0.75 mol). Then 73 mL of $POCl_3$ (0.75 mol) was added with stirring. The reactor was sealed and heated to 180 °C, and the pressure reached 0.14 MPa. After 1 h, the pressure dropped to 0.09 MPa. Heating was stopped after 2 h while the pressure was 0.03 MPa. After cooling, the reaction mixture was poured into 500 mL of cold water and gave a light yellow crystalline solid. The product was collected by filtration, washed with 20 mL of toluene, and dried: yield 132 g (72%); purity 96.5% (HPLC, 230 nm); mp 152−154 °C; ^{1}H NMR ($CDCl_3$, δ, ppm) 9.33 (overlap, 2H), 8.80 (d, 1H); ^{13}C NMR ($CDCl_3$, δ, ppm) 162.2, 160.2, 157.10, 136.4, 120.6, 120.2; HRMS *m*/*e* 242.8932 $[M]^+$ (calcd for $C_7H_3BrClN_3$, 242.9919); MS (EI, *m*/*e*) 244.9 (100), 242.9 (84), 246.9 (25).

6-Bromo-2,4-dichloropyrido[2,3-*d*]pyrimidine (12): reaction scale 0.75 mol with 9 h reaction time; yield 159 g (76%); purity 98% (HPLC, 230 nm); mp 176−177 °C; ^{1}H NMR ($CDCl_3$, δ, ppm) 9.32 (d, 1H), 8.77 (d, 1H); ^{13}C NMR ($CDCl_3$, δ, ppm) 163.5, 161.1, 159.1, 157.9, 136.6, 120.6, 118.6; HRMS *m*/*e* 276.8783 $[M]^+$ (calcd for $C_7H_2BrCl_2N_3$, 276.8809); MS (EI, *m*/*e*) 278.9 (100), 276.9 (67), 280.9 (46).

4-Chloropyrido[2,3-*d*]pyrimidine (9): reaction scale 1.3 mol with 5 h reaction time; yield 153 g (73%); purity 97.5% (by HPLC, wavelength 230 nm); mp 145−147.5 °C (lit.[23] mp 240 °C, lit.[9] mp 137 °C dec); MS (EI, *m*/*e*) 165.0 (100), 167.0 (32). Spectroscopic data matched literature reported data: ^{1}H NMR.[13,23]

2,4-Dichloropyrido[2,3-*d*]pyrimidine (10): reaction scale 1.3 mol with 9 h reaction time; yield 190 g (75%); purity 98% (by HPLC, wavelength 230 nm); mp 154−156 °C (lit.[9] mp 157−158 °C); ^{1}H NMR ($CDCl_3$, δ, ppm) 9.3 (br, s, 1H), 8.66 (dd, 1H), 7.75 (dd, 2H); ^{13}C NMR ($CDCl_3$, δ, ppm) 164.7, 159.8, 159.6, 159.0, 135.5, 124.7, 117.9; HRMS *m*/*e* 198.8998 $[M]^+$ (calcd for $C_7H_3Cl_2N_3$, 198.9704); MS (EI, *m*/*e*) 198.87 (100), 200.87 (64).

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra of new compounds or known compounds with no previous report of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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