Facile Synthesis of 2,4-Diamino-6-alkyl- or 6-Aryl-Pyrimidine Derivatives

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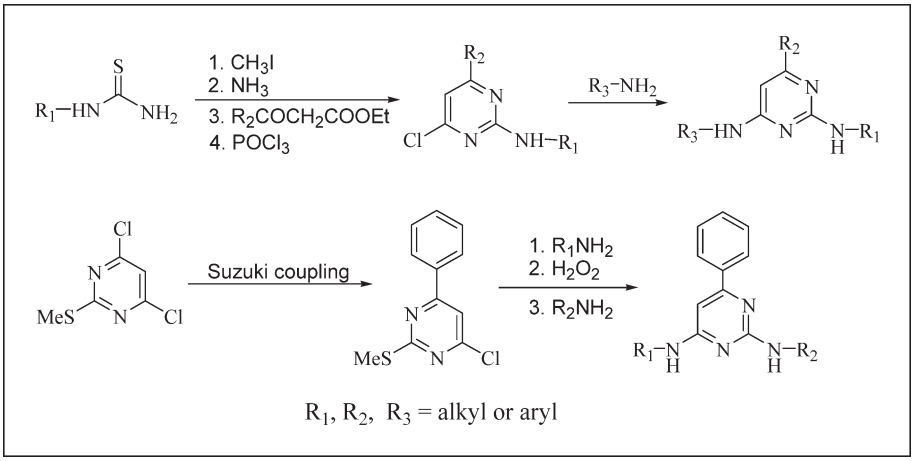

Facile methods were developed to prepare a series of 6-phenyl and 6-alkyl-2,4-diaminopyrimidine derivatives. The pyrimidine ring of the final products was constructed by treatment of a 1,3-dicarbonyl derivative with an amidine or guanidine. The 6-phenyl-pyrimidine derivatives were also prepared by Suzuki coupling reaction, using 2-methylthio-4,6-dichloropyrimidine as the starting material.

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INTRODUCTION

As part of our efforts in search of malaria prophylactic and/or therapeutic agents, a series of imidazolidinedione (IZ) derivatives was found to possess profound activity against liver stage malarias in rodent and nonhuman primate models [1–4]. Subsequently, the IZ compounds were found to metabolize to *s*-triazine derivatives in microsomal preparations and in rodents [4]. Active in mice tests, the *s*-triazines were considered the active metabolite of the IZ compounds. This finding prompted us to develop methods to prepare a series of *N,N′*-di-substituted 2,4-diamino-1,3,5-triazines and 2,4-diamino-pyrimidine derivatives as potential antimalarial agents. This report focused on the method development for the synthesis of the latter class of compounds.

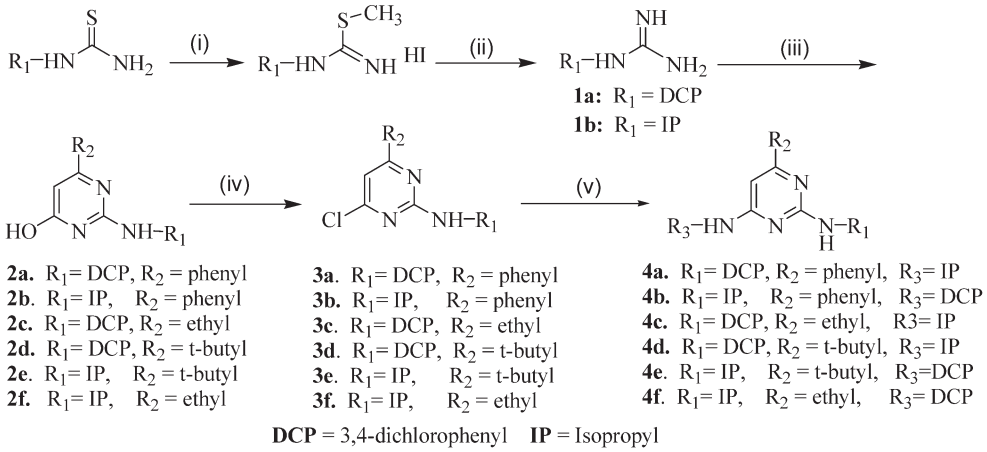
Polyamino-pyrimidines play a very important role in biological and pharmaceutical chemistry. A number of applications as therapeutic agents have been documented [5]. The most general method for the synthesis of 2,4,6-trisubstituted pyrimidines involves the treatment of two essential starting materials, a 1,3-dicarbonyl component and a N—C—N fragment such as urea, amidine, or guanidine [6,7]. The other method involved Suzuki coupling or Grignard reactions to insert various aryl or alkyl groups into 2,4,6-trichloropyrimidine [8] followed by stepwise amination with appropriate amines.

In this study, facile methods were developed to prepare substituted 6-alkyl or 6-aryl-2,4-diaminopyrimidines.

RESULTS AND DISCUSSION

Methods were developed to prepare substituted 6-alkyl or 6-arylpyrimidine-2,4-diamines. The pyrimidine ring of the desired products was constructed by condensation of a 1,3-dicarbonyl component with an amidine, isopropylguanidine, or 3,4-dichloroguanidine as shown in Scheme 1. The hydroxypyrimidines (**2a–f**) obtained were converted to the corresponding chloropyrimidines (**3a–f**) in high yields with phosphorus oxychloride [9–11]. The amination of chloropyrimidine derivatives was achieved via acid- or base-mediated nucleophilic substitution [12]. Hartung et al. reported that the chloro group of chloropyrimindines can be easily displaced with an aromatic amine under acidic conditions, but it can only be displaced by an aliphatic amino group under basic

Scheme 1. Synthesis of 6-phenyl or alkyl-2,4-diaminopyrimidine derivatives.

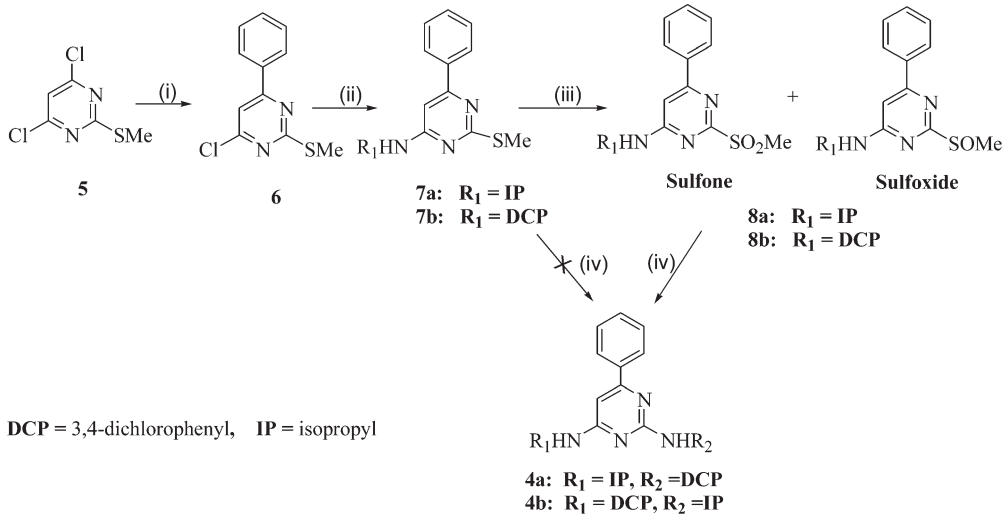


Reagents and Conditions: (i) CH_3I, acetone, reflux; (ii) NH_3, EtOH, 100 °C; (iii) R_2COCH_2COOEt, DMF, 100 °C, 48hr; (iv) $POCl_3$; (v) R_3NH_2, 110 °C.

conditions [12]. The method was adapted to insert the 3, 4-dichloroanilino, and the isopropylamino groups into the pyrimidine ring in high yield under the acidic and basic conditions, respectively (Scheme 1). Likewise, 4-alkyl analogs **4c–f** were prepared using ethyl propionylacetate or ethyl pivaloylacetate as 1,3-dicarbonyl component.

The Suzuki coupling method was an alternative approach used to make the 2,4-diamino-6-phenylpyrimidine derivatives (**4a** and **4b**) (Scheme 2). Initially, the Suzuki coupling reaction was attempted using 2,4,6-trichloropyrimidine as the starting material to introduce a phenyl group at either the 4- or 6-position, followed by amination. However, the success of this approach depends on the relative reactivity of the 2- and 4-chloro groups toward amination reactions, allowing for insertion of an amino group selectively to either 2- or 4-position of the pyrimidine ring. Although the Suzuki reaction of 2,4,6-trichloropyrimidine gave a good yield of 2,4-dichloro-6-phenyl-pyrimidine, the followed up

Scheme 2. Method involved Suzuki reaction on 4,6-dichloro-2-methylthiopyrimidine.



Reagents and Conditions: (i) $C_6H_5B(OH)_2$, $Pd(OAC)_2II$, TPP, Na_2CO_3, Glyme, reflux, 18h; (ii) R_1NH_2, 1-butanol, reflux, 6h; (iii) 30% H_2O_2, $NaWO_4$, EtOAc/toluene (1:1 v/v), 0 °C for 30 min then RT for 2h; (iv) R_2NH_2, neat, 140 °C, 2h.

amination gave a mixture consisting almost equal amount of 2-amino- and 4-aminopyrimidine derivatives. The low selectivity of 2,4-dichloro-6-phenyl-pyrimidine in the amination reaction led us to use 4,6-dichloro-2-methylthio-pyrimidine as the starting material. On treatment with phenylboronic acid in the presence of triphenylphosphine and palladium acetate, 4,6-dichloro-2-methylthio-pyrimidine (**5**) gave 4-chloro-2-methylthio-6-phenylpyrimidine (**6**) in very high yield. The first amination of compound **6** gave intermediate **7a** or **7b** readily, whereas the second amination on the 2-methylthio group failed to produce the desired products **4a** and **4b** [13–15]. Thus, oxidative activation of the 2-methylthio group in **7a** and **7b** was necessary before the amination reaction on the 2-position can be carried out. The oxidation was achieved by treatment of the 2-methylthiopyrimidine derivative with hydrogen peroxide under the catalysis of sodium tungstate dehydrate [14,15]. The mixture of sulfone and sulfoxide (**8**) formed was used without purification for further reactions with 3, 4-dichloroaniline or isopropylamine to give the products **4a** (11%) and **4b** (84%), respectively. The striking disparity in yields between **4a** and **4b** is, most likely, a result of difference in nucleophilicity of the two amines used.

The major difference between the two methods used in Scheme 1 (Method 1) and Scheme 2 (Method 2) to prepare compounds **4a** and **4b** is the order of introduction of 2-amino, 4-amino-, and 6-phenyl groups to the pyrimidine ring. The former method assembled the 2-amino and the 6-phenyl groups during the formation of the pyrimidine ring followed by insertion of the arylamino or alkylamino group at either 2- or 4-posion under the acidic or basic conditions, respectively. The overall yield of the Method 1 is good and the reaction conditions are mild. The latter method as described in Scheme 2 started from the commercially available starting material 4,6-dichloro-2-methylthio-pyrimidine. The 6-phenyl substituent was constructed first by the Suzuki coupling reaction followed by stepwise amination reactions to yield the substituted 2, 4-diamino-6-phenylpyrimidines **4a** or **4b**. The yield of the 2nd nucleophilic substitution reaction is good when alkylamines were used, but poor when aromatic amines were the nucleophiles.

In conclusion, the method described in Scheme 1 is superior to that of Scheme 2 for the preparation of the desired pyrimidine derivatives **4a-f**, with better yield, milder reaction conditions and cheaper reagents.

EXPERIMENTAL

Melting points were determined on a Mettler FP62 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed using HPTLC-HLF normal phase 150 microns silica gel plates (Analtech, Newark, DE). Visualization of the developed chromatogram was performed by UV absorbance, or spreading with aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using a Horizon HPFC System (Biotage, Charlottesville, VA) with Flash 25M or 40M cartridges (KP-Sil™ Silica, 32–63 μm, 60 Å). Preparative TLC was performed using silica gel GF Tapered Uniplates (Analtech, Newark, DE). ^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform, unless otherwise noted, on a Bruker Avance 300 spectrometer (Bruker Instruments, Wilmington, DE). Chemical shifts are reported in parts per million on the δ scale from an internal standard of tetramethylsilane. Combustion analyses were performed by Atlantic Microlab, (Norcross, GA). Where analyses are indicated by symbols of the elements, the analytical results obtained were within +/− 0.4% of the theoretical values.

2-(3,4-Dichlorophenylamino)-4-hydroxy-6-phenylpyrimidine (2a). Ethyl benzoylacetate (15 mL) was added dropwise to a suspension of 3,4-dichlorophenylguanidine (**1a**, 7.23g. 35.4 mmol) [2] in 100 mL of anhydrous DMF. The mixture was heated at 100°C for 48 h. After cooling, the reaction mixture was poured into 500 mL of ice water. The precipites were collected, washed with water, and dried to give 64% yield of compound **2a** as a pink solid. The product was used for further reactions without purification. ^{1}H NMR (CD_3OD): δ 8.24 (d, 1H, J = 2.4Hz), 8.00 (m, 2H), 7.57 (m, 2H), 7.47 (m, 3H), 6.45 (s, 1H). ms: m/z 331 (M^+).

4-Hydroxy-2-isopropylamino-6-phenylpyrimidine (2b). Ethyl benzoylacetate (11.7 mL) was added dropwise to a suspension of isopropylguanidine (**1b**) [2] (2.3 g, 22.7 mmol) in 50 mL of anhydrous DMF. The reaction mixture was heated at 100°C for 3 days. After cooling, the solution was poured into crushed ice water. The mixture was extracted with EtOAc three times and the EtOAc extracts were combined, washed with water, and brine successively, dried over Na_2SO_4 and evaporated to dryness in vacuole. The residue was applied to a silica gel flash column and eluted with 2.5% MeOH in $CHCl_3$ to give 35% yield of compound **2b** as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 2H, J = 3.6 Hz), 7.48 (m, 3H), 6.24 (s, 1H), 4.37 (m, 1H), 1.36 (d, 6H, J = 6.6 Hz). ms: m/z 229 (M^+).

2-(3,4-Dichlorophenylamino)-6-ethyl-4-hydroxy-pyrimidine (2c). Compound **2c** was prepared by the same method for the preparation of **2a**, using ethyl propionylacetate as starting material to yield 75% of **2c** as a white solid. ^{1}H NMR (CD_3OD) δ 8.06 (d, 1H, J = 2.2 Hz), 7.46 (dd, 1H, J = 2.2 Hz, 8.7 Hz), 7.42 (d, 1H, J = 8.7 Hz), 5.82 (s, 1H), 2.54 (q, 2H, J = 7.5 Hz), 1.25 (t, 3H, J = 7.5 Hz). ms: m/z 283 (M^+).

6-*t*-Butyl-2-(3,4-dichlorophenylamino)-4-hydroxy-pyrimidine (2d). The title compound was prepared by the same method as for the preparation of **2a**, using ethyl pivaloylacetate as starting material to yield 60% of **2d** as an off-white solid. ^{1}H NMR (CD_3OD): δ 8.22 (s, 1H), 7.41 (m, 2H), 5.93 (s, 1H), 1.28 (s, 9H). ms: m/z 311 (M^+).

6-*t*-Butyl-4-hydroxy-2-isopropylamino-pyrimidine (2e). Compound **2e** was prepared by the same method as for the preparation of **2b**, using ethyl pivaloylacetate as starting material to afford the product as a white solid (33% yield). ^{1}H NMR ($CDCl_3$): δ 5.73 (s, 1H), 4.17 (m, 1H), 1.21 (m, 15H). ms: m/z 209 (M^+).

6-Ethyl-4-hydroxy-2-isopropylamino-pyrimidine (2f). Compound **2f** was prepared by the same method as for the preparation of **2b**, using ethyl propionylacetate as starting material to give 31% yield of the desired product as a white solid. ^{1}H NMR ($CDCl_3$): δ 6.04 (s, 1H), 4.17 (m, 1H), 2.45 (q, 2H, J = 7.2 Hz), 1.25 (t, 3H, J = 7.2 Hz), 1.21 (d, 6H, J = 6.6 Hz). ms: m/z 181 (M^+).

4-Chloro-2-(3,4-dichlorophenylamino)-6-phenylpyrimidine (3a). 2-(3, 4-Dichlorophenylamino)-4-hydroxy-6-phenylpyrimidine (**2a**) in 100 mL of $POCl_3$ was stirred at room temperature overnight. The excess $POCl_3$ was removed under reduced pressure to give a gummy residue which solidified upon addition of excessive amount of crushed ice. The solid was purified by silica gel flash column chromatography, eluting with 10% EtOAc in hexane to afford the desired compound **3a** in 82% yield as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.07 (m, 3H), 7.56 (m, 3H), 7.46 (m, 1H), 7.42 (d, 1H, J = 8.7 Hz), 7.24 (s, 1H). ms: m/z 349 (M^+).

4-Chloro-2-isopropylamino-6-phenylpyrimidine (3b). The title compound was prepared by the same method for the preparation of **3a**, using hydroxyl intermediate **2b** as the starting material giving the desired 4-chloro product **3b** as light yellow oil in 47% yield. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 2H, J = 3.6 Hz), 7.48 (m, 3H), 6.97 (s, 1H), 4.28 (m, 1H), 1.27 (d, 6H, J = 6.5 Hz). ms: m/z 247 (M^+).

2-(3,4-Dichlorophenylamino)-4-chloro-6-ethylpyrimidine (3c). The title compound was prepared by the same method as for the preparation of **3a**, using compound **2c** as the starting material, to give 75% yield of the desired compound as off-white solid. ^{1}H NMR ($CDCl_3$,): δ 8.06 (s, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 6.70 (s, 1H), 2.70 (q, 2H, J = 7.5 Hz), 1.30 (t, 3H, J = 7.5 Hz). ms: m/z 301 (M^+).

6-*t*-Butyl-4-chloro-2-(3,4-dichlorophenylamino)-pyrimidine (3d). Compound **3d** was prepared by the same method as for the preparation of **3a**, using **2d** as the starting material to give 83% yield of the product as off-white solid. ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.38 (s, 2H), 6.83 (s, 1H), 1.38 (s, 9H). ms: m/z 329 (M^+).

6-*t*-Butyl-4-chloro-2-isopropylamino-pyrimidine (3e). Compound **3e** was prepared from **2e** using the same method as for the preparation of **3a**; giving 50% yield of the desired compound as white oil. ^{1}H NMR ($CDCl_3$): δ 6.55 (s, 1H), 4.97 (brs, 1H), 4.15 (m, 1H), 1.25 (m, 15H). ms: m/z 227 (M^+).

4-Chloro-6-ethyl-2-isopropylamino-pyrimidine (3f). Compound **3f** was prepared by the same method as for the preparation of **3a**, starting from **2f** to get the desired compound as white oil in 47% yield. ^{1}H NMR ($CDCl_3$): δ 6.44 (s, 1H), 5.04 (brs, 1H), 4.15 (m, 1H), 2.58 (q, 2H, J = 7.2 Hz), 1.25 (m, 9H). ms: m/z 199 (M^+).

2-(3,4-Dichlorophenylamino)-4-isopropylamino-6-phenylpyrimidine.HCl (4a)

Method 1. 4-Chloro-2-(3,4-dichlorophenylamino)-6-phenylpyrimidine (**3a**, 5g) in 100 mL of isopropylamine was heated in a sealed tube at 110°C overnight. Upon cooling, the reaction mixture was poured into ice water and the mixture was extracted with EtOAc three times. The EtOAc extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue was applied to a silica gel flash column and eluted with hexane: EtOAc (10:1, v/v) to give the desired product **4a** as light yellow solid in 90% yield, mp 277.6°C (decomposed). ^{1}H NMR ($CDCl_3$): δ 8.16 (br, 1H), 7.95 (m, 2H), 7.47 (m, 3H), 7.33 (d, 2H, J = 1.8 Hz), 7.00 (brs, 1H), 6.28 (s, 1H), 4.72 (s, 1H), 4.14 (m, 1H), 1.32 (d, 6H, J = 6.4Hz). ms: m/z 372 (M^+). *Anal*. calcd. for $C_{19}H_{18}Cl_2N_4$.HCl: C, 55.69; H, 4.67; N, 13.67; Cl, 25.96. Found: C, 55.80; H, 4.65; N, 13.66; Cl, 25.90.

Method 2. A mixture of sulfone/sulfoxide **8a** (2.0 g) and 3,4-dichloroaniline (3.34 mL, 3.0 equiv) was heated in a sealed tube at 140°C for 2 h. The mixture was cooled and the crude product was purified by a silica gel flash column, eluting with hexane/EtOAc (4:1 v/v) to give the desired compound **4a** in 11% yield. The NMR and MS spectra data are identical to compound **4a** prepared by method 1 as shown in Scheme 1.

4-(3,4-Dichlorophenylamino)-2-isopropylamino-6-phenylpyrimidine (4b)

Method 1. Concentrated hydrochloric acid (1.5 mL) was added to a solution of 4-chloro-2-isopropylamino-6-phenylpyrimidine (**3b**) (886 mg) and 3,4-dichloroaniline (815 mg, 1.5 equiv) in 15 mL of isopropanol. The reaction mixture was heated at 100°C overnight. The crude product was purified by silica gel flash column chromatography and eluted with 2.5% MeOH in CH_2Cl_2 to give the desired compound as an off-white solid, yield 97%, mp 79.7°C. ^{1}H NMR ($CDCl_3$): δ 7.93 (m, 3H), 7.43 (m, 2H), 7.37 (s, 1H), 7.28 (d, 1H, J = 2.6 Hz), 7.25 (d, 1H, J = 2.6 Hz), 6.48 (s, 1H), 6.36 (s, 1H), 4.98 (br, 1H), 4.25 (m, 1H), 1.32 (d, 6H, J = 6.4 Hz). ^{13}C NMR: ($CDCl_3$) δ 163.21, 161.89, 161.74, 141.51, 138.41, 131.35, 130.68, 130.27, 129.01, 126.74, 122.72, 120.45, 119.27, 92.51, 79.64, 42.77, 23.00. ms: m/z 374 (M^+). *Anal*. calcd. for $C_{19}H_{18}Cl_2N_4$.HCl: C, 55.69; H, 4.67; N, 13.67; Cl, 25.96. Found: C, 55.40; H, 4.62; N, 13.50; Cl, 25.69.

Method 2. The mixture of sulfone/sulfoxide **8b** (3.0g) and isopropylamine (6.21mL, 10.0 equiv) was heated in a sealed tube at 140°C for 20 min. The mixture was cooled and the crude product was purified by silica gel flash column chromatography and eluted with hexane/EtOAc (4:1 v/v) to give compound **4b** in 84% yield. The NMR and MS spectra data are identical to compound **4b** prepared by method 1 as shown in Scheme 1.

2-(3,4-Dichlorophenylamino)-6-ethyl-4-isopropylamino-pyrimidine (4c). Compound **4c** was prepared by the same method as for the preparation of **4a**, using **3c** as starting material to give the gummy desired compound. The product was dissolved in anhydrous ether and 2.0*M* HCl ether solution was added to form HCl salt. The HCl salt was recrystallized from hexanes/$CHCl_3$ to give a white solid in 95% yield, mp 211.3°C. ^{1}H NMR (CD_3OD): δ 8.02 (s, 1H), 7.55 (d, 1H, J = 8.7 Hz), 7.42 (d, 1H, J = 8.7 Hz), 6.05 (s, 1H), 4.24 (m, 1H), 2.65 (q, 2H, J = 7.5 Hz), 1.31 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 170.9, 162.9, 159.3, 140.2, 132.2, 129.9, 123.8, 120.0, 117.8, 94.0, 42.8, 30.7, 22.8, 12.7. ms: m/z 324 (M^+). *Anal*. calcd. for $C_{15}H_{18}Cl_2N_4$: C, 55.39; H, 5.58; N, 17.23; Cl, 21.80. Found: C, 55.18; H, 5.67; N, 16.95; Cl, 22.05.

6-*t*-Butyl-2-(3,4-dichlorophenylamino)-4-isopropylamino-pyrimidine (4d). Compound **4d** was prepared by the same method as for the preparation of **4a**, starting from **3d** to give the desired compound in 99% yield as an off-white solid, mp 125.8–126.5°C. ^{1}H NMR ($CDCl_3$): δ 8.20 (s, 1H), 7.30 (m, 2H), 7.05 (br, 1H), 5.88 (s, 1H), 4.59 (s, 1H), 4.08 (m, 1H), 1.30 (s, 9H), 1.25 (d, 6H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$): δ 177.1, 162.9, 158.9, 140.5, 132.2, 129.9, 123.5, 119.9, 117.5, 91.9, 42.7, 37.1, 19.3, 22.9. ms: m/z 352 (M^+). *Anal*. calcd.

for $C_{17}H_{22}Cl_2N_4$: C, 57.79; H, 6.28; N, 15.86; Cl, 20.07. Found: C, 58.01; H, 6.18; N, 15.80; Cl, 20.05.

6-*t*-Butyl-4-(3,4-dichlorophenylamino)-2-isopropylamino-pyrimidine (4e). Compound **4e** was prepared by the same method as for the preparation of **4b**, using 6-t-butyl-4-chloro-2-isopropylamino-pyrimidine (**3e**) as starting material to give the desired compound as a white solid in 71% yield, mp 249.5–250.8°C. ^{1}HNMR ($CDCl_3$): δ 11.94 (s, 1H), 11.04 (s, 1H), 8.30 (d, 1H, J = 6.9 Hz), 8.25 (s, 1H), 7.71 (d, 1H, J = 8.7 Hz), 7.33 (d, 1H, J = 6.9 Hz), 6.78 (s, 1H), 4.14 (m, 1H), 1.36 (s, 9H), 1.32 (t, 6H, J = 6.5 Hz). ms: m/z 352 (M^+). *Anal*. calcd. for $C_{17}H_{22}Cl_2N_4$.HCl: C, 52.39; H, 5.95; N, 14.38; Cl, 27.29. Found: C, 52.46; H, 5.96; N, 14.33; Cl, 27.16.

4-(3,4-dichlorophenylamino)-6-ethyl-2-isopropylamino-pyrimidine (4f). Compound **4f** was prepared by the same method as for the preparation of **4b**, using compound **3f** as the starting material to afford the desired compound as a pink solid in 92% yield, mp 251.3°C (decomposed).^{1}H NMR ($CDCl_3$): δ 7.92 (d, 1H, J = 2.5 Hz), 7.33 (d, 1H, J = 8.7 Hz), 7.20 (dd, 1H, J = 2.5Hz, 8.7Hz), 6.47 (br, 1H), 5.80 (s, 1H), 4.82 (d, 1H, J = 7.0 Hz), 4.11 (m, 1H), 2.48 (q, 2H, J = 7.6 Hz), 1.25 (d, 6H, J = 6.5 Hz), 1.21 (t, 3H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 161.7, 158.8, 154.1, 138.7, 131.5, 131.1, 126.3, 122.7, 121.4, 95.9, 43.9, 25.8, 22.3, 11.8. ms: m/z 324 (M^+). *Anal*. calcd. for $C_{15}H_{18}Cl_2N_4$.HCl: C, 49.81; H, 5.29; N, 15.49; Cl, 29.41. Found: C, 49.98; H, 5.28; N, 15.52; Cl, 29.31.

4-Chloro-2-methylthio-6-phenylpyrimidine (6). A catalytic amount of palladium acetate (0.286 g, 0.05 equiv) and triphenylphosphine (0.668 g, 0.10 equiv) were added to the solution of 4,6-dichloro2-methylthio-pyrimidine (**5**) (5.0 g, 25.42 mmol), phenylboronic acid (3.10 g, 1.0 equiv), and sodium carbonate (8.3 g, 3.1 equiv dissolved in a minium amount of water) in 250 mL of glyme. The reaction mixture was heated to reflux for 18 h, and the solvent was removed under reduced pressure. The crude product was extracted with methylene chloride and the extracts were combined, washed with water three times, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography, using hexane/ethyl acetate as eluent to yield compound **6** as a white solid in 84% yield, mp 59.8°C. ^{1}H NMR ($CDCl_3$): δ 8.06 (m, 2H), 7.68 (m, 3H), 7.38 (s, 1H), 1.54 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 173.55, 165.29, 161.53, 135.31, 131.66, 128.98, 127.35, 111.70, 14.41. ms: m/z 236 (M^+).

4-Isopropyl-amino-2-methylthio-6-phenylpyrimidine (7a). A suspension of 4-chloro-2-methylthio-6-phenylpyrimidine (**6**, 2.0g) and isopropylamine (1.0 mL, 1.5 equiv) in 100 mL of 1-BuOH was heated under reflux for 6 h. The solution was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with hexane/EtOAc (8:2 v/v) to yield 68% of the desired compound **7a**, mp 89.6°C. ^{1}H NMR ($CDCl_3$): δ 7.98 (d, 2H, J = 6.0 Hz), 7.43 (m, 3H), 6.38 (s, 1H), 4.77 (br, 1H), 4.10 (m, 1H), 1.54 (s, 3H), 1.27 (d, 6H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$): δ 171.5, 162.7, 162.0, 137.7, 94.9, 42.8, 22.7, 14.0. ms: m/z 259 (M^+).

4-(3,4-Dichlorophenylamino)-2-methylthio-6-phenylpyrimidine (7b). The title compound was prepared by the same method as for the preparation of **7a** using 3,4-dichloroaniline as nucleophile to give compound **7b** in 65% yield. ^{1}H NMR (CD_3OD): δ 8.13 (d, 1H, J = 2.4 Hz), 7.82 (m, 2H), 7.62 (m, 3H), 7.57 (s, 1H), 7.54 (d, 1H, J = 2.4 Hz), 6.85 (s, 1H), 2.73 (s, 3H). ^{13}C NMR (CD_3OD):: δ 169.6, 160.3, 157.5, 137.3, 132.1, 131.8, 130.4, 129.1, 127.9 127.1, 123.3, 121.1, 99.7, 13.1. ms: m/z: 361 (M^+). *Anal*. calcd. for $C_{17}H_{13}Cl_2N_3S$: C, 56.36, H, 3.62, Cl, 19.57, N, 11.60. Found: C, 56.74, H, 3.98, Cl, 20.08, N, 12.10.

4-Isopropylamino-2-methanesulfonyl/sulfinyl-6-phenylpyrimidine (mixture of sulfone and sulfoxide) (8a). 4-Isopropylamino-2-methylthio-6-phenylpyrimidine (**7a)** (2.0g, 7.7 mmol) was dissolved in 50 mL of ethyl acetate/toluene mixture. Water (2 ml) was added to the solution followed by a catalytic amount of sodium tungstate dihydrate (0.18 g, 0.1 equiv). The mixture was cooled to 0°C and hydrogen peroxide (30% aqueous solution, 1.69 mL, 10 equiv) was added dropwise. The reaction was stirred for 30 min, warmed to room temperature, and monitored by TLC until the disappearance of the starting material **7a** (~2 h). The mixture was cooled to 0°C again and excess H_2O_2 was decomposed carefully by addition of saturated sodium sulfide (20 mL). The organic layer was separated, concentrated under vacuum at 50°C to a volume of 100 mL. The mixture was cooled to room temperature and diluted with hexanes (20 mL). Compound **8a**, as a mixture of sulfone and sulfoxide, precipitated out from the solution, was collected and washed with hexanes to give **8a** in yield 71%. The product was used for further reaction without purification. ^{1}H NMR (CD_3OD): δ 7.50 (d, 2H, J = 6.0 Hz), 7.27 (m, 3H), 6.77 (s, 1H), 4.77 (m, 1H), 1.59 (s, 6H), 1.32 (d, 6H, J = 6.4 Hz). ^{13}C NMR (DMSO-d6): δ 166.3, 163.2, 160.7, 136.2, 131.2, 129.4, 127.5, 126.9, 103.1, 98.8, 42.7, 22.4. ms: m/z 291 (M^+).

4-(3,4-Dichlorophenylamino)-2-methanesulfonyl/sulfinyl-6-phenylpyrimidine (mixture of sulfone and sulfoxide) (8b). Compound **8b** was prepared from **7b** according to the same method for the preparation of **8a** to give the desired product in 74 % yield. ^{1}H NMR (DMSO-d6): δ 10.59 (s, 1H), 8.18 (d, 1H, J = 2.8 Hz), 8.10 (m, 2H), 7.64 (m, 3H), 7.60 (d, 1H, J = 2.8 Hz), 7.40 (s, 1H), 2.73 (s, 3H). ms: m/z 393 (M^+).

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