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A practical strategy for the synthesis of 2-dialkylamino-4-arylamino-6-aminopyrimidines

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ABSTRACT

Starting from commercially available 4-amino-2,6-dichloropyrimidine, a practical four steps synthesis of 2-dialkylamino-4-arylamino-6-aminopyrimidines was developed. This strategy could introduce a diverse set of secondary amines and arylamines to displace the 2- and 4-chloro groups. The products of this route are otherwise difficult to access. In addition, 6-amino arylation was carried out to demonstrate the reactivity and utility of 2-dialkylamino-4-arylamino-6-aminopyrimidines as building blocks for assembling interesting aminopyrimidine molecules.

Having presence in all naturally occurring nucleobases, pyrimidines[1] are arguably the most important diazines for living organisms. Since the discovery of the first pyrimidine derivative in 1818,[2] the use of pyrimidines as components in agrochemicals[3] and pharmaceuticals has gained great interest.

Aminopyrimidines, where one or more (up to four) pyrimidine hydrogens are substituted with amino or functionalized amino groups, can be found in a large number of natural products,[4] such as vitamine B1, and many pharmaceutical agents.[5] Aminopyrimidines are present in widely used classes of drugs including BCR-ABL tyrosine kinase inhibitor imatinib (Gleevec, **1**), dihydrofolate reductase inhibitor trimethoprim (Triprim, **2**), 5-HT 1A receptor agonist Buspirone (Buspar, **3**), HMG-CoA reductase inhibitor Rosuvastatin (Crestor, **4**), and alpha-1 adrenergic receptor blocker Doxazosin (Cardura, **5**). As indicated in Figure 1, these aminopyrimidine therapeutics have a wide range of indications including leukemia, bacterial infection, and hypertension management. In addition, many pharmaceutical agents in development also contain aminopyrimidine frameworks.[6]

During the course of a medicinal chemistry program, the synthesis of an aminopyrimidine intermediate represented by 2-dialkylamino-4-arylamino-6-aminopyrimidine **6a** (Fig. 2) became important for further transformation. Despite the simple structural feature of this compound and a literature report[7] on the synthesis of a related structure, our synthetic efforts toward **6a** met with significant setbacks. For example, the corresponding chloride precursor **7a** failed to effectively produce product **6a** in attempted direct nucleophilic displacement reactions with aniline under either basic or acidic conditions.[8] Transition metal catalyzed C–N coupling with this substrate was also unsuccessful in our hands.[9] Attempts to access **6a** though an alternative route[10] did not yield productive outcomes.

Given the electron-rich nature imparted by two amino substitutions in **7a**, we anticipated that protection of the **7a** amine with an electronwithdrawing group such as *tert*-butoxycarbonyl (Boc) could (1) block potential reactivity (dimerization) from the NH_2 group at the 4-position, (2) enhance the reactivity of chloride in C–N bond formation either through S_NAr fashion or transition metal catalyzed coupling reaction and (3) be easily removed following the C–N bond formation. Herein, we report the development of such a practical strategy for the preparation of 2-dialkylamino-4-arylamino-6-aminopyrimidines (see Table 1).

The syntheses of the chloropyrimidine precursors **7** were achieved following the known literature precedent[11] by reacting commercially available 4-amino-2,6-dichloropyrimidine **8** with secondary amines **9** in nearly 90% yields. Bis-Boc protection[12] of **7** was then realized with Boc_2O (NaH, DMF) to the afforded intermediates **10**. To our delight, a C–N bond formation was readily achieved when **10** was reacted with a wide range of arylamine substrates under typical Buchwald coupling conditions.[9] Ortho substitutions (examples 6 and 7) on the arylamino building block were tolerated. Encouragingly, heteroarylamines such as aminopyridine (example 8), aminopyrimidines (example 9 and 10), aminothiazole (example 11), and aminooxadiazole (example 12) all reacted to give good yields. Final deprotection of the 4-amino group was, as we expected, quantitative and led to the efficient production of a diverse set of 2-dialkylamino-4-arylamino-6-aminopyrimidines (see Scheme 1).

To further explore the utility of **6** in generating drug-like aminopyrimidine structures, we carried out Buchwald–Hartwig couplings (Scheme 2) of representative compound **6a** with a few arylbromides. As can be seen from Table 2, the standard coupling reactions gave regioselective coupling products with very high

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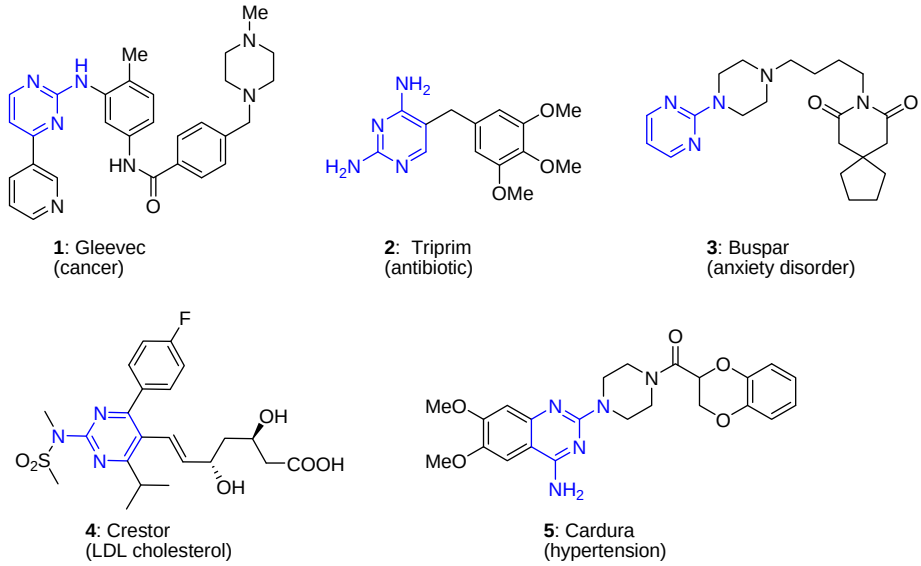


Figure 1. Drugs with aminopyrimidine framework.

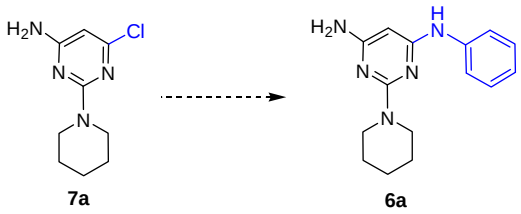


Figure 2.

yields. This reaction tolerated electron-donating groups (**14b, 14c**) and ortho substitution (**14c**) on the benzene ring. More interestingly, heteroarylbromides such as bromopyridines (**14d**, **14e**) and bromopyrimidine (**14f**) all reacted and gave high yielding reactions.

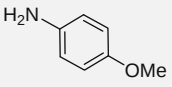
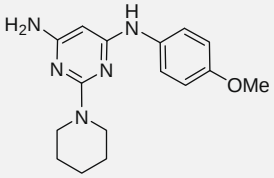
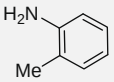
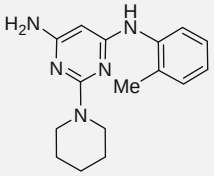
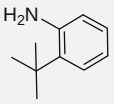
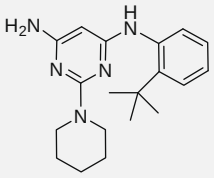
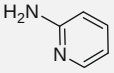
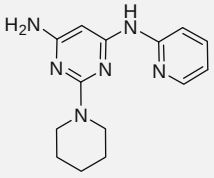
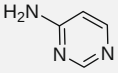
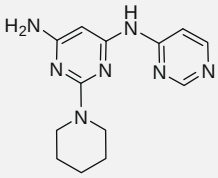
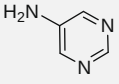
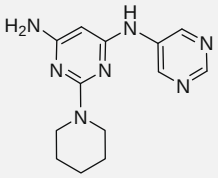
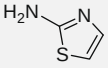
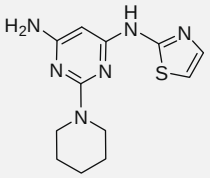
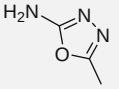
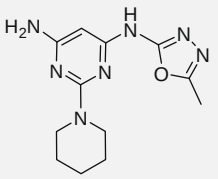
In summary, a practical strategy for the synthesis of 2-dialkylamino-4-arylamino-6-aminopyrimidines was developed. This strategy uses commercially available 4-amino-2,6-dichloropyrimidine as starting material and could introduce a diverse set of secondary

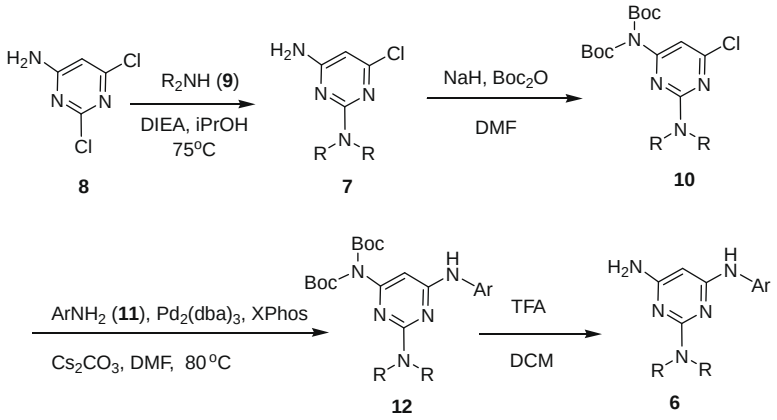
Table 1
Yields for the synthesis of 2-dialkylamino-4-arylamino-6-aminopyrimidines starting from 4-amino-2,6-dichloropyrimidine

Entry	Secondary amines	Yields (%) for steps **8**→**7** and **7**→ **10**[13,14]	Arylamines	Final products	Yields (%) for steps **10**→**12**[15]
1	**9a**	90/87	**11a**	**6a**	78
2	**9b**	90/87	**11a**	**6b**	71
3	**9c**	91/87	**11a**	**6c**	92
4	**9d**	90/85	**11a**	**6d**	75

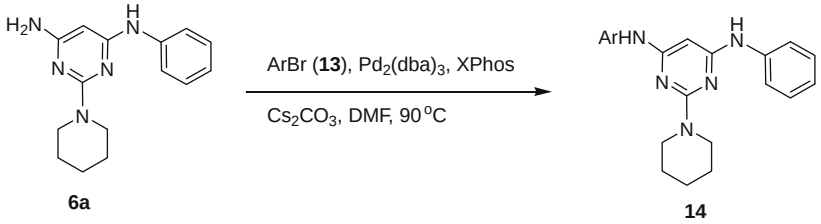
(*continued on next page*)

Table 1 (*continued*)

Entry	Secondary amines	Yields (%) for steps **8**→**7** and **7**→ **10**[13,14]	Arylamines	Final products	Yields (%) for steps **10**→**12**[15]
5	 **9a**	90/87	 **11b**	 **6e**	87
6	 **9a**	90/87	 **11c**	 **6f**	87
7	 **9a**	90/87	 **11d**	 **6g**	73
8	 **9a**	90/87	 **11e**	 **6h**	77
9	 **9a**	90/87	 **11f**	 **6i**	83
10	 **9a**	90/87	 **11g**	 **6j**	85
11	 **9a**	90/87	 **11h**	 **6k**	78
12	 **9a**	90/87	 **11i**	 **6l**	77

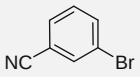
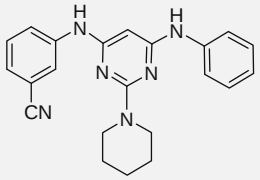
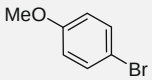
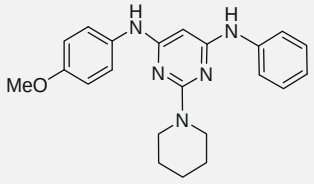
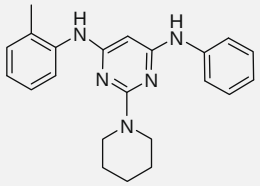
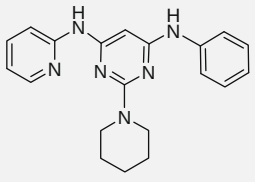


Scheme 1. Synthetic route toward 2-dialkylamino-4-arylamino-6-aminopyrimidines.



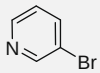
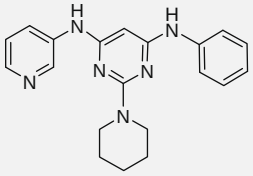
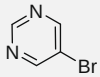
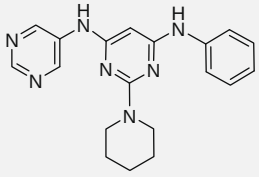
Scheme 2. Synthesis of 2-dialkylamino-4,6-bisarylaminopyrimidines.

Table 2
Yields for coupling of **6a** with aryl bromide[16]

Entry	Aryl bromide	Product	Yields (%)
1	 **13a**	 **14a**	94
2	 **13b**	 **14b**	90
3	 **13c**	 **14c**	94
4	 **13d**	 **14d**	87

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl bromide	Product	Yields (%)
5	 **13e**	 **14e**	98
6	 **13f**	 **14f**	87

amines and arylamines to displace the 2- and 4-chloro groups which are otherwise difficult to access. In addition, 6-amino arylation was carried out to demonstrate the reactivity and utility of 2-dialkylamino-4-arylamino-6-aminopyrimidines as building blocks for assembling interesting aminopyrimidine molecules.

Acknowledgments

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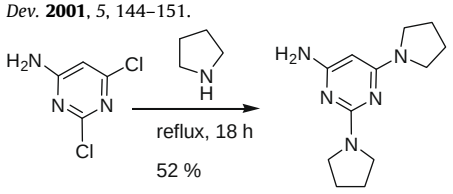

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12. Bis-Boc protection was chosen over Mono-Boc due to the attempted Mono-Boc protection giving a mixture of both products and starting material. In terms of reactivity for the subsequent coupling reaction, Mono-Boc protected **7a** showed a comparable reactivity with **10a**.
13. *Representative procedure for the synthesis of chloroaminopyrimidine* **7**: 6-chloro-2-(piperidin-1-yl)pyrimidin-4-amine (**7a**). To a solution of dichloride **8** (5.0 g, 30.5 mmol) in anhydrous 2-propanol (30.5 mL) were added *N*,*N*′-diisopropylethylamine (26.6 mL, 152 mmol) and piperidine (3.62 mL, 36.6 mmol). The resulting solution was heated to 75 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature before being diluted with water (100 mL), and extracted with ethyl acetate (100 mL). The organic extract was washed with water (100 mL × 2) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield the crude product. The product was then purified by flash chromatography (0→100% ethyl acetate in hexanes over 10 column volumes) to yield pure **7a** (5.85 g, 90.2%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.55 (s, 2H), 3.71–3.66 (m, 4H), 1.64–1.58 (m, 2H), 1.57–1.50 (m, 4H). ESIMS (*m*/*z*): 213 (M+H).
14. *Representative procedure for the synthesis of bis-bocaminopyrimidine* **10**: di-*tert*-butyl [6-chloro-2-(piperidin-1-yl)pyrimidin-4-yl]imidodicarbonate (**10a**). To a solution of **7a** (1 g, 4.70 mmol) in anhydrous *N*,*N*-dimethylformamide (23.5 mL), at 0 °C, was added sodium hydride (1.128 g, 28.2 mmol, 60%). The resulting solution was allowed to stir for 10 min before di-*tert*-butyl dicarbonate (4.10 g, 18.81 mmol) was added along with additional *N*,*N*-dimethylformamide (23.5 mL) to facilitate stirring of the foamy mixture. The solution was allowed to stir overnight while warming to ambient temperature. The reaction mixture was cooled to 0 °C before water was added very carefully to quench the remaining sodium hydride, after which ethyl acetate (100 mL) was used to extract the product. The extract was washed with water (2 × 100 mL) before being concentrated in vacuo. The residue was redissolved in dichloromethane (20 mL) and water (20 mL) before potassium carbonate (3.90 g, 28.2 mmol) and 2-(aminomethyl)pyridine (4.81 mL, 47.0 mmol) were added. The mixture was stirred for 30 min to allow complete reaction with the remaining Boc_2O (otherwise it is very difficult to separate the product from Boc_2O using silica gel chromatography). More DCM was added and the organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (0→30% ethyl acetate in hexanes over 15 column volumes) to yield **10a** (1.43 g, 86.8%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (s, 1H), 3.67 (m, 4H), 1.69–1.47 (m, 24H). ESIMS (*m*/*z*): 413 (M+H).
15. *Representative procedure for the synthesis of 2-dialkylamino-4-arylamino-6-amino pyrimidines* **6**: *N*-phenyl-2-(piperidin-1-yl)pyrimidine-4,6-diamine (**6a**). To a solution of **10a** (100 mg, 0.242 mmol) in anhydrous *N*,*N*-dimethylformamide (1.62 mL), under an atmosphere of nitrogen, were added cesium carbonate (237 mg, 0.727 mmol), aniline (**11a**) (33.2 μL, 0.363 mmol), XPhos (34.6 mg, 0.073 mmol), and tris(dibenzylideneacetone) dipalladium (24.39 mg, 0.027 mmol). The resulting solution was heated to 80 °C for 3 h before being allowed to cool to ambient temperature. Sat. ammonium chloride (40 mL) was added to quench the reaction before the product was extracted into ethyl acetate (50 mL). The organic extract was washed with satd ammonium chloride (2 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude bis-Boc protected product. The residue was purified by flash chromatography (0→80% ethyl acetate in hexanes over 10 column volumes) to yield pure bis-Boc product **12a** (88.7 mg, 77.8%). ^{1}H NMR (600 MHz, DMSO) δ 9.26 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.22 (s, 1H), 3.63–3.58 (m, 4H), 1.56 (dd, *J* = 12.4, 5.7 Hz, 2H), 1.44 (m, 22H). ESIMS (*m*/*z*): 470 (M+H).The bis-Boc product (100 mg) was redissolved in dichloromethane (1.42 mL) along with trifluoroacetic acid (1.64 mL, 21.30 mmol). The resulting solution was allowed to stir for 1 h before satd sodium bicarbonate was added

slowly to the reaction to quench the remaining acid (2 mL). Ethyl acetate was added to extract the product before being washed with satd sodium bicarbonate (2 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield the desired deprotected product **6a** (57.4 mg, quantitative). ^{1}H NMR (600 MHz, DMSO) δ 8.50 (s, 1H), 7.46 (d, J = 7.9 Hz, 2H), 7.18 (t, J = 7.8 Hz, 2H), 6.81 (t, J = 7.3 Hz, 1H), 5.84 (s, 2H), 5.14 (s, 1H), 3.66–3.54 (m, 4H), 1.55 (d, J = 5.1 Hz, 2H), 1.43 (m, 4H). ESIMS (m/z): 270 (M+H).

16. *Representative procedure for the synthesis of 2-dialkylamino-4-arylamino-6-arylamino pyrimidines* **14:** *3-{[6-(phenylamino)-2-(piperidin-1-yl)pyrimidin-4-yl]amino}benzonitrile* (**14a**). To a solution of **6a** (30 mg, 0.111 mmol) in anhydrous *N*,*N*-dimethylformamide (1.0 mL), under an atmosphere of nitrogen, were added cesium carbonate (72.6 mg, 0.223 mmol), 3-bromobenzonitrile (24.3 mg, 0.134 mmol), XPhos (13.3 mg, 0.028 mmol), and tris(dibenzylideneacetone) dipalladium (10.2 mg, 0.011 mmol). The resulting solution was heated to 90 °C for 3 h before being allowed to cool to ambient temperature. Satd ammonium chloride was added to quench the reaction before the product was extracted into ethyl acetate. The organic extract was washed with satd ammonium chloride and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford the crude product. The residue was purified by flash chromatography (0→60% ethyl acetate in hexanes over 12 column volumes) to yield **14a** (39 mg, 94 %). ^{1}H NMR (600 MHz, DMSO) δ 9.22 (s, 1H, NH), 8.89 (s, 1H, NH), 8.22 (s, 1H), 7.72 (dd, J = 1.8, 7.8 Hz, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.45 (m, 1 H), 7.29 (m, 3H), 6.92 (m, 1H), 5.52 (s, 1H, pyrimidine CH), 3.71 (m, 4H), 1.64 (m, 2H), 1.54 (m, 4H). ESIMS (m/z): 371 (M+H).