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Regioselective Control of the S_NAr Amination of 5-Substituted-2,4-Dichloropyrimidines Using Tertiary Amine Nucleophiles

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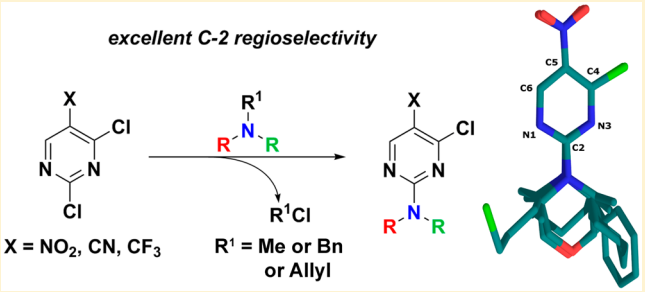
Supporting Information

ABSTRACT: The S_NAr reaction of 2,4-dichloropyrimidines, further substituted with an electron-withdrawing substituent at C-5, has selectivity for substitution at C-4. Here we report that tertiary amine nucleophiles show excellent C-2 selectivity. In situ N-dealkylation of an intermediate gives the product that formally corresponds to the reaction of a secondary amine nucleophile at C-2. This reaction is practical (fast under simple reaction conditions, with good generality for tertiary amine structure and moderate to excellent yields) and significantly expands access to pyrimidine structures.



S_NAr reactions of halopyrimidines are a proven route to diverse pyrimidine-containing structures. 2,4-Dichloropyrimidines that are further substituted at C-5 with an electron-withdrawing substituent (notably cyano, nitro, or trifluoromethyl) are particularly useful starting materials, yielding (upon further synthetic transformation) pyrimidine-containing structures with biological activity. The breadth of biologically active pyrimidine, and pyrimidine-derived, structures is expansive.[1,2] The synthetic objectives of several examples are cited herein: adenosine A_{2A} receptor antagonist;[3] HIV non-nucleoside reverse transcriptase inhibitor;[4] VLA-4 integrin antagonist;[5] inhibitor of falcipain protease;[6] inhibitor of stearoyl-CoA desaturase;[7] and inhibitors of human kinases.[8−21] The S_NAr reactions of these pyrimidines (whether with carbon, nitrogen, or oxygen nucleophiles) invariably occur rapidly (often in minutes) at low temperatures (ambient and below), with excellent yields and outstanding regioselectivity for nucleophilic displacement of the C-4 halogen.[22] Indeed, with many amine nucleophiles, this regioselectivity is so good that the accompanying experimentals often fail to acknowledge the possible presence of a minor product from competing substitution at C-2. Where the ratio for C-4 compared to C-2 substitution of 2,4-dichloro-5-nitropyrimidine **1** has been measured with sterically unencumbered amines, ratios between 9:1 to 19:1 are observed.[3,23−25] As the initial reaction of longer synthetic sequences, this reaction dictates the overall synthetic strategy. As the C-4 regioselectivity is not always desirable, effort has been given to the use of a Lewis acid (such as $ZnCl_2$) to direct amine nucleophiles toward preferential substitution at C-2 of the pyrimidine.[2,11] Here, we report a simple alternative toward this same objective: the use of a tertiary amine as the S_NAr nucleophile.

This strategy is exemplified by the contrast between the reactions of diethylamine (representing a secondary amine, such as is used customarily for S_NAr) and triethylamine (as a tertiary amine nucleophile) with 2,4-dichloro-5-nitropyrimidine **1** as the pyrimidine electrophile. Reaction of **1** with 1 equiv of diethylamine (CH_2Cl_2 solvent, 0 °C, 1 h) gave **2a** (C-4 substitution) as the major product, along with **3a** (C-2 substitution) and unreacted **1** with ratio of 5:1:4 (Figure 1A). The addition of iPr_2NEt base allowed complete consumption of **1** with formation of the three products **2a**, **3a**, and **4a** (C-2 and C-4 disubstitution) in a ratio of **2a**:**3a**:**4a** of 10/0.2/1.6, as determined by the integration of the H-6 resonance in the ^1H NMR spectrum of the final reaction mixture. This result is in accord with the extensive literature precedent for preferential nucleophilic substitution at C-4 in these S_NAr reactions (citing recent literature examples of C-4 selective S_NAr and where the presence of a product from competing C-2 substitution is not noted).[1,4−10,12,14−16,18−21]

In contrast, under identical reaction conditions but with NEt_3 (2 equiv) as the amine nucleophile, the pyrimidin-2-amine **3a** (Figure 1B) was the main product (91%). Isomer **2a** was not detected by NMR. Notwithstanding the use of 2 equiv of NEt_3, the reaction did not proceed further to give **4a**. The implicit *N*-dealkylation that occurred from a cationic quaternary amine intermediate, presumably involving the liberated halide as the nucleophile, is a phenomenon observed previously in selected azine S_NAr chemistry,[26−29] as well as in less related synthetic transformations.[30,31] To our knowledge, our study is the first study to emphasize the regiochemical advantage of this S_NAr approach to pyrimidine functionalization. The identity of **3a** as the product of this S_NAr reaction with NEt_3 was confirmed by X-ray analysis (Figure 1). The lack of reactivity of pyrimidinamine **3a** to this tertiary amine under these conditions was confirmed by independent experiment. Pyrimidinediamine **4a** was prepared either by reaction of diethylamine with **3a** (1

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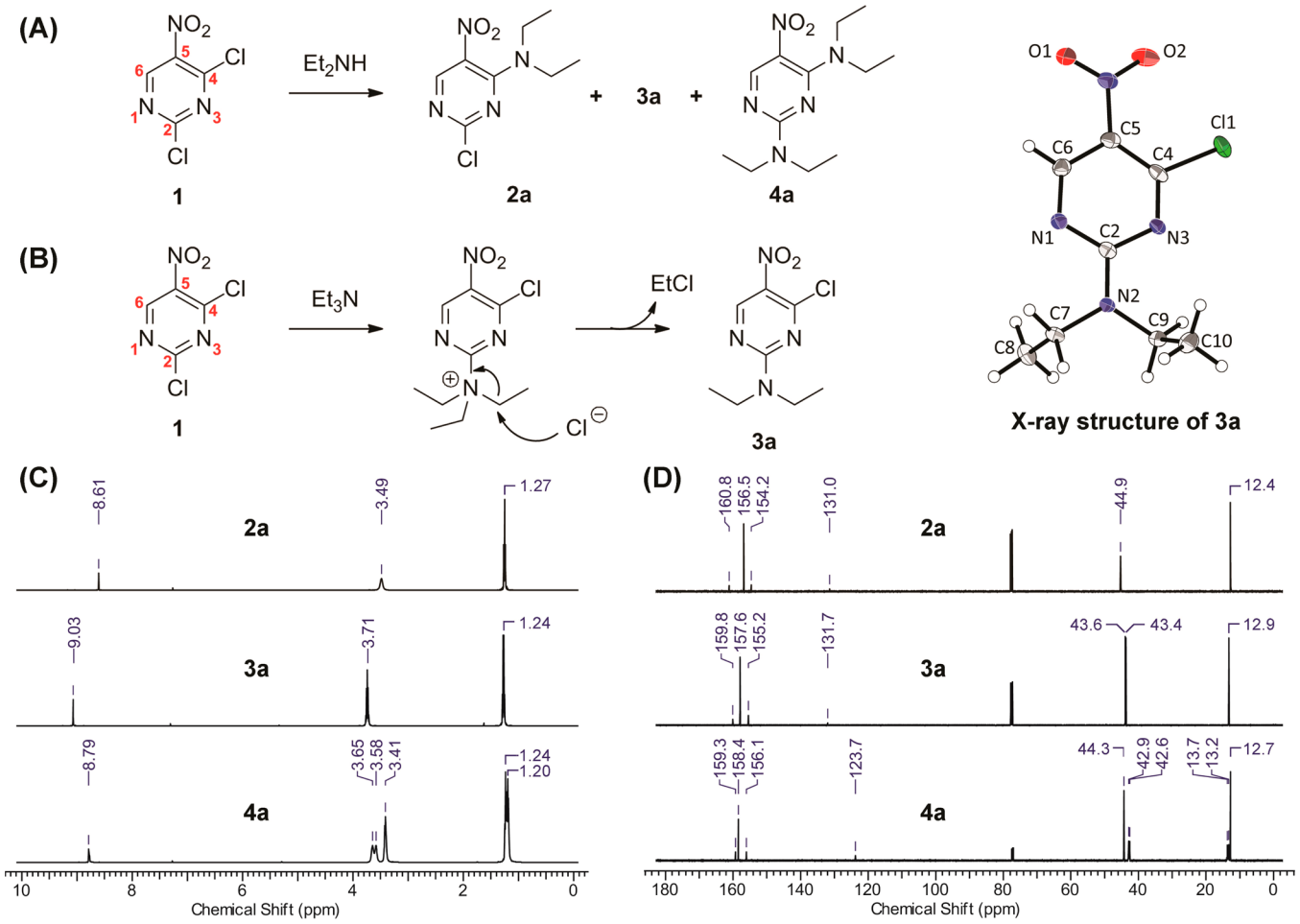

Figure 1. Reaction of 2,4-dichloro-5-nitropyrimidine (**1**) with diethylamine (A) and triethylamine (B). ^{1}H NMR spectra (C) and ^{13}C NMR spectra (D) of the purified reaction products **2a**, **3a**, and **4a**.

equiv, 5 min, rt, CH_2Cl_2) or by the reaction of **1** with excess diethylamine (5 equiv, iPr$_2$NEt, 3 h, 40 °C, CH_2Cl_2).

The NMR spectra (both ^{1}H and ^{13}C) of **2a**, **3a**, and **4a** show that the two ethyl moieties of each are magnetically distinct (Figure 1C and D). This magnetic inequivalence is more apparent in the spectra of **3a** and **4a** than in the spectra of **2a**. In other respects the NMR spectra (of **2a**, **3a**, and **4a**) are very similar. This similarity is problematic, in the absence of synthetic standards, to the assignment of structure to these pyrimidinamines. As a result of this potential ambiguity, we used X-ray crystallography for the routine confirmation of the structure of the products obtained from the reaction of **1a** with tertiary amines.

The breadth of this reaction was evaluated using 14 trialkylamines (**5a**−**5n**, Table 1). The yields of the 4-chloro-5-nitropyrimidin-2-amine product ranged from 25% (*N*-methylpyrroline) to 91% (for NEt_3).

The C-2 regioselectivity was general. We emphasize that the yields reported in this table are for the pure 4-chloro-5-nitropyrimidin-2-amine, obtained by chromatographic purification. The literature offers conflicting (against our own observations) advice on the properties of the chloro-5-nitropyrimidin-2-amine products, such as high yields following silica chromatography and high purity following crystallization from 2-propanol solvent. Our observations follow closely the observations of Taylor and Thompson.[22] In our hands the latent reactivities of both the 4-chloro-5-nitropyrimid-2-amine and the 2-chloro-5-nitropyrimid-4-amine are sufficient to make advisible their prompt use in the ensuing reaction (as is indeed often the literature circumstance). When silica gel chromatography of these chloro-5-nitropyrimidines is necessary, the shortest possible flash column should be used. The removal of small amounts of the 2-chloro-5-nitropyrimidin-4-amine by exploiting the generally greater solubility in organic solvents of the 2-chloro-5-nitropyrimidin-4-amine compared to the 4-chloro-5-nitropyrimidin-2-amine may be advisible.[1,19,22] Last, 4-chloro-5-nitropyrimid-2-amines are not shelf-stable (stored in a vial at room temperature, without explicit effort to exclude atmospheric moisture, results in significant levels of decomposition over a period of months) and they react with certain solvents (such as DMF and DMSO) at elevated temperatures.

Several additional comments are in order with respect to the examples of Table 1. The yield from the reaction with tri-*n*-butylamine (entry 2) was nearly the yield value seen for triethylamine. The reaction outcome with unsymmetrically substituted amines is more complicated. The moiety that is lost from the quaternary amine intermediate during the reaction with *N*-methylmorpholine (entry 3) is the methyl group. A trend emerges for the preferred shedding of the smaller *N*-alkyl moieties in the course of this reaction (entries 3−4, 7−8). The outcome with *N*-methylpyrrolidine as the amine nucleophile (entry 5) was different. Instead of loss of the methyl moiety, nucleophilic attack by the chloride ion opens the pyrrolidine ring to give compound **3e** as a major product (along with two

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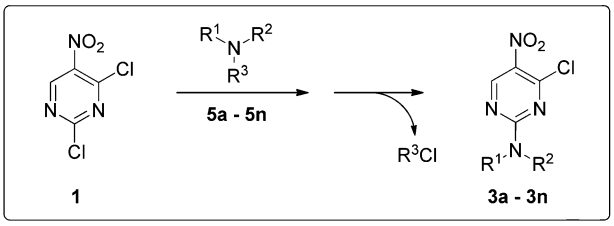
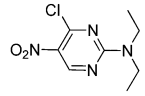
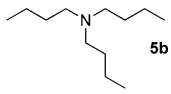
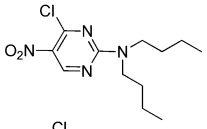
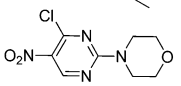
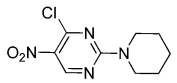
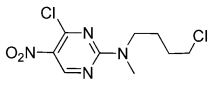
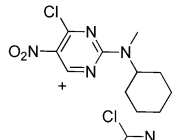
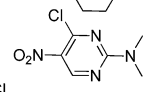
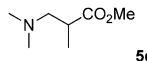
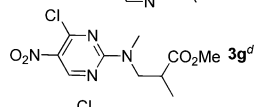
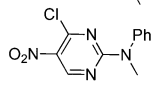
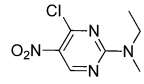
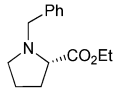
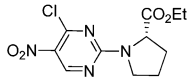
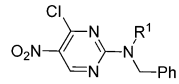
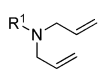
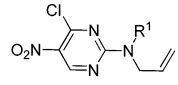
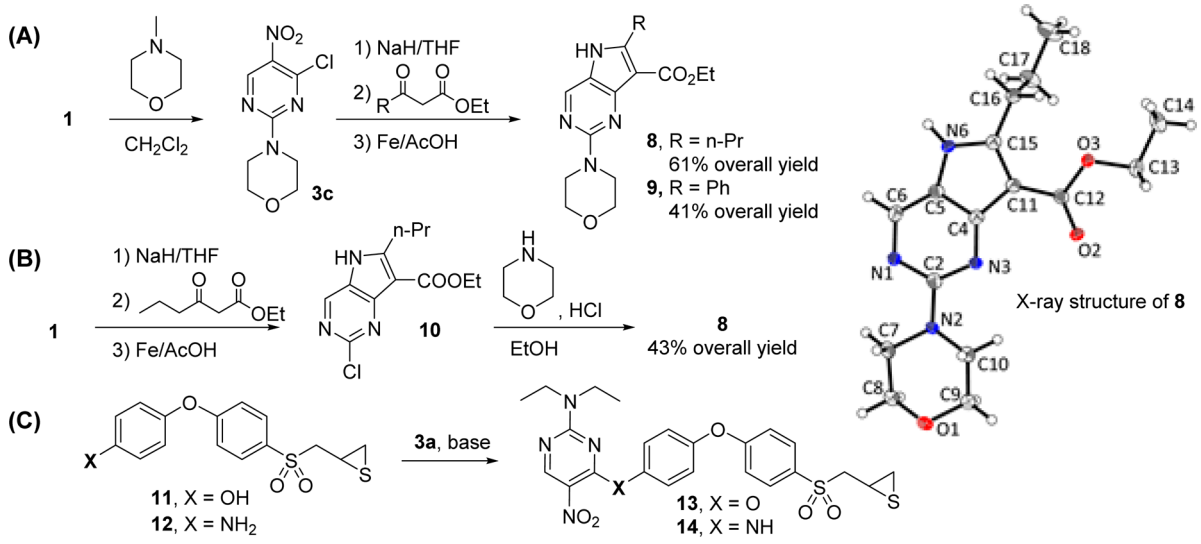
Table 1. Reactions of Pyrimidine 1 with Trialkylamines (5a−5n)[a,b]



Entry	Amine		Product[b]		Yield (%)[c]
1		5a		3a	91
2		5b		3b[d]	87
3		5c		3c	79
4		5d		3d	49
5		5e		3e	25
6		5f		3f-1	33
				3f-2	15
7		5g		3g[d]	45
8[b]		5h		3h	73
9		5i		3i	55
10[b]		5j		3j[d]	60
11[b]		5k, R1 = Me		3k[d]	84
12[b]		5l, R1 = Et		3l	86
13		5m, R1 = Me		3m[d]	86
14		5n, R1 = allyl		3n[d]	84

[a]Condition A: CH_2Cl_2, 1 h, room temperature (except for the entries with footnote *b*). [b]As condition A gives a slow reaction, condition B ($ClCH_2CH_2Cl$, 90 °C) was used. [c]Yields were not optimized. [d]Structure assigned by NMR.

Scheme 1. Examples of Functionalization of Pyrimidin-2-Amines 3c and 3a[a]



[a]Synthesis of compound **8** by the modified approach using **3c** (A) and by Zhao et al.[25] (B). Synthesis of compounds **13** and **14** using **3a** (C).

additional minor products, whose structures were not determined). With *N*,*N*-dimethylcyclohexylamine as the amine (entry 6), the *N*-methyl-*N*-cyclohexyl-2-pyrimidinamine (**3f-1**) was the major product and the *N*,*N*-dimethyl-2-pyrimidinamine (**3f-2**) was the minor product. With *N*-ethyl-*N*-methylbenzylamine as the amine nucleophile (entry 9), the benzyl moiety is preferentially lost to give **3i** as the main product. The same trend was observed with the reaction of benzylproline (**5j**).

Selectivity for nucleophilic substitution at C-2 in the presence of $ZnCl_2$ has been reported.[2] The reaction of diethylamine with **1** using $ZnCl_2$ in our hands gave a mixture of C-2 and C-4 products in a ratio of 1:9, respectively. The reaction of morpholine with **1** using $ZnCl_2$ gave a product mixture comprising C-2 substitution, C-4 substitution, and bis-substitution to the pyrimidinediamine, in a respective ratio of 1:7:2. These two examples emphasize the limitations of the

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$ZnCl_2$ method with respect to amine and pyrimidine structures, as also discussed by Richter et al.[2]

While entries 1−10 of Table 1 exemplify useful synthetic transformations, the class of product is entirely tertiary pyrimidinamines. *N*-Unsubstituted and *N*-monosubstituted pyrimidinamines are often desired products. With respect to the latter objective, entries 9 and 10 open the possibility of using an *N*,*N*-dibenzylalkylamine nucleophile, which can be readily transformed to the monoalkyl pyrimidinamine by catalytic hydrogenation. Thus, reactions of *N*,*N*-dibenzylmethylamine (entry 11) and *N*-dibenzylethylamine (entry 12) gave the *N*-alkyl-*N*-benzylpyrimidinamines (**3k** and **3l**, respectively) in excellent yields, as did the use of *N*,*N*-diallylmethylamine (**5m**, entry 13) to give *N*-allyl-*N*-methylpyrimidinamine (**3m**) as product. Likewise, the reaction of triallylamine (**5n**, entry 14) went smoothly to give *N*,*N*-diallylpyrimidinamine (**3n**), as a masked primary amine product. Highly sterically hindered amines (such as diisopropylethylamine, tribenzylamine, and tricyclohexylamine) are unreactive, both at ambient temperature and at reflux.

Since an authentic product was not available for any of these entries, X-ray crystallography was the method of choice for structure assignment. Nine products (**3a**, **3c**, **3d**, **3e**, **3f-1**, **3f-2**, **3h**, **3i**, and **3l**) in Table 1 and five additional compounds (**7a**, **7b**, **8**, **13**, and **14**, discussed later) were so characterized (Supporting Information).

We evaluated the reaction outcome for two other 5-substituted 2,4-dichloropyrimidines using NEt_3 as the amine nucleophile. Both the 5-cyano (**6a**) and 5-trifluoromethyl (**6b**) pyrimidines preserved the S_NAr preference for C-2 reactivity, as confirmed by X-ray crystal analysis of the respective products **7a** and **7b** (Supporting Information). In both cases the NMR spectrum of the crude reaction product showed the absence (<5%) of the C-4 isomer. In contrast, neither 2,4-dichloropyrimidine **6c** nor 2-chloropyrimidine (**6d**) reacts with this tertiary amine (either at room temperature or at reflux).

The value of this new strategy to control the S_NAr regioselectivity of reactive 5-substituted-2,4-dichloropyrimidines is illustrated. A common transformation following successive S_NAr reactions of 2,4-dichloro-5-nitropyrimidine is reduction of the nitro moiety.[17] Pyrimidine **3c** is a useful intermediate toward the synthesis of pyrrolo[3,2-*d*]pyrimidine structures, a relatively unexplored class of biologically active heterocycles (Scheme 1A).

The C-2 selective S_NAr with *N*-methylmorpholine as the tertiary amine gave ultimately **8** in an overall yield (three steps from **1**) of 61%. The cognate structure **9** was obtained in 41% overall yield (Scheme 1A). In contrast, Zhao et al. prepared **8** by substitution first at C-4 of **1**, followed by substitution at C-2 of **10**, in an overall yield of 43% (Scheme 1B).[25] Not only was the yield improved by the new route, but the new route is simpler. As a further example, pyrimidin-2-amine **3a** was transformed into thiirane-based inhibitors of matrix metalloproteinases (Scheme 1C). The reaction of HO- or H_2N-containing thiirane derivatives **11** (preparation[32−34]) and **12** (preparation[35]) with **3a** gave smooth substitution to yield the desired products (**13** and **14**, respectively), notwithstanding the base sensitivity of the thiirane moiety. Both **13** and **14** are crystalline (Supporting Information).

The pyrimidine ring is the core of numerous valuable organic structures. The decisive ability of compounds **1**, **6a**, and **6b** to undergo clean regioselective substitution of their 2-chloro substituents, using tertiary amine nucleophiles, opens a new strategy toward these pyrimidines. Moreover, we anticipate general usefulness for this strategy, as demonstrated by the excellent C-2 S_NAr selectivity retained by the *N*-benzyl and *N*-allyl tertiary amines.

EXPERIMENTAL SECTION

General Procedure A. Reaction was carried out on a 10 mmol scale unless otherwise noted. Compound **1** (1.95 g, 10.0 mmol) was dissolved in CH_2Cl_2 (40 mL). To this room-temperature solution is added dropwise the amine (20.0 mmol). The reaction flask warms slightly as the amine is added. After a period of 1 h, the reaction mixture was filtered through a pad of silica gel. The filtrate was concentrated under the reduced pressure. The resulting residue was purified by silica chromatography using an EtOAc/hexanes mixture as the chromatography solvent.

General Procedure B. Same conditions as with general procedure A, except 1,2-dichloroethane was the solvent at a reaction temperature of 90 °C.

*2-Chloro-N,N-diethyl-5-nitro-4-pyrimidinamine (**2a**).* Prepared using the general procedure A (5.0 mmol scale) except using 1 equiv of diethylamine (0.5 mL, 5 mmol) and *i*Pr_2NEt (0.9 mL, 5 mmol). Compound **2a** was obtained in 67% (0.8 g) as a yellow oil and 0.4 g of a mixture of **2a** and dimer **4a**. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 9H), 3.49 (br s, 6H), 8.61 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.4, 44.9, 131.0, 154.2, 156.5, 160.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{12}ClN_4O_2$ 231.0643; found 231.0664.

*4-Chloro-N,N-diethyl-5-nitro-2-pyrimidinamine (**3a**).* Prepared using the general procedure A with triethylamine **5a** in 91% yield (2.1 g) as a light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.24, 1.25 (2 × t, J = 7.2 Hz, 4H), 3.70, 3.72 (2 × q, J = 7.2 Hz, 4H), 9.03 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9, 43.4, 43.6, 131.7, 155.2, 157.6, 159.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{12}ClN_4O_2$ 231.0643; found 231.0655.

*N,N,N′,N′-Tetraethyl-5-nitro-2,4-pyrimidinediamine (**4a**).* Prepared using the general procedure A from **3a** and diethylamine on a 5 mmol scale (0.7 g, 50% yield), or using **1** and diethylamine (2.5 mL, 25 mmol) and $EtNiPr_2$ (4.5 mL, 25 mmol) in refluxing condition on a 5 mmol scale (0.7 g, 51%) as a light orange solid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.13−1.27 (m, 11H), 3.32−3.49 (m, 4H), 3.52−3.61 (m, 2H), 3.64 (br s, 2H), 8.72−8.79 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 13.2, 13.7, 42.6, 42.9, 44.3, 123.7, 156.1, 158.4, 159.3; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{22}N_5O_2$ 268.1768; found 268.1739.

*4-Chloro-N,N-dibutyl-5-nitro-2-pyrimidinamine (**3b**).* Prepared using the general procedure A with tri(*n*-butyl)amine **5b** (2.5 g, 87%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.73−1.13 (m, 6H), 1.18−1.44 (m, 4H), 1.49−1.67 (m, 4H), 3.40−3.72 (m, 4H), 9.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 13.8, 19.95, 19.99, 29.4, 29.5, 48.4, 48.5, 131.3, 154.7, 157.3, 159.9; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{20}ClN_4O_2$ 287.1269; found 287.1294.

*4-(4-Chloro-5-nitro-2-pyrimidinyl)morpholine (**3c**).* Compound **3c** was prepared by general procedure A using *N*-methylmorpholine **5c** on a 5 mmol scale (1.0 g, 79%) as a light yellow solid. ^1H NMR (600 MHz, $CDCl_3$) δ 3.76 (t, J = 4.5 Hz, 4H), 3.93 (m, 2H), 3.95−3.99 (m, 2H), 9.02 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 45.0, 45.2, 66.6, 132.0, 155.4, 157.6, 159.7; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_8H_{10}ClN_4O_3$ 245.0436; found 245.0458.

*4-Chloro-5-nitro-2-(1-piperidinyl)-pyrimidine (**3d**).* Compound **3d** was prepared by general procedure A using *N*-methylpiperidine **5d** (1.2 g, 49%) as a light yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.59−1.68 (m, 4H), 1.68−1.75 (m, 2H), 3.88, 3.91 (2 × t, J = 5.6 Hz,4H), 8.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.2, 25.77, 25.81, 45.7, 46.0, 131.0, 155.1, 157.5, 159.3; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_9H_{12}ClN_4O_2$ 243.0643; found 243.0660.

*4-Chloro-N-(4-chlorobutyl)-N-methyl-5-nitro-2-pyrimidinamine (**3e**).* Compound **3e** was prepared by general procedure A using *N*-methylpyrrolidine **5e** (0.7 g, 25%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.80 (br s, 4H), 3.25, 3.26 (2 × s, 3H), 3.54−3.66 (m,

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2H), 3.66−3.83 (m, 2H), 8.99, 9.01 (2 × s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3, 24.4, 29.37, 29.42, 35.8, 36.1, 44.37, 44.39, 49.2, 49.3, 131.7, 154.8, 154.9, 157.2, 157.4, 160.2, 160.3; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_9H_{13}Cl_2N_4O_2$ 279.0410; found 279.0421.

*4-Chloro-N-cyclohexyl-N-methyl-5-nitro-2-pyrimidinamine (**3f-1**) and 4-chloro-N,N-dimethyl-5-nitro-2-pyrimidinamine (**3f-2**).* Reaction of **1** and *N*,*N*-dimethylcyclohexylamine **5f** by general procedure A gave **3f-1** (0.9 g, 33%) as a light yellow solid and **3f-2** (0.3 g, 15%) as a white solid. **3f-1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (m, 1H), 1.36−1.56 (m, 4H), 1.71 (br s, 3H), 1.84 (d, J = 11.4 Hz, 2H), 3.11 (br s, 3H), 4.60, 4.67 (2 × t, J = 11.1 Hz), 8.99, 9.00 (2 × s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.3, 25.4, 25.5, 29.68, 29.74, 29.8, 30.0, 55.7, 55.9, 131.21, 131.24, 154.6, 154.7, 157.1, 157.3, 159.8, 159.9; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{11}H_{16}ClN_4O_2$ 271.0956; found 271.0974. **3f-2**:Compound **3f-2** is known in the literature,[36] but its spectral data is not reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29, 3.30 (2 × s, 6H), 9.01 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.6, 37.9, 131.5, 154.8, 157.2, 160.4; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_6H_8ClN_4O_2$ 203.0330; found 203.0345.

*(±)-2-Methyl-3-[methyl-(4-chloro-5-nitro-2-pyrimidinylamino)]-propanoic acid, methyl ester (**3g**).* Compound **3g** was prepared by general procedure A using methyl β-(dimethylamino)isobutyrate **5g** (1.3 g, 45%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14, 1.16 (2 × d, J = 3.8 Hz, 3H), 2.93 (q, J = 7.2 Hz, 1H), 3.22, 3.23 (2 × s, 3H), 3.61, 3.62 (2 × s, 3H), 3.71−3.88 (m, 2H), 8.95, 8.97 (2 × s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 14.9, 37.1, 37.4, 37.8, 51.9, 53.2, 53.4, 131.9, 154.5, 154.8, 156.9, 157.1, 157.2, 160.3, 174.9; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{14}ClN_4O_4$ 289.0698; found 289.0708.

*4-Chloro-N-methyl-N-phenyl-5-nitro-2-pyrimidinamine (**3h**).* Compound **3h** was prepared by general procedure B using *N*,*N*-dimethylaniline **5h** on 5 mmol scale (1.0 g, 73%) as a light orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3H), 7.28 (m, 2H), 7.37 (m, 1H), 7.48 (m, 2H), 8.95 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.2, 126.5, 128.0, 129.9, 133.3, 143.3, 157.5, 160.8; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{11}H_{10}ClN_4O_2$ 265.0487; found 265.0515.

*4-Chloro-N-ethyl-N-methyl-5-nitro-2-pyrimidinamine (**3i**).* Compound **3i** was prepared by the general procedure A using *N*-ethyl-*N*-methylbenzylamine **5i** (1.2 g, 55%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15, 1.17 (2 × t, J = 7.1 Hz, 3H), 3.18 and 3.19 (2 × s, 3H), 3.63−3.75 (m, 2H), 8.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 35.2, 35.5, 45.0, 45.2, 131.5, 154.8, 154.9, 157.28, 157.32, 159.88, 159.94; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_7H_{10}ClN_4O_2$ 217.0487; found 217.0508.

*1-(4-Chloro-5-nitro-2-pyrimidinyl)-L-proline ethyl ester (**3j**).* Compound **3j** was prepared using *N*-benzylproline ethyl ester **5j** by general procedure A except reaction temperature was 40 °C instead of room temperature (1.8 g, 60%, a light brown oil). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 and 1.24 (2 × t, J = 7.1 Hz, 3H), 1.99−2.18 (m, 3H), 2.28−2.41 (m, 1H), 3.69−3.77 (m, 1H), 3.79−3.91 (m, 1H), 4.06−4.25 (m, 2H), 4.61 (ddd, J = 19.6, 8.7, 3.8 Hz, 1H), 8.93 and 9.00 (2 × s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 14.1, 23.6, 23.7, 30.1, 30.2, 48.0, 48.2, 60.2, 60.4, 61.3, 132.4, 154.4, 154.9, 156.9, 157.3, 158.37, 158.42, 171.3; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{11}H_{14}ClN_4O_4$ 301.0698; found 301.0712.

*4-Chloro-N-benzyl-N-methyl-5-nitro-2-pyrimidinamine (**3k**).* Compound **3k** was prepared by the general procedure B using *N*,*N*-dibenzylmethylamine **5k** on a 5 mmol scale (1.2 g, 84%) as a while solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 (s, 3H), 4.95, 4.99 (2 × s, 2H), 7.19−43 (m, 5H), 9.06, 9.07 (2 × s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.8, 36.1, 53.4, 53.7, 127.8, 128.1, 128.19, 128.24, 129.1, 136.0, 136.1, 155.2, 155.4, 157.6, 157.8, 160.8, 160.9; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{12}ClN_4O_2$ 279.0643; found 279.0633.

*4-Chloro-N-benzyl-N-ethyl-5-nitro-2-pyrimidinamine (**3l**).* Compound **3l** was prepared by the general procedure B using *N*,*N*-dibenzylethylamine **5l** on a 5 mmol scale (1.3 g, 86%) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20, 1.22 (2 × t, J = 7.0 Hz, 3H), 3.67−3.76 (m, 2H), 4.93 and 4.96 (2 × s, 2H), 7.19−7.42 (m, 5H), 9.05, 9.08 (2 × s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.4, 43.1, 43.4, 51.0, 51.3, 127.7, 128.07, 128.09, 128.13, 129.0, 136.5, 136.6, 155.3, 155.5, 157.7, 157.9, 160.46, 160.55; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{14}ClN_4O_2$ 293.0800; found 293.0786.

*4-Chloro-N-allyl-N-methyl-5-nitro-2-pyrimidinamine (**3m**).* Compound **3m** was prepared by the general procedure A using *N*,*N*-diallylmethylamine **5m** on a 5 mmol scale (1.0 g, 86%) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (s, 3H), 4.33 (dd, J = 13.1, 5.7 Hz, 2H), 5.12−5.30 (m, 2H), 9.00 (s, 1H), 9.03 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.5, 35.9, 52.5, 52.7, 118.2, 118.5, 131.5, 132.0, 155.0, 155.2, 157.5, 157.6, 160.4, 160.5; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_8H_{10}ClN_4O_2$ 229.0487; found 229.0486.

*4-Chloro-N,N-diallyl-5-nitro-2-pyrimidinamine (**3n**).* Compound **3n** was prepared by the general procedure A using triallylamine **5n** on a 5 mmol scale (1.1 g, 84%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ^1 4.29 (dd, J = 11.3, 5.7 Hz, 4H), 5.15−5.30 (m, 4H), 5.75−5.87 (m, 2H), 9.02 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.9, 50.2, 118.2, 118.6, 131.67, 131.70, 132.3, 155.2, 157.7, 160.2; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{12}ClN_4O_2$ 255.0643; found 255.0651.

*4-Chloro-2-(diethylamino)pyrimidine-5-carbonitrile (**7a**).* Compound **7a** was prepared by general procedure using pyrimidine **6a** and triethylamine **5a** on a 1.1 mmol scale (0.21 g, 91%) as a while solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (2 × t, J = 6.7 Hz, 6H), 3.65 (2 × q, J = 6.7 Hz, 4H), 8.39 (s, 1H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 and 1.21 (2 × t, J = 7.0 Hz, 6H), 3.64 and 3.86 (2 × q, J = 7.1 Hz, 4H), 8.39 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9, 43.1, 95.0, 115.5, 160.1, 162.0, 162.1; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_9H_{12}ClN_4$ 211.0745; found 211.0762.

*4-Chloro-N,N-diethyl-5-trifluoromethyl-2-pyrimidinamine (**7b**).* Compound **7b** was prepared by the general procedure using pyrimidine **6b** and triethylamine **5a** on a 1.1 mmol scale (0.25 g, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 3.5 Hz, 6H), 3.64 (q, J = 6.9 Hz, 4H), 8.41 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.96, 12.98, 42.8, 42.9, 110.0 (d, J = 33.2 Hz), 123.6 (q, J = 269.9 Hz), 157.2 (q, J = 4.9 Hz), 158.9, 161.4; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_9H_{12}ClF_3N_3$ 254.0666; found 254.0683.

*Ethyl 2-(4-Morpholinyl)-6-propyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate (**8**).* Compound **8** was prepared by the literature procedure[25] using pyrimidine **5c** and ethyl butyrylacetate in 0.8 mmol scale (0.20 g, 77%) as a light yellow solid. The ^{1}H NMR and ^{13}C NMR spectra matched to the literature.[25]

*Ethyl 2-(4-Morpholinyl)-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate (**9**).* Compound **9** was prepared by the literature procedure[25] using pyrimidine **5c** and ethyl benzoylacetate on a 0.8 mmol scale (0.15 g, 51%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 3.74−3.91 (m, 8H), 4.28 (q, J = 7.1 Hz, 2H), 7.38−7.50 (m, 3H), 7.53−7.63 (m, 2H), 8.49 (s, 1H), 8.95 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 45.3, 60.3, 67.3, 122.2, 128.5, 128.9, 129.5, 130.2, 131.4, 141.1, 149.7, 151.8, 159.5, 164.3; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{21}N_4O_3$ 353.1608; found 353.1630.

*(±)-2-[[[4-[4-[(2-Diethylamino-5-nitropyrimidin-4-yl)oxy]-phenoxy]phenyl]sulfonyl]methyl]thiirane (**13**).* Compound **11** (0.27 g, 0.8 mmol) was dissolved in THF (5 mL) and the solution was cooled in ice−water bath. NaH (0.04 g, 1.0 mmol, 60% in oil) was added and the resulting suspension was stirred for 2 min. Compound **3a** (0.25 g, 1.1 mmol) was added. After 20 min, the reaction mixture was poured into ice−water, and was extracted with EtOAc. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica chromatography to give **13** as a pure product (0.13 g, 30%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.1 Hz, 4H), 2.17 (dd, J = 5.2, 1.6 Hz, 1H), 2.55 (m, J = 6.2, 1.2 Hz, 1H), 3.06 (m, J = 5.8 Hz, 1H), 3.21 (dd, J = 14.4, 7.6 Hz, 1H), 3.27 (q, J = 7.0 Hz, 2H), 3.50 (dd, J = 14.4, 5.8 Hz, 1H), 3.67 (q, J = 7.2 Hz, 2H), 7.08 (m, J = 8.8 Hz, 2H), 7.15 (m, J = 9.0 Hz, 2H), 7.24 (m, J = 9.0 Hz, 2H), 7.88 (m, J = 9.0 Hz, 2H), 9.09 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 13.2, 24.4, 26.3, 43.3, 43.6, 62.8, 117.6, 121.5, 122.7, 124.3, 131.0,

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132.3, 149.1, 152.4, 158.9, 160.4, 162.5, 163.2; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{23}H_{25}N_4O_6S_2$ 517.1210; found 517.1196.

*(±)-2-[[[4-[4-[(2-Diethylamino-5-nitropyrimidin-4-yl)amino]-phenoxy]phenyl]sulfonyl]methyl]thiirane (**14**).* Compound **14** was prepared in the same way for **13** except using **12** and iPr$_2$NEt instead of **11** and NaH on a 0.7 mmol scale (0.23 g, 62%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (q, J = 6.8 Hz, 6H), 2.17 (dd, J = 5.0, 1.5 Hz, 1H), 2.55 (d, J = 6.2 Hz, 1H), 3.07 (m, J = 6.2 Hz, 1H), 3.20 (dd, J = 14.2, 7.8 Hz, 1H), 3.51 (dd, J = 14.2, 5.7 Hz, 1H), 3.60 (q, J = 7.0 Hz, 2H), 3.73 (q, J = 7.0 Hz, 2H), 7.11 (dd, J = 9.0, 2.5 Hz, 4H), 7.71 (d, J = 9.1 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 9.11 (s, 1H), 10.42 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 12.9, 13.6, 24.4, 26.3, 43.2, 43.5, 62.8, 117.8, 120.1, 121.0, 124.4, 131.0, 132.3, 134.8, 151.6, 154.0, 158.4, 160.4, 163.2; HRMS (ESI-QTOF) m/z $[M + H]^+$ Calcd for $C_{23}H_{26}N_5O_5S_2$ 516.1370; found 516.1355.

■ ASSOCIATED CONTENT

Supporting Information

Supplementary table and figures; ^{1}H and ^{13}C NMR spectra for all compounds; crystallographic information files (CIFs) for compounds **3a**, **3c**, **3d**, **3e**, **3f-1**, **3f-2**, **3h**, **3i**, **3l**, **7a**, **7b**, **8**, **13**, and **14**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01044.

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Notes

The authors declare no competing financial interest.

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