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Design and development of arrayable syntheses to accelerate SAR studies of pyridopyrimidinone and pyrimidopyrimidinone

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ABSTRACT

Chemoselectivity of chlorine versus methylthio (–SCH_3), methylsulfinyl (–$SOCH_3$), or methylsulfonyl [–$S(O)_2CH_3$] in either functionalization or substitution of pyridopyrimidinone and pyrimidopyrimidinone was studied. Utilization to prepare final targets for accelerated SAR studies via two-dimensional array syntheses has been demonstrated in both systems.

Heterocyclic small molecules have been extensively explored by the pharmaceutical industry for the treatment of various health problems.[1] Most of the time very intense synthetic efforts have been involved in order to establish structure–activity relationships (SARs). This process is quite time-consuming, and adds significantly to the cycle-time for drug discovery. Accelerated SAR studies have thus played an important role to progress lead identification and optimization programs in a timely and competitive manner.[2] Therefore, synthesis allowing structural diversity introduced later in a sequence if not in the last step is ideally sought. This has been considered very challenging when there are two or more points of diversity to be studied. Selection of chemically reactive substituents (e.g., leaving groups) with different reaction preferences is envisioned critical for the success of these studies.[3]

Our success in this area has been recently realized in pyridopyrimidinone system (**I**, Fig. 1), whose SAR was initially explored through a stepwise synthesis allowing rapid optimization of substituents (e.g., amines) at C2.[4] A second generation synthetic route was later developed to optimize substituents at C4 on the basis of chemoselectivity displayed by 4-chlorine versus 2-methylsulfinyl (–$SOCH_3$).[5] The pyrimidopyrimidinone (**II**), a template with a structure similar to **I**, has been studied by GlaxoSmithKline and others to identify compounds that display anti-inflammatory activity.[6,7] We are interested in developing synthetic strategies that can be utilized to optimize substituents at C2 and C4 in both systems, ideally starting from a common intermediate. From the perspective of retrosynthetic analysis, identification of two leaving groups (LG_2 and LG_4) with different reaction preferences has been considered vital for success. Chlorine and methylthio (–SCH_3) have been chosen due to the early success achieved in **I**. This Letter reports our research of the relative reactivity of LG_2 (–SCH_3, –$SOCH_3$, and –SO_2CH_3) versus LG_4 (–Cl) in both templates (**III** and **IV**). Final development of arrayable syntheses leading toward **I** and **II** is also described.

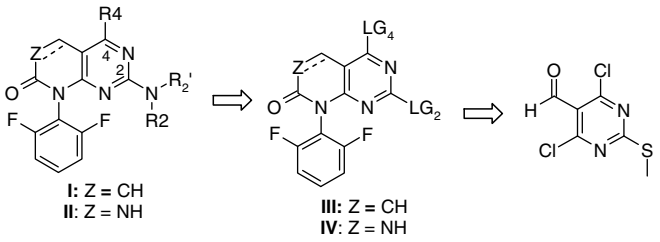

Figure 1. Retrosynthetic analysis.

Compounds in this Letter were prepared from 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde **1** (Scheme 1).[8] Nucleophilic displacement with 2,6-difluoroaniline afforded **2**. Amide formation followed by intramolecular condensation under the assistance of microwave irradiation provided **3**. Oxidation to the methyl sulfoxide **4** or the methyl sulfone **5** was achieved by controlling the amount of oxidant (e.g., *m*-CPBA) used. The pyrimidopyrimidinone ring was also prepared from **1**. Oxime formation followed by dehydration with $SOCl_2$ provided the pyrimidine nitrile **6**. Displacement with 2,6-difluoroaniline, reduction of the nitrile to a benzylamine, and ring construction with carbonyl diimidazole then furnished compound **8**. Oxidation of the sulfide to sulfoxide **9** or sulfone **10** was accomplished once again by manipulating the amount of *m*-CPBA.

With the six substrates **3**–**5** and **8**–**10** available, we were ready to investigate the chemoselectivity of 2-SMe, 2-SOMe, and 2-$S(O)_2$Me relative to 4-Cl in the two tri-substituted pyrimidinones

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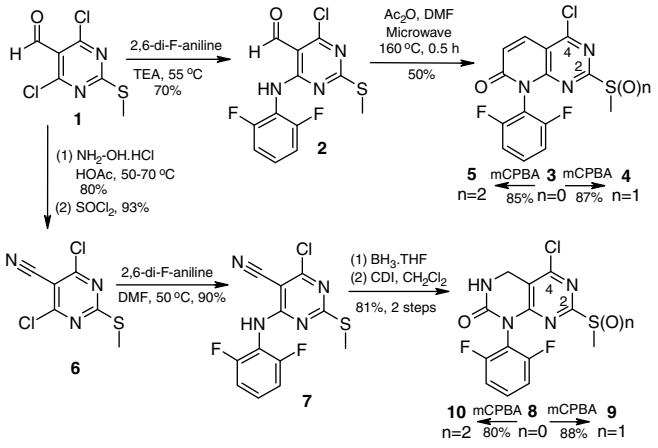
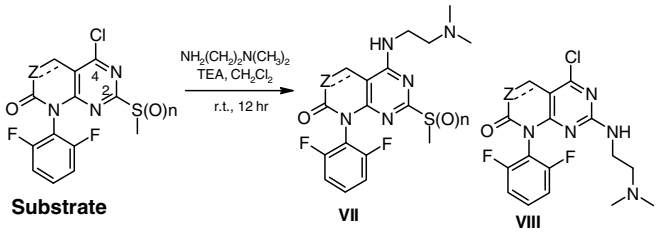


Scheme 1.

Table 2
Results of nucleophilic displacement at C2



Sub	Z	*n*	**VII**:**VIII**[a]	Yield
3	CH	0	**VII** only	81% **VII**
4	CH	1	**VIII** only	75% **VIII**
5	CH	2	1:2	—
8	NH	0	**VII** only[b]	19% **VII**
9	NH	1	**VIII** only	85% **VIII**
10	NH	2	1:1.5	—

[a] Product ratios are based on LC–MS measurement of the crude mixture.
[b] About 70% of **8** was recovered.

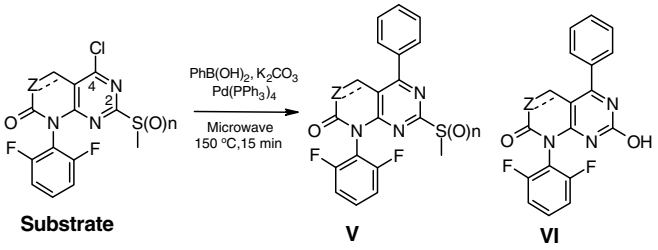
I and **II**. Reactions that were studied were the Suzuki cross-coupling at C4 and the nucleophilic displacement at C2 with amines. Standard experimental conditions have been adapted for the purpose of demonstrating application with more of general interests. Palladium-catalyzed [e.g., 0.05 equiv $Pd(PPh_3)_4$] cross-coupling with a phenyl boronic acid [1.2 equiv $PhB(OH)_2$] in the presence of K_2CO_3 (3 equiv) under microwave irradiation (150 °C, 15 min) was investigated first (Table 1).[9] The best selectivity has been demonstrated between the 4-Cl and the 2-SMe in both heterocycles, and very good yield of the desired product **V** has been achieved. Both 2-SOMe and 2-$S(O)_2$Me are labile enough to hydrolyze under the reaction conditions with a notable amount of compound **VI** being formed.

Nucleophilic displacement with amines (e.g., 1 equiv $NH_2CH_2CH_2N(CH_3)_2$) in the presence of triethyl amine (3 equiv) was studied (rt, 12 h) next (Table 2).[10] The best selectivity over 4-Cl was achieved by the 2-$SOCH_3$ substituent, and the desired compound **VIII** has been isolated with a very good yield in both templates. Limited selectivity has been displayed between the 2-$S(O)_2$Me and the 4-Cl, and approximate equal amounts of **VII** and **VIII** were formed. The 4-Cl is more reactive than the 2-SMe, and displacement at C4 (**VII**) was the major reaction in both systems. The reaction preferences of 4-Cl observed in the two fused pyrimidines are different from a simple pyrimidine system, where excellent selectivity has been achieved between a 4-Cl and a 2-SMe, 2-S(O)Me and 2-$S(O)_2$Me substituent.[11]

After 2-SMe/4-Cl and 2-SOMe/4-Cl have been identified as the best combinations for Suzuki coupling at C4 and substitution at C2, respectively, attention was directed toward developing arrayable syntheses in both systems. Starting from **3** (**Strategy A**, Scheme 2), Suzuki cross-coupling afforded the sulfide **11**. Oxidation to a mixture of sulfone/sulfoxide, followed by nucleophilic displacement then afforded the target **12**.[12] Rapid optimization of substituents (e.g., amines) at C2 have been achieved through this strategy. On the other hand, rapid optimization at C4 has been accomplished via **Strategy B.** Oxidation of **3** to the sulfoxide followed by displacement with an amine then furnished compound **13**, which is a key intermediate for rapid optimization of substituents at C4 as exemplified by a Suzuki cross-coupling reaction affording **12**. Similarly, both strategies have been readily expanded to pyrimidopyrimidinone system (Scheme 3) furnishing the desired product **15**[13] in an arrayable fashion.

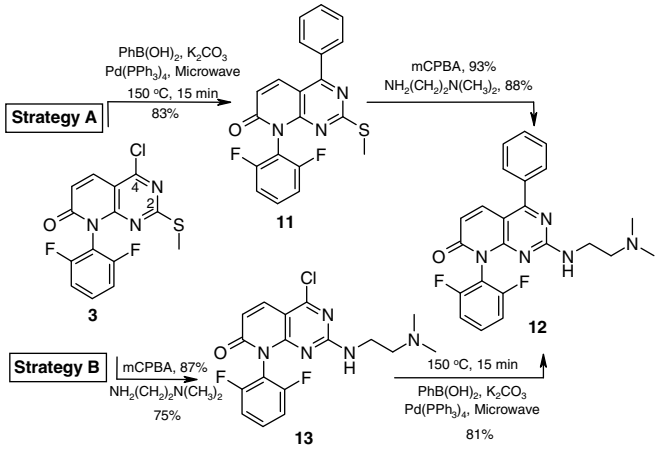
In summary, advanced pyrimidinone templates with 2-SCH_3 and 4-Cl have been prepared from a common intermediate **1**. Arrayable syntheses allowing rapid and facile access to various substituents at either C2 or C4 have been developed for both systems.

Table 1
Results of Suzuki cross-coupling at C4

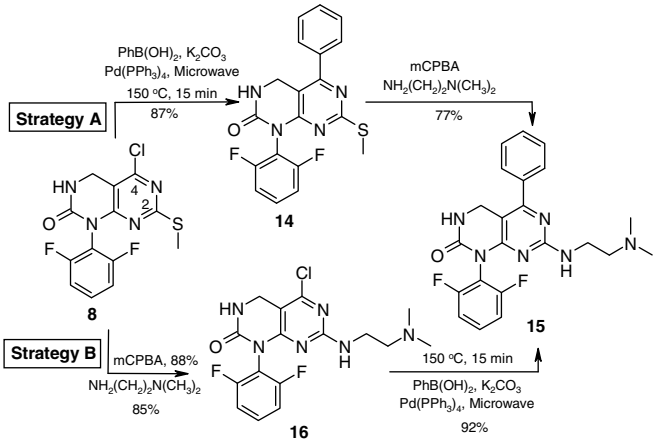


Sub	Z	*n*	**V**:**VI**[a]	Yield
3	CH	0	**V** only	83% **V**
4	CH	1	1:4	—
5	CH	2	1:17	79% **VI**
8	NH	0	**V** only	87% **V**
9	NH	1	**VI** only	64% **VI**
10	NH	2	1:27	78% **VI**

[a] Product ratios are based on LC–MS measurement of the crude mixture.



Scheme 2.



Scheme 3.

Acknowledgment

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8. Compounds **1** and **6** could be prepared according to the procedure published by: Santilli, A. A.; Dong, H. K.; Wander, S. K. *J. Heterocycl. Chem.* **1971**, *8*, 445.
9. A solution of the substrate (0.27 mmol, 1 equiv) and $PhB(OH)_2$ (1.2 equiv) in dioxane–water (3:1, 4 mL) was mixed with K_2CO_3 (3 equiv). The resultant mixture was bubbled with N_2 for 5 min before $Pd(PPh_3)_4$ (0.05 equiv) was added. The reaction vessel was sealed and irradiated using microwave irradiation at 150 °C for 15 min. Solids in the mixture were filtered off, and the relative percentage of components in this crude solution was measured with LC–MS. Separation via reverse phase HPLC where applicable then provided the product. 8-(2,6-Difluorophenyl)-2-(methylthio)-4-phenylpyrido-[2,3-*d*]pyrimidin-7(8*H*)-one (**V**, Z = CH, *n* = 0): ^{1}H NMR (400 MHz, DMSO): δ 2.3 (s, 3H), 6.8 (d, 1H, *J* = 12 Hz), 7.4–7.8 (m, 8H), 8.1 (d, 1H, *J* = 12 Hz). LC–MS (*m*/*e*) = 382 (MH+). 8-(2,6-Difluorophenyl)-2-hydroxy-4-phenylpyrido[2,3-*d*]-pyrimidin-7(8*H*)-one (**VI**, Z = CH): ^{1}H NMR (400 MHz, DMSO): δ 6.4 (d, 2H, *J* = 8 Hz), 7.4–7.7 (m, 9H). LC–MS (*m*/*e*) = 352 (MH+). 1-(2,6-Difluorophenyl)-7-(methylthio)-5-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (**V**, Z = NH, *n* = 0): ^{1}H NMR (400 MHz, DMSO): δ 2.1 (s, 3H), 4.5 (s, 2H), 7.3–7.7 (m, 8H), 8.0 (s, 1H). LC–MS (*m*/*e*) = 385 (MH+). 1-(2,6-Difluorophenyl)-7-hydroxy-5-phenyl-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (**VI**, Z = NH): ^{1}H NMR (400 MHz, DMSO): δ 4.2 (s, 2H), 7.3–7.6 (m, 8H), 8.0 (s, 1H). LC–MS (*m*/*e*) = 355 (MH+).
10. A solution of the substrate (0.2 mmol) in CH_2Cl_2 (3 mL) was mixed with triethylamine (3 equiv) and *N*,*N*-dimethyl-1,2-ethanediamine (1 equiv). The resultant solution was stirred at room temperature for about 12 h. Percentage of components in this crude solution was measured with LC–MS. Separation via reverse phase HPLC where applicable then provided the product. 8-(2,6-Difluorophenyl)-4-{[2-(dimethylamino)ethyl]amino}-2-(methylthio)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**VII**, Z = CH, *n* = 0): ^{1}H NMR (400 MHz, DMSO): δ 2.2 (s, 3H), 2.5 (s, 6H), 3.3 (t, 2H, *J* = 8 Hz), 4.0 (t, 2H, *J* = 8 Hz), 6.5 (d, 1H, *J* = 12 Hz), 7.3–7.7 (m, 3H), 8.3 (d, 1H, *J* = 12 Hz). 8.5 (br s, 1H). LC–MS (*m*/*e*) = 392 (MH+). 4-Chloro-8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)-ethyl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**VIII**, Z = CH): ^{1}H NMR (400 MHz, MeOD): δ 2.8 (s, 3H), 2.9 (s, 3H), 3.3 (m, 2H), 4.0 (m, 2H), 6.6 (d, 1H, *J* = 12 Hz), 7.2–7.6 (m, 3H), 8.1 (d, 1H, *J* = 12 Hz). LC–MS (*m*/*e*) = 380 (MH+). 1-(2,6-Difluorophenyl)-5-{[2-(dimethylamino)ethyl]-amino}-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (**VII**, Z = NH, *n* = 0): ^{1}H NMR (400 MHz, DMSO): δ 2.1 (s, 3H), 2.5 (s, 6H), 3.2 (m, 2H), 3.8 (m, 2H), 4.6 (s, 2H), 7.2 (m, 2H), 7.5 (m, 1H), 7.9 (br s, 1H), 8.3 (br s, 1H). LC–MS (*m*/*e*) = 395 (MH+).
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12. *8-(2,6-Difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-4-phenylpyrido[2,3-d]-pyrimidin-7(8H)-one* (**12**): ^{1}H NMR (400 MHz, MeOD): δ 2.6 (br s, 3H), 2.9 (br s, 3H), 3.3 (br s, 2H), 4.0 (br s, 2H), 6.5 (d, 2H, *J* = 8 Hz), 7.2–7.8 (m, 8H), 8.0 (d, 2H, *J* = 8 Hz). LC–MS (*m*/*e*) = 422 (MH+).
13. *1-(2,6-Difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-5-phenyl-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one* (**15**): ^{1}H NMR (400 MHz, MeOD): δ 2.8 (s, 6H), 3.2 (br s, 2H), 3.6 (br s, 2H), 4.5 (s, 2H), 7.2–7.7 (m, 8H). LC–MS (*m*/*e*) = 425 (MH+).