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CHEMOSELECTIVE DISPLACEMENT OF METHYLSULFINYL GROUP WITH AMINES TO PROVIDE 2-ALKYLAMINO-4,6-DISUBSTITUTED PYRIMIDINE-5-CARBOXYLIC ACID

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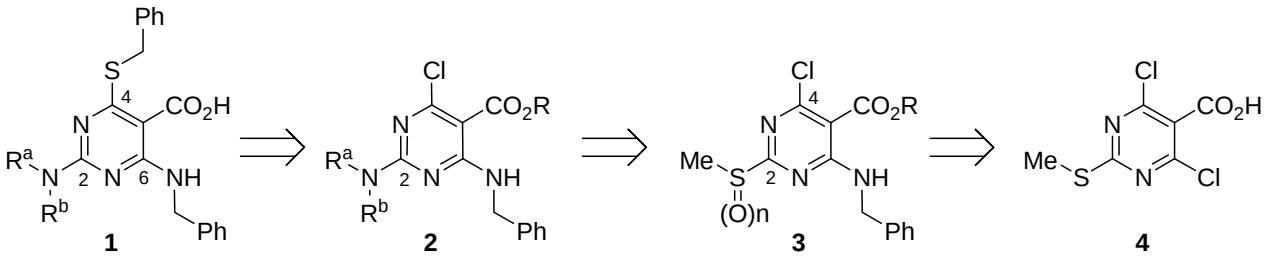
Abstract – An efficient and rapid method for introducing various kinds of alkylamines at C2 of methyl 6-(benzylamino)-4-chloro-2-(methylsulfinyl)pyrimidine-5-carboxylate using the chemoselective displacement of the methylsulfinyl group (SOMe) against a chlorine atom with amines was investigated. Further transformation led to the synthesis of 2-alkylamino-4,6-disubstituted pyrimidine-5-carboxylic acids that are of biological interest.

INTRODUCTION

Polyfunctionalized pyrimidines are attractive core structures in many biologically active compounds such as phosphodiesterase V inhibitors, protein tyrosine kinase inhibitors, and protein kinase C inhibitors.[1] In our ongoing drug research program to synthesize a novel peroxysome proliferator-activated receptor γ (PPARγ) agonist, we are focusing our attention on 2-alkylamino-4,6-disubstituted pyrimidine-5-carboxylic acid (**1**).[2] In order to explore the structural activity relationships of this scaffold, we introduced a variety of substituents at C4 and C6 using a nine-step procedure starting from pyrrolidine, which can be the substituent at C2.[3] However, this synthetic method is not efficient for introducing various kinds of substituted amino groups at C2 instead of using the pyrrolidino group. As such we planned a retrosynthetic analysis of the target compound (**1**) as shown in Scheme 1. The target compound **1** could be derived from **2**, which was constructed by chemoselective displacement of the methylsulfonyl (SO_2Me) or methylsulfinyl group (SOMe) at C2 of **3** with amines in a competitive environment with the chlorine atom at C4. Although such nucleophilic amination of pyrimidines bearing SO_2Me or SOMe has been demonstrated,[4,5] the broad scope and

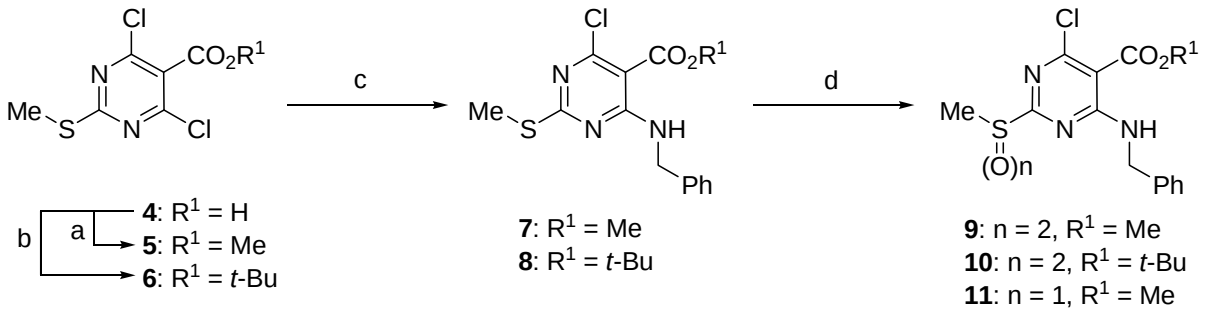
synthetic utility of this method has not been explored. Intermediate **3** could be prepared from 4,6-dichloro-2-(methylthio) pyrimidine-5-carboxylic acid (**4**)[6] in a three-step procedure. Herein, we wish to report the synthesis of 2-alkylamino-4,6-disubstituted pyrimidine-5-carboxylic acid (**1**) using chemoselective displacement of the SOMe in **3** with various kinds of amine nucleophiles as a key reaction step.



Scheme 1. Retrosynthetic analysis of target compound (*1*).

RESULTS AND DISCUSSION

The intermediate **9**–**11** was obtained by the following method as shown in Scheme 2. Esterification of **4** with methyl iodide in the presence of K_2CO_3 or with *tert*-butylacetoacetate using *c*H_2SO_4[7] afforded methyl ester **5** or *tert*-butyl ester **6** in good yield (99%, 82%, respectively). Treatment of **5** or **6** with benzylamine resulted in the displacement of the chlorine atom at C4 with a benzylamino group. Oxidation of **7** or **8** with *m*CPBA (2.2 eq of *m*CPBA was used for the preparation of **9** and **10**, 1.1 eq of *m*CPBA was used for the preparation of **11**) yielded the corresponding SO_2Me compounds (**9** and **10**) and SOMe compound (**11**).

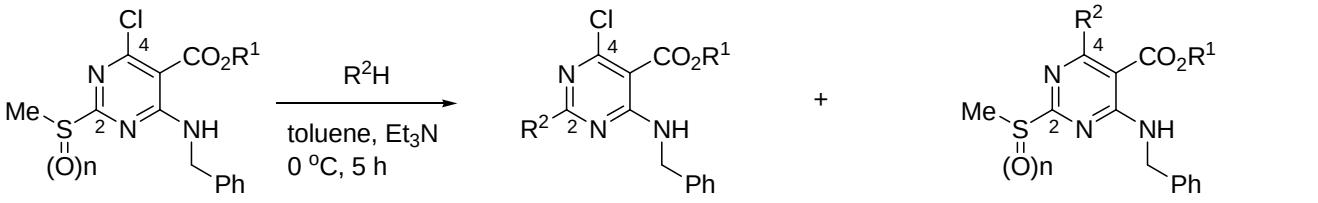


Scheme 2. *Reagent and conditions*: (a) MeI, K_2CO_3, DMF, rt, 2 h, 99%; (b) *t*-butyl acetoacetate, *c*-H_2SO_4, rt, 24 h, 82%; (c) benzylamine, Et_3N, THF, 0 °C, 1 h, 95% (for **7**), 99% (for **8**); (d) *m*CPBA (2.2 eq for **9** and **10**; 1.1 eq for **11**), THF, 0 °C, 5 h, 90% (for **9**), 85% (for **10**), 82% (for **11**).

In order to investigate a suitable pyrimidine substrate for the chemoselective displacement reaction at C2, we demonstrated the reaction with pyrrolidine or dibutylamine as an amine nucleophile in the presence of

triethylamine in toluene (Table 1). The displacement of SOMe in **9** with pyrrolidine afforded a 2-pyrrolidino derivative **12a** (59%) and a 4-pyrrolidino derivative **14a** (17%) (entry 1); however, when dibutylamine was used, this reaction provided only a modest yield of 2-butylamino derivative **12b** (23%) compared to 4-butylamino derivative **14b** (52%) (entry 2). Based on these results, we assumed that a steric effect is important for selectivity between C2 and C4. Therefore, sterically hindered *tert*-butyl ester was introduced at C5, with the aim of interrupting a C4 attack with an amine nucleophile instead of C2 (entry 3 and 4). But no significant steric effect was observed (31:69, C2:C4 for Me (entry2); 14:86 C2:C4 for *tert*-Bu (entry 4)). By contrast, there was a dramatic improvement in the ratio when SOMe compound **11** was used as a substrate (96:4 and 89:11; C2:C4 for entry 5 and 6, respectively) instead of SO_2Me compound **9** (78:22 and 31:69; C2:C4 for entry 1 and 2, respectively). This improvement effect of SOMe for the ratio is consistent with the reported results.[5]

Table 1. Amination at C2 position with pyrrolidine or dibutylamine



9: n = 2, R^1 = Me
10: n = 2, R^1 = *t*-Bu
11: n = 1, R^1 = Me

12a: R^1 = Me, R^2 = pyrrolidino
12b: R^1 = Me, R^2 = dibutylamino
13a: R^1 = *t*-Bu, R^2 = pyrrolidino
13b: R^1 = *t*-Bu, R^2 = dibutylamino

14a: n = 2, R^1 = Me, R^2 = pyrrolidino
14b: n = 2, R^1 = Me, R^2 = dibutylamino
15a: n = 2, R^1 = *t*-Bu, R^2 = pyrrolidino
15b: n = 2, R^1 = *t*-Bu, R^2 = dibutylamino
16a: n = 1, R^1 = Me, R^2 = pyrrolidino
16b: n = 1, R^1 = Me, R^2 = dibutylamino

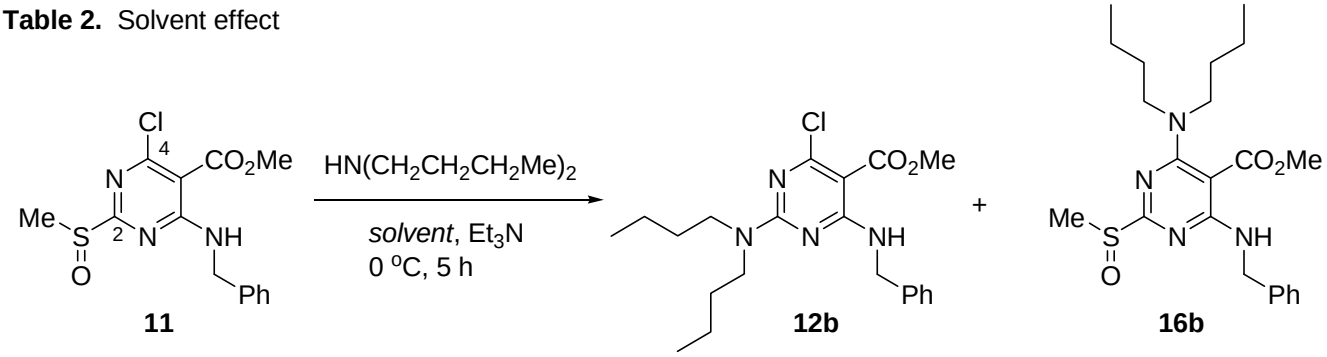
Entry	Substrate	n	R^1	R^2H	C2 displacemetnt product	C4 displacemetnt product	Ratio[a] of C2:C4
1	9	2	Me		**12a** (59%)	**14a** (17%)	78 : 22
2	9	2	Me	$HN(CH_2CH_2CH_2Me)_2$	**12b** (23%)	**14b** (52%)	31 : 69
3	10	2	tBu		**13a** (68%)	**15a** (19%)	78 : 22
4	10	2	tBu	$HN(CH_2CH_2CH_2Me)_2$	**13b** (13%)	**15b** (81%)	14 : 86
5	11	1	Me		**12a** (76%)	**16a** (3%)	96 : 4
6	11	1	Me	$HN(CH_2CH_2CH_2Me)_2$	**12b** (70%)	**16b** (9%)	89 : 11

[a] Ratio are based on isolated yield.

To explore a more optimal condition for this reaction, the solvent effect was examined as shown in Table

2. Using toluene as a solvent, the reaction gave good selectivity for C2 versus C4 (89:11, C2:C4, entry 1). However, when DMF was used as a solvent, the reaction provided only a modest level of selectivity (50:50, C2:C4, entry 3). These results indicate that a less polar solvent can be effective for the chemoselective displacement of SOMe with amine nucleophiles.

Table 2. Solvent effect



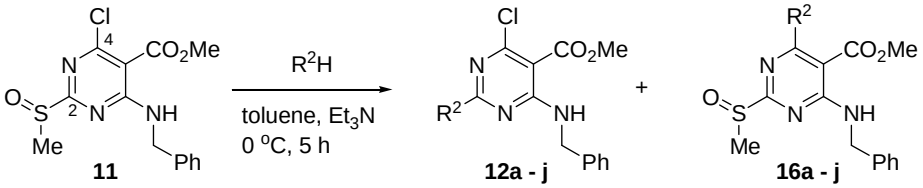
11 **12b** **16b**

Entry	Solvent	**12b**	**16b**	Ratio[a]
1	toluene	70%	9%	89 : 11
2	EtOH	49%	35%	58:42
3	DMF	40%	40%	50:50

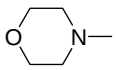
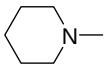
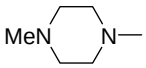
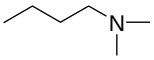
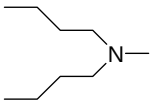
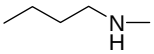
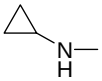
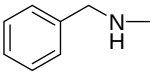
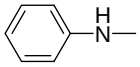
[a] Ratio are based on isolated yield.

With the optimal reaction condition achieved for the chemoselective displacement reaction of SOMe at C2, we proceeded to study the generality and efficacy of this method using methyl 6-(benzylamino)-4-chloro-2-(methylsulfinyl)pyrimidine-5-carboxylate (**11**) and a variety of amine nucleophiles (Table 3). As shown in entries 1–9, the reaction with the alkylamines afforded a series of 2-alkylamino pyrimidine-5-carboxylate derivatives in a good yield (70–92%) and with good C2 selectivity versus C4. Interestingly, a 2-anilino derivative was the sole product of this reaction when aniline was used as an amine nucleophile (entry 10), although the reason is unclear.

Table 3. Amination of methyl 4-chloro-2-(methylsulfinyl)pyrimidine-5-carboxylate (**11**)

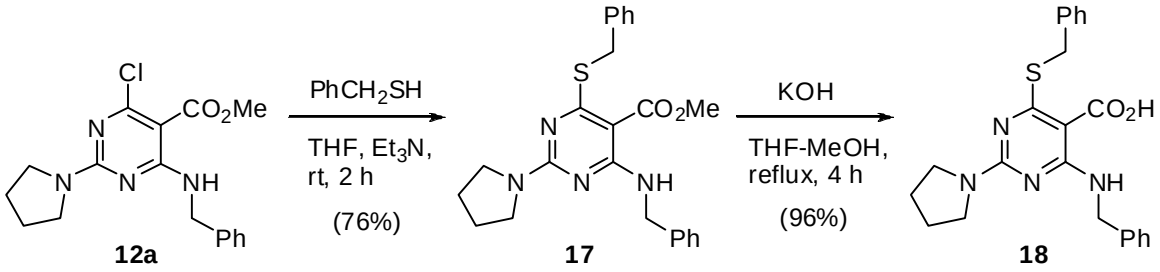


11 **12a - j** **16a - j**

Entry	R^2	C2 displacemetnt product	C4 displacemetnt product	Ratio[a]
1		**12a** (76)	**16a** (3)	96 : 4
2		**12c** (92)	**16c** (5)	95 : 5
3		**12d** (92)	**16d** (3)	97 : 3
4		**12e** (79)	**16e** (5)	94 : 6
5		**12f** (75)	**16f** (8)	90 : 10
6		**12b** (70)	**16b** (9)	89 : 11
7		**12g** (70)	**16g** (-)[b]	100 : 0
8		**12h** (75)	**16h** (7)	94 : 6
9		**12i** (75)	**16i** (4)	95 : 5
10		**12j** (-)[b]	**16j** (84)	0 : 100

[a] Ratio are based on isolated yield.
[b] Compound was not detected by TLC.

Finally, treatment of chloride **12a** with benzyl mercaptan in the presence of triethylamine, and subsequent hydrolysis of ester **17** with potassium hydroxide afforded target compound **18** in good yield.



12a **17** **18**

Scheme 3. Synthesis of new PPARγ agonist

In summary, we investigated an efficient method for introducing various kinds of amine nucleophiles at C2 of methyl 6-(benzylamino)-4-chloro-2-(methylsulfinyl)pyrimidine-5-carboxylate using a chemoselective displacement of SOMe with amines. This methodology is suitable for construction of a small library of 2-alkylamino-4,6-disubstituted pyrimidine-5-carboxylic acid derivatives that are of biological interest. The biological activity of these compounds will be reported in due course.

EXPERIMENTAL

General.

Melting points were determined with a Yamato MP-500 melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS and the solvent peak as internal standards, on a JEOL ECA-400 (400 MHz) spectrometer. Mass spectra (MS) were obtained on a Hitachi M-2000 mass spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60F254 plates, and the compounds were visualized by UV illumination (254 nm) or by heating after spraying with phosphomolybdic acid in ethanol. The data for elemental analysis are within ±0.4% of theoretical values and were determined by a Yanaco CHN corder MT-5.

Methyl 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylate (5). To a solution of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (16.7 g, 69.9 mmol) in DMF (150 mL) was added potassium carbonate (11.6 g, 83.9 mmol) and iodomethane (5.50 mL, 88.3 mmol) at 0 ^{o}C. The mixture was stirred at the same temperature for 0.5 h, and then rt for 2 h. The resulting mixture was diluted with AcOEt, and then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 10:1) of the residue gave **5** as a solid (17.6 g, 99%). Mp 48–49 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.59 (3H, s), 3.98 (3H, s). IR (neat) ν_{max} 1742, 1546, 1479, 1355, 1294, 1219 1065 cm^{-1}. HRMS (EI) calcd for $C_7H_6Cl_2N_2O_2S$ (M^+) 251.9527, found 251.9538. Anal. Calcd for $C_7H_6Cl_2N_2O_2S$: C, 33.22; H, 2.39; N, 11.07. Found: C, 32.97; H, 2.18; N, 11.05.

***tert*-Butyl 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylate (6).** To a mixture of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (2.39 g, 10.0 mmol) *tert*-butyl acetoacetate (10.3 g, 65.1 mmol) and concentrated H_2SO_4 (50 μL, 0.938 mmol) was stirred at room temperature for 24 h. The resulting mixture was diluted with ethyl acetate, then washed with water and saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 10:1) of the residue gave **6** as a solid (2.41 g, 82%). Mp 91–93 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61 (9H, s), 2.58 (3H, s). IR (neat) ν_{max}

1729, 1556, 1483, 1358, 1238, 1151, 1073 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{12}Cl_2N_2O_2S$ (M^+) 293.9997, found 293.9970. Anal. Calcd for $C_{10}H_{12}Cl_2N_2O_2S$: C, 40.69; H, 4.10; N, 9.49. Found: C, 40.15; H, 3.90; N, 9.23.

Methyl 6-(benzylamino)-4-chloro-2-(methylthio)pyrimidine-5-carboxylate (7). To a solution of methyl 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylate (**5**) (900 mg, 3.56 mmol) in THF (10 mL) was added triethylamine (0.60 mL, 4.30 mmol) and benzylamine (381 mg, 3.56 mmol) at 0 °C. The mixture was stirred at same temperature for 1 h. The resulting mixture was diluted with AcOEt, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 5:1) of the residue gave **7** as a solid (1.10 g, 95%). Mp 94–97 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.47 (3H, s), 3.89 (3H, s), 4.74 (2H, d, *J* = 6.1 Hz), 7.22–7.38 (5H, m), 8.70–8.78 (1H, br). IR (neat) ν_{max} 3320, 1670, 1571, 1542, 1385, 1313, 1195, 1060, cm^{-1}. HRMS (EI) calcd for $C_{14}H_{14}ClN_3O_2S$ (M^+) 323.0495, found 323.0500. Anal. Calcd for $C_{14}H_{14}ClN_3O_2S$: C, 51.93; H, 4.36; N, 12.98. Found: C, 51.94; H, 4.26; N, 12.98.

***tert*-Butyl 6-(benzylamino)-4-chloro-2-(methylthio)pyrimidine-5-carboxylate (8).** To a solution of *tert*-butyl 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylate (**6**) (2.30 g, 7.79 mmol) in THF (20 mL) was added triethylamine (1.30 mL, 9.33 mmol) and benzylamine (877 mg, 8.18 mmol) at 0 °C. The mixture was stirred at same temperature for 1 h. The resulting mixture was diluted with AcOEt, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 5:1) of the residue gave **8** as a solid (2.84 g, 99%). Mp 93–96 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.57 (9H, s), 2.45 (3H, s), 4.73 (2H, d, *J* = 6.1 Hz), 7.25–7.37 (5H, m), 8.61 (1H, t, *J* = 6.1 Hz). IR (neat) ν_{max} 3302, 1671, 1567, 1545, 1384, 1322, 1204, 1148 cm^{-1}. HRMS (ESI^+) calcd for $C_{17}H_{21}ClN_3O_2S$ ($M+H^+$) 366.10430, found 366.10498. Anal. Calcd for $C_{17}H_{20}ClN_3O_2S$: C, 55.81; H, 5.51; N, 11.48. Found: C, 55.44; H, 5.45; N, 11.27.

Methyl 6-(benzylamino)-4-chloro-2-(methylsulfonyl)pyrimidine-5-carboxylate (9) To a solution of methyl 4-chloro-6-(benzylamino)-2-(methylthio)pyrimidine-5-carboxylate (**7**) (4.17 g, 12.9 mmol) in THF (120 mL) was added *m*CPBA (5.00 g, 29.0 mmol) portionwise under ice cooling. The mixture was stirred for 5 h at 0 °C. The resulting mixture was diluted with AcOEt, then washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 2:1) of the residue gave **9** as a colorless solid (4.12 g, 90%). Mp 137–139 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.23 (3H, s), 3.96 (3H, s), 4.77 (2H, d, *J* = 5.5 Hz), 7.25–7.40 (5H, m), 8.72–8.81 (1H, br). IR (neat) ν_{max} 3374, 1716, 1639, 1600, 1453, 1312, 1222, 1159, 1120, 1044 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{14}ClN_3O_4S$ (M^+) 355.0394, found 355.0352. Anal. Calcd for $C_{14}H_{14}ClN_3O_4S$: C, 47.26; H, 3.97; N, 11.81. Found: C, 47.15; H, 3.81; N,

11.82.

***tert*-Butyl 6-(benzylamino)-4-chloro-2-(methylsulfonyl)pyrimidine-5-carboxylate (10)** To a solution of *tert*-butyl 4-chloro-6-(benzylamino)-2-(methylthio)pyrimidine-5-carboxylate (**8**) (1.28 g, 3.50 mmol) in CH_2Cl_2 (8 mL) was added *m*CPBA (1.51 g, 8.75 mmol) portionwise under ice cooling. The mixture was stirred for 5 h at 0 °C. The resulting mixture was diluted with AcOEt, and then washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 2:1) of the residue gave **10** as a colorless solid (1.19 g, 85%). Mp 116–119 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.59 (9H, s), 3.21 (3H, s), 4.76 (2H, d, *J* = 5.5 Hz), 7.27–7.40 (5H, m), 8.60–8.68 (1H, br). IR (neat) ν_{max} 3323, 1683, 1574, 1536, 1509, 1319, 1270, 1184, 1156, 1137, 1096, 1061 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{17}H_{21}ClN_3O_4S$ (M+H$^+$) 398.09413, found 398.09078. Anal. Calcd for $C_{17}H_{20}ClN_3O_4S$: C, 51.32; H, 5.07; N, 10.56. Found: C, 51.14; H, 4.97; N, 10.29.

Methyl 6-(benzylamino)-4-chloro-2-(methylsulfinyl)pyrimidine-5-carboxylate (11) To a solution of methyl 4-chloro-6-(benzylamino)-2-(methylthio)pyrimidine-5-carboxylate (**7**) (480 mg, 1.48 mmol) in CH_2Cl_2 (3 mL) was added *m*CPBA (289 mg, 1.67 mmol) portionwise under ice cooling. The mixture was stirred at 0 °C for 5 h. The resulting mixture was diluted with AcOEt, and then washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 2:1) of the residue gave **11** as a colorless solid (411 mg, 82%). Mp 98–100 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.87 (3H, s), 3.45 (3H, s), 4.73–4.85 (2H, m), 7.27–7.39 (5H, m), 8.72–8.80 (1H, br). IR (neat) ν_{max} 3007, 1721, 1643, 1571, 1542, 1437, 1385, 1314, 1225, 1181, 1119, 1059 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{14}H_{15}ClN_3O_3S$ (M+H$^+$) 340.05226, found 340.05320. Anal. Calcd for $C_{14}H_{14}ClN_3O_3S$: C, 49.49; H, 4.15; N, 12.37. Found: C, 49.67; H, 4.12; N, 12.08.

General procedure for displacement reaction with amine nucleophile

To a solution of methyl 4-chloro-6-(benzylamino)-2-(methylsulfinyl)pyrimidine-5-carboxylate (**11**) (0.100 mmol) in toluene (0.5 mL) were added a mixture of triethylamine (20 μL) and amine (0.101 mmol) in toluene (0.5 mL) portionwise under ice cooling. The mixture was stirred at 0 °C for 5 h. The resulting mixture was diluted with AcOEt, and then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 5:1–1:2) of the residue gave C2 displacement compounds **12a–i** and (or) C4 displacement compounds **16a–f, h–j**.

Methyl 6-(benzylamino)-4-chloro-2-pyrrolidinopyrimidine-5-carboxylate (12a)

Colorless solid; Mp 110–111 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.89–1.96 (4H, m), 3.51 (2H, t, *J* = 6.7 Hz), 3.60 (2H, t, *J* = 6.7 Hz), 3.83 (3H, s), 4.67 (2H, d, *J* = 5.5 Hz), 7.22–7.35 (5H, m), 8.77 (1H, t, *J* = 5.5 Hz). IR (neat) ν_{max} 3321, 1665, 1563, 1539, 1435, 1381, 1321, 1279, 1194, 1142, 1064 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{19}ClN_4O_2$ (M^+) 346.1197, found 346.1167. Anal. Calcd for $C_{17}H_{19}ClN_4O_2$: C, 58.87; H, 5.52; N, 16.15. Found: C, 58.87; H, 5.49; N, 16.04.

Methyl 6-(benzylamino)-2-(dibutylamino)-4-chloropyrimidine-5-carboxylate (12b)

Colorless solid; Mp 47–49 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, t, *J* = 7.3 Hz), 0.93 (3H, t, *J* = 7.3 Hz), 1.16–1.37 (4H, m), 1.42–1.60 (4H, m), 3.43 (2H, t, *J* = 7.9 Hz), 3.54 (2H, t, *J* = 7.9 Hz), 3.83 (3H, s), 4.65 (2H, d, *J* = 5.5 Hz), 7.21–7.35 (5H, m), 8.73 (1H, t, *J* = 5.5 Hz). IR (neat) ν_{max} 3320, 1654, 1563, 1531, 1436, 1418, 1372, 1312, 1260, 1227, 1198, 1123, 1058 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{29}ClN_4O_2$ (M^+) 404.1979, found 404.1955. Anal. Calcd for $C_{21}H_{29}ClN_4O_2$: C, 62.29; H, 7.22; N, 13.84. Found: C, 62.21; H, 7.26; N, 13.69.

Methyl 6-(benzylamino)-4-chloro-2-morpholinopyrimidine-5-carboxylate (12c)

Colorless solid; Mp 105–107 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.65–3.72 (4H, m), 3.75–3.83 (4H, br), 3.84 (3H, s), 4.64 (2H, d, *J* = 5.5 Hz), 7.23–7.35 (5H, m), 8.75–8.85 (1H, br). IR (neat) ν_{max} 3321, 1663, 1559, 1532, 1474, 1435, 1353, 1316, 1228, 1195, 1110 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{19}ClN_4O_3$ (M^+) 362.1146, found 362.1132. Anal. Calcd for $C_{17}H_{19}ClN_4O_3$: C, 56.28; H, 5.28; N, 15.44. Found: C, 56.43; H, 5.23; N, 15.14.

Methyl 6-(benzylamino)-4-chloro-2-piperidinopyrimidine-5-carboxylate (12d)

Colorless solid; Mp 92–93 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.47–1.68 (6H, m), 3.70–3.82 (4H, m), 3.03 (3H, s), 4.64 (2H, d, *J* = 5.5 Hz), 7.22–7.35 (5H, m), 8.72–8.80 (1H, br). IR (neat) ν_{max} 3314, 1661, 1560, 1526, 1473, 1418, 1365, 1313, 1236, 1215, 1193, 1131 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{21}ClN_4O_2$ (M^+) 360.1353, found 360.1377. Anal. Calcd for $C_{18}H_{21}ClN_4O_2$: C, 59.91; H, 5.87; N, 15.53. Found: C, 60.07; H, 5.86; N, 15.15.

Methyl 6-(benzylamino)-4-chloro-2-(4-methylpiperazinyl)pyrimidine-5-carboxylate (12e)

Colorless solid; Mp 86–88 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 2.35–2.44 (4H, br), 3.75–3.90 (4H, br), 3.84 (3H, s), 4.65 (2H, d, *J* = 5.5 Hz), 7.22–7.35 (5H, m), 8.74–8.82 (1H, br). IR (neat) ν_{max} 3315, 1672, 1564, 1531, 1436, 1363, 1303, 1238, 1217 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{22}ClN_5O_2$ (M^+) 375.1462, found 375.1467. Anal. Calcd for $C_{18}H_{22}ClN_5O_2$: C, 57.52; H, 5.90; N, 18.63. Found: C, 57.54; H, 5.85; N, 18.54.

Methyl 6-(benzylamino)-2-(*N*-butyl-*N*-methylamino)4-chloro-pyrimidine-5-carboxylate (12f)

Colorless solid; Mp 51–54 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82–0.98 (3H, m), 1.15–1.35 (2H, m), 1.40–1.63 (2H, m), 3.06 and 3.13 (3H, each s), 3.45–3.65 (2H, m), 3.84 (3H, s), 4.62–4.70 (2H, m),

7.21–7.35 (5H, m), 8.75 (1H, t, J = 5.5 Hz). IR (neat) ν_{max} 3326, 1665, 1571, 1533, 1432, 1404, 1306, 1211, 1123 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{23}ClN_4O_2$ (M^+) 362.1510, found 362.1532. Anal. Calcd for $C_{18}H_{23}ClN_4O_2$: C, 59.58; H, 6.39; N, 15.44. Found: C, 59.85; H, 6.45; N, 15.43.

Methyl 6-(benzylamino)-2-(butylamino)-4-chloropyrimidine-5-carboxylate (12g)

Colorless solid; Mp 109–110 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85–0.98 (3H, m), 1.25–1.60 (4H, m), 3.30–3.47 (2H, m), 3.84 (3H, s), 4.59–4.73 (2H, m), 5.05–5.27 (1H, m), 7.21–7.37 (5H, m), 8.59–8.95 (1H, m). IR (neat) ν_{max} 3330, 3267, 1660, 1598, 1547, 1434, 1353, 1312, 1256, 1152 cm^{-1}. HRMS (ESI^+) for $C_{17}H_{22}ClN_4O_2$ ($M+H^+$): calcd, 349.14313; found, 349.14052. Anal. Calcd for $C_{17}H_{21}ClN_4O_2$: C, 58.53; H, 6.07; N, 16.06. Found: C, 58.50; H, 6.00; N, 15.96.

Methyl 6-(benzylamino)-4-chloro-2-(cyclopropylamino)pyrimidine-5-carboxylate (12h)

Colorless solid; Mp 119–121 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.45–0.57 (2H, m), 0.68–0.84 (2H, m), 2.68–2.85 (1H, br), 3.84 (3H, s), 4.60–4.80 (2H, m), 5.27–5.42 (1H, br), 7.21–7.40 (5H, m), 8.80–8.98 (1H, br). IR (neat) ν_{max} 3260, 1660, 1563, 1523, 1438, 1348, 1254, 1139 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{17}ClN_4O_2$ (M^+) 332.1040, found 332.1048. Anal. Calcd for $C_{16}H_{17}ClN_4O_2$: C, 57.75; H, 5.15; N, 16.84. Found: C, 57.91; H, 5.10; N, 16.71.

Methyl 2,6-bis(benzylamino)-4-chloropyrimidine-5-carboxylate (12i)

Colorless solid; Mp 142–145 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (3H, s), 4.57 (2H, d, J = 5.5 Hz), 4.64 (2H, d, J = 5.5 Hz), 5.31–5.72 (1H, br), 7.17–7.40 (10H, m), 8.60–8.97 (1H, br). IR (neat) ν_{max} 3277, 1663, 1594, 1570, 1543, 1316, 1263, 1228, 1143 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{19}ClN_4O_2$ (M^+) 382.1197, found 382.1188. Anal. Calcd for $C_{20}H_{19}ClN_4O_2$: C, 62.74; H, 5.00; N, 14.63. Found: C, 62.87; H, 5.02; N, 14.60.

Methyl 6-(benzylamino)-2-(methylsulfinyl)-4-pyrrolidinopyrimidine-5-carboxylate (16a)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.85–1.95 (4H, m), 2.80 (3H, s), 3.35–3.65 (4H, br), 3.85 (3H, s), 4.66–4.78 (2H, m), 7.22–7.35 (5H, m), 8.11–8.18 (1H, br). IR (neat) ν_{max} 3347, 1670, 1572, 1505, 1455, 1337, 1218, 1073 cm^{-1}. HRMS (ESI^+) for $C_{18}H_{23}N_4O_3S$ ($M+H^+$): calcd, 375.14909; found, 375.14841.

Methyl 6-(benzylamino)-4-(dibutylamino)-2-(methylsulfinyl)pyrimidine-5-carboxylate (16b)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, t, J = 7.3 Hz), 1.22–1.33 (4H, m), 1.52–1.63 (4H, m), 2.80 (3H, s), 3.44 (4H, t, J = 7.3 Hz), 3.80 (3H, s), 4.66–4.78 (2H, m), 7.23–7.35 (5H, m), 8.22 (1H, t, J = 5.5 Hz). IR (neat) ν_{max} 3346, 1671, 1571, 1507, 1433, 1348, 1214, 1119, 1076 cm^{-1}. HRMS (ESI^+) calcd for $C_{22}H_{33}N_4O_3S$ ($M+H^+$) 433.22734, found 433.22416.

Methyl 6-(benzylamino)-2-(methylsulfinyl)-4-morpholinopyrimidine-5-carboxylate (16c)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.80 (3H, s), 3.60–3.66 (4H, m), 3.72 (4H, t, J = 4.9 Hz),

3.84 (3H, s), 4.65–4.77 (2H, m), 7.22–7.36 (5H, m), 8.35–8.42 (1H, br). IR (neat) ν_{max} 3342, 1669, 1574, 1506, 1451, 1433, 1267, 1228, 1113, 1076 cm^{-1}. HRMS (ESI^+) for $C_{18}H_{23}N_4O_4S$ ($M+H^+$): calcd, 391.14400; found, 391.14469.

Methyl 6-(benzylamino)-2-(methylsulfinyl)-4-piperidinopyrimidine-5-carboxylate (16d)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.23–1.37 (2H, m), 1.52–1.72 (4H, m), 2.80 (3H, s), 3.48–3.60 (4H, m), 3.82 (3H, s), 4.66–4.77 (2H, m), 7.21–7.35 (5H, m), 8.34 (1H, t, J = 5.5 Hz). IR (neat) ν_{max} 3341, 1669, 1573, 1506, 1442, 1377, 1346, 1244, 1202, 1076 cm^{-1}. HRMS (ESI^+) for $C_{19}H_{25}N_4O_3S$ ($M+H^+$): calcd, 389.16474; found, 389.16516.

Methyl 6-(benzylamino)-4-(4-methylpiperazinyl)-2-(methylsulfinyl)pyrimidine-5-carboxylate (16e)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.44 (4H, t, J = 4.9 Hz), 2.80 (3H, s), 3.58–3.70 (4H, m), 3.83 (3H, s), 4.65–4.78 (2H, m), 7.20–7.38 (5H, m), 8.36 (1H, t, J = 5.5 Hz). IR (neat) ν_{max} 3336, 1659, 1571, 1509 1433, 1347, 1225, 1134, 1059 cm^{-1}. HRMS (ESI^+) for $C_{19}H_{26}N_5O_3S$ ($M+H^+$): calcd, 404.17563; found, 404.17486.

Methyl 6-(benzylamino)-4-(*N*-butyl-*N*-methylamino)-2-(methylsulfinyl)pyrimidine-5-carboxylate (16f)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.3 Hz), 1.24–1.40 (2H, m), 1.57–1.66 (2H, m), 2.80 (3H, s), 2.93 (3H, s), 3.57–3.73 (2H, m), 3.11 (3H, s), 4.67–4.86 (2H, m), 7.22–7.36 (5H, m), 8.24 (1H, t, J = 5.5 Hz). IR (neat) ν_{max} 3346, 1670, 1571, 1507, 1411, 1349, 1203, 1116, 1071 cm^{-1}. HRMS (ESI^+) for $C_{19}H_{27}N_4O_3S$ ($M+H^+$): calcd, 391.18039; found, 391.18119.

Methyl 6-(benzylamino)-4-(cyclopropylamino)-2-(methylsulfinyl)pyrimidine-5-carboxylate (16h)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.50–0.60 (2H, m), 0.80–0.90 (2H, m), 2.85 (3H, s), 3.05–3.13 (1H, m), 3.87 (3H, s), 4.73–4.86 (2H, m), 7.22–7.40 (5H, m), 8.17–8.27 (1H, br), 8.40–8.52 (1H, br). IR (neat) ν_{max} 3382, 3288, 1665, 1576, 1520, 1454, 1359, 1247, 1210, 1068 cm^{-1}. HRMS (ESI^+) for $C_{17}H_{21}N_4O_3S$ ($M+H^+$): calcd, 361.13344; found, 361.13280.

Methyl 4,6-bis(benzylamino)-2-(methylsulfinyl)pyrimidine-5-carboxylate (16i)

Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.75 (3H, s), 3.87 (3H, s), 4.73–4.86 (2H, m), 7.25–7.38 (10H, m), 8.52–8.60 (2H, br). IR (neat) ν_{max} 3345, 1664, 1575, 1522, 1453, 1410, 1361, 1246, 1217 cm^{-1}. HRMS (ESI^+) for $C_{21}H_{23}N_4O_3S$ ($M+H^+$): calcd, 411.14909; found, 411.14959.

Methyl 4-anilino-6-(benzylamino)-2-(methylsulfinyl)pyrimidine-5-carboxylate (16j)

Colorless solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.82 (3H, s), 3.97 (3H, s), 4.78–4.90 (2H, m), 7.13 (1H, t, J = 7.3 Hz), 7.25–7.40 (7H, m), 7.64 (2H, d, J = 7.3 Hz), 8.40–8.50 (1H, br), 10.40–10.48 (1H, br). IR (neat) ν_{max} 3342, 1676, 1605, 1573, 1500, 1449, 1408, 1365, 1261, 1201, 1072 cm^{-1}. HRMS (ESI^+) for $C_{20}H_{21}N_4O_3S$ ($M+H^+$): calcd, 397.13344; found, 397.13327.

General procedure for the preparation of carboxylic acids 18

Step 1: To a solution of chloride **12a** (0.191 mmol) in THF (0.5 mL) were added triethylamine (50 μL, 0.359 mmol) and phenylmethanethiol (28.5 mg, 0.229 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with AcOEt, then washed with water and brine, and dried over Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 5:1) of the residue gave **17.**

Step 2: To a solution of ester **17** (0.140 mmol) in THF-MeOH (1 mL; 1:1 v/v) was added 3mol/L KOH (0.5 mL) at rt and the mixture was refluxed for 4 h. The resulting mixture was cooled to rt, then added water and 2N HCl (1 mL). The precipitate was formed and collected by filtration, and dried in vacuo to give **18.**

4-(Benzylamino)-6-(benzylthio)-2-pyrrolidinopyrimidine-5-carboxylic acid (18)

Colorless solid; Mp 164–166 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.80–1.95 (4H, m), 3.37–3.48 (2H, m), 3.48–3.62 (2H, m), 4.27 (2H, s), 4.63 (2H, d, J = 5.5 Hz), 7.17–7.40 (10H, m), 8.85–9.05 (1H, br), 12.70–13.20 (1H, br). IR (neat) ν_{max} 3351, 1623, 1561, 1526, 1423, 1336, 1304, 1284, 1191 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{23}H_{25}N_4O_2S$ (M^++1) 421.1698, found 421.1694. Anal. Calcd for $C_{23}H_{24}N_4O_2S$ 0.2H_2O: C, 65.13; H, 5.70; N, 13.21. Found: C, 64.84; H, 5.65; N, 12.95.

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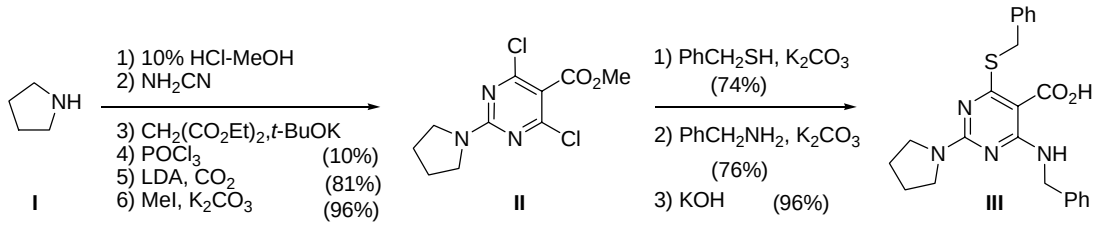

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