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Nucleophilic Substitution Reaction of Pyrimidin-2-yl Phosphates Using Amines and Thiols as Nucleophiles Mediated by PEG-400 as an Environmentally Friendly Solvent

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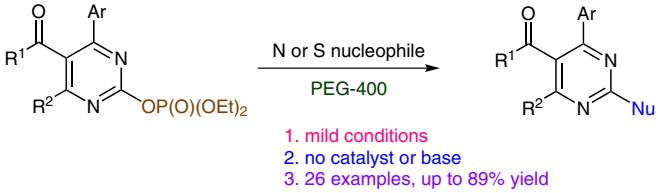

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Abstract A metal-free synthesis of C2-functionalized pyrimidines via the reaction of pyrimidin-2-yl phosphates with amines and thiophenols in PEG-400 has been developed. The desired products can be generated in good to excellent yields in the environmentally friendly PEG-400, without any catalysts or other additives.

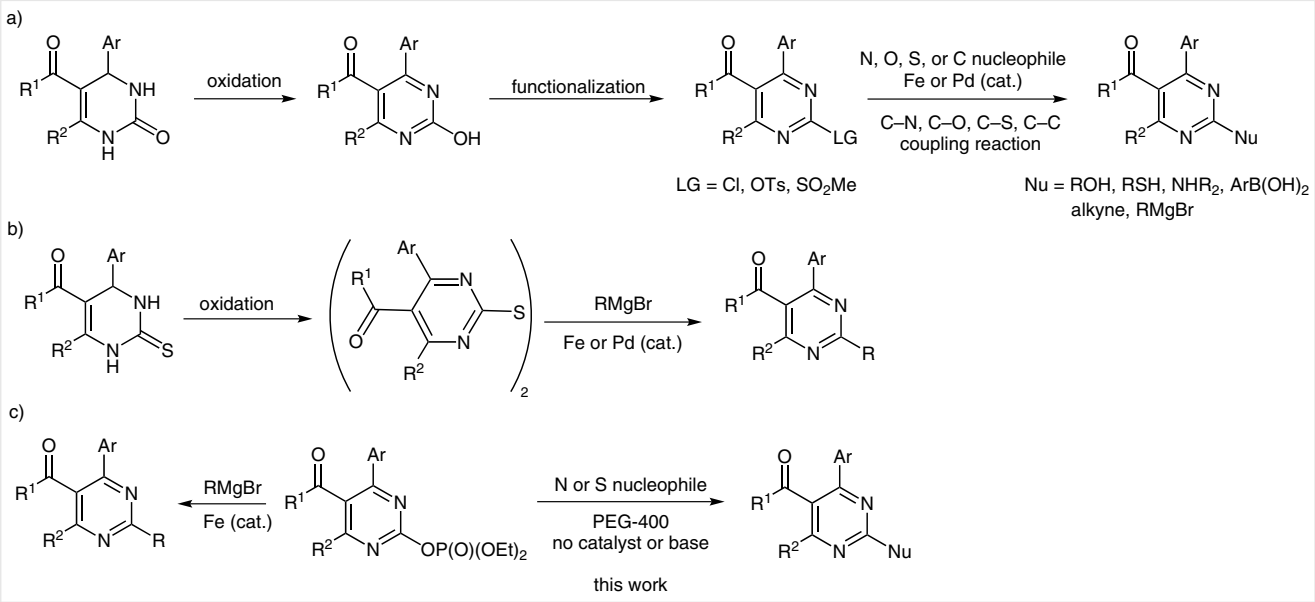
Key words C2-functionalized pyrimidines, pyrimidin-2-yl phosphates, amines, thiophenols, cross-coupling, metal-free

Developing green chemical reactions is one of the most important aims of modern organic synthesis. Poly(ethylene glycol) 400 (PEG-400) is an interesting solvent system which has many advantages over other solvents, such as thermal stability, commercial availability, nonvolatility, and immiscibility with a number of organic solvents. PEG is inexpensive, non-halogenated, and easily degradable, and possesses low toxicity.[1] Thus, PEG has received considerable attention in synthetic organic chemistry as a green organic solvent.[1d,2]

In recent years, much attention has been paid to coupling with C–O electrophiles[3] due to their ready availability from natural sources and chemical synthesis. So far, unreactive substrates such as phosphates have been identified as competent coupling partners in cross-coupling reactions. The use of phosphates has various advantages such as easy preparation and environmental friendliness. In addition, phosphates can be involved in a series of reactions, such as the Stille,[4] Negishi,[5] Suzuki–Miyaura,[6] Kumada,[7] Sonogashira,[8] and Heck reactions,[9] providing a reliable alternative to environmentally unfriendly halides.

3,4-Dihydropyrimidin-2(1*H*)-one (DHPM) is a privileged heterocyclic scaffold. Compounds containing this scaffold exhibit a wide range of pharmacological properties,[10] such as activity as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and hepatitis B virus replication inhibitors.[11] Among the DHPM derivatives, most of the pharmacologically attractive derivatives are N3- and C2-functionalized analogues.[12] The synthesis of pyrimidine derivatives[13] has attracted much attention among the many scientific research workers. However, there are only a few reports in the literature for the efficient synthesis of C2-substituted pyrimidines. In the traditional methods, C2-substituted pyrimidines have been obtained by a multistep strategy involving sequential dehydrogenation, tautomerization, activation, and base-, palladium-, or iron-catalyzed cross-coupling with a nucleophile (Scheme 1, a).[14–17] Thus, developing a new and simple methodology to prepare C2-substituted pyrimidines from the easily available Biginelli DHPM is more attractive than other methods. In 2008, Srinivasan and co-workers reported an efficient regioselective approach to the synthesis of tetrasubstituted pyrimidines by sequential functionalization of easily available Biginelli DHPMs via dehydrogenation and chlorination, followed by a palladium-catalyzed Suzuki/Sonogashira coupling reaction (Scheme 1, a).[14c] In 2010, our group reported the synthesis of 4-arylpyrimidin-2-yl tosylates and their utilization in the formation of C2-substituted pyrimidines.[16a] Then, we developed procedures for the synthesis of C2-substituted pyrimidines via the cross-coupling reactions of pyrimidin-2-yl sulfonates.[16b–d] We also developed the iron- or palladium-catalyzed C–S or C–C cross-coupling reaction of 1,2-di(pyrimidin-2-yl) disulfides with Grignard reagents (Scheme 1, b).[17]

More recently, we expanded the synthetic method for C2-substituted pyrimidines by a Kumada cross-coupling reaction of pyrimidin-2-yl phosphates with Grignard reagents (Scheme 1, c).[18] Herein, we explored the possible application of pyrimidin-2-yl phosphates in the diversification of the pyrimidine motif by functionalization with



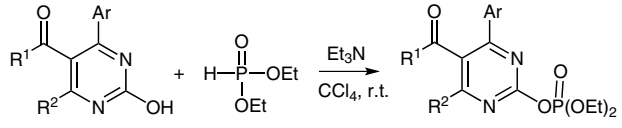
Scheme 1 Synthesis of C2-functionalized pyrimidines derived from DHPMs

amino and thioether groups (Scheme 1, c). Notably, the reaction delivered the desired C2-substituted pyrimidines under mild reaction conditions, with no requirement for catalysts, additives, or bases, and an easy-to-handle procedure which make this method more attractive than other methods.

According to our previous report,[18] the pyrimidin-2-yl phosphates **3** were prepared by the reaction of 2-hydroxypyrimidines **1** with diethyl phosphonate (**2**) in the presence of a triethylamine in carbon tetrachloride system (Table 1).

Initially, the cross-coupling reaction between pyrimidin-2-yl phosphate **3a** and piperidine (**4a**) was explored as the model reaction (Table 2). At first, we tested a diverse set of temperatures (Table 2, entries 1–4). When the reaction was carried out at room temperature, the starting material

Table 1 Preparation of the Pyrimidin-2-yl Phosphates **3**[a]

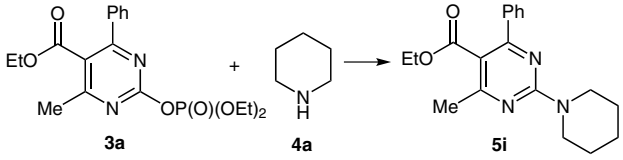


1 **2** **3**

Entry	Ar	R^1	R^2	Product **3**	Yield[b] (%)
1	Ph	OEt	Me	**3a**	82
2	4-Tol	OEt	Me	**3b**	76
3	4-$MeOC_6H_4$	OEt	Me	**3c**	70
4	4-FC_6H_4	OEt	Me	**3d**	79
5	4-ClC_6H_4	OEt	Me	**3e**	84
6	4-BrC_6H_4	OEt	Me	**3f**	75
7	4-$O_2NC_6H_4$	OEt	Me	**3g**	80
8	2-Tol	OEt	Me	**3h**	82
9	2-ClC_6H_4	OEt	Me	**3i**	83
10	Ph	OEt	*i*-Pr	**3j**	78
11	Ph	OMe	Me	**3k**	88

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.9 mmol), Et_3N (1.8 mmol), CCl_4 (2 mL), r.t., 20 min.
[b] Isolated yield after column chromatography.

Table 2 Optimization of the Reaction of Pyrimidin-2-yl Phosphate **3a** with Piperidine (**4a**)[a]

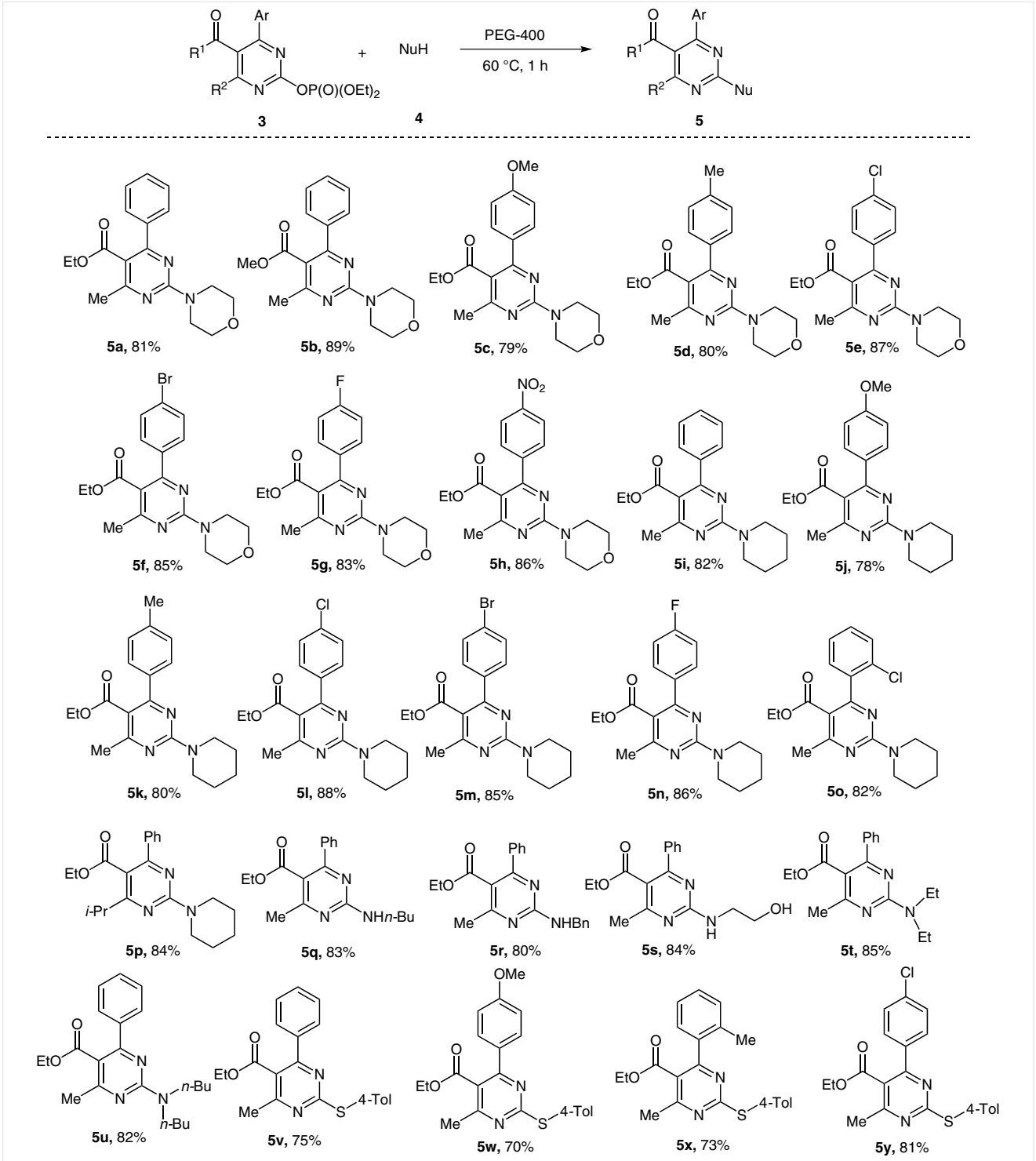


3a **4a** **5i**

Entry	Solvent	Temp (°C)	Yield[b] (%)	Entry	Solvent	Temp (°C)	Yield[b] (%)
1	PEG-400	r.t.	75	8	PEG-6000[c]	60	65
2	PEG-400	60	82	9	DMSO	60	80
3	PEG-400	80	83	10	DMF	60	81
4	PEG-400	110	85	11	dioxane	60	70
5	PEG-400	60	82[d]	12	THF	60	72
6	PEG-2000[c]	60	68	13	H_2O	60	50
7	PEG-4000[c]	60	73	14	EtOH	60	78

[a] Reaction conditions: **3a** (1.0 mmol), **4a** (1.5 mmol), solvent (3 mL), 1 h.
[b] Isolated yield after column chromatography.
[c] PEG (2 g) was used.
[d] Reaction time was prolonged to 2 h.

was not completely consumed and the yield was only 75%. The starting material was consumed when the temperature was increased to 60 °C, 80 °C, or 110 °C; however, increasing the temperature to 80 °C or 110 °C only resulted in a slight further increase in the yield. So, we chose 60 °C as the optimum temperature. Then, when the reaction time was prolonged from 1 hour to 2 hours, the yield was unchanged (Table 2, entry 5 vs 2). Finally, the effect of the solvent on



Scheme 2 Cross-coupling reactions of pyrimidin-2-yl phosphates **3** with N and S nucleophiles

this reaction was also investigated. Different kinds of solvents (such as PEG-2000, DMSO, DMF, dioxane, THF, H_2O, and EtOH) were tested, as well as PEG-400 which proved superior (Table 2, entry 2 vs 6–14). From the perspective of environmental protection and the productivity, we finally selected PEG-400 as the best solvent. Thus, on the basis of all of these results, PEG-400 as solvent at 60 °C for 1 hour was selected as our optimized reaction conditions for the cross-coupling reaction between pyrimidin-2-yl phosphate **3a** and piperidine (**4a**).

With the optimized conditions in hand, various pyrimidin-2-yl phosphates **3** and a diverse set of nucleophiles **4** were used to test the scope of the reaction (Scheme 2). In general, moderate to good yields (70–89%) of the C2-functionalized pyrimidines **5** were obtained under the standard reaction conditions. The nature of substituents on the heterocyclic fragment of the phosphate esters did not play a significant role in this reaction. We found that pyrimidin-2-yl phosphates **3** bearing an electron-withdrawing group (Cl, Br, F, NO_2) on the phenyl ring provided higher yields than those compounds containing an electron-donating group (OMe, Me). Cyclic secondary amines (morpholine or piperidine) as the nucleophile were the most successful in this process, being completely consumed to provide **5a**–**p**. Acyclic amines also gave promising results; thus, primary amines and secondary amines gave satisfactory results (see **5q**–**u**). However, aromatic amines failed to react, even under higher temperatures and longer reaction times (not shown in Scheme 2). We next turned our attention to sulfur and oxygen nucleophiles by treating pyrimidin-2-yl phosphates **3** with 1.5 equivalents of S and O nucleophiles in PEG-400 at 60 °C. The reaction of phosphates **3** and *p*-thiocresol proceeded smoothly without base, to give **5v**–**y**.

Furthermore, diethyl 6-methyl-2-(phenylamino)pyrimidin-4-yl phosphate (**3l**) was prepared[18] and treated with *p*-thiocresol, giving the C–S coupling product **5z** in 80% yield (Scheme 3).

When alcohols were involved, the reaction with pyrimidin-2-yl phosphates **3** failed. When sodium *tert*-butoxide, potassium carbonate, or tripotassium phosphate was added to the system, most of the corresponding starting 2-hydroxypyrimidine **1** was recovered, which shows that hydrolysis of the phosphates may occur. From our previous work,[16a] the cross-coupling reactions of pyrimidin-2-yl sulfonates with alcohols can proceed upon prolonging the reaction time and the use of strongly basic conditions; however, the hydrolysis of phosphates can take place in the presence of alkali.

We also examined the cross-coupling reactions of pyrimidin-2-yl phosphates **3** with other nitrogenated nucleophiles, such as benzamide, carbamates, and sulfonamides. Unfortunately, we found that we could not obtain the target products in PEG-400, even when different kinds of bases were added to the system.[19]

In summary, we have developed a simple, rapid, and environmentally benign methodology for the synthesis of C2-substituted pyrimidines via the nucleophilic substitution reaction of reactive pyrimidin-2-yl phosphates with different nitrogen and sulfur nucleophiles. The reaction is carried out in PEG-400 as an environmentally friendly solvent and proceeds efficiently to give various C2–N- and C2–S-functionalized products in high yields under catalyst-, base-, and ligand-free conditions.

Commercially available reagents were used without further purification, unless otherwise stated. Melting points were measured on an XT-4 apparatus and are uncorrected. IR spectra were recorded using KBr pellets on a Nicolet Avatar 360 FT-IR spectrophotometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on either a Varian V-NMRS 600 or Mercury Plus-400 instrument using $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEX II 47e mass spectrometer. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were performed on silica gel GF254 plates.

Pyrimidin-2-yl Phosphates 3a–3l; General Procedure

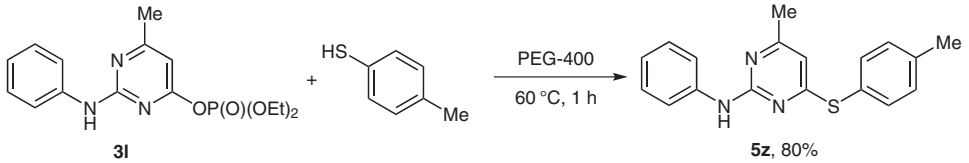
Et_3N (0.25 mL, 1.8 mmol) was slowly added to a mixture of a 2-hydroxypyrimidine **1** (0.6 mmol), diethyl phosphonate (**2**; 124.3 mg, 0.9 mmol), and CCl_4 (2 mL), and then the mixture was stirred at r.t. for 20 min. After the starting material **1** had been consumed (monitored by TLC), the product was purified by flash chromatography on silica gel using petroleum ether–EtOAc (4:1) to EtOAc as eluent to provide the corresponding pyrimidin-2-yl phosphate **3**.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-methyl-6-phenylpyrimidine-5-carboxylate (3a)[18]

Yield: 194 mg (82%); yellow oil.

IR (KBr): 2980 (m), 1718 (s), 1595 (s), 1570 (s), 1492 (s), 1448 (s), 1386 (s), 1208 (s), 1163 (m), 1080 (s), 1030 (vs) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 6.8 Hz, 2 H, ArH), 7.40–7.37 (m, 3 H, ArH), 4.32 [q, *J* = 7.6 Hz, 4 H, $P(O)(OCH_2CH_3)_2$], 4.14–4.10 (m, 2 H, OCH_2), 2.54 (s, 3 H, CH_3), 1.31 [t, *J* = 6.4 Hz, 6 H, $P(O)(OCH_2CH_3)_2$], 0.99 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).



3l **5z**, 80%

Scheme 3 Cross-coupling reaction of pyrimidin-2-yl phosphate **3l** with *p*-thiocresol

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.94, 166.92, 166.47, 158.55, 136.43, 130.15, 128.12 (2 C), 128.01 (2 C), 122.65, 64.87, 64.81, 61.56, 22.08, 15.62, 15.55, 13.13.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.37.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{24}N_2O_6P$: 395.1366; found: 395.1368.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-methyl-6-(*p*-tolyl)pyrimidine-5-carboxylate (3b)[18]

Yield: 192 mg (76%); yellow oil.

IR (KBr): 2980 (m), 1720 (s), 1610 (w), 1560 (s), 1510 (s), 1438 (s), 1038 (vs), 576 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.6 Hz, 2 H, ArH), 7.25 (d, *J* = 7.2 Hz, 2 H, ArH), 4.41–4.36 [m, 4 H, P(O)(OCH_2CH_3)$_2$], 4.22 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.60 (s, 3 H, Ar-CH_3), 2.40 (s, 3 H, CH_3), 1.38 [t, *J* = 6.8 Hz, 6 H, P(O)(OCH_2CH_3)$_2$], 1.11 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.85, 167.43, 166.46, 158.67, 140.74, 133.65, 128.98 (2 C), 128.20 (2 C), 122.52, 65.05, 64.99, 61.72, 22.30, 21.14, 15.85, 15.78, 13.42.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.12.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}N_2O_6P$: 409.1523; found: 409.1525.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (3c)[18]

Yield: 177 mg (70%); yellow oil.

IR (KBr): 2983 (m), 1716 (s), 1610 (s), 1580 (s), 1510 (s), 1476 (w), 1448 (s), 1260 (s), 1034 (vs), 958 (m), 570 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.2 Hz, 2 H, ArH), 6.95 (d, *J* = 7.2 Hz, 2 H, ArH), 4.39 [q, *J* = 7.2 Hz, 4 H, P(O)(OCH_2CH_3)$_2$], 4.24 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 2.59 (s, 3 H, CH_3), 1.38 [t, *J* = 6.8 Hz, 6 H, P(O)(OCH_2CH_3)$_2$], 1.15 (t, *J* = 6.0 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.77, 167.72, 165.76, 161.53, 158.64, 130.04 (2 C), 128.73, 122.09, 113.75 (2 C), 65.11, 65.05, 61.82, 55.19, 22.36, 15.92, 15.84, 13.58.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.10.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}N_2O_7P$: 425.1472; found: 425.1470.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (3d)[18]

Yield: 194 mg (79%); yellow oil.

IR (KBr): 2984 (m), 1716 (s), 1610 (s), 1560 (s), 1544 (s), 1448 (s), 1090 (s), 1034 (vs), 560 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 4.0 Hz, 2 H, ArH), 7.14 (t, *J* = 7.6 Hz, 2 H, ArH), 4.39 [q, *J* = 7.2 Hz, 4 H, P(O)(OCH_2CH_3)$_2$], 4.22 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.61 (s, 3 H, CH_3), 1.38 [t, *J* = 6.8 Hz, 6 H, P(O)(OCH_2CH_3)$_2$], 1.12 (t, *J* = 6.0 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.46, 167.40, 165.54, 162.96, 158.88, 132.84, 130.66 (2 C), 130.58 (2 C), 122.74, 115.78 (2 C), 115.56 (2 C), 65.32, 65.26, 62.07, 22.59, 16.06, 15.99, 13.66.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.14.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}FN_2O_6P$: 413.1272; found: 413.1278.

Ethyl 4-(4-Chlorophenyl)-2-[(diethoxyphosphoryl)oxy]-6-methylpyrimidine-5-carboxylate (3e)[18]

Yield: 215 mg (84%); yellow solid; mp 80–82 °C.

IR (KBr): 2984 (m), 1720 (s), 1596 (s), 1544 (s), 1492 (w), 1438 (s), 1396 (s), 1090 (s), 1032 (vs), 578 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.62 (m, 2 H, ArH), 7.45–7.42 (m, 2 H, ArH), 4.42–4.35 [m, 4 H, P(O)(OCH_2CH_3)$_2$], 4.25–4.21 (m, 2 H, OCH_2), 2.62 (s, 3 H, CH_3), 1.39 [t, *J* = 6.8 Hz, 6 H, P(O)(OCH_2CH_3)$_2$], 1.13 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.55, 167.18, 165.40, 158.87, 136.89, 135.10, 129.76 (2 C), 128.73 (2 C), 122.73, 65.26, 65.20, 62.06, 22.54, 16.00, 15.93, 13.59.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.15.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}ClN_2O_6P$: 429.0977; found: 429.0980.

Ethyl 4-(4-Bromophenyl)-2-[(diethoxyphosphoryl)oxy]-6-methylpyrimidine-5-carboxylate (3f)[18]

Yield: 211 mg (75%); white solid; mp 93–95 °C.

IR (KBr): 2980 (m), 1715 (s), 1594 (s), 1580 (s), 1514 (s), 1448 (s), 1255 (s), 1035 (vs), 690 (m), 575 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.54 (m, 4 H, ArH), 4.40–4.38 [m, 4 H, P(O)(OCH_2CH_3)$_2$], 4.22 (q, *J* = 6.8 Hz, 2 H, OCH_2), 2.62 (s, 3 H, CH_3), 1.39 [t, *J* = 6.4 Hz, 6 H, P(O)(OCH_2CH_3)$_2$], 1.13 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.58, 167.14, 165.46, 158.87, 135.53, 131.69 (2 C), 129.94 (2 C), 125.26, 122.68, 65.26, 65.20, 62.07, 22.55, 16.00, 15.93, 13.59.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.17.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}BrN_2O_6P$: 473.0472; found: 473.0476.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-methyl-6-(4-nitrophenyl)pyrimidine-5-carboxylate (3g)

Yield: 210 mg (80%); white solid; mp 70–72 °C.

IR (KBr): 2984 (m), 1720 (s), 1560 (m), 1544 (m), 1256 (s), 1032 (m), 580 (m), 508 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.32 (m, 2 H, ArH), 7.86–7.84 (m, 2 H, ArH), 4.42–4.39 [m, 4 H, P(O)(OCH_2CH_3)$_2$], 4.24 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.67 (s, 3 H, CH_3), 1.41 [t, *J* = 7.2 Hz, 6 H, P(O)(OCH_2CH_3)$_2$], 1.13 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.32, 166.51, 164.51, 158.94, 148.84, 142.64, 129.51 (2 C), 123.59 (2 C), 123.08, 65.37, 65.33, 62.30, 22.75, 16.01, 15.96, 13.61.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.27.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}N_3O_8P$: 440.1217; found: 440.1215.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-methyl-6-(*o*-tolyl)pyrimidine-5-carboxylate (3h)

Yield: 200 mg (82%); yellow oil.

IR (KBr): 2950 (w), 1718 (s), 1610 (s), 1565 (s), 1516 (s), 1448 (s), 1034 (vs), 575 (m) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 1 H, ArH), 7.25–7.23 (m, 1 H, ArH), 7.19–7.16 (m, 1 H, ArH), 7.10 (d, *J* = 5.2 Hz, 1 H, ArH), 4.36–4.33 [m, 4 H, P(O)$(OCH_2CH_3)_2$], 4.01–3.99 (m, 2 H, OCH_2), 2.63 (s, 3 H, Ar-CH_3), 2.25 (s, 3 H, CH_3), 1.36–1.33 [m, 6 H, P(O)$(OCH_2CH_3)_2$], 0.86–0.84 (m, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.62, 169.38, 166.47, 136.76, 135.93, 130.38 (2 C), 129.34 (2 C), 127.88 (2 C), 125.39 (2 C), 65.35, 65.29, 61.62, 22.86, 19.55, 16.04, 15.97, 13.34.

^{31}P NMR (243 MHz, $CDCl_3$): δ = –7.07.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}N_2O_6P$: 409.1523; found: 409.1520.

Ethyl 4-(2-Chlorophenyl)-2-[(diethoxyphosphoryl)oxy]-6-methylpyrimidine-5-carboxylate (3i)

Yield: 212 mg (83%); yellow oil.

IR (KBr): 2980 (m), 1715 (s), 1603 (s), 1565 (s), 1544 (s), 1252 (m), 1098 (s), 1032 (vs), 556 (m) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 5.2 Hz, 1 H, ArH), 7.35–7.34 (m, 1 H, ArH), 7.31 (s, 2 H, ArH), 4.35 [q, *J* = 4.8 Hz, 4 H, P(O)$(OCH_2CH_3)_2$], 4.04 (q, *J* = 4.8 Hz, 2 H, OCH_2), 2.68 (s, 3 H, CH_3), 1.34 [t, *J* = 4.4 Hz, 6 H, P(O)$(OCH_2CH_3)_2$], 0.89 (t, *J* = 4.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.72, 167.12, 165.53, 158.81, 136.70, 131.89, 130.45 (2 C), 129.98 (2 C), 129.38 (2 C), 126.64 (2 C), 123.51, 65.42, 65.38, 61.64, 23.47, 16.02, 15.97, 13.34.

^{31}P NMR (243 MHz, $CDCl_3$): δ = –7.30.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}ClN_2O_6P$: 429.0977; found: 429.0982.

Ethyl 2-[(Diethoxyphosphoryl)oxy]-4-isopropyl-6-phenylpyrimidine-5-carboxylate (3j)

Yield: 197 mg (78%); colorless oil.

IR (KBr): 2976 (w), 1720 (s), 1544 (s), 1398 (m), 1244 (s), 1030 (s), 828 (w), 622 (w) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2 H, ArH), 7.43–7.38 (m, 3 H, ArH), 4.36–4.32 [m, 4 H, O$(CH_2CH_3)_2$], 4.14 (q, *J* = 4.8 Hz, 2 H, OCH_2), 3.22–3.15 (m, 1 H, CH), 1.34 [t, *J* = 4.8 Hz, 6 H, CH$(CH_3)_2$], 1.30 [d, *J* = 4.8 Hz, 6 H, P(O)$(OCH_2CH_3)_2$], 1.02 (t, *J* = 4.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.09, 167.58, 167.56, 166.78, 159.39, 159.37, 136.90, 130.32, 128.41 (2 C), 128.33 (2 C), 122.32, 65.06, 65.02, 61.92, 33.29, 21.55 (2 C), 16.05, 16.00, 13.53.

^{31}P NMR (243 MHz, $CDCl_3$): δ = –8.13.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{28}N_2O_6P$: 423.1679; found: 423.1685.

Methyl 2-[(Diethoxyphosphoryl)oxy]-4-methyl-6-phenylpyrimidine-5-carboxylate (3k)[18]

Yield: 200 mg (88%); colorless oil.

IR (KBr): 2983 (m), 1716 (s), 1598 (s), 1498 (s), 1445 (s), 1383 (s), 1218 (s), 1160 (m), 1050 (s), 1035 (vs), 802 (m), 585 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 2 H, ArH), 7.48–7.45 (m, 3 H, ArH), 4.41–4.37 [m, 4 H, $(OCH_2CH_3)_2$], 3.71 (s, 3 H, OCH_3), 2.61 (s, 3 H, CH_3), 1.40–1.37 [m, 6 H, $(OCH_2CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.26, 167.86, 166.60, 158.84, 136.46, 130.49, 128.41 (2 C), 128.13 (2 C), 122.41, 65.18, 65.12, 52.56, 22.48, 15.92, 15.84.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –7.15.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}N_2O_6P$: 381.1210; found: 381.1214.

Diethyl 6-Methyl-2-(phenylamino)pyrimidin-4-yl Phosphate (3l)[18]

Yield: 172 mg (85%); white solid; mp 100–102 °C.

IR (KBr): 3215 (s), 2980 (m), 1715 (s), 1610 (s), 1575 (s), 1498 (s), 1440 (s), 1350 (s), 1030 (vs), 585 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.64 (m, 2 H, ArH), 7.35–7.27 (m, 2 H, ArH), 7.20 (s, 1 H, ArH), 7.06–7.03 (m, 1 H, ArH), 6.31 (s, 1 H, NH), 4.30–4.25 [m, 4 H, $(OCH_2CH_3)_2$], 2.40 (s, 3 H, CH_3), 1.35 [t, *J* = 7.2 Hz, 6 H, $(OCH_2CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.20, 164.73, 164.68, 159.42, 138.98, 128.78 (2 C), 122.73, 119.48 (2 C), 99.53, 99.46, 64.99, 64.93, 24.15, 16.04, 15.97.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –6.86.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}N_3O_4P$: 338.1254; found: 338.1251.

C2-Functionalized Pyrimidines 5a–z; General Procedure

To a stirred mixture of a pyrimidin-2-yl phosphate **3**[18] (0.4 mmol) in PEG-400 (3 mL) was added a nucleophile (0.6 mmol) at 60 °C. After the reaction mixture was stirred at 60 °C for 1 h (TLC monitoring), it was extracted with water (10 mL) and EtOAc (30 mL). Then, the organic layers were dried over Na_2SO_4. The crude product was purified by flash chromatography using petroleum ether–EtOAc (15:1) to EtOAc as eluent for **5a**–**u**, and petroleum ether–EtOAc (30:1) to EtOAc as eluent for **5v**–**z**, to give the pure product **5**.

Ethyl 4-Methyl-2-morpholino-6-phenylpyrimidine-5-carboxylate (5a)[16a]

Yield: 106 mg (81%); white solid; mp 118–119 °C.

IR (KBr): 2964 (w), 1718 (vs), 1560 (s), 1512 (s), 1492 (s), 1444 (s), 1232 (s), 690 (vw), 576 (vw) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.40 (m, 5 H, ArH), 4.08–4.03 (m, 2 H, OCH_2), 3.94–3.92 [m, 4 H, N$(CH_2)_2$], 3.76 [t, *J* = 4.80 Hz, 4 H, O$(CH_2)_2$], 2.50 (s, 3 H, CH_3), 0.95 (t, *J* = 7.60 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.96, 167.03, 165.66, 160.20, 139.30, 129.46, 128.16 (2 C), 128.06 (2 C), 114.48, 66.87 (2 C), 60.99, 44.10 (2 C), 23.14, 13.54.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}N_3O_3$: 328.1656; found: 328.1661.

Methyl 4-Methyl-2-morpholino-6-phenylpyrimidine-5-carboxylate (5b)

Yield: 111 mg (89%); colorless oil.

IR (KBr): 2952 (w), 1718 (vs), 1638 (s), 1560 (s), 1490 (s), 1458 (s), 1068 (s), 1024 (m), 766 (vw) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.58 (m, 2 H, ArH), 7.41 (d, *J* = 4.8 Hz, 3 H, ArH), 3.93–3.91 [m, 4 H, N$(CH_2)_2$], 3.76–3.74 [m, 4 H, O$(CH_2)_2$], 3.58 (s, 3 H, OCH_3), 2.49 (s, 3 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.51, 167.05, 165.41, 160.29, 139.17, 129.54, 128.19 (2 C), 128.00 (2 C), 114.19, 66.84 (2 C), 51.86, 44.13 (2 C), 23.16.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O_3$: 314.1499; found: 314.1501.

Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (5c)[16a]

Yield: 113 mg (79%); white solid; mp 72–74 °C.

IR (KBr): 2960 (w), 1715 (vs), 1592 (s), 1581 (s), 1492 (s), 1446 (s), 1230 (s), 1050 (s), 1034 (s), 850 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 9.20 Hz, 2 H, ArH), 6.93 (d, *J* = 8.40 Hz, 2 H, ArH), 4.11–4.10 (m, 2 H, OCH_2), 3.93–3.91 [m, 4 H, $N(CH_2)_2$], 3.84 (s, 3 H, OCH_3), 3.75 [t, *J* = 4.80 Hz, 4 H, $O(CH_2)_2$], 2.47 (s, 3 H, CH_3), 1.05 (t, *J* = 7.20 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.32, 166.63, 164.68, 160.88, 160.15, 131.50, 129.69 (2 C), 114.19, 113.58 (2 C), 66.86 (2 C), 55.34, 55.30, 44.10 (2 C), 23.05, 13.74.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}N_3O_4$: 358.1761; found: 358.1768.

Ethyl 4-Methyl-2-morpholino-6-(*p*-tolyl)pyrimidine-5-carboxylate (5d)[16a]

Yield: 109 mg (80%); white solid; mp 68–70 °C.

IR (KBr): 2964 (s), 1716 (vs), 1584 (s), 1560 (vs), 1510 (s), 1448 (m), 1234 (s), 1016 (s), 796 (s), 594 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.00 Hz, 2 H, ArH), 7.22 (d, *J* = 8.00 Hz, 2 H, ArH), 4.12–4.07 (m, 2 H, OCH_2), 3.92 [t, *J* = 4.40 Hz, 4 H, $N(CH_2)_2$], 3.75 [t, *J* = 4.40 Hz, 4 H, $O(CH_2)_2$], 2.48 (s, 3 H, Ar-CH_3), 2.38 (s, 3 H, CH_3), 1.01 (t, *J* = 6.80 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.16, 166.74, 165.43, 160.22, 139.64, 136.36, 128.86 (2 C), 128.03 (2 C), 114.45, 66.86 (2 C), 60.98, 44.12 (2 C), 23.04, 21.29, 13.61.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}N_3O_3$: 342.1812; found: 342.1815.

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (5e)[16a]

Yield: 126 mg (87%); white solid; mp 80–83 °C.

IR (KBr): 2950 (w), 1715 (vs), 1605 (s), 1580 (s), 1490 (s), 1454 (s), 1050 (s), 1025 (m), 830 (s), 650 (s), 540 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.37 (m, 4 H, ArH), 4.12–4.07 (m, 2 H, OCH_2), 3.92 [t, *J* = 5.6 Hz, 4 H, $N(CH_2)_2$], 3.76 [t, *J* = 5.20 Hz, 4 H, $O(CH_2)_2$], 2.50 (s, 3 H, CH_3), 1.02 (t, *J* = 7.60 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.68, 167.23, 164.45, 160.04, 137.70, 135.65, 129.47 (2 C), 128.40 (2 C), 114.27, 66.82 (2 C), 61.14, 44.10 (2 C), 23.17, 13.65.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}ClN_3O_3$: 362.1266; found: 362.1268.

Ethyl 4-(4-Bromophenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (5f)[16a]

Yield: 138 mg (85%); white solid; mp 92–93 °C.

IR (KBr): 2950 (w), 1718 (vs), 1596 (s), 1575 (s), 1482 (s), 1456 (s), 1034 (m), 650 (s), 585 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.43 (m, 4 H, ArH), 4.12–4.06 (m, 2 H, OCH_2), 3.91 [t, *J* = 4.4 Hz, 4 H, $N(CH_2)_2$], 3.75 [t, *J* = 4.8 Hz, 4 H, $O(CH_2)_2$], 2.49 (s, 3 H, CH_3), 1.02 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.65, 167.30, 164.53, 160.11, 138.25, 131.35 (2 C), 129.75 (2 C), 123.95, 114.28, 66.83 (2 C), 61.12, 44.15 (2 C), 23.17, 13.66.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}BrN_3O_3$: 406.0761; found: 406.0765.

Ethyl 4-(4-Fluorophenyl)-6-methyl-2-morpholinopyrimidine-5-carboxylate (5g)[16a]

Yield: 114 mg (83%); white solid; mp 86–88 °C.

IR (KBr): 2964 (s), 1716 (vs), 1602 (s), 1560 (vs), 1508 (s), 1448 (s), 1226 (vs), 848 (s), 800 (s), 592 (m), 566 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.07 (m, 4 H, ArH), 4.12–4.06 (m, 2 H, OCH_2), 3.92 [t, *J* = 4.80 Hz, 4 H, $N(CH_2)_2$], 3.76 [t, *J* = 4.80 Hz, 4 H, $O(CH_2)_2$], 2.49 (s, 3 H, CH_3), 1.02 (t, *J* = 7.20 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.85, 167.12, 164.86, 164.41, 162.38, 160.12, 135.33, 130.14 (2 C), 130.05, 115.31 (2 C), 114.34, 66.84 (2 C), 61.07, 44.10 (2 C), 23.15, 13.66.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}FN_3O_3$: 346.1561; found: 346.1556.

Ethyl 4-Methyl-2-morpholino-6-(4-nitrophenyl)pyrimidine-5-carboxylate (5h)

Yield: 128 mg (86%); yellow solid; mp 100–102 °C.

IR (KBr): 2856 (w), 1718 (vs), 1560 (m), 1522 (m), 1446 (m), 1348 (s), 1236 (vs), 864 (m), 802 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.26 (m, 2 H, ArH), 7.73–7.70 (m, 2 H, ArH), 4.08 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.93 [t, *J* = 4.8 Hz, 4 H, $N(CH_2)_2$], 3.78–3.76 [m, 4 H, $O(CH_2)_2$], 2.54 (s, 3 H, CH_3), 1.01 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.02, 167.95, 163.82, 160.04, 148.20, 145.77, 129.10 (2 C), 123.28 (2 C), 114.20, 66.76 (2 C), 61.16, 44.12 (2 C), 23.47, 13.66.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}N_4O_5$: 373.1506; found: 373.1510.

Ethyl 4-Methyl-6-phenyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5i)[16a]

Yield: 107 mg (82%); white solid; mp 69–70 °C.

IR (KBr): 2950 (w), 1715 (vs), 1565 (s), 1550 (s), 1495 (s), 1450 (s), 1270 (s), 1164 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 2 H, ArH), 7.42–7.38 (m, 3 H, ArH), 4.06–4.01 (m, 2 H, OCH_2), 3.89 [t, *J* = 5.60 Hz, 4 H, $N(CH_2)_2$], 2.49 (s, 3 H, CH_3), 1.68–1.60 [m, 6 H, $(CH_2)_3$], 0.93 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.20, 166.91, 165.73, 160.15, 139.75, 129.20, 128.06 (2 C), 113.18 (2 C), 60.77, 44.64, 25.84 (2 C), 24.83, 23.20 (2 C), 13.51.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}N_3O_2$: 326.1863; found: 326.1867.

Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5j)[16a]

Yield: 111 mg (78%); white solid; mp 87–88 °C.

IR (KBr): 2922 (s), 1270 (s), 1235 (m), 1080 (s), 1065 (s), 1045 (s), 1024 (m), 564 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.8 Hz, 2 H, ArH), 6.91 (d, *J* = 8.8 Hz, 2 H, ArH), 4.13–4.07 (m, 2 H, OCH_2), 3.88 [t, *J* = 5.2 Hz, 4 H, $N(CH_2)_2$], 3.84 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3), 1.68–1.60 [m, 6 H, $(CH_2)_3$], 1.03 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.57, 166.55, 164.77, 160.75, 132.03, 129.72 (2 C), 113.52 (2 C), 60.82, 55.32, 44.65 (2 C), 25.85 (2 C), 24.87, 23.13, 13.75.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{20}H_{26}N_3O_3$: 356.1969; found: 356.1970.

Ethyl 4-Methyl-2-(piperidin-1-yl)-6-(*p*-tolyl)pyrimidine-5-carboxylate (5k)[16a]

Yield: 109 mg (80%); white solid; mp 68–69 °C.

IR (KBr): 2925 (w), 1718 (vs), 1598 (s), 1568 (s), 1540 (s), 1230 (s), 1063 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.0 Hz, 2 H, ArH), 7.19 (d, J = 8.0 Hz, 2 H, ArH), 4.10–4.04 (m, 2 H, OCH_2), 3.88 [t, J = 5.2 Hz, 4 H, $N(CH_2)_2$], 2.47 (s, 3 H, Ar-CH_3), 2.38 (s, 3 H, CH_3), 1.67–1.59 [m, 6 H, $(CH_2)_3$], 0.99 (t, J = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.42, 166.61, 165.52, 139.35, 136.83, 128.77 (2 C), 128.08 (2 C), 60.79, 44.67 (2 C), 25.85 (2 C), 24.87, 23.19, 21.32, 13.63.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{20}H_{26}N_3O_2$: 340.2020; found: 340.2015.

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5l)[16a]

Yield: 126 mg (88%); white solid; mp 54–55 °C.

IR (KBr): 2948 (w), 1716 (vs), 1594 (s), 1588 (s), 1520 (s), 1455 (s), 1230 (m), 845 (s), 550 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.4 Hz, 2 H, ArH), 7.36 (d, J = 8.4 Hz, 2 H, ArH), 4.10–4.04 (m, 2 H, OCH_2), 3.88 [t, J = 5.2 Hz, 4 H, $N(CH_2)_2$], 2.48 (s, 3 H, CH_3), 1.68–1.60 [m, 6 H, $(CH_2)_3$], 1.01 (t, J = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.42, 166.61, 165.52, 139.35, 136.83, 128.77 (2 C), 128.09 (2 C), 113.19, 60.79, 44.67 (2 C), 25.85 (2 C), 24.88, 23.19, 13.63.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{19}H_{23}ClN_3O_2$: 360.1473; found: 360.1471.

Ethyl 4-(4-Bromophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5m)[16a]

Yield: 137 mg (85%); white solid; mp 61–62 °C.

IR (KBr): 2928 (w), 1714 (vs), 1578 (s), 1558 (s), 1510 (s), 1458 (s), 1064 (s), 645 (m), 573 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 8.4 Hz, 2 H, ArH), 7.43 (d, J = 8.0 Hz, 2 H, ArH), 4.09–4.04 (m, 2 H, OCH_2), 3.88 [t, J = 5.2 Hz, 4 H, $N(CH_2)_2$], 2.49 (s, 3 H, CH_3), 1.68–1.60 [m, 6 H, $(CH_2)_3$], 1.00 (t, J = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.89, 167.21, 164.59, 160.04, 138.70, 131.21 (2 C), 129.76 (2 C), 123.67, 60.89, 44.67 (2 C), 25.85 (2 C), 24.82, 23.29, 13.66.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{19}H_{23}BrN_3O_2$: 404.0968; found: 404.0970.

Ethyl 4-(4-Fluorophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5n)[16a]

Yield: 118 mg (86%); white solid; mp 51–52 °C.

IR (KBr): 2938 (w), 1715 (vs), 1598 (s), 1578 (s), 1505 (s), 1455 (s), 1350 (s), 1060 (s), 730 (s), 640 (m), 575 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.06 (m, 4 H, ArH), 4.10–4.04 (m, 2 H, OCH_2), 3.88 [t, J = 5.60 Hz, 4 H, $N(CH_2)_2$], 2.48 (s, 3 H, CH_3), 1.69–1.54 [m, 6 H, $(CH_2)_3$], 1.00 (t, J = 6.80 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.37, 165.00, 164.74, 162.53, 160.35, 136.05, 130.49, 130.22, 115.45, 115.40, 113.28, 61.12, 44.90 (2 C), 26.10 (2 C), 25.08, 23.47, 13.87.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{19}H_{23}FN_3O_2$: 344.1769; found: 344.1775.

Ethyl 4-(2-Chlorophenyl)-6-methyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5o)

Yield: 118 mg (82%); colorless oil.

IR (KBr): 2932 (s), 1716 (vs), 1560 (s), 1542 (s), 1510 (s), 1458 (s), 1092 (s), 1066 (s), 806 (s), 760 (s), 574 (s) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.37 (m, 1 H, ArH), 7.28 (d, J = 2.4 Hz, 3 H, ArH), 3.94 (q, J = 4.8 Hz, 2 H, OCH_2), 3.85 [t, J = 3.6 Hz, 4 H, $N(CH_2)_2$], 2.58 (s, 3 H, CH_3), 1.68–1.56 [m, 6 H, $(CH_2)_3$], 0.83 (t, J = 4.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.54, 167.20, 165.69, 159.97, 139.89, 131.94, 129.72 (2 C), 129.17 (2 C), 129.15 (2 C), 126.34 (2 C), 113.07, 60.34, 44.70 (2 C), 25.82 (2 C), 24.80, 24.40, 13.38.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{19}H_{23}ClN_3O_2$: 360.1473; found: 360.1475.

Ethyl 4-Isopropyl-6-phenyl-2-(piperidin-1-yl)pyrimidine-5-carboxylate (5p)

Yield: 119 mg (84%); white solid; mp 92–94 °C.

IR (KBr): 2932 (s), 1718 (s), 1560 (s), 1524 (s), 1446 (s), 1236 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.57 (m, 2 H, ArH), 7.39–7.38 (m, 3 H, ArH), 4.03 (q, J = 7.2 Hz, 2 H, OCH_2), 3.89 [t, J = 5.6 Hz, 4 H, $N(CH_2)_2$], 3.31–3.21 (m, 1 H, CH), 1.68–1.64 (m, 2 H, CH_2), 1.62–1.58 [m, 4 H, $(CH_2)_2$], 1.27 [s, 3 H, $CH(CH_3)_2$], 1.26 [s, 3 H, $CH(CH_3)_2$], 0.94 (t, J = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.26, 169.53, 165.33, 160.65, 139.91, 129.11, 128.09 (2 C), 128.07 (2 C), 112.93, 60.88, 44.70 (2 C), 32.63, 25.80 (2 C), 24.94, 21.74 (2 C), 13.56.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{21}H_{28}N_3O_2$: 354.2176; found: 354.2179.

Ethyl 2-(Butylamino)-4-methyl-6-phenylpyrimidine-5-carboxylate (5q)

Yield: 104 mg (83%); white solid; mp 76–78 °C.

IR (KBr): 3242 (vs), 1715 (vs), 1598 (s), 1570 (s), 1512 (s), 1446 (s), 1250 (s), 1085 (vs), 1028 (s), 775 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 2 H, ArH), 7.42 (s, 3 H, ArH), 5.53 (s, 1 H, NH), 4.04 (q, J = 7.2 Hz, 2 H, OCH_2), 3.47 (q, J = 6.4 Hz, 2 H, $NHCH_2$), 2.49 (s, 3 H, CH_3), 1.61–1.54 (m, 2 H, $CH_2CH_2CH_3$), 1.44–1.35 (m, 2 H, $CH_2CH_2CH_3$), 0.94 [t, J = 7.2 Hz, 6 H, OCH_2CH_3 (3 H), CH_2CH_3 (3 H)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.80, 166.11, 161.19, 139.28, 139.25, 129.27, 128.11 (2 C), 127.90 (2 C), 114.94, 60.88, 40.98, 31.68, 19.97, 13.78, 13.74, 13.49.

HRMS (EI): m/z [M + H]$^+$ calcd for $C_{18}H_{24}N_3O_2$: 314.1863; found: 314.1865.

Ethyl 2-(Benzylamino)-4-methyl-6-phenylpyrimidine-5-carboxylate (5r)[14c]

Yield: 111 mg (80%); colorless oil.

IR (KBr): 3252 (vs), 1716 (vs), 1598 (s), 1560 (s), 1532 (s), 1448 (s), 1256 (vs), 1166 (w), 1080 (vs), 1026 (s), 770 (s) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 4.4 Hz, 2 H, ArH), 7.41–7.39 (m, 3 H, ArH), 7.32–7.30 (m, 4 H, ArH), 7.26–7.25 (m, 1 H, ArH), 6.12 (s, 1 H, NH), 4.66 (d, *J* = 4.0 Hz, 2 H, CH_2), 4.06 (q, *J* = 4.8 Hz, 2 H, OCH_2), 2.48 (s, 3 H, CH_3), 0.95 (t, *J* = 4.4 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.80, 161.12, 139.10, 129.43, 128.49 (2 C), 128.31 (2 C), 128.19, 128.05, 128.00, 127.80, 127.52 (2 C), 127.16 (2 C), 115.51, 61.03, 45.25, 22.69, 13.55.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N_3O_2$: 348.1707; found: 348.1712.

Ethyl 2-[(2-Hydroxyethyl)amino]-4-methyl-6-phenylpyrimidine-5-carboxylate (5s)[16a]

Yield: 101 mg (84%); white solid; mp 100–102 °C.

IR (KBr): 3420 (s), 3260 (vs), 1714 (vs), 1598 (s), 1558 (s), 1524 (s), 1438 (s), 1258 (vs), 1082 (s), 708 (s), 620 (vw) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.38 (m, 5 H, ArH), 6.02 (s, 1 H, NH), 4.08–4.02 (m, 2 H, OCH_2), 3.78 (t, *J* = 4.0 Hz, 2 H, CH_2), 3.56 (d, *J* = 4.4 Hz, 2 H, $NHCH_2$), 2.48 (s, 3 H, CH_3), 0.94 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.43, 167.39, 161.62, 138.76, 129.58, 128.30 (2 C), 127.82 (2 C), 115.77, 63.39, 61.11, 44.56, 22.87, 13.50.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}N_3O_3$: 302.1499; found: 302.1501.

Ethyl 2-(Diethylamino)-4-methyl-6-phenylpyrimidine-5-carboxylate (5t)

Yield: 106 mg (85%); colorless oil.

IR (KBr): 2972 (s), 1718 (s), 1560 (m), 1522 (m), 1494 (m), 1458 (m), 1438 (m), 1260 (s), 1194 (m), 1080 (s), 1046 (m) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H, ArH), 7.40–7.39 (m, 3 H, ArH), 4.03 (q, *J* = 4.8 Hz, 2 H, OCH_2), 3.70 [q, *J* = 4.8 Hz, 4 H, $N(CH_2CH_3)_2$], 2.49 (s, 3 H, CH_3), 1.20 [t, *J* = 4.8 Hz, 6 H, $N(CH_2CH_3)_2$], 0.94 (t, *J* = 4.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.46, 166.77, 165.52, 159.87, 139.94, 129.08, 128.08 (2 C), 128.00 (2 C), 113.09, 60.73, 41.82 (2 C), 23.28, 13.55, 13.16 (2 C).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{24}N_3O_2$: 314.1863; found: 314.1860.

Ethyl 2-(Dibutylamino)-4-methyl-6-phenylpyrimidine-5-carboxylate (5u)

Yield: 121 mg (82%); colorless oil.

IR (KBr): 2928 (s), 1718 (vs), 1560 (m), 1544 (m), 1524 (m), 1492 (m), 1458 (m), 1438 (s), 1226 (vs), 1180 (m), 1088 (s), 1058 (s), 775 (s) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59–7.58 (m, 2 H, ArH), 7.40–7.39 (m, 3 H, ArH), 4.05–4.04 (m, 2 H, OCH_2), 3.65–3.64 [m, 4 H, $N(CH_2)_2$], 2.49 (s, 3 H, CH_3), 1.63–1.59 [m, 4 H, $(CH_2CH_2CH_3)_2$], 1.37–1.34 [m, 4 H, $(CH_2CH_2CH_3)_2$], 0.96–0.94 [m, 9 H, OCH_2CH_3 (3 H), $(CH_2CH_3)_2$ (6 H)].

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.51, 166.68, 165.37, 160.34, 139.96, 129.07, 128.11 (2 C), 127.97 (2 C), 112.92, 60.71 (2 C), 47.16 (2 C), 29.99, 23.30, 20.17 (2 C), 13.98 (2 C), 13.56.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{32}N_3O_2$: 370.2489; found: 370.2495.

Ethyl 4-Methyl-6-phenyl-2-(*p*-tolylthio)pyrimidine-5-carboxylate (5v)[16a]

Yield: 109 mg (75%); white solid; mp 65–66 °C.

IR (KBr): 2930 (s), 1714 (vs), 1591 (s), 1582 (s), 1510 (s), 1455 (s), 1370 (w), 1070 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 4.8 Hz, 4 H, ArH), 7.40 (d, *J* = 4.8 Hz, 1 H, ArH), 7.37–7.34 (m, 2 H, ArH), 7.21 (d, *J* = 5.2 Hz, 2 H, ArH), 4.15 (q, *J* = 4.4 Hz, 2 H, OCH_2), 2.49 (s, 3 H, Ar-CH_3), 2.39 (s, 3 H, CH_3), 1.04 (t, *J* = 4.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.37, 168.10, 165.82, 163.51, 139.16, 137.40, 135.07 (2 C), 130.07, 129.68 (2 C), 128.38 (2 C), 128.31 (2 C), 125.89, 121.37, 61.70, 22.59, 21.33, 13.58.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2S$: 365.1318; found: 365.1315.

Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-(*p*-tolylthio)pyrimidine-5-carboxylate (5w)[16a]

Yield: 110 mg (70%); white solid; mp 85–87 °C.

IR (KBr): 2935 (s), 1717 (vs), 1595 (s), 1581 (s), 1505 (s), 1453 (s), 1265 (s), 1150 (m), 1040 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–6.85 (m, 8 H, ArH), 4.21–4.19 (m, 2 H, OCH_2), 3.82 (s, 3 H, OCH_3), 2.48 (s, 3 H, Ar-CH_3), 2.40 (s, 3 H, CH_3), 1.13 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.01, 168.50, 165.49, 162.55, 161.38, 139.11, 135.10 (2 C), 130.11 (2 C), 129.66 (2 C), 129.53, 125.90, 120.69, 113.76 (2 C), 61.73, 55.31, 22.50, 21.35, 13.76.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_3S$: 395.1424; found: 395.1428.

Ethyl 4-Methyl-6-(*o*-tolyl)-2-(*p*-tolylthio)pyrimidine-5-carboxylate (5x)

Yield: 110 mg (73%); colorless oil.

IR (KBr): 2980 (s), 1722 (vs), 1524 (s), 1491 (s), 1440 (s), 1377 (s), 1218 (vs), 1182 (m), 1086 (s), 807 (s) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2 H, ArH), 7.26–7.23 (m, 1 H, ArH), 7.18 (d, *J* = 5.2 Hz, 3 H, ArH), 7.15–7.12 (m, 1 H, ArH), 7.08 (d, *J* = 5.2 Hz, 1 H, ArH), 3.98–3.95 (m, 2 H, OCH_2), 2.52 (s, 3 H, Ar-CH_3), 2.36 (s, 3 H, CH_3), 2.13 (s, 3 H, Ph-CH_3), 0.85–0.83 (m, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.17, 167.14, 166.14, 166.05, 139.21, 137.33, 136.12, 135.14 (2 C), 130.35, 129.74 (2 C), 129.01, 128.18, 125.70, 125.29, 122.75, 61.32, 22.84, 21.32, 19.62, 13.37.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_2S$: 379.1475; found: 379.1478.

Ethyl 4-(4-Chlorophenyl)-6-methyl-2-(*p*-tolylthio)pyrimidine-5-carboxylate (5y)[16a]

Yield: 129 mg (81%); white solid; mp 92–93 °C.

IR (KBr): 2935 (s), 1716 (vs), 1590 (s), 1583 (s), 1515 (s), 1454 (s), 1024 (s), 595 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.49 (m, 2 H, ArH), 7.46–7.44 (m, 2 H, ArH), 7.34–7.32 (m, 2 H, ArH), 7.21 (d, *J* = 5.2 Hz, 2 H, ArH), 4.18 (q, *J* = 4.8 Hz, 2 H, OCH_2), 2.49 (s, 3 H, Ar-CH_3), 2.39 (s, 3 H, CH_3), 1.10 (t, *J* = 4.8 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.59, 167.91, 166.02, 162.11, 139.31, 136.47, 135.79, 135.13 (2 C), 129.76 (2 C), 129.72 (2 C), 128.59 (2 C), 125.70, 121.15, 61.86, 22.61, 21.34, 13.69.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}ClN_2O_2S$: 399.0929; found: 399.0932.

4-Methyl-*N*-phenyl-6-(*p*-tolylthio)pyrimidin-2-amine (5z)

Yield: 98 mg (80%); colorless oil.

IR (KBr): 3430 (s), 2920 (s), 1640 (s), 1593 (s), 1585 (s), 1510 (s), 1265 (s), 1240 (s), 1040 (s), 880 (s) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 5.6 Hz, 2 H, ArH), 7.39–7.38 (m, 2 H, ArH), 7.28 (s, 1 H, ArH), 7.17–7.15 (m, 2 H, ArH), 7.08 (s, 1 H, ArH), 6.95–6.93 (m, 1 H, ArH), 6.23 (s, 1 H, ArH), 2.45 (s, 3 H, Ar-CH_3), 2.25 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.56, 166.53, 158.83, 139.91, 139.53, 136.10 (2 C), 130.35 (2 C), 128.62 (2 C), 124.80, 121.85, 118.52 (2 C), 107.76, 23.93, 21.40.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}N_3S$: 308.1216; found: 308.1221.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560175.

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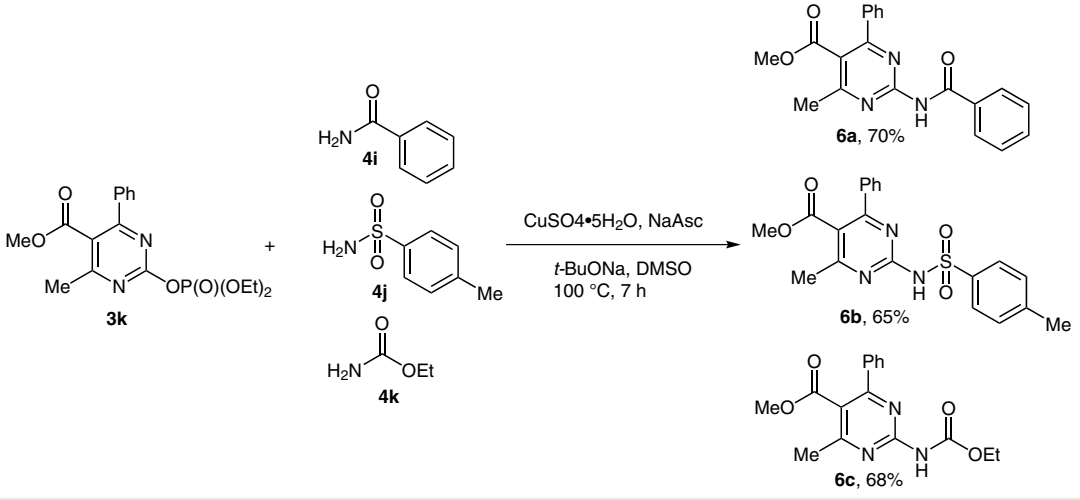
(19) We can obtain satisfactory results via the $CuSO_4 \cdot 5H_2O$-catalyzed NaAsc-mediated cross-coupling of pyrimidin-2-yl phosphates **3** with amides **4**. Using this method, we have successfully achieved the further functionalization of pyrimidin-2-yl phosphate **3k** (Scheme 4).



Scheme 4