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Cross-Coupling Reactions of Pyrimidin-2-yl Sulfonates with Phenols and Anilines: An Efficient Approach to C2-Functionalized Pyrimidines

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Pyrimidin-2-yl sulfonates, as an efficient reaction partner, which can be easily prepared from cheap commercial materials, were coupled with phenols and anilines to give a wide array of C2-aryloxy- and arylaminopyrimidines in good to excellent yields under mild reaction conditions.

Keywords cross-coupling, pyrimindine-2-yl sulfonates, C2-aryloxypyrimidines, C2-arylaminopyrimidines

Introduction

Heterobiaryl compounds as a prevalent structural motif in many pharmaceuticals and other biologically active molecules, have been focused on the development of significant nature's heterocyclic products.[1] Dihydropyrimidinones (DHPMs), a class of heterocyclic compounds that have been previously established *N*-acyl-/*N*-benzoyl- and C2-DHPM derivatives display more interesting pharmacological properties than other derivatives.[2] C2-DHPM derivatives have attracted considerable interest due to their interesting pharmacological properties, such as calcium channel modulator, antihypertensive activity, α_{1a}-adrenergic agonists mitotic kinesin inhibitor and hepatitis B virus replication suppressor.[3]

Although some synthetic approaches have now been established, the methods to synthesize C2-DHPM derivatives are still limited.[4] In the conversion of pyrimidin-2(1*H*)-one to C2-substituted pyrimidine, conventional tautomerization-activation-coupling process would normally include chlorination or sulfonylation, followed by coupling with a nucleophile.[5] Chlorination using $POCl_3$ at high temperatures could be problematic for substrates with sensitive functionalities,[5b,5c] and *S*-alkylation was necessary for sulfide oxidation.[5e,5h] Kappe group have developed an efficient carbon-carbon coupling reaction between 3,4-dihydropyrimidine-2-thiones and boronic acids under modified Liebeskind-Srogl reaction conditions.[6,7] Kang *et al*.[8] have reported a novel and efficient synthesis of multifunctionalized pyrimidines through Kappe dehydrogenation and PyBroP-mediated coupling with nucleophiles. More recently, we have developed a approach to highly substituted and functionalized pyrimidines by a domino desulfitative coupling/acylation/hydration process cocatalyzed by copper(I) and palladium(II).[9]

Therefore, a method easily available for the starting materials generating small amount of by-product to streamline organic synthesis and to improve the diversity of product is still needed in this area. In 2010, we have developed a mild and rapid procedure to the synthesis of C2-substituted pyrimidines by cross-coupling reaction of pyrimidin-2-yl sulfonates, which were easily available from DHPMs *via* oxidation, esterification,[10] with N, S and O nucleophiles at room temperature. The results showed that the method is not essential for phenols to provide phenolic pyrimidines. Alternatively, in 2011, we have developed a novel and efficient synthetic method to prepare C2-multifunctionalized pyrimidines by the Mitsunobu reaction between 2-hydroxy pyrimidine and N, S and O nucleophiles.[11] Unfortunately, it was unefficient to afford aniline pyrimidine derivative *via* these two approaches.

Herein, we report a general process for the synthesis of C2-aryloxy- and arylaminopyrimidines by cross-coupling reactions of pyrimidin-2-yl sulfonates with phenols and anilines.

Experimental

General methods

Melting points were measured on an XT-4 apparatus and are uncorrected. NMR spectra were recorded at 400

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(^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian 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 on silica gel GF254 plates. Solvent was purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted.

General procedure for the synthesis of 2-aryloxypyrimidines (3a－3k)

A mixture of pyrimidin-2-yl sulfonates (**1**, 1.0 mmol), phenols (**2**, 1.5 mmol), K_2CO_3 (2.5 mmol) and acetone (4 mL) was stirred at 60 ℃ for 7 h until the **1** were completely consumed (monitored by TLC). The mixture was cooled to r.t. and quenched with saturated NH_4Cl aqueous solution (3 mL), extracted with diethyl ether (10 mL×2). The organic solvents were combined and washed with NaOH aqueous solution (2 mmol/mL, 2 mL), brine and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2), eluting with petroleum ether/EtOAc (30∶1) to afford the corresponding 2-aryloxypyrimidines **3**. The spectroscopic data for compounds **3d**, **3g**, **3h**, **3i** and **3j** were consistent with those reported in the literature.[11]

Ethyl 4-methyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (3a) Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49－7.47 (m, 2H), 7.31－7.25 (m, 5H), 7.16－7.08 (m, 3H), 4.05 (q, J=7.1 Hz, 2H), 2.45 (s, 3H), 0.92 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.91, 167.77, 166.36, 163.69, 152.52, 136.98, 130.06, 129.11, 128.17, 128.08, 124.96, 121.31, 115.20, 61.57, 22.46, 13.35; HRMS calcd for $C_{20}H_{18}N_2O_3$ $[M+H]^+$ 335.1396; found 335.1399.

Ethyl 4-methyl-6-phenyl-2-(*p*-tolyloxy)pyrimidine-5-carboxylate (3b) Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65－7.55 (m, 2H), 7.50－7.36 (m, 3H), 7.23－7.18 (m, 2H), 7.16－7.10 (m, 2H), 4.23－4.13 (m, 2H), 2.63－2.51 (m, 3H), 2.36 (s, 3H), 1.08－1.03 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.03, 168.05, 166.56, 164.02, 150.51, 137.32, 134.64, 130.18, 129.80, 128.34, 128.16, 121.18, 120.87, 61.71, 22.60, 20.73, 13.57. HRMS calcd for $C_{21}H_{20}N_2O_3$ $[M+H]^+$ 349.1552; found 349.1550.

Ethyl 4-methyl-6-phenyl-2-(*m*-tolyloxy)pyrimidine-5-carboxylate (3c) Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64－7.54 (m, 2H), 7.48－7.35 (m, 3H), 7.29－7.21 (m, 2H), 7.20－7.10 (m, 2H), 4.22－4.13 (m, 2H), 2.60－2.51 (m, 3H), 2.28－2.17 (m, 3H), 1.12－1.00 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.12, 168.13, 166.59, 163.83, 151.29, 137.29, 131.07, 130.52, 130.18, 128.36, 128.31, 126.77, 125.41, 121.82, 120.78, 61.74, 22.68, 16.37, 13.58. HRMS calcd for $C_{21}H_{20}N_2O_3$ $[M+H]^+$ 349.1552; found 349.1549.

Ethyl 2-(4-chlorophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (3e) White solid, m.p. 66－68 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64－7.54 (m, 2H), 7.50－7.33 (m, 5H), 7.24－7.14 (m, 2H), 4.21－4.16 (m, 2H), 2.57 (s, 3H), 1.08－1.06 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.23, 167.87, 166.61, 163.59, 151.25, 137.09, 130.41, 130.38, 129.37, 128.43, 128.28, 122.94, 121.28, 61.81, 22.69, 13.57. HRMS calcd for $C_{20}H_{17}ClN_2O_3$ $[M+H]^+$ 369.1006; found 369.1009.

Ethyl 2-(2-chlorophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (3f) White solid, m.p. 76－78 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J=6.9 Hz, 2H), 7.51－7.34 (m, 4H), 7.28 (dd, J=11.5, 5.7 Hz, 2H), 7.23－7.13 (m, 1H), 4.23－4.11 (m, 2H), 2.56 (d, J=3.0 Hz, 3H), 1.11－0.96 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.25, 167.97, 166.51, 163.26, 148.85, 137.13, 130.32, 128.49, 128.34, 128.13, 127.73, 127.35, 126.49, 123.71, 121.23, 61.79, 22.67, 13.58. HRMS calcd for $C_{20}H_{17}ClN_2O_3$ $[M+H]^+$ 369.1006; found 369.1003.

Ethyl 2-(4-chlorophenoxy)-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (3k) White solid, m.p. 70－72 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J=8.8 Hz, 2H), 7.36 (d, J=8.8 Hz, 2H), 7.18 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 4.25 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 2.55 (s, 3H), 1.16 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.40, 165.70, 163.56, 161.68, 151.32, 130.41, 130.23, 130.02, 129.26, 123.01, 120.69, 114.18, 113.77, 61.93, 55.67, 22.55, 14.01. HRMS calcd for $C_{21}H_{19}ClN_2O_4$ $[M+H]^+$ 399.1112; found 399.1114.

General procedure for the synthesis of 2-arylaminopyrimidines (5a－5h)

All reactions were conducted under nitrogen atmosphere in a dual-manifold Schlenk tube. A seal tube (15 mL) initially fitted with a septum containing $PdCl_2$ (8.8 mg, 0.05 mmol) and PPh_3 (52.0 mg, 0.2 mmol) was evacuated and purged with nitrogen gas three times. Pyrimidin-2-yl sulfonates (**1**, 1.0 mmol), anilines (**4,** 1.5 mmol), K_3PO_4 (2.5 mmol) and 1.4-dioxane (4 mL), were added to the system and the reaction mixture was stirred at 110 ℃ for 10 h until complete consumption of **1** (based on TLC monitoring). Then, the mixture was cooled to r.t. and quenched with saturated NH_4Cl aqueous solution (3 mL), extracted with ethoxyethane (10 mL×2). The organic solvents were combined and washed with NaOH aqueous solution (2 mmol/mL, 2 mL), brine and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2), eluting with EtOH/EtOAc (1∶100) to afford the corresponding 2-arylaminopyrimidins **5**. The spectroscopic data for compound **5a** were consistent with those reported in the literature.[5h]

Ethyl 4-methyl-6-phenyl-2-(*p*-tolylamino)pyrimidine-5-carboxylate (5b) Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.64－7.56 (m, 2H), 7.50 (dd, J=8.3, 1.5 Hz, 2H), 7.42 (dd, J=4.3, 2.6 Hz, 3H), 7.10 (d, J=7.5 Hz, 2H), 4.12－4.06 (m, 2H), 2.55 (d,

J=1.8 Hz, 3H), 2.30 (s, 3H), 0.99−0.95 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.48, 167.17, 165.76, 158.79, 138.62, 136.38, 132.19, 129.55, 129.22, 128.21, 127.96, 119.42, 116.64, 61.15, 22.91, 20.70, 13.47. HRMS calcd for $C_{21}H_{21}N_3O_2$ $[M+H]^+$ 348.1712; found 348.1708.

Ethyl 4-methyl-6-phenyl-2-(*o*-tolylamino)pyrimidine-5-carboxylate (5c) Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J=8.1 Hz, 1H), 7.61−7.46 (m, 2H), 7.35 (dd, J=5.1, 1.8 Hz, 3H), 7.20−7.10 (m, 2H), 6.97 (dd, J=8.5, 11.1 Hz, 2H), 4.02 (q, J=7.1 Hz, 2H), 2.47 (s, 3H), 2.26 (s, 3H), 0.91 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.51, 167.26, 165.88, 159.09, 138.59, 136.98, 130.40, 129.63, 128.30, 127.99, 126.50, 121.51, 117.02, 61.23, 22.92, 18.16, 13.53. HRMS calcd for $C_{21}H_{21}N_3O_2$ $[M+H]^+$ 348.1712; found 348.1715.

Ethyl 2-(4-chlorophenylamino)-4-methyl-6-phenylpyrimidine-5-carboxylate (5d) Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.71−7.57 (m, 2H), 7.56−7.47 (m, 2H), 7.41 (d, J=5.8 Hz, 3H), 7.24−7.17 (m, 2H), 4.11 (q, J=7.1 Hz, 2H), 2.55 (s, 3H), 0.98 (dd, J=7.7, 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.28, 167.24, 165.70, 158.53, 138.30, 137.63, 129.75, 128.60, 128.29, 127.95, 127.32, 120.40, 117.25, 61.30, 22.88, 13.52. HRMS calcd for $C_{20}H_{18}ClN_3O_2$ $[M+H]^+$ 368.1166; found 368.1169.

Ethyl 4-methyl-2-(4-nitrophenylamino)-6-*p*-tolylpyrimidine-5-carboxylate (5e) Yellow solid, m.p. 175−177 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (d, J=6.9 Hz, 2H), 8.03 (s, 1H), 7.80 (d, J=6.9 Hz, 2H), 7.54 (d, J=6.3 Hz, 2H), 7.25 (d, J=6.3 Hz, 2H), 4.22−4.17 (m, 2H), 2.58 (s, 3H), 2.40 (s, 3H), 1.11−1.08 (t, J=5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.20, 167.15, 165.47, 157.95, 145.34, 141.92, 140.55, 134.95, 129.22, 128.06, 125.08, 118.81, 117.87, 61.63, 22.81, 21.32, 13.64. HRMS calcd for $C_{21}H_{20}N_4O_4$ $[M+H]^+$ 393.1563; found 393.1566.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(phenylamino)pyrimidine-5-carboxylate (5f) Claybank oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, J=10.1 Hz, 1H), 7.34 (d, J=8.5 Hz, 4H), 7.06−6.95 (m, 2H), 6.72 (t, J=7.4 Hz, 1H), 6.68−6.61 (m, 2H), 3.88 (q, J=7.1 Hz, 2H), 3.52 (s, 3H), 2.24 (s, 3H), 0.80 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.90, 166.83, 164.88, 161.05, 158.78, 139.26, 130.80, 129.77, 128.75, 122.55, 119.27, 116.67, 113.75, 61.30, 55.28, 22.83, 13.75. HRMS calcd for $C_{21}H_{21}N_3O_3$ $[M+H]^+$ 364.1661; found 364.1659.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-(phenylamino)pyrimidine-5-carboxylate (5g) White solid, m.p. 129−130. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (s, 1H), 7.46−7.27 (m, 4H), 7.19−7.14 (m, 2H), 7.09−7.04 (m, 2H), 6.87−6.75 (m, 1H), 3.98−3.86 (m, 2H), 2.42−2.26 (m, 3H), 0.92−0.74 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.38, 167.60, 164.61, 158.92, 139.08, 137.15, 136.02, 129.62, 128.93, 128.65, 122.98, 119.50, 116.97, 61.52, 23.12, 13.78. HRMS calcd for $C_{21}H_{18}ClN_3O_2$ $[M+H]^+$ 368.1166; found 368.1168.

Ethyl 4-methyl-2-(2-nitrophenylamino)-6-phenylpyrimidine-5-carboxylate (5h) Yellow solid, m.p. 177−180 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.58 (s, 1H), 9.12 (dd, J=8.7, 1.0 Hz, 1H), 8.27 (dd, J=8.5, 1.5 Hz, 1H), 7.69−7.63 (m, 3H), 7.57−7.45 (m, 3H), 7.16−7.05 (m, 1H), 4.17 (q, J=7.1 Hz, 2H), 2.63 (s, 3H), 1.06 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.13, 167.32, 165.46, 158.18, 138.06, 136.70, 135.98, 135.43, 130.04, 128.47, 128.22, 126.08, 121.22, 121.20, 119.34, 61.59, 22.86, 13.61. HRMS calcd for $C_{20}H_{18}N_4O_4$ $[M+H]^+$ 379.1006; found 379.1408.

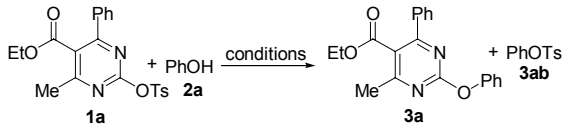
Results and Discussion

C−O coupling reaction of pyrimidin-2-yl sulfonates with phenols

We began this study by choosing pyrimidin-2-yl sulfonate (**1a**) and phenol (**2a**) as model substrates (Table 1). Initially, different bases were tested at r.t. In the presence of K_2CO_3 or K_3PO_4, no reaction was detected. The strong bases NaOH and NaO^{t}Bu resulted in a low conversion to give only a trace of the target coupling compound **3a**, but with formation of the O−S cleavage product **3ab** in high yield (Table 1, Entries 1−6). To our delight, using acetone as solvent and K_2CO_3 or K_3PO_4 as base under refluxing for 7 h obtained the cross-coupling product **3a** in 86% isolated yield (Table 1, Entries 7 and 8). The reaction could also conduct smoothly in THF and dioxane as solvents using K_2CO_3 as base to give product **3a** (Table 1, Entries 11−12). It revealed that the reaction was best conducted in the presence of 2.5 equivalents of K_2CO_3 in acetone at 60 ℃ for 7 h, and the desired product was isolated in the best yield. It is noteworthy that O−S cleavage products (**3ab**) were obtained under strong bases (Table 1, Entries 3, 4, 9, 10) and high temperature (Table 1, Entry 6). Our previous work has reported analogous results,[10] and Lee *et al*. disclosed the competitive reaction pathways in the nucleophilic substitution reactions of aryl benzenesulfonates with benzylamines in acetonitrile.[12] In this study, we have also observed two competitive reaction pathways (*i.e*., C−O bond cleavage path vs. the S−O bond-cleavage path). The S−O bond cleavage reaction is favored with strong base and high temperature. Reaction of **1a** with phenols produced C2-substituted pyrimidines via cleavage of C−O bond in high yields.

Under the optimized conditions, various pyrimidin-2-yl sulfonates (**1**) with a diverse set of phenols (**2**) were tested in the reaction scope (Table 2). In general, good to excellent yields (67%−92%) were obtained under the standard reaction conditions (Table 2, Entries 1−11). The reaction tolerated a variety of pyrimidin-2-yl sulfonates and phenols containing an electron-withdrawing group (Cl and NO_2) as well as an electron-donating group (Me) on the phenyl ring.

Table 1 Optimization of reaction conditions for compound **3a**[a]



Entry	Base	Solvent	Temp./℃	Time/h	Yield[b]/%	
					3a	**3ab**
1	K_2CO_3	Acetone	r.t.	48	0	0
2	K_3PO_4	Acetone	r.t.	48	0	0
3	NaOH	Dioxane	r.t.	48	12	85
4	NaO^{t}Bu	Dioxane	r.t	48	trace	87
5	K_2CO_3	THF	r.t.	48	trace	0
6	K_2CO_3	Dioxane	110	48	0	65
7	K_2CO_3	Acetone	60	7	86	8
8	K_3PO_4	Acetone	60	7	80	trace
9	NaOH	Acetone	60	7	0	56
10	NaO*t*-Bu	Acetone	60	7	0	60
11	K_2CO_3	THF	70	7	85	trace
12	K_2CO_3	Dioxane	60	7	82	trace

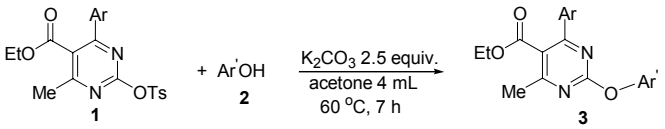
[a] Reactants and reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), base (2.5 equiv.), and solvent (4 mL). [b] Isolated yield of pure product after column chromatography.

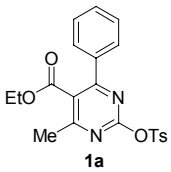
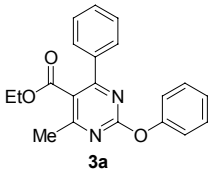
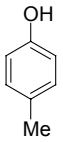
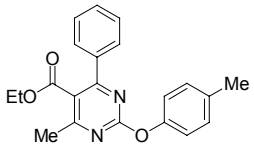
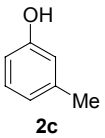
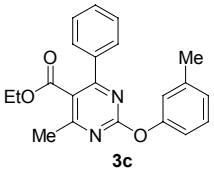
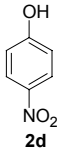
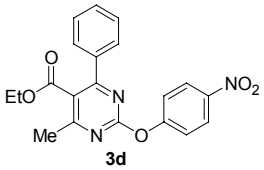
C—N coupling reaction of pyrimidin-2-yl sulfonates with anilines

Next, coupling reaction of pyrimidin-2-yl sulfonates with anilines was examined. In our preliminary study to optimize the reaction conditions, the coupling of pyrimidin-2-yl sulfonates (**1a)** and aniline (**4a**) was selected as the model reaction in the presence of various bases (Table 3). It indicated that the bases play an important role in the coupling reaction.[13] Among the tested bases, only K_3PO_4 gave the product in dioxane or DMSO, albeit in low yield (Table 3, Entries 1—9). To our delight, the yield was dramatically increased to 88% when $PdCl_2$ (5 mol%) was used as the catalyst and PPh_3 (20 mol%) was used as ligand (Table 3, Entry 10). Further study showed that the catalysts and ligands have slight influence on the yield (Table 3, Entries 11—14). In summary, the optimal conditions for cross-coupling reaction of pyrimidin-2-yl sulfonates with aniline were achieved by using 5 mol% $PdCl_2$, 20 mol% PPh_3, 2.5 equiv. K_3PO_4 in 1,4-dioxane at 110 ℃ for 10 h.

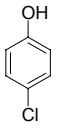
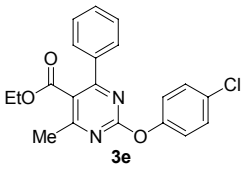
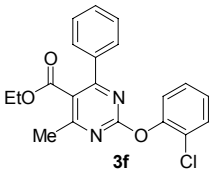
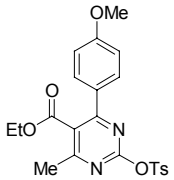
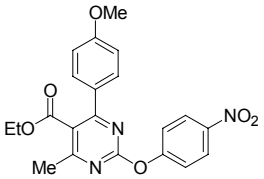
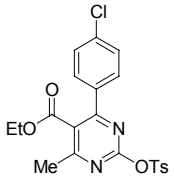
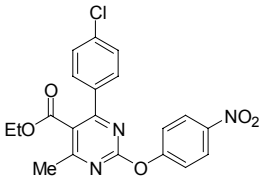
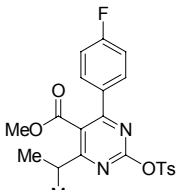
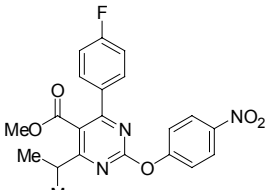
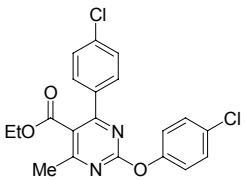
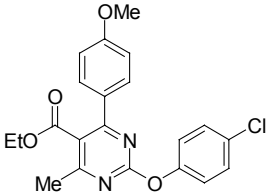
The generality of the optimized reaction conditions was examined by treating various pyrimidin-2-yl sulfonates with different anilines. In general, good to excellent yields of C2-arylaminopryrimindes **5a**—**5h**

Table 2 C—O coupling of pyrimidin-2-yl sulfonates with phenols



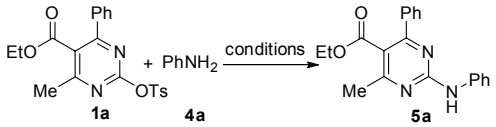
Entry	Sulfonate **1**	Ar'OH **2**	Product **3**	Yield[a]/%
1	 **1a**	 **2a**	 **3a**	86
2	**1a**	 **2b**	 **3b**	92
3	**1a**	 **2c**	 **3c**	89
4	**1a**	 **2d**	 **3d**	80

Continued

Entry	Sulfonate **1**	Ar'OH **2**	Product **3**	Yield[a]/%
5	**1a**	 **2e**	 **3e**	85
6	**1a**	 **2f**	 **3f**	70
7	 **1b**	**2d**	 **3g**	67
8	 **1c**	**2d**	 **3h**	72
9	 **1d**	**2d**	 **3i**	76
10	**1c**	**2e**	 **3j**	75
11	**1b**	**2e**	 **3k**	70

[a] Isolated yield of pure product after column chromatography.

Table 3 Optimization of reaction conditions for compound **5a**[a]

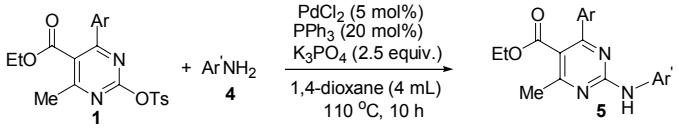


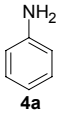
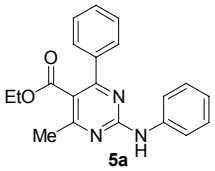
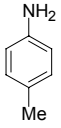
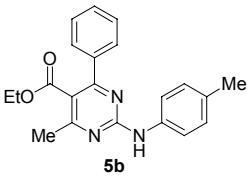
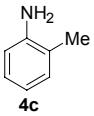
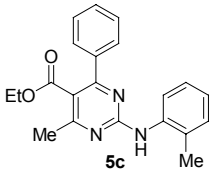
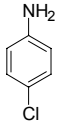
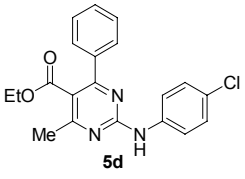
Entry	Base	Solvent	Temp./℃	Time/h	Yield[b]/%	Entry	Base	Solvent	Temp./℃	Time/h	Yield[b]/%
1	K_2CO_3	Acetone	60	48	0	8	K_3PO_4	Dioxane	110	48	55
2	K_2CO_3	THF	68	48	0	9	K_3PO_4	DMSO	110	48	40
3	K_2CO_3	Dioxane	110	48	0	10	K_3PO_4	Dioxane	110	10	88[c]
4	K_2CO_3	DMSO	110	48	0	11	K_3PO_4	DMSO	120	10	86[c]
5	Na_2CO_3	Dioxane	110	48	0	12	K_3PO_4	Dioxane	110	10	80[d]
6	NaAc	Dioxane	110	48	0	13	K_3PO_4	Dioxane	110	10	60[e]
7	DBU	Dioxane	110	48	0	14	K_3PO_4	Dioxane	110	10	65[f]

[a] Reactants and reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), base (2.5 equiv.), and solvent (4 mL). [b] Isolated yield of pure product after column chromatography. [c] 5 mol% $PdCl_2$ and 20 mol% PPh_3. [d] 2.5 mol% $PdCl_2$ and 10 mol% PPh_3. [e] 5 mol% $NiCl_2$ and 20 mol% PPh_3. [f] 10 mol% CuI_2 and 20 mol% PPh_3.

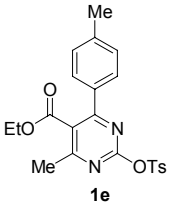
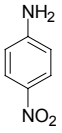
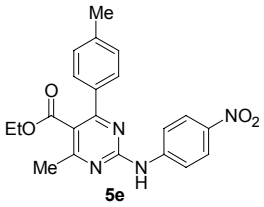
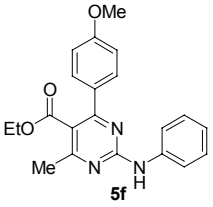
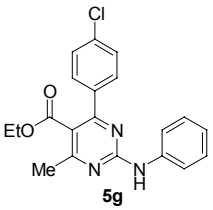
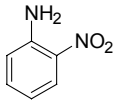
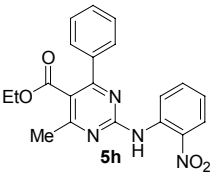
were obtained (Table 4). The reaction tolerated a variety of anilines containing an electron-withdrawing group (Cl and NO_2) as well as an electron-donating group (Me) on the phenyl ring, although the reaction of electro-deficient nitroanilines **4e** and **4f** gave lower yields of the products (Table 4, Entries 5 and 8).

Table 4 C—N coupling of pyrimidin-2-yl sulfonates with anilines



Entry	Sulfonate **1**	Ar'NH_2 **4**	Produt **5**	Yield[a]/%
1	**1a**	 **4a**	 **5a**	88
2	**1a**	 **4b**	 **5b**	96
3	**1a**	 **4c**	 **5c**	68
4	**1a**	 **4d**	 **5d**	84

Continued

Entry	Sulfonate **1**	Ar'NH_2 **4**	Produt **5**	Yield[a]/%
5	 **1e**	 **4e**	 **5e**	55
6	**1b**	**4a**	 **5f**	80
7	**1c**	**4a**	 **5g**	90
8	**1a**	 **4f**	 **5h**	78

[a] Isolated yield of pure product after column chromatography.

Conclusions

In summary, we have developed a general approach to C2-substituted pyrimidines *via* the cross-coupling of pyrimidin-2-yl sulfonates. A wide range of C2-substituted pyrimidines were obtained in good to excellent yields. Noteworthy is the use of easily prepared pyrimidin-2-yl sulfonates as an attractive reaction partner for the synthesis of novel C2-substituted C—O/C—N systems. Compared with previous procedures,[10,11] this method avoids the formation of S—O bond-cleavage by-product to give phenolic pyrimidine as the sole product. Furthermore, some novel structures of aniline pyrimidine derivatives, which are difficultly obtained by the classical methods, were prepared, which make this approach attractive. Synthesis and screening of desired compounds based on pyrimidine scaffolds may lead to the discovery of interesting biological activities.

Acknowledgement

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