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Palladium-catalyzed oxidative C–H/C–H cross-couplings of thiazolo[5,4-*d*]pyrimidine with aromatic (hetero)cycles

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ABSTRACT

A novel Pd(II)-catalyzed dehydrogenative cross-coupling reaction of thiazolo[5,4-*d*]pyrimidine with unactivated (hetero)arenes via C–H bond activation was achieved. This protocol provides a straightforward and operationally simple method for the synthesis of 2-arylsubstituted thiazolo[5,4-*d*]pyrimidines of interest in pharmaceutical sciences.

1. Introduction

Classical transition-metal-catalyzed methods for the direct C-arylation, such as Kumada, Negishi, Stille, Suzuki, and Hiyama–Denmark reactions, require functionalized groups in at least one of the two coupling partners prior to cross-coupling.[1] Recently, the direct functionalization of C–H bonds of organic compounds has emerged as a powerful and ideal method for carbon–carbon (C–C) bond formation.[2] During the last few decades, much effort has been made towards reliable transition-metal-catalyzed intermolecular oxidative C–H cross-coupling reactions.[3] In this context, direct C–H/C–H cross-coupling between two unfunctional groups provides an alternative and potentially more efficient synthetic methodology. Generally, although C–H oxidative cross-coupling between two unactivated (hetero)arenes are most challenging, they still represent significant progress toward the stated goals of Green Chemistry. To date, intermolecular C–H oxidative cross-coupling of many motifs with (hetero)arenes has been developed, including indoles,[4] benzofurans,[5] benzazoles,[6] benzoxazoles,[7] xanthines,[8] pyridin-*N*-oxides,[9] anilides,[10] perfluoroarenes.[11]

2-Arylsubstituted thiazolo[5,4-*d*]pyrimidines have been explored as an array of pharmacologically active compounds, such as Tie-2 inhibitors,[12] phosphatidylinositide 3-kinases (PI3K) inhibitors,[13] immunosuppressive agents[14] and human membrane phosphatidylinositol 4-kinase inhibitors.[15] By using the classic synthesis methods of heterocyclic chemistry, C-2 arylated thiazolo[5,4-*d*]pyrimidines can only be achieved by cyclization of benzoic anhydride with 5-amino-6-mercaptopyrimidine,[16] dehydrocyclization of 4-amino-5-arylamido-pyrimidines with polyphosphoric acid or ring closure of benzoyl aminopyrimidines with phosphorus pentasulfide.[17] As these procedures require some toxic reagents and harsh conditions, their applications are always limited. Thus, the development of new synthetic methodologies for the synthesis of this motif is of major importance.

As a continuing effort of our work in the construction of heterocycles by transition-metal-catalyzed cross-coupling reactions,[18] we herein disclose a novel Pd-catalyzed C–H oxidative cross-couplings of thiazolo[5,4-*d*]pyrimidine with aromatic (hetero)cycles for the synthesis of C-2 arylated thiazolopyrimidines.

2. Results and discussion

In our investigation of the direct coupling reaction between 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (**1a**) and benzene (**2a**), a twofold C–H functionalization occurs between **1a** and benzene to form 4-(5-methyl-2-phenyl-thiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (**3a**) in the presence of $Pd(OAc)_2$(Table 1, entry 1). So we focused on the cross-coupling of **1a** and benzene with $Pd(OAc)_2$ as a catalyst and screened several parameters including oxidant, additive and solvent. On the outset of our study, the direct coupling reaction between **1a** and **2a** was performed in the presence of 20 mol % of $Pd(OAc)_2$ in DMF at 120 °C, with $Cu(OAc)_2$ and

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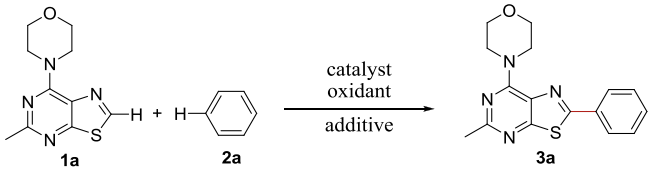
Table 1
Pd-catalyzed C–H oxidative cross-coupling reaction of 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (**1a**) with benzene (**2a**)[a]



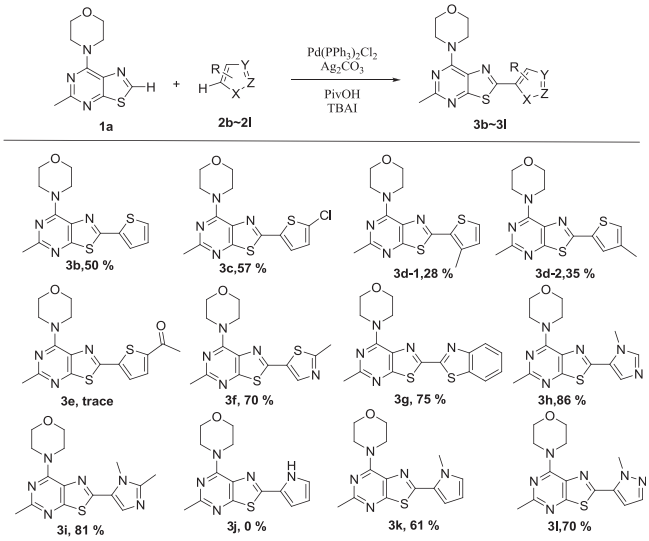
Entry	Catalyst (mol %)	Oxidant	Additive	Solvent	Yield (%)[c]
1	$Pd(OAc)_2$(20)	—	—	DMF	<10
2	$Pd(OAc)_2$(20)	$Cu(OAc)_2$	PivOH	DMF	24
3	$Pd(OAc)_2$(20)	AgOAc	PivOH	DMF	30
4	$Pd(OAc)_2$(20)	Ag_2CO_3	PivOH	DMF	45
5	$Pd(OAc)_2$(20)	Ag_2CO_3	Pyridine	DMF	18
6	$Pd(OAc)_2$(20)	Ag_2CO_3	PivOH	DMSO	46
7	$Pd(OAc)_2$(20)	Ag_2CO_3	PivOH	Dioxane	42
8	$Pd(OAc)_2$(20)	Ag_2CO_3	PivOH	Benzene	64
9	$Pd(OAc)_2$(20)	Ag_2CO_3	PivOH+TBAB	Benzene	60
10	$Pd(OAc)_2$(20)	Ag_2CO_3	PivOH+TBAI	Benzene	75
11	$Pd(OAc)_2$(10)	Ag_2CO_3	PivOH+TBAI	Benzene	62
12	$Pd(OAc)_2$(40)	Ag_2CO_3	PivOH+TBAI	Benzene	77
13	$PdCl_2$(20)	Ag_2CO_3	PivOH+TBAI	Benzene	69
14	$Pd(dppf)Cl_2$[b](20)	Ag_2CO_3	PivOH+TBAI	Benzene	56
15	$Pd(PPh_3)_2Cl_2$(20)	Ag_2CO_3	PivOH+TBAI	Benzene	80

[a] Reaction conditions: entry 1–6: **1a** (0.1 mmol), **2a** (1 mmol), catalyst (0.02 mmol), oxidant (0.3 mmol), additive (0.6 mmol), Solvent: 2 mL dry DMF, in a sealed tube, 120 °C, 20 h, unless otherwise indicated. Entry 7–12: **1a** (0.1 mmol), catalyst (0.02 mmol), oxidant (0.3 mmol), additive: PivOH(0.6 mmol), TBAI(0.02 mmol), Solvent: 2 mL dry benzene, in a sealed tube, 120 °C, 20 h.
[b] Dppf=1,1′-bis-(diphenylphosphino)ferrocene, TBAB=tetrabutyl-ammonium bromide, TBAI=tetrabutylammonium iodide.
[c] All the yield was isolated yield.

PivOH as oxidant and additive, respectively. The yield was only 24% (Table 1, entry 2). When replacing $Cu(OAc)_2$ with AgOAc, the yield of **3a** can be improved to 30% (Table 1, entry 3). In comparison, Ag_2CO_3 give a higher yield of 45% (Table 1, entry 4). In consideration of yield, Ag_2CO_3 is the favorable oxidant. Then PivOH was replaced by pyridine, the yield was decreased to only 18% (Table 1, entry 5). Other bases, including Cs_2CO_3, K_3PO_4, also gave a lower yield at trace or 10%, respectively. When PivOH was replaced by AcOH and TFA, the yield of coupling was only 31% and 20%. In addition, we noticed that when DMF was replaced with other solvent, such as DMSO and dioxane, the yields of **3a** were almost the same (Table 1, entry 4, 6, 7). Remarkably, a moderate yield was achieved when **2a** was used as solvent (Table 1, entry 8). Gong, Li, and co-workers reported that added TBAB helps to mediate and stabilize the Ag_2CO_3 oxidant.[19] Therefore we used TBAB or TBAI as another additive. The yield of the **3a** could be increased to 75% by adding TBAI to the reaction system and TBAB was inferior to TBAI (Table 1, entry 9, 10). Reduce the amount of catalyst gave a lower yield and an increase in the catalyst loading to 40 mol % made no significant difference to the yield(Table 1, entry 11, 12). In addition, we noticed that the cross-coupling reaction of **1a** and **2a** was not restricted to using $Pd(OAc)_2$ as a catalyst, so other Pd complexes, including $PdCl_2$, $PdCl_2$(dppf) and $Pd(PPh_3)_2Cl_2$ were used as well (Table 1, entry 13–15). Finally, the best yield of **3a** (80%) was obtained when the reaction was performed with 20 mol % of $Pd(PPh_3)_2Cl_2$, 3 equiv of Ag_2CO_3, 6 equiv of PivOH and 20 mol % TBAI in dry benzene (**2a**) (Table 1, entry 15).

With this optimal catalytic system, different substituted heteroarenes, including thiophene, thiazole, imidazole, pyrazole, and pyrrole, were explored as coupling partners for **1a** to test the versatility of this direct oxidative C–H/C–H cross-coupling methodology (Table 2). Compared with other heteroarenes, imidazole offered a higher yield. Thiazole, pyrazole, thiophene, pyrrol could also offer a moderate yield. The cross-coupling of **1a**

Table 2
Pd-catalyzed C-2 or C-5 arylation of **1a** with heteroarenes[a]

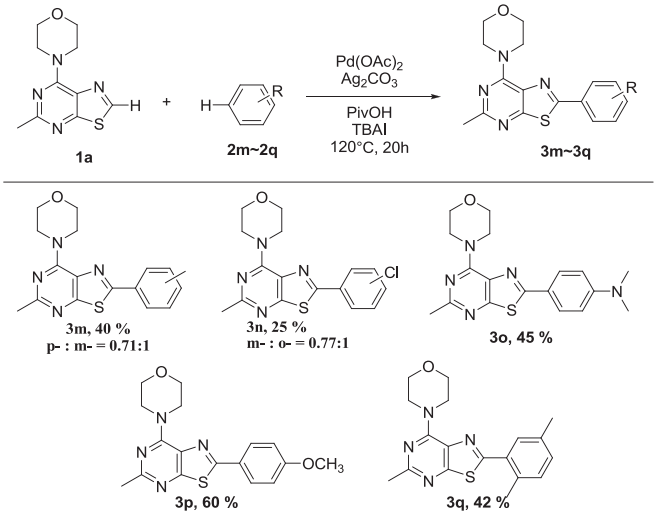


with *N*-methylimidazole (**2h**) furnished **3h** in excellent yield at 86%. Heteroarenes bearing electron-donating functionalities offered the products in moderate to excellent yields, and the slightly electron-withdrawing groups furnished the desired products in good yields inferior to that of electron-rich groups. However, a poor result was obtained when heteroarenes bearing a strong electron-withdrawing group, –Ac. The reaction between **1a** and pyrrole (**2j**) failed to give any coupling product. This result cohered with our previous study that the Ag+ can crystallize with the NH fragment and lead to this phenomenon.[18] Interestingly, all the substituted heteroarenes, which have at least two sites for C–H activation, reacted with **1a** selectively at C-2 or C-5 positions to give the desire product. This phenomenon was especially evident in the coupling of **1a** with 3-methylthiophene (**2d**). Two different products, which have similar amount were obtained in the reaction. The regioselectivity of the cross-couplings may be governed by the C–H acidity at C-2 and C-5 positions of the aromatic heterocycles.[6,20]

To further ascertain the scope of this methodology, a variety of substituted arenes were also investigated. To our surprise, with this optimal catalytic system, coupling reactions between **1a** and substituted arenes (toluene, chlorobenzene, anisole, *N*,*N*-dimethylaniline, 1,4-dimethylbenzene) afforded **3a** as the major product, even no benzene was provided. According to the previous reports that olefins and some simple arenes could be arylated by triphenylphosphine in the presence of palladium through $C(sp^2)$–P/$C(sp^2)$–H bond cleavage.[21] Our experiment revealed that the $Pd(PPh_3)_2Cl_2$ could also directly coupled with 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (**1a**). Based on the results that $Pd(PPh_3)_2Cl_2$ catalyzed double C–H activation between thiazolo[5,4-*d*]pyrimidine and heteroarenes can afford the desire product, we concluded that the priority of coupling with thiazolo[5,4-*d*]pyrimidine was heteroarenes>$PdCl_2(PPh_3)_2$ or PPh_3>>substituted arenes.

Next, we examined direct C–H activation of **1a** with substituted arenes to form **3m**–**q** under the reaction conditions of entry 10 in Table 1 (Table 3). Most substituted arenes were well tolerated under this condition. The arylated thiazolo[5,4-*d*]pyrimidine (**3m**–**q**) could be obtained with yields ranging from 25% to 60 %. As expected, good yields were generally obtained with electron-rich arenes (**3o**, **3p**). Electron-poor motifs afforded slightly lower yields (**3m**).

Table 3
Pd-catalyzed C–H cross-coupling reaction of **1a** with substituted arenes



3. Conclusions

In conclusion, we have developed a straightforward and practical method for direct Pd-catalyzed oxidative cross-coupling of thiazolo[5,4-*d*]pyrimidine with aromatic (hetero) cycles via two-fold C–H functionalization. This catalyzed system is notable for its synthetic simplicity and inexpensive palladium catalytic system. Furthermore, the arylation of thiazolo[5,4-*d*]pyrimidine is not restricted to benzene itself but can also be conducted with other substituted heteroarenes. The most important is that this synthetic protocol provides a concise access to afford 2-arylsubstituted thiazolo[5,4-*d*]pyrimidine derivatives, which are meaningful to pharmaceutical art.

4. Experimental section

4.1. General methods

A variety of chemical reagents were commercially purchased and used without further purification. Analytical TLC was carried out on pre-coated plates and visualized with UV. ^{1}H and ^{13}C NMR spectra were collected on BRUKER AV-300 (300 MHz) spectrometer. Chemical shifts were reported in δ (parts per million), relative to the internal standard of TMS. The signals observed were described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The number of protons (n) for a given resonance was indicated as nH. Coupling constants are reported as J value in Hertz. ^{13}C NMR is reported as δ (ppm) in downfield from TMS and relative to the signal of chloroform-*d* (δ 77.00, triplet). Mass spectrometry was obtained using a Q-tof high resolution mass spectrometer.

4.2. General procedure and characterization data of all compounds

*4.2.1. 4-(5-Methyl-2-phenylthiazolo[5,4-d]pyrimidin-7-yl) morpholine (**3a**).* To a solution of **1a** (24 mg, 0.1 mmol) in anhydrous benzene (2.0 mL) was added Ag_2CO_3 (82 mg, 0.3 mmol), TBAI (15 mg, 0.04 mmol), PivOH (61 mg, 0.6 mmol), and $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol) in a sealed tube. The reaction mixture was stirred at 120 °C for 20 h, during, which the reaction was monitored by means of TLC. Then the mixture was concentrated in vacuo, and the residue was subjected to column chromatography over silica gel (EtOAc-PE, 1/4) to give **3a**. Yield: 25 mg, 80%, white solid; Spectral data of **3a** are reported previously.[18c]

*4.2.2. 4-(5-Methyl-2-(thiophen-2-yl)thiazolo[5,4-d]pyrimidin-7-yl) morpholine (**3b**).* Yield: 15.9 mg (50%) white solid. Mp 195–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J=3.12 Hz, 1H), 7.45 (d, J=4.83 Hz, 1H), 7.10 (t, J=4.08 Hz, 1H), 4.38 (s, 4H), 3.85 (t, J=4.47 Hz, 4H), 2.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 163.1, 154.0, 153.1, 137.5, 130.8, 128.8, 128.0, 126.9, 67.1, 46.3, 25.8. FTIR (KBr, cm^{-1}) ν 3133, 1637, 1565, 1544, 1400, 1114, 692. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{14}N_4OS_2$ 319.0682; found 319.0672.

*4.2.3. 4-(2-(5-Chlorothiophen-2-yl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3c**).* Yield: 20.1 mg (57%) white solid. Mp 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J=4.02 Hz, 1H), 6.94 (d, J=4.02 Hz, 1H), 4.37 (s, 4H), 3.87 (t, J=4.95 Hz, 4H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 163.4, 153.9, 152.8, 135.9, 134.1, 128.7, 127.2, 127.0, 67.1, 46.3, 25.8. FTIR (KBr, cm^{-1}) ν 3124, 1637, 1561, 1400, 1138, 1116, 999. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}ClN_4OS_2$ 353.0292; found: 353.0274.

*4.2.4. 4-(5-Methyl-2-(3-methylthiophen-2-yl)thiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3d-1**).* Yield: 9.3 mg (28%) white solid. Mp 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J=5.07 Hz, 1H), 6.96 (d, J=5.07 Hz, 1H), 4.40 (s, 4H), 4.10 (t, J=4.82 Hz, 4H), 3.26 (s, 3H), 2.57 (s, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}N_4OS_2$ 333.0838; found 333.0824.

*4.2.5. 4-(5-Methyl-2-(4-methylthiophen-2-yl)thiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3d-2**).* Yield: 11.6 mg (35%) white solid. Mp 141–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.06 (s, 1H), 4.40 (s, 4H), 4.10 (t, J=4.82 Hz, 4H), 2.59 (s, 3H), 2.25 (s, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}N_4OS_2$ 333.0838; found 333.0824.

*4.2.6. 4-(5-Methyl-2-(2-methylthiazol-5-yl)thiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3f**).* Yield: 23.4 mg (70%) white solid. Mp 215–216 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 4.38 (s, 4H), 3.87 (t, J=4.95 Hz, 4H), 2.79 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 163.5, 154.0, 150.8, 143.5, 132.8, 130.8, 128.8, 67.0, 46.3, 27.7, 25.8. FTIR (KBr, cm^{-1}) ν 3125, 1664, 1565, 1400, 1264, 1121, 1070. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_5OS_2$ 334.0791; found 334.0780.

*4.2.7. 4-(2-(Benzo[d]thiazol-2-yl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3g**).* Yield: 27.7 mg (75%) white solid. Mp 254–255 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J=0.57, 7.86 Hz, 1H), 7.95 (dd, J=0.75, 6.45 Hz, 1H), 7.49–7.57 (m, 2H), 4.46 (s, 4H), 3.91 (t, J=4.71 Hz, 4H), 2.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 161.4, 154.4, 153.5, 135.3, 133.2, 129.3126.8, 126.5, 124.1, 123.9, 121.788, 67.1, 46.3, 26.0. FTIR (KBr, cm^{-1}) ν 3123, 3003, 1562, 1535, 1400, 1121, 997, 753. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_5OS_2$ 370.0791; found 370.0786.

*4.2.8. 4-(5-Methyl-2-(1-methyl-1H-imidazol-5-yl)thiazolo[5,4-d] pyrimidin-7-yl)morpholine(**3h**).* Yield: 27.3 mg (86%) white solid. Mp 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.06 (s, 1H), 4.40 (s, 4H), 4.09 (s, 3H), 3.87 (t, J=4.68 Hz, 3H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 163.5, 154.3, 152.4, 140.2, 129.7, 129.1, 125.1, 67.0, 46.2, 35.5, 25.8. FTIR (KBr, cm^{-1}) ν 3124, 1663, 1571, 1400, 1139, 1068, 953. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}N_6OS$ 317.1179; found 317.1155.

*4.2.9. 4-(2-(1,2-Dimethyl-1H-imidazol-5-yl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3i**).* Yield: 28.6 mg (81%) white solid. Mp 190–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.28 (s, 1H), 4.54 (t, J=4.5 Hz, 4H), 3.92 (s, 3H), 3.84 (t, J=4.74 Hz, 4H), 2.57

(s, 3H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 163.0, 153.9, 150.7, 149.3, 132.1, 130.8, 128.6, 66.9, 46.2, 32.7, 29.6, 25.7. FTIR (KBr, cm^{-1}) ν 3124, 1654, 1637, 1560, 1400, 1139, 1068. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}N_6OS$ 331.1336; found 331.1312.

*4.2.10. 4-(5-Methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3k**).* Yield: 19.3 mg (61%) white solid. Mp 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (t, J=2.3°Hz, 1H), 6.76 (dd, J=1.71, 3.93 Hz, 1H), 6.20 (dd, J=1.29, 3.93 Hz, 1H), 4.37 (t, J=4.83 Hz, 4H), 4.00 (s, 3H), 3.85 (t, J=4.77 Hz, 4H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 162.5, 153.9, 152.9, 129.1, 128.1, 126.2, 114.8, 108.9, 67.1, 46.3, 37.0, 25.8. FTIR (KBr, cm^{-1}) ν 3123, 3007, 1637, 1570, 1400, 1119, 1068, 955. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_5OS$ 316.1227; found 316.1215.

*4.2.11. 4-(5-Methyl-2-(1-methyl-1H-pyrrol-2-yl)thiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3l**).* Yield: 22.1 mg (70%) white solid. Mp 222–223 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J=3.6°Hz, 1H), 6.73 (d, J=3.6 Hz, 1H), 4.39 (s, 4H), 4.24 (s, 3H), 3.85 (t, J=4.65 Hz, 4H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 163.7, 154.6, 149.8, 138.6, 134.9, 128.9, 109.0, 67.0, 46.3, 39.7, 25.9. FTIR (KBr, cm^{-1}) ν 3125, 2919, 1655, 1576, 1400, 1069, 954. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}N_6OS$ 317.1179; found 317.1144.

4.3. General procedure of 3m–q

*4.3.1. 4-(5-Methyl-2-p-tolylthiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3m-1**) and 4-(5-methyl-2-m-tolylthiazolo[5,4-d]pyrimidin-7-yl) morpholine (**3m-2**).* To a solution of **1a** (24 mg, 0.1 mmol) in anhydrous toluene (2.0 mL) was added Ag_2CO_3 (82 mg, 0.3 mmol), TBAI (15 mg, 0.04 mmol), PivOH (61 mg, 0.6 mmol), and $Pd(OAc)_2$ (8 mg, 0.02 mmol) in a sealed tube. The reaction mixture was stirred at 120 °C for 20 h, during, which the reaction was monitored by means of TLC. Then the mixture was concentrated in vacuo, and the residue was subjected to column chromatography over silica gel (EtOAc-PE, 1/4) to give **3m**. Yield: 12.5 mg (40%).

3m-1: White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J=8.16°Hz, 2H), 7.36 (d, J=7.48 Hz, 2H), 4.46 (s, 4H), 3.89 (t, J=4.47 Hz, 4H), 2.62 (s, 3H), 2.43 (s, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_4OS$ 327.1274; found 327.1228.

3m-2: White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.03 (t, J=4.26°Hz, 2H), 4.46 (s, 4H), 3.89 (t, J=4.47 Hz, 4H), 2.62 (s, 3H), 2.46 (s, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_4OS$ 327.1274; found 327.1228.

*4.3.2. 4-(2-(3-Chlorophenyl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl) morpholine (**3n-1**) and 4-(2-(2-chlorophenyl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl) morpholine (**3n-2**).* Yield: 8.7 mg (25%).

3n-1: White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–8.02 (m, 4H), 4.45 (s, 4H), 3.89 (t, J=4.5 Hz, 4H), 2.62 (s, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}ClN_4OS$ 347.0728; found 347.0707. **3n-2**: White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.55 (m, 4H), 4.45 (s, 4H), 3.89 (t, J=4.5 Hz, 4H), 2.61 (s, 3H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}ClN_4OS$ 347.0728; found 347.0707.

*4.3.3. N,N-Dimethyl-4-(5-methyl-7-morpholinothiazolo[5,4-d]pyrimidin-2-yl) aniline (**3o**).* Yield: 14.2 mg (45%). White solid. Mp 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J=8.97 Hz, 2H), 6.74 (d, J=9.0 Hz, 2H), 4.45 (s, 4H), 3.89 (t, J=4.77 Hz, 4H), 3.07 (m, 6H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, CDCl3, ppm) δ 168.8, 163.5, 154.0, 150.8, 142.1, 141.7, 132.8, 130.8, 128.7, 67.0, 41.2, 27.7. FTIR (KBr, cm^{-1}) ν 3123, 1611, 1400, 1119, 1068, 951. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_5OS$ 356.1540; found 356.1526.

*4.3.4. 4-(2-(4-Methoxyphenyl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3p**).*[18c] Yield: 20.6 mg (60%). White solid. Mp 206–207 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J=8.85 Hz, 2H), 6.98 (d, J=8.85 Hz, 2H), 4.42 (s, 4H), 3.84–3.88 (m, 7H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, CDCl3, ppm) δ 166.0, 162.7, 161.9, 160.1, 154.1, 146.5, 128.5, 126.3, 114.3, 67.1, 55.5, 46.3, 25.8. FTIR (KBr, cm^{-1}) ν 3119, 1605, 1559, 1400, 1259, 1069, 996. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_4O_2S$ 343.1223; found 343.1241.

*4.3.5. 4-(2-(2,5-Dimethylphenyl)-5-methylthiazolo[5,4-d]pyrimidin-7-yl)morpholine (**3q**).* Yield: 14.3 mg (42%) white solid. Mp 215–216 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.22 (s, 1H), 7.21 (s, 1H), 4.45 (s, 4H), 3.86 (t, J=4.08 Hz, 4H), 2.63 (s, 3H), 2.62 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, CDCl3, ppm) δ 165.1, 163.5, 153.9, 150.8, 143.5, 142.1, 141.7, 132.1, 130.9, 128.8, 128.7, 67.0, 46.3, 25.8, 19.5, 19.1. FTIR (KBr, cm^{-1}) ν 3215, 1637, 1559, 1400, 1119, 1069. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}N_4OS$ 341.1431; found 341.1452.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.103.

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