Unexpected C—O Bond Formation in Suzuki Coupling of 4-Chlorothieno[2,3-*d*]pyrimidines

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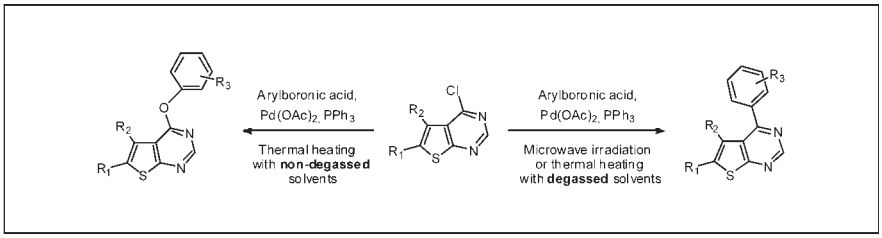

Palladium-catalyzed Suzuki reactions were performed on 4-chlorothieno[2,3-*d*]pyrimidines under classical heating conditions and under microwave irradiation. Some unexpected results were obtained during this study as two kinds of compounds were isolated depending on the conditions used. A careful investigation of experimental details has shown that the expected C—C bond formation occurred when degassed solvents were used (both in classical and microwave heating) whereas an unexpected C—O bond formation happened when solvents were not degassed with argon-bubbling before use.

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INTRODUCTION

Kinase insert domain (KDR)-containing receptor is one of the human tyrosine kinases that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor-induced angiogenesis [1]. Compounds which influence the KDR kinase have attracted much attention and are of great interest as potential therapeutic agents. Several compounds with a quinazoline moiety have shown effective antitumor activity and have found clinical applications such as gefitinib (Iressa® from AstraZeneca) or erlotinib (Tarceva® from Genentech) [2].

For many years, thieno[3,2-*d*]pyrimidines and thieno[2,3-*d*]pyrimidines are known to be pharmacophoric elements in numerous active compounds such as analgesic [3], anticancer [4], mGluR1 antagonists [5], or molecules having antimicrobial and anti-inflammatory activities [6] (Fig. 1). Munchhof et al. [7] reported the design and structure activity relationship (SAR) of thieno[3,2-*d*]-pyrimidines and -pyridines as selective VEGFR-2 kinase inhibitors. Since then, many patents were filed and consequently, thienopyrimidines have become a well-sought privileged class of compounds in drug discovery programs and practical strategies for the construction of libraries have been developed [8].

RESULTS AND DISCUSSION

The interest in this heterocyclic core prompted us to set up a short and efficient route toward this nucleus. In 2007, we have reinvestigated the synthesis of thieno[2,3-*d*]pyrimidinone **1a** and 4-chlorothieno[2,3-*d*]pyrimidine **2a** using microwave-assisted procedure [9]. We now extended this procedure to compound **2b** (Scheme 1).

Aiming to extend thienopyrimidine libraries, we then wanted to functionalize those compounds on position 4. Usually, functionalities are introduced at C-4 via nucleophilic substitution reaction of the chlorothienopyrimidine with amines [10]. In this study, we have decided to focus our attention on the introduction of aromatics and heterocycles at this position. Indeed, we thought that easy modulation at C-4 could be done by palladium-catalyzed cross-coupling of 4-chlorothieno[2,3-*d*]pyrimidines **2a**,**b** with different arylboronic acids.

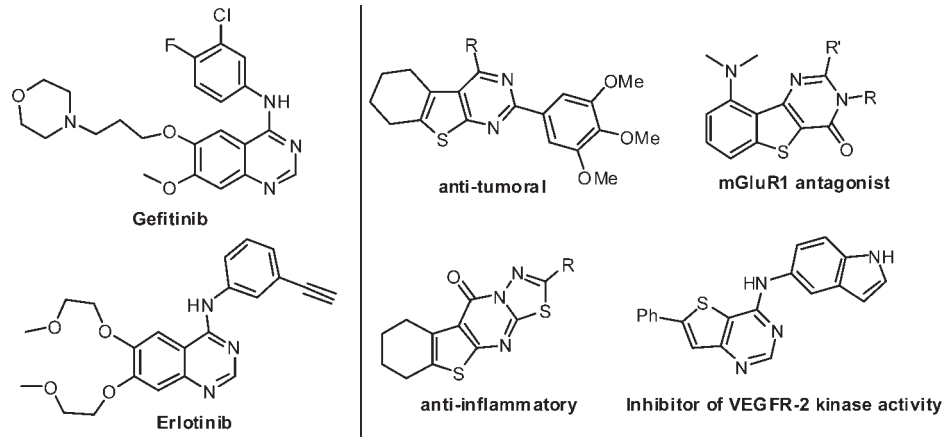


Figure 1. Structures of quinazolines and thienopyrimidines with biological activities.

The electron-deficient nature of the pyrimidine ring makes this system far more reactive in Suzuki coupling compared with the analogous benzenoid halides. 2,4,6-Trichloropyrimidines, 2,4- and 4,6-dihalo pyrimidines have been successfully arylated under classical Suzuki conditions ($Pd(OAc)_2$, PPh_3, Na_2CO_3, benzene/ethanol/water or $Pd(PPh_3)_4$, toluene, Na_2CO_3 2*M*) [11,12]. A sequential Suzuki coupling/amination reaction was recently described on 4,6-dichloropyrimidines under microwave irradiation [13]. Some studies were also done on condensed halopyrimidines as for example on 2,4-dichloropyridopyrimidines [14] or on 4-chloro-2-trichloromethylquinazoline [15]. To the best of our knowledge, there is only one publication with one example on Suzuki coupling on 4-chlorothieno[2,3-*d*]pyrimidine [4a].

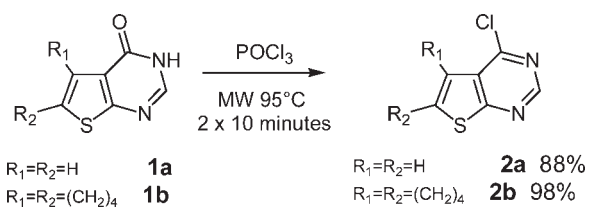
First, we investigated the reactivity of 4-chlorothieno[2,3-*d*]pyrimidine **2a** with 4-methoxyphenylboronic acid under classical Suzuki conditions. The reaction was performed in DME with $Pd(OAc)_2/PPh_3$ catalysis in the presence of Na_2CO_3 2*M* as base at 75–85°C. The reaction was stopped when the starting material had completely disappeared (TLC control) and the product was isolated by column chromatography (Scheme 2).

We then carried out the same Suzuki coupling under microwave irradiation hoping to enhance the yields and decrease reaction times. $Pd(OAc)_2/PPh_3$ was used as catalytic system, with Cs_2CO_3 as base and DME/EtOH/H_2O as solvent. We worked under temperature/time control with 150°C/30 min as parameters. At the end of the time, the TLC control indicated that all starting material was consumed. However, after purification, the ^1H NMR spectrum was not consistent with the one obtained under classical conditions (Fig. 2). Two different products were obtained. First of all, to control these results, we applied under microwave irradiation exactly the same conditions as for classical heating (DME/H_2O was used as solvent and Na_2CO_3 as base). The same product as before was obtained, different from the one resulting from classical heating.

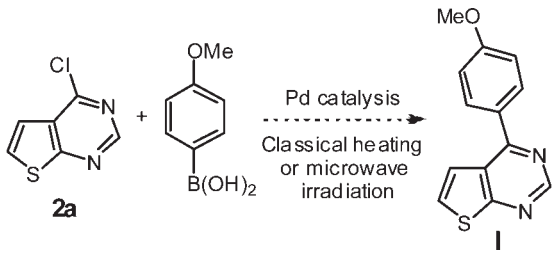
As shown in Figure 2, in both ^1H NMR spectra, the same signals were present although their δ values were slightly different. The thiophene ring seemed to remain unchanged in both compounds (two doublets at 7.63 and 7.94 ppm in compound **A**; two doublets at 7.75 and 8.01 ppm in compound **B**). The presence of an AB signal let us suppose that the *p*-disubstituted phenyl ring was still present in both structures too (two doublets at 7.01 and 7.22 ppm in compound **A**, two doublets at 7.15 and 8.01 ppm in compound **B**). Moreover, NOESY experiment and HMBC sequence showed that the pyrimidine proton was isolated and placed between the two nitrogen atoms in both structures.

The same coupling with 4-methoxyphenylboronic acid was realized on chlorothienopyrimidine **2b** in classical

Scheme 1



Scheme 2



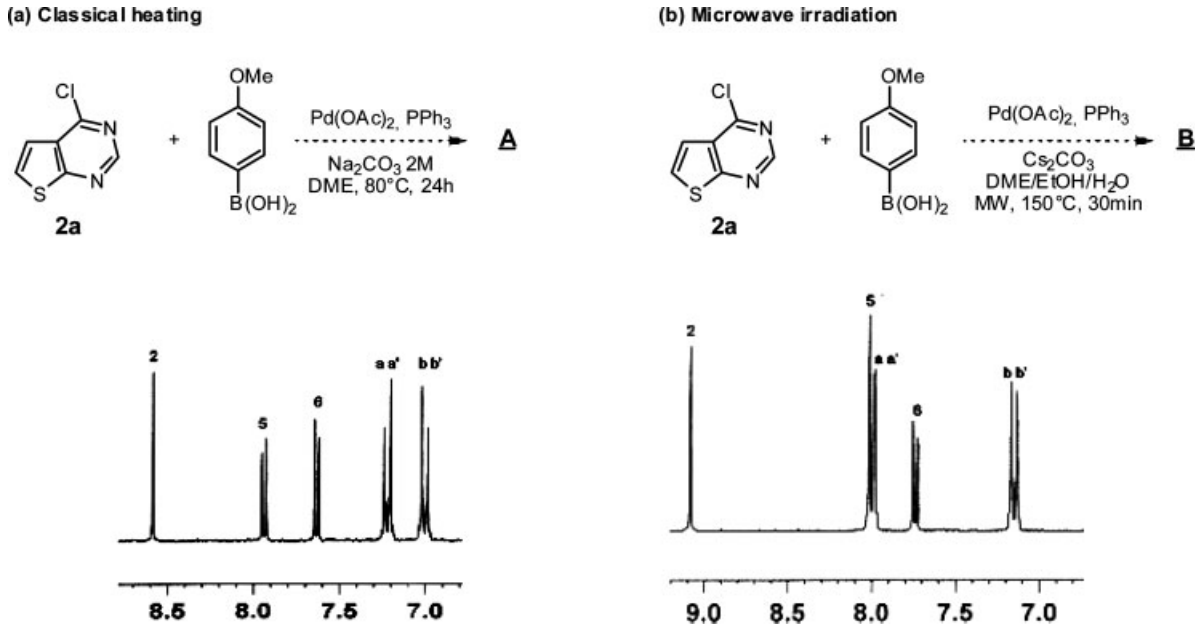


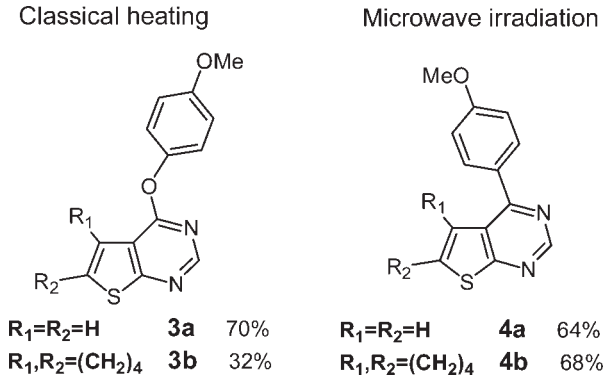
Figure 2. [1]H NMR spectra (aromatic part) of compound obtained by classical heating and under microwave irradiation: (a) classical heating and (b) microwave irradiation.

conditions and under microwave irradiation. Two different compounds were obtained and after several attempts, we succeeded in isolating crystals. Those crystallographic data showed that the expected product was obtained under microwave irradiation (with formation of the C—C bond between chlorothienopyrimidine and boronic acid), whereas the classical heating led to the formation of a C—O bond. The compounds obtained are shown in Scheme 3.

Once the structures were elucidated, we tried to explain the formation of compounds **3**. During those first experiments, we have noticed that *p*-methoxyphenol was detected as trace in the crude material. So, we postulated that the boronic acid must have been transformed into *p*-methoxyphenol and after, the phenol would have reacted with the chloropyrimidine under SNAr process giving compounds **3**. As a verification, compound **3b** was synthesized directly by the action of *p*-methoxyphenate on 4-chloropyrimidine **2b** in 55% yield (Scheme 4).

Regarding the yield obtained for compound **3a** (70%), it would mean that the boronic acid was converted into phenol near completely. It is well known that oxygen should be avoided when working with boronic acids since they could be oxidized to the corresponding phenols [16,17]. That is why our reactions were performed under an argon atmosphere both under classical heating and under microwave irradiation. However, there was a very small difference of manipulation when doing those reactions. Under classical heating, the reactions were performed in a Schlenk tube flushed with argon whereas in microwave irradiation, a one-necked round-bottom

Scheme 3



Scheme 4

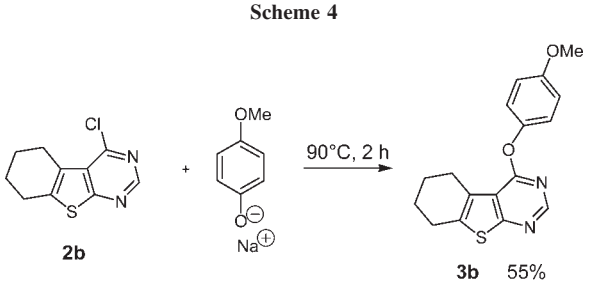
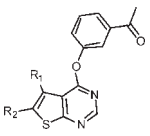
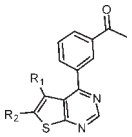
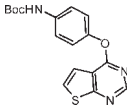
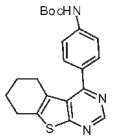
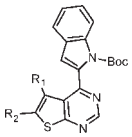


Table 1

Suzuki coupling of 4-chlorothienopyrimidines under classical heating and microwave irradiation.

Entry	Method	Product	Yield		
1	A		$R_1 = R_2 = H$ $R_1,R_2 = (CH_2)_4$	**5a** **5b**	77% 25%[a]
2	B for **6a** C for **6b**		$R_1 = R_2 = H$ $R_1,R_2 = (CH_2)_4$	**6a** **6b**	44% 75%
3	A			**7**	67%
4	C			**8**	61%
5	C		$R_1 = R_2 = H$ $R_1,R_2 = (CH_2)_4$	**9a** **9b**	36% 51%

Method A: Classical heating, nondegassed solvents (75°C, 24 h); Method B: Microwave irradiation (150°C, 30 min); Method C: Classical heating, DME, and H_2O degassed (75°C, 24 h).

[a] Reaction was performed at room temperature.

flask was used and argon was bubbled directly in the solution while loading the reagents. So, we performed the Suzuki cross-coupling under classical heating conditions but this time, solvents (DME and water) were degassed with argon bubbling before being introduced in the reaction mixture. In this case, we only observed C—C bond formation. Compounds **6**, **8**–**9** were synthesized in good yields under classical heating with degassed solvents whereas the formation of C—O bond occurred when nondegassed solvents were used for compounds **5** and **7** (Table 1).

CONCLUSIONS

In summary, we have demonstrated that 4-chlorothieno[2,3-*d*]pyrimidines undergo Suzuki coupling under both classical heating and microwave irradiation in moderate to good yields. Moreover, because of unexpected results obtained under classical heating, we have shown the importance to use degassed solvents in those reactions and not working only under an argon stream. Further investigation of the mechanism of C—O bond formation in cross-coupling with boronic acid as well as its application to other substrates are ongoing in our laboratory.

EXPERIMENTAL

General methods. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^{1}H NMR spectra were measured at 250 MHz, and ^{13}C NMR spectra were measured at 62.9 MHz on a Bruker AC 250 spectrometer at 25°C in DMSO-d_6. IR spectra were recorded for neat samples on KBr plates on a Perkin Elmer Spectrum Bx FTIR spectrophotometer. Standard mass spectrometry data were acquired by using GC-MS system in EI mode with a maximum *m*/*z* range of 400 on a GC Varian CP 3800 spectrometer and triple quadrupole 1200 Varian detector. HMRS were collected on a Bruker MICROTOF-Q ESI/QqTOF spectrometer. Elemental analyses were determined with a Thermofinnigan FlashEA 1112 elemental analyzer. Microwave monomode synthesizer, (CEM Corporation) Discover model was used in open-vessel mode for the microwave-assisted synthesis; the temperature was monitored by an infrared sensor located in the microwave cavity floor. When required, all solvents and reagents were purified by standard techniques. All Suzuki cross-coupling reactions were conducted under a positive pressure of argon. Chromatographic separations were carried out with silica gel 60 Å (70–200 μm) or alumina. Yields reported are for chromatographically pure isolated product.

Details of synthesis, purification, and characterization of starting materials **1a**,**b** and **2a**,**b** can be found in literature [9].

CCDC 716544 and CCDC 716545 contain the supplementary crystallographic data for this article (compounds **4b** and **3b**, respectively). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for Suzuki cross-coupling. ***Method A.*** To a solution of 4-chlorothienopyrimidine (**2a**: 171 mg, **2b**: 225 mg, 1 mmol), boronic acid (1.2 mmol) and PPh_3 (39 mg, 0.15 mmol) in DME (12 mL) were added 2*M* Na_2CO_3 (10 mL) and $Pd(OAc)_2$ (10 mg, 0.04 mmol).The reaction mixture was stirred at 75–80°C for 24 h under argon. After filtration, the aqueous layer was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with 10% NaOHaq and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give products **3a**, **3b**, **5a**, **5b**, and **7**.

Method B. A 50-mL round-bottomed flask was charged with 4-chlorothienopyrimidine (**2a**: 171 mg, **2b**: 225 mg, 1 mmol), boronic acid (1.5 mmol), Cs_2CO_3 (1.01 g, 3.1 mmol), PPh_3 (66 mg, 0.25 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and DME/EtOH/$H_2$0 (30 mL, ratio: 1/1/1) flushed with argon. The reaction mixture was placed in a microwave synthesizer. The

microwave vial was purged three times with argon and then heated under microwave irradiation (150°C) for 30 min. After this time, the reaction mixture was allowed to cool to room temperature and was quenched with AcOEt/H_20 (20 mL, ratio: 1/1). The water layer was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give products **4a**, **4b**, and **6a**.

Method C. Same procedure as Method A but with DME and water degassed with argon bubbling.

4-(4-Methoxyphenoxy)thieno[2,3-d]pyrimidine (3a). Compound **3a** was obtained according to Method A from **2a** (171 mg, 1 mmol) and 4-methoxyphenylboronic acid (182 mg, 1.2 mmol) and isolated by column chromatography (Silica, CH_2Cl_2 as eluent); the yield was 155 mg (64%), beige solid, mp 111–112°C; IR: 1572, 1534, 1503 cm^{-1}; ^1H NMR: δ 3.78 (s, 3H), 7.01 (d, J = 9.1 Hz, 2H), 7.22 (d, J = 9.1 Hz, 2H), 7.63 (d, J = 6 Hz, 1H), 7.94 (d, J = 6 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR: δ 55.3, 114.2, 118.4, 118.5, 122.8, 127.1, 145.3, 152.9, 156.9, 163.4, 168.8; GC MS (t_R 9.19 min) m/z (%) = 257 (100, M^+), 244 (19), 134 (94); HRMS calcd for [M + H^+] $C_{13}H_{11}N_2O_2S$ 259.0536, found 259.0534. *Anal*. Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.59; H, 3.88; N, 10.89.

4-(4-Methoxyphenoxy)-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (3b). Compound **3b** was obtained according to Method A from **2b** (225 mg, 1 mmol) and 4-methoxyphenylboronic acid (182 mg, 1.2 mmol) and isolated by column chromatography (Silica, CH_2Cl_2 as eluent); the yield was 101 mg (34%), brown solid, mp 83–84°C, IR: 1570, 1560, 1498 cm^{-1}; ^1H NMR: δ 1.85 (m, 4H), 2.85 (m, 2H), 3.00 (m, 2H), 6.99 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 2H), 8.45 (s, 1H); ^{13}C NMR: δ 21.8, 22.3, 24.9, 25.4, 55.4, 114.5, 118.3, 122.8, 126.9, 135.5, 145.4, 152.0, 156.7, 163.1, 167.4; GC MS (t_R 11.62 min) m/z (%) = 313 (100, M^+), 298 (40), 205 (44). *Anal*. Calcd. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.60; H, 5.21; N, 9.06.

4-(4-Methoxyphenyl)thieno[2,3-d]pyrimidine (4a). Compound **4a** was obtained according to the general procedure B from **2a** (171 mg, 1 mmol) and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) and isolated after purification by chromatography on silica gel (CH_2Cl_2 as eluent), the yield was 155 mg (64%), beige solid, mp 136–137°C, IR: 1609, 1540, 1514 cm^{-1}; ^1H NMR: δ 3.85 (s, 3H), 7.15 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 6 Hz, 1H), 7.98–8.02 (m, 3H), 9.08 (s, 1H); ^{13}C NMR: δ 55.4, 114.4, 121.1, 126.7, 128.3, 129.3, 130.8, 152.9, 159.3, 161.2, 169.1; GC MS (t_R 9.34 min) m/z (%) = 242 (100, M^+), 211 (66), 134 (5); HRMS calcd for [M + H^+] $C_{13}H_{11}N_2OS$ 243.0587, found 243.0601. *Anal*. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.62; H, 4.17; N, 11.49.

4-(4-Methoxyphenyl)-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (4b). Compound **4b** was obtained according to the general procedure B from **2b** (225 mg, 1 mmol) and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) and isolated after purification by column chromatography on silica gel (CH_2Cl_2 as eluent), the yield was 201 mg (68%), white solid, mp 101–102°C, IR: 1608, 1508 cm^{-1}; ^1H NMR: δ 1.56–1.60 (m, 2H), 1.79–1.83 (m, 2H), 2.13–2.18 (m, 2H), 2.85–2.90 (m, 2H), 3.83 (s, 3H), 7.06 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 8.95 (s, 1H); ^{13}C NMR: δ 21.9, 22.1, 25.4, 26.8, 55.2, 113.2, 127.2, 128.0, 130.5, 130.6, 130.7, 137.6, 151.5, 160.1, 168.0; GC MS (t_R 11.32 min) m/z (%) = 296 (100, M^+), 265 (12), 211 (9). *Anal*. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 69.10; H, 5.36; N, 9.53.

1-[3-(Thieno[2,3-d]pyrimidin-4-yloxy)phenyl]ethanone (5a). Compound **5a** was prepared according to Method A from **2a** (171 mg, 1 mmol) and 3-acetylphenylboronic acid (197 mg, 1.2 mmol) and purified by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 208 mg (77%), white solid, mp 140–141°C; IR: 1694, 1571, 1526 cm^{-1}; ^1H NMR: δ 2.59 (s, 3H), 7.64 (m, 2H), 7.69 (d, J = 6 Hz, 1H), 7.90 (m, 2H), 7.99 (d, J = 6 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR: δ 26.8, 118.4, 118.6, 121.6, 125.7, 127.0, 127.5, 130.2, 138.5, 152.2, 152.8, 163.0, 169.1, 197.2; GC MS (t_R 9.82 min) m/z (%) = 270 (100, M^+), 255 (99), 242 (29), 227 (98), 135 (97); HRMS calcd for [M + H^+] $C_{14}H_{11}N_2O_2S$ 271.0536, found 271.0516. *Anal*. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.48; H, 3.75; N, 10.55.

1-[3-(5,6,7,8-Tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl-oxy)-phenyl]ethanone (5b). Compound **5b** was prepared from **2b** (225 mg, 1 mmol) and 3-acetylphenylboronic acid (197 mg, 1.2 mmol) according to Method A working at room temperature and purified by column chromatography (Silica, Cyclohexane/AcOEt 98:2 as eluent), the yield was 80 mg (25%), white solid, mp 148–149°C, IR: 1683, 1571, 1558 cm^{-1}; ^1H NMR: δ 1.85 (m, 4H), 2.58 (s, 3H), 2.86 (m, 2H), 3.02 (m, 2H), 7.55–7.65 (m, 2H), 7.83–7.90 (m, 2H), 8.47 (s, 1H); ^{13}C NMR: δ 21.7, 22.3, 25.0, 25.4, 26.8, 118.4, 121.5, 125.5, 126.9, 127.0, 130.0, 135.9, 138.4, 151.9, 152.3, 162.6, 167.7, 197.2; HRMS calcd for [M + H^+] $C_{18}H_{17}N_2O_2S$ 325.1005, found 325.0985. *Anal*. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.87; H, 4.90; N, 8.64.

1-(3-Thieno[2,3-d]pyrimidin-4-ylphenyl)ethanone (6a). Compound **6a** was prepared from **2a** (171 mg, 1 mmol) and 3-acetylphenylboronic acid (246 mg, 1.5 mmol) according to Method B. The pure product was obtained by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 111 mg (44%), white solid, mp 129–130°C, IR: 1683, 1603, 1545 cm^{-1}; ^1H NMR: δ 2.74 (s, 3H), 7.83 (m, 2H), 8.13–8.32 (m, 3H), 8.56 (s, 1H), 9.25 (s, 1H); ^{13}C NMR: δ 26.9, 120.7, 127.3, 128.7, 129.3, 129.4, 130.0, 133.5, 137.3, 137.4, 153.0, 158.9, 169.4, 197.5; GC MS (t_R 9.76 min) m/z (%) = 254 (100, M^+), 239 (64), 211 (68); HRMS calcd for [M + H^+] $C_{14}H_{11}N_2OS$ 255.0587, found 255.0572. *Anal*. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found: C, 66.26; H, 3.88; N, 10.99.

1-[3-(5,6,7,8-Tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl) phenyl]ethanone (6b). Compound **6b** was prepared from **2b** (225 mg, 1 mmol) and 3-acetylphenylboronic acid (197 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 231 mg (75%), pale brown solid, mp 121–122°C, IR: 1684, 1579, 1560, 1523 cm^{-1}; ^1H NMR: δ 1.53–1.58 (m, 2H), 1.77–1.82 (m, 2H), 2.02–2.07 (m, 2H), 2.63 (s, 3H), 2.86–2.91 (m, 2H), 7.68 (m, 1H), 7.80 (m, 1H), 8.10 (m, 1H), 8.30 (s, 1H), 9.02 (s, 1H); ^{13}C NMR: δ 21.2, 22.0, 25.4, 26.6, 26.8, 126.8, 128.1, 128.4, 128.6, 128.9, 133.6, 136.3, 138.4, 138.5, 151.6, 159.3, 168.1, 197.6; GC MS (t_R 11.78 min) m/z (%) = 307 (100, M^+), 293 (56), 280 (93), 266 (16); HRMS calcd for [M + H^+] $C_{18}H_{17}N_2OS$ 309.1056, found 309.1030. *Anal*. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.17; H, 5.35; N, 9.12.

tert-Butyl 4-(thieno[2,3-d]pyrimidin-4-yloxy)phenylcarbamate (7). Compound **7** was prepared from **2a** (171 mg, 1 mmol) and 4-[(*tert*-butoxycarbonyl)amino]phenylboronic acid (285 mg, 1.2 mmol) according to Method A. The pure product was obtained by column chromatography (Silica, CH_2Cl_2 as eluent), the yield was 230 mg (67%), pale yellow solid, mp 141–142°C, IR: 1702, 1573, 1535 cm^{-1}; ^1H NMR: δ 1.46 (s, 9H), 7.17 (d, $J = 9$ Hz, 2H), 7.49 (d, $J = 9$ Hz, 2H), 7.61 (d, $J = 6$ Hz, 1H), 7.91 (d, $J = 6$ Hz, 1H), 8.56 (s, 1H), 9.41 (s, 1H); ^{13}C NMR: δ 28.0, 79.2, 115.0, 118.4, 118.5, 119.2, 122.0, 127.2, 137.1, 146.5, 152.9, 163.3, 168.8; GC MS (t_R 9.74 min) *m*/*z* (%) = 243 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{17}H_{18}N_3O_3S$ 344.1063, found 344.1042. *Anal*. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.62; H, 4.88; N, 12.29.

tert-Butyl 4-(5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl)phenylcarbamate (8). Compound **8** was prepared from **2b** (225 mg, 1 mmol) and 4-[(*tert*-butoxycarbonyl)amino]phenylboronic acid (285 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Alumina, cyclohexane/AcOEt 98:2 as eluent), the yield was 231 mg (61%), white solid, mp 173–174°C, IR: 1702, 1612, 1513 cm^{-1}, ^1H NMR: δ 1.46 (s, 9H), 1.61 (m, 2H), 1.79 (m, 2H), 2.15 (m, 2H), 2.87 (m, 2H), 7.44 (m, 2H), 7.60 (m, 2H), 8.95 (s, 1H), 9.62 (s, 1H); ^{13}C NMR: δ 22.0, 25.4, 26.2, 26.8, 28.1, 79.3, 116.9, 127.2, 128.3, 129.9, 131.7, 137.6, 140.7, 151.5, 152.7, 160.1, 168.0; GC MS (t_R 12.23 min) *m*/*z* (%) = 280 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{21}H_{24}N_3O_2S$ 382.1584, found 382.1545. *Anal*. Calcd. for $C_{21}H_{23}N_3O_2S$: C, 66.12; H, 6.08; N, 11.01. Found: C, 66.35; H, 6.10; N, 10.95.

tert-Butyl 2-thieno[2,3-d]pyrimidin-4-yl-1H-indole-1-carboxylate (9a). Compound **9a** was prepared from **2a** (171 mg, 1 mmol) and 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid (313 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Alumina, cyclohexane/AcOEt 98:2 as eluent), the yield was 127 mg (36%), pale brown oil, IR: 1727, 1565, 1539, 1515 cm^{-1}; ^1H NMR: δ 1.11 (s, 9H), 7.29 (s, 1H), 7.34 (m, 1H), 7.47 (m, 1H), 7.57 (d, $J = 6$ Hz, 1H), 7.74 (d, $J = 7.7$ Hz, 1H), 8.05 (d, $J = 6$ Hz, 1H), 8.13 (d, $J = 8.3$ Hz, 1H), 9.17 (s, 1H); ^{13}C NMR: δ 26.7, 83.9, 113.6, 114.4, 120.5, 121.9, 123.4, 126.1, 128.2, 128.3, 129.2, 134.7, 137.1, 148.9, 152.6, 154.2, 168.3; GC MS (t_R 10.97 min) *m*/*z* (%) = 251 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{19}H_{18}N_3O_2S$ 352.1114, found 352.1099. *Anal*. Calcd. for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96. Found: C, 65.21; H, 4.88; N, 11.89.

tert-Butyl 2-(5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4-yl)-1H-indole-1-carboxylate (9b). Compound **9b** was prepared from **2b** (225 mg, 1 mmol) 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid (313 mg, 1.2 mmol) according to Method C. The pure product was obtained by column chromatography (Alumina, cyclohexane/AcOEt 98:2 as eluent), the yield was 207 mg (51%), yellow oil, IR: 1735, 1574, 1512 cm^{-1}; ^1H NMR: δ 0.99 (s, 9H), 1.56 (m, 2H), 1.76 (m, 2H), 2.09 (m, 2H), 2.87 (m, 2H), 6.94 (s, 1H), 7.32 (m, 1H), 7.42 (m, 1H), 7.69 (d, $J = 7.2$ Hz, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 9.04 (s, 1H); ^{13}C NMR: δ 21.6, 22.2, 24.2, 25.3, 26.6, 83.8, 111.6, 115.0, 121.5, 123.5, 125.4, 126.8, 128.3, 129.4, 134.4, 135.6, 138.8, 148.6, 151.5, 153.4, 167.2; GC MS (t_R 13.97 min) *m*/*z* (%) = 305 (100, M^+); HRMS calcd for $[M + H^+]$ $C_{23}H_{24}N_3O_2S$ 406.1584, found 406.1560. *Anal*. Calcd. for $C_{23}H_{23}N_3O_2S$: C, 68.12; H, 5.72; N, 10.36. Found: C, 68.13; H, 5.71; N, 10.40.

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