Tetrahedron 68 (2012) 5445–5452

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Combination of the Suzuki–Miyaura cross-coupling and nucleophilic aromatic substitution of hydrogen (S_N^H) reactions as a versatile route to pyrimidines bearing thiophene fragments

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ARTICLE INFO

Article history:
Received 19 January 2012
Received in revised form 13 March 2012
Accepted 24 April 2012
Available online 3 May 2012

Keywords:
Suzuki–Miyaura reaction
Nucleophilic aromatic substitution of hydrogen
Pyrimidines
Thiophenes
Microwave-assisted synthesis

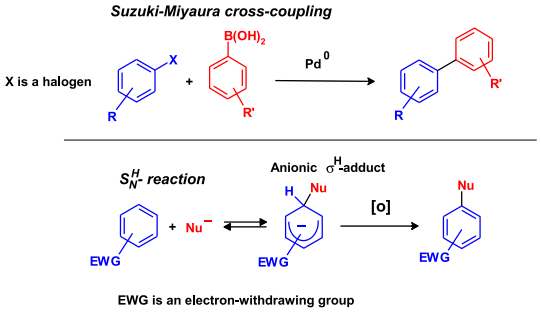
ABSTRACT

It has been shown that combination of the Suzuki–Miyaura cross-coupling and nucleophilic aromatic substitution of hydrogen is a versatile method for the synthesis of 4-(thiophen-2-yl)-, 5-(thiophen-2-yl)-, and 4,5-di(thiophen-2-yl) substituted pyrimidines from the commercially available 5-bromopyrimidine. The S_N^H (AE)- and S_N^H (AO)-reactions of 5-bromopyrimidine with thiophene and 2-bromothiophene have been studied by gas–liquid chromatography/mass-spectrometry. The structures of intermediate σ^H-adducts, as well as thiophene-(thiophenyl)pyrimidine and bithiophene-(thiophenyl)pyrimidine dyads have first been established by X-ray crystallography analysis.

1. Introduction

The reactions leading to the formation of new carbon–carbon bonds are of great importance for synthetic organic chemistry. The Suzuki–Miyaura palladium-catalyzed cross-coupling reactions of aryl halides with organoboronic acids proved to be a versatile approach for the selective formation of carbon–carbon bonds, which is used in particular for the synthesis of biaryls.[1] Another approach to the formation of C–C and C–X (X is a heteroatom) bonds with an aromatic ring is based on nucleophilic aromatic substitution of hydrogen (S_N^H) (Scheme 1).[2] The advantage of this method is that it does require neither the presence of a halogen atom in aromatic substrate nor an expensive metal catalyst.

Pyrimidines belong to an important class of heteroaromatic compounds, which have found wide applications as effective pharmaceuticals, agrochemicals, and organic materials.[3] A number of pyrimidines are known to exhibit antimicrobial and antitumor activities. Besides that, pyrimidines possess interesting coordinating characteristics as ligands for a variety of transition metals and have proved to be useful for construction of supramolecules.[4] Electron-deficient nature of the pyrimidine ring provides a highly electron-accepting properties for the pyrimidine-conjugated monomers and polymers.[5] Indeed, conjugated molecules bearing pyrimidine units as the key fragments attract a considerable attention of chemists and physicists as promising candidates for light-emitting diodes.[6]



Scheme 1.

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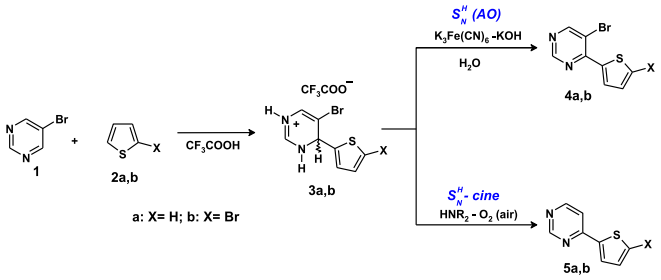
doi:10.1016/j.tet.2012.04.095

In this paper a new approach to the synthesis of (thiophen-2-yl) substituted pyrimidines is described. These π-conjugated heterocyclic systems consisting of thiophene/bithiophene units, as electron-donating fragments attached to the pyrimidine ring, as electron acceptor, are rather interesting for elucidation of their photophysical and electrochemical properties.[7] One of the traditional methods for the synthesis of such compounds is the Suzuki–Miyaura cross-coupling reaction.[7,8] In this communication we wish to report a new convenient approach to (thiophen-2-yl) substituted pyrimidines by using a combination of two C–C coupling reactions, i.e., the Suzuki–Miyaura palladium-catalyzed cross-coupling and the nucleophilic aromatic substitution of hydrogen.

2. Results and discussion

It has been shown earlier that pyrimidine, 5-methylpyrimidine and their benzoanneleted analogs react in the presence of trifluoroacetic acid with a number of aromatic compounds, such as phenols, pyrroles, indoles, and thiophenes, to form rather stable 4-aryl substituted 3,4-dihydropyrimidinium salts.[9]

Indeed, when thiophene **2a** or 2-bromothiophene **2b** was added to a solution of 5-bromopyrimidine **1** in CF_3COOH, and the reaction mixture was stirred at room temperature for 24 h, thiophenyl substituted dihydropyrimidines **3a** or **3b** were obtained as white crystalline products in high yields (65–80%) (Scheme 2).



Scheme 2.

The structure of thiophenyl substituted dihydropyrimidines **3a**,**b** has been established by X-ray crystallography analysis (Figs. 1 and 2).

Dihydropyrimidines **3a**,**b** are considered to be intermediate σ^H-adducts and, indeed, they can be transformed into S_N^H-products **4** and **5**. Use of KOH/$K_3Fe(CN)_6$ in water as the oxidative system enabled us to transform dihydropyrimidines **3a**,**b** into the products of nucleophilic aromatic substitution of hydrogen **4a**,**b**. The reaction proceeds via the classical two-step "Addition–Oxidation" pathway S_N^H (AO). On the contrary, in the presence of secondary amines (diethylamine, piperidine or morpholine) aromatization of compounds **3a**,**b** takes place due to the elimination of HBr, thus yielding 4-(thiophen-2-yl) (**5a**) and 4-(5-bromothiophen-2-yl) substituted pyrimidine (**5b**), as products of *cine*-substitution of hydrogen (Table 1).

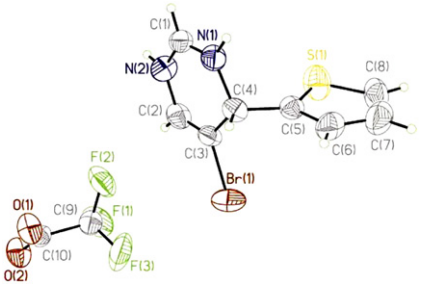


Fig. 1. X-ray structure of **3a**.

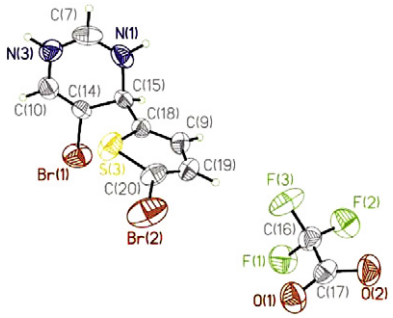


Fig. 2. X-ray structure of **3b**.

Attempts to react compounds **5a**,**b** with thiophene **2a** or 2-bromothiophene **2b** in CF_3COOH to obtain the products of double nucleophilic substitution of hydrogen have failed. No traces of 4,6-disubstituted pyrimidines **6a**–**c** have been observed in the reaction mixtures by GC–MS (Scheme 3). A low reactivity of **5a**,**b** toward thiophenes **2a**,**b** is probably due to the presence of the electron-donating thienyl group at C(4) of the pyrimidine ring.

Compounds **4a**,**b** have further been involved in the Suzuki–Miyaura cross-coupling reaction with 2-thienylboronic acid (**2c**) under microwave irradiation, thus resulting in the formation of 4,5-di(thiophen-2-yl)pyrimidine (**8a**) and 4-([2,2′]-bithiophenyl-5-yl)-5-(thiophen-2-yl)pyrimidine (**9**) in good yields (Scheme 4, Table 2). The structure of compounds **8a** and **9** has unequivocally been established by X-ray crystallography (Figs. 3 and 4).

It is worth noting that in the reaction of 5-bromo-4-(5-bromothiophen-2-yl)pyrimidine (**4b**) with 2-thienylboronic acid (**2c**) the compound (**10**) is formed as by-product. Molecular ion $[M]^+$ for **10** is *m*/*z* 244, and it coincides with the molecular weight of **8a**, however the difference in retention times for these compounds is about 2 min. In order to distinguish these compounds, the synthesis of **10** was carried out by reacting 4-(5-bromothiophen-2-yl) pyrimidine (**5b**) with 2-thienylboronic acid (**2c**) under the same reaction conditions. The retention time for the obtained compound **10** proved to coincide with that for by-product derived from the reaction of **4b** with **2c**. Moreover, the crystal structure of 4-([2,2′]-bithiophenyl-5-yl)pyrimidine (**10**) was confirmed by X-ray diffraction (see Fig. 5).

The method for obtaining of 4,5-dithiophenyl substituted pyrimidines described above is not unique one, and can be complemented with the inverted sequence of the S_N^H and cross-coupling reactions. In order to realize it, we have obtained 5-(thiophen-2-yl)pyrimidine (**11**), and its reactivity in the S_N^H-reactions with thiophene **2a** and 2-bromothiophene **2b** in CF_3COOH have been investigated.

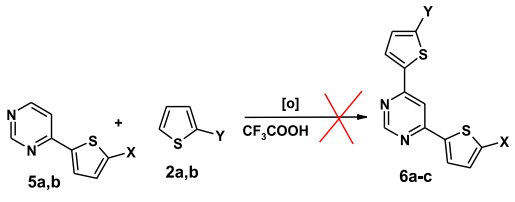
Compound **11** was obtained in 55% yield according to a similar cross-coupling procedure under microwave activation at 150 °C in THF/H_2O (3:4) (Scheme 5).

Pyrimidine **11** was dissolved in trifluoroacetic acid, the corresponding thiophene **2a** or **2b** was added, and the reaction mixture was stirred under room temperature for 24 h (Scheme 6). According to GC–MS spectra the major components in these mixtures proved to be the corresponding 1,2-dihydropyrimidines **12a**,**b**. Besides that, the presence of 4-(5-bromothiophen-2-yl)-5-(thiophen-2-yl)-3,4-dihydropyrimidin-1-ium (**12b**) trifluoroacetate was confirmed by ^1H NMR spectroscopic analysis, as clearly indicated by the characteristic signal at 6.13 ppm, which corresponds to the proton resonance at sp^3-carbon of C(4) atom of the pyrimidine ring. Reaction mixtures containing **12a** or **12b** without additional purification were oxidized with $K_3Fe(CN)_6$ (1.0 mmol) in 33% aqueous solution KOH for 2 h (Scheme 6). These reaction mixtures have also been analyzed by GLC–MS. Unfortunately, 4,5-dithiophenyl

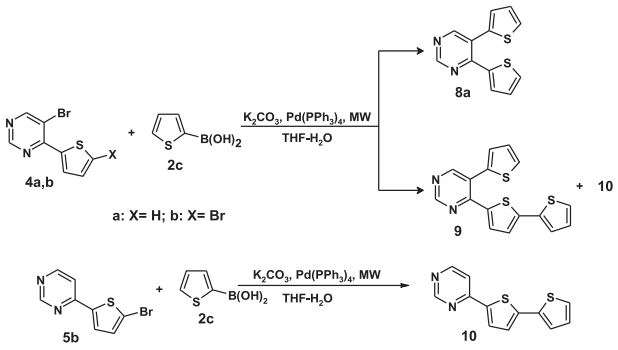
Table 1
Effects of reaction conditions on structure and yields of S_N^H-products (**4a**,**b** or **5a**,**b**) derived from σ^H-adducts **3a**,**b**

Entry	σ^H-Adducts	Oxidative system	Time, h	S_N^H-Products	Isolated yields (%)	Reaction mixtures[a] GC–MS (%)
1	**3a**	KOH–$K_3Fe(CN)_6$–H_2O	1	**4a**	42	**4a**—95 **3a**—5
2	**3a**	KOH–$K_3Fe(CN)_6$–H_2O	2	**4a**	75	—
3	**3b**	KOH–$K_3Fe(CN)_6$–H_2O	1	**4b**	39	**4b**—76 **5b**—7 **3b**—17
4	**3b**	KOH–$K_3Fe(CN)_6$–H_2O	2	**4b**	69	—
5	**3b**	Oxygen of air/diethylamine	24	**5a**	38	**5a**—55 **4a**—11 **3a**—34
6	**3a**	Oxygen of air/piperidine	24	**5a**	75	**5a**—82 Impurities—18
7	**3a**	Oxygen of air/morpholine	24	**5a**	82	**5a**—87 Impurities—13
8	**3b**	Oxygen of air/diethylamine	24	**5b**	67	**5b**—74 **4b**—17 **3b**—9
9	**3b**	Oxygen of air/piperidine	24	**5b**	78	**5b**—98 Impurities—2
10	**3b**	Oxygen of air/morpholine	24	**5b**	77	**5b**—96 Impurities—4

[a] For the reaction mixtures to study the solvent was distilling off solvent and the residue was analyzed by GC–MS.



Scheme 3.



Scheme 4.

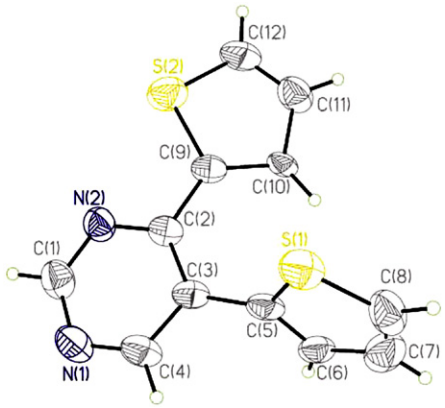


Fig. 3. X-ray structure of **8a**.

substituted pyrimidines **8a**,**b** were obtained in moderate yields (30–70%). The results of the S_N^H-reactions performed are summarized in Table 3.

3. Conclusion

A combination of the cross-coupling and S_N^H-reactions proved to be a versatile tool for the synthesis of pyrimidines bearing thiophene fragments. The X-ray crystallography data for a number of mono- and di(thiophenyl) substituted pyrimidines support the proposed structures.

Table 2
The microwave-assisted Suzuki–Miyaura cross-coupling reaction of monothiophenyl substituted pyrimidines (**4a**,**b** and **5b**) with 2-thienylboronic acid (**2c**)[a]

Entry	Monothiophenyl substituted pyrimidine	Isolated yields (%)	Reaction mixtures, according to the data of GC–MS (%)
1	**4a**	**8a**—57	**8a**—63 **Ph_3PO**—37
2[b]	**4b**	**9**—59 **10**—11	**9**—62 **10**—13 **Ph_3PO**—25
3	**5b**	**10**—68	**10**—71 **Ph_3PO**—29

[a] Unless otherwise indicated, the reaction conditions were as follows: starting S_N^H-compound (0.5 mmol), **2c** (0.6 mmol), $Pd(PPh_3)_4$ (5 mol %), and K_2CO_3 (2.5 equiv) in a mixture of THF (3 mL) and H_2O (4 mL) at 150 °C.
[b] The reaction conditions were as follows: starting S_N^H-compound (0.5 mmol), **2c** (1.2 mmol), $Pd(PPh_3)_4$ (10 mol %), and K_2CO_3 (5.0 equiv) in a mixture of THF (3 mL) and H_2O (4 mL) at 150 °C.

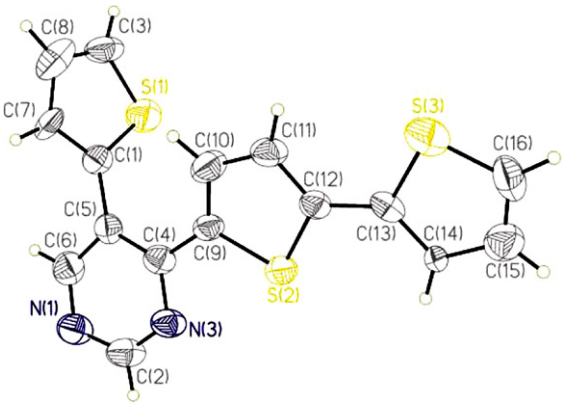


Fig. 4. X-ray structure of **9**.

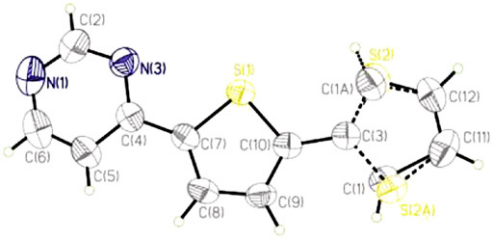


Fig. 5. X-ray structure of **10**.

4. Experimental section

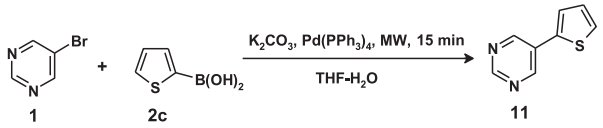
4.1. General information

Solvents and reagents were dried and purified according to the described procedures.[10]

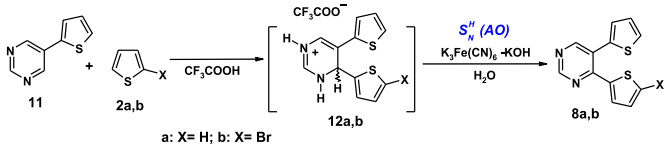
Products **4a**, **5a**, **9** and **11** have previously[7,8c,11] been characterized, and the data obtained corresponded satisfactorily with NMR and MS data, and comparison with authentic samples.

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker DRX-400 and AVANCE-500 instruments using Me_4Si and C_6F_6 as an internal standards. All signals in the ^{1}H and ^{13}C NMR spectra were assigned on the basis of 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and HMBC experiments. Elemental analysis was carried on a Eurovector EA 3000 automated analyzer. Melting points were determined on Boetius combined heating stages and were not corrected.

The GC–MS analysis of all samples was carried out using an Agilent GC 7890A MS 5975C Inert XL EI/CI GC–MS spectrometer with a quadrupole mass-spectrometric detector with electron ionization (70 eV) and scan over the total ionic current in the range



Scheme 5.



Scheme 6.

m/*z* 20–1000 and a quartz capillary column HP-5MS (30 m×0.25 mm, film thickness 0.25 mm). Helium served as a carrier gas, the split ratio of the flow was 1:50, and the consumption through the column was 1.0 mL min^{-1}; the initial temperature of the column was 40 °C (storage 3 min), programming rate was 10 °C min^{-1}–290 °C (storage 20 min), the temperature of the evaporator was 250 °C, the temperature of the source was 230 °C, the temperature of the quadrupole was 150 °C, and the temperature of the transition chamber was 280 °C. Solutions of the samples with a concentration of 3–4 mg mL^{-1} were prepared in acetonitrile. Samples of 1 mL of the obtained solutions were analyzed.

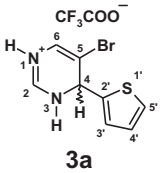
Column chromatography was carried out using Lancaster silica gel 0.040–0.063 mm (230–400 mesh), eluting with ethyl acetate/hexane, 1:2. The progress of reactions and the purity of compounds were checked by TLC on Sorbfil plates (Russia), in which the spots were visualized with UV light (λ 254 or 365 nm).

Microwave experiments were carried out in a Discover unimodal microwave system (CEM, USA) with a working frequency of 2.45 GHz and the power of microwave radiation ranged from 0 to 300 W. The reactions were carried out in a 10 mL reaction tube with the hermetic Teflon cork. The temperature of the reaction was monitored using an inserted IR sensor by the external surface of the reaction vessel.

X-ray intensity data were collected with a Xcalibur CCD diffractometer using Mo-*Kα* (*λ*=0.71069 Å) radiation at *T*=295(2) K. Crystal data and data collection parameters are summarized in Table 4. Unit cell parameters were refined using all collected spots after the integration process. For **3a** and **10** multi-scan methods of absorption data correction, and for **3b** and **8a** the analytical absorption data correction were used.[12] Structures were solved by direct methods with SHELX97.[13] All the structures were refined by full-matrix least squares on F^2 using SHELX97. All the non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms were calculated with AFIX. The H atoms were included in the refinement with an isotropic temperature factor. The details of the refinement and the final *R* indices are presented in Table 4. Deposition numbers CCDC 863232 for **3a**, CCDC 863233 for **3b**, CCDC 863235 for **8a**, CCDC 863234 for **9**, and CCDC 863236 for **10** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.2. General procedure for the synthesis of σ^H-adducts—trifluoroacetate 5-bromo-4-(5-X-thiophen-2-yl)-3,4-dihydropyrimidiniums (3a,b)

Thiophene (**2a**) (50 μL, 2.0 mmol) or 2-bromothiophene (**2b**) (64 μL, 2.0 mmol) was added to a solution of 5-bromopyrimidine (**1**) (159 mg, 1.0 mmol) in CF_3COOH (4 mL). The reaction mixture was stirred for 24 h, evaporated, and the residue was washed with EtOAc (3×10 mL). The precipitate that formed was filtered off and dried.



*4.2.1. Trifluoroacetate 5-bromo-4-thiophen-2-yl-3,4-dihydropyrimidiniums (**3a**).* Yield (286 mg, 80%), white crystal powder; mp 165–166 °C. δ_H (500 MHz, CD_3CN) 2.20–5.60 (br s, 2H, NH), 5.87 (m, 1H, H-4, *J*=0.6 Hz), 6.84 (dd, 1H, H-6, *J*=0.8, 0.6 Hz), 7.07 (dd, 1H,

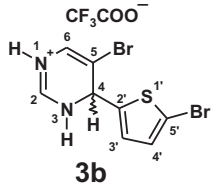
Table 3
Composition of the reaction mixtures for the reaction of 5-(thiophen-2-yl)pyrimidine (**11**) with thiophenes **2a**,**b** and yields of 4,5-dithiophenyl substituted pyrimidines (**4a**,**b**)

Entry	Reactants	Reaction mixtures, GLC–MS (%)	Reaction mixtures after oxidation with $K_3Fe(CN)_6$, GLC–MS (%)	Isolated yields (%)
1	**11**+**2a**	**8a**—5 **12a**—43 Impurities—52	**8a**—61 Impurities—39	**8a**—32
2	**11**+**2b**	**8b**—9 **12b**—91	**8a**—1 **12b**—9 **8b**—90	**8b**—73

Table 4
Crystal data and structure refinement for compounds **3a**,**b**, **8a**, **9** and **10**

Compound	**3a**	**3b**	**8a**	**9**	**10**
Crystal size, mm	0.24×0.19×0.15	0.30×0.19×0.03	0.22×0.12×0.05	0.24×0.19×0.08	0.25×0.15×0.05
Crystal color	Colorless	Colorless	Colorless	Yellow	Colorless
Empirical formula	$C_{10}H_8BrF_3N_2O_2S$	$C_{10}H_7Br_2F_3N_2O_2S$	$C_{12}H_8N_2S_2$	$C_{16}H_{10}N_2S_3$	$C_{12}H_8N_2S_2$
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/c$
a, Å	12.3961(6)	14.2706(18)	5.6728(4)	7.5862(6)	9.7914(7)
b, Å	9.4931(12)	9.8243(11)	13.1845(8)	5.9836(9)	5.7843(4)
c, Å	11.2026(10)	11.0938(10)	14.9097(9)	32.368(4)	19.7378(14)
α	90	90	90	90	90
β	93.745(6)	111.888(9)	94.127(5)	95.199(8)	95.026(6)
γ	90	90	90	90	90
Volume (Å^3), Z	1315.5(2), 4	1443.2(3), 4	1112.25(12), 4	1463.2(3), 4	1113.58(14), 4
μ, mm^{-1}	3.318	5.795	0.448	0.499	0.448
Reflections collected	7707	7276	5948	7802	5645
Independent reflections (R_{int})	3132 (0.0287)	2864 (0.0313)	2250 (0.0304)	2988 (0.0517)	2716 (0.0241)
Reflections with $I>2\sigma(I)$	1424	1445	1264	1316	1392
S	1.000	1.001	1.001	1.000	1.000
R_1 [$I>2\sigma(I)$]	0.0400	0.0430	0.0486	0.0450	0.0347
wR_2 [$I>2\sigma(I)$]	0.0781	0.0882	0.1218	0.0631	0.0584
R_1 (all data)	0.1030	0.1025	0.0845	0.1235	0.0845
wR_2 (all data)	0.0827	0.0958	0.1288	0.0688	0.0618
Largest diff. peak and hole, ē/Å^3	0.521 and −0.595	0.717 and −0.718	0.471 and −0.294	0.271 and −0.295	0.248 and −0.185
Completeness to θ (deg.)	98.0% (26.00)	97.5% (26.00)	99.1% (26.37)	98.9% (26.40	98.8% (26.00)

H-4′, J=5.1, 3.6 Hz), 7.22 (ddd, 1H, H-3′, J=3.6, 1.3, 0.5 Hz), 7.54 (ddd, 1H, H-5′, J=5.1, 1.3, 0.5 Hz), 8.13 (d, 1H, H-2, J=0.8 Hz); δ_C (126 MHz, CD_3CN) 55.52 (C-4), 105.80 (C-5), 118.16 (q, CF_3, $^1J_{CF}$=294.1 Hz), 123.73 (C-6), 128.51 (C-4′), 129.22 (C-3′), 129.36 (C-5′), 143.82 (C-2), 161.95 (q, COO, ^2JCF=33.6 Hz); δ_F (470.5 MHz, CD3CN) 88.60 (s, CF_3); Anal. Calcd for $C_{10}H_8BrF_3N_2O_2S$ (357.15): C, 33.63; H, 2.26; N, 7.84; S, 8.98. Found: C, 33.82; H, 2.29; N, 8.00; S, 8.95.

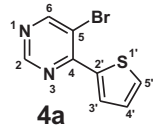


3b

*4.2.2. Trifluoroacetate 5-bromo-4-(5-bromothiophen-2-yl)-3,4-dihydropyrimidiniums (**3b**).* Yield (283 mg, 65%), white crystal powder; mp 163–165 °C. δ_H (500 MHz, CD_3CN) 2.20–5.50 (2H, br s, NH), 5.82 (s, 1H, H-4), 6.84 (s, 1H, H-6), 7.03 (d, 1H, H-3′, J=3.9 Hz), 7.10 (d, 1H, H-4′, J=3.9 Hz), 8.11 (s, 1H, H-2); δ_C (126 MHz, CD_3CN) 55.66 (C-4), 104.93 (C-5), 115.33 (C-5′), 118.17 (q, CF_3, $^1J_{CF}$=294.1 Hz), 124.22 (C-6), 129.96 (C-3′) 131.76 (C-4′), 145.57 (C-2′), 148.43 (C-2), 161.89 (q, COO, $^2J_{CF}$=33.9 Hz); δ_F (470.5 MHz, CD_3CN) 88.56 (s, CF_3); Anal. Calcd for $C_{10}H_7Br_2F_3N_2O_2S$ (436.05): C, 27.55; H, 1.62; N, 6.42; S, 7.35. Found: C, 27.53; H, 1.41; N, 6.52; S, 7.64.

4.3. General procedure for the synthesis of 5-bromo-4-(5-X-thiophen-2-yl)-pyrimidines (4a,b)

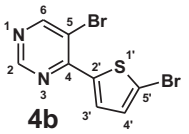
Compound **3a** (or **3b**) (0.5 mmol) was added to 3 mL of 33% KOH aqueous solution. After that a solution of $K_3Fe(CN)_6$ (329 mg, 1.0 mmol) in 2 mL water was added. The resulting mixture was stirred for an appropriate time (see Table 1, entries 1–4). After all starting material was consumed, the reaction mixture was poured into $CHCl_3$ (10 mL), washed with water, extracted with $CHCl_3$ (2×5 mL), dried with anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired $S_N{}^H$-products (**4a**,**b**).



4a

*4.3.1. 5-Bromo-4-thiophen-2-yl-pyrimidine (**4a**).*[11] Yield (see Table 1, entries 1–2), pale yellow powder; mp 50–52 °C (lit.[11] 208–210 °C). δ_H (500 MHz, $CDCl_3$) 7.20 (dd, 1H, H-4′, J=5.0, 3.9 Hz), 7.63 (dd, 1H, H-5′, J=5.0, 1.0 Hz), 8.43 (dd, 1H, H-3′, J=3.9, 1.0 Hz), 8.84 (s, 1H, H-6), 9.02 (s, 1H, H-2); δ_C (126 MHz, $CDCl_3$) 115.42 (C-5), 128.26 (C-4′), 131.81 (C-3′), 131.98 (C-5′), 140.71 (C-2′),

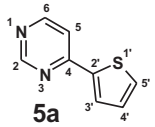
156.23 (C-2), 156.30 (C-4), 160.82 (C-6); GC t_R 19.11 min; MS *m*/*z* (rel intensity) 240 (M^+, 100) for ^{79}Br, 242 (M^+, 100) for 81Br; Anal. Calcd for $C_8H_5BrN_2S$ (241.11): C, 39.85; H, 2.09; N, 11.62; S, 13.30. Found: C, 39.94; H, 2.39; N, 11.51; S, 13.05.



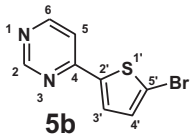
*4.3.2. 5-Bromo-4-(5-bromothiophen-2-yl)-pyrimidine (**4b**).* Yield (see Table 1, entries 3–4), pale yellow powder; mp 132–133 °C. δ_H (500 MHz, $CDCl_3$) 7.15 (d, 1H, H-4′, *J*=4.2 Hz), 8.18 (d, 1H, H-3′, *J*=4.2 Hz), 8.83 (s, 1H, H-6), 8.98 (s, 1H, H-2); δ_C (126 MHz, $CDCl_3$) 114.86 (C-5), 120.53 (C-5′), 131.30 (C-4′), 132.34 (C-3′), 142.20 (C-2′), 155.17 (C-4), 156.20 (C-2), 160.92 (C-6); GC t_R 21.90 min; MS *m*/*z* (rel intensity) 319 (M^+, 100) for both ^{79}Br, 320 (M^+, 50) for ^{79}Br and ^{81}Br, 321 (M^+, 50) for both ^{81}Br; Anal. Calcd for $C_8H_4Br_2N_2S$ (320.01): C, 30.03; H, 1.26; N, 8.75; S, 10.02. Found: C, 30.28; H, 1.18; N, 8.67; S, 9.89.

4.4. General procedure for the synthesis of 4-(5-X-thiophen-2-yl)-pyrimidines (5a,b)

Compound **3a** (or **3b**) (0.5 mmol) was dissolved in 3 mL of the corresponding secondary amine (diethylamine, piperidine or morpholine). The resulting solution was stirred for 24 h at room temperature, the solvent was distilled off in vacuo, and the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired S_N^H-*cine*-products (**5a**,**b**).



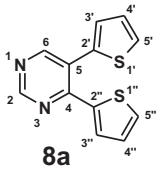
*4.4.1. 4-Thiophen-2-yl-pyrimidine (**5a**).*[7] Yield (see Table 1, entries 5–7), pale yellow powder; mp 61–63 °C (lit.[7] 54–56 °C). δ_H (400 MHz, $CDCl_3$) 7.17 (dd, 1H, H-4′, *J*=5.0, 3.7 Hz), 7.55 (dd, 1H, H-5′, *J*=5.0, 1.2 Hz), 7.58 (dd, 1H, H-5, *J*=5.3, 1.4 Hz), 7.78 (dd, 1H, H-3′, *J*=3.7, 1.2 Hz), 8.68 (d, 1H, H-6, *J*=5.3 Hz), 9.14 (d, 1H, H-2, *J*=1.4 Hz); GC t_R 16.40 min; MS *m*/*z* (rel intensity) 162 (M^+, 100); Anal. Calcd for $C_8H_6N_2S$ (162.21): C, 59.24; H, 3.73; N, 17.27; S, 19.77. Found: C, 59.14; H, 3.59; N, 17.40; S, 19.87.



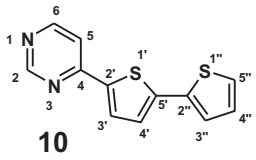
*4.4.2. 4-(5-Bromothiophen-2-yl)-pyrimidine (**5b**).* Yield (see Table 1, entries 8–10), beige powder; mp 149–151 °C. δ_H (400 MHz, $CDCl_3$) 7.13 (d, 1H, H-3′(4′), *J*=4.0 Hz), 7.50 (dd, 1H, H-5, *J*=5.5, 1.4 Hz), 7.51 (d, 1H, H-4′(3′), *J*=4.0 Hz), 8.69 (d, 1H, H-6, *J*=5.5 Hz), 9.11 (d, 1H, H-2, *J*=1.4 Hz); GC t_R 19.47 min; MS *m*/*z* (rel intensity) 240 (M^+, 100) for ^{79}Br, 242 (M^+, 100) for ^{81}Br; Anal. Calcd for $C_8H_5BrN_2S$ (241.11): C, 39.85; H, 2.09; N, 11.62; S, 13.30. Found: C, 39.77; H, 2.12; N, 11.36; S, 13.63.

4.5. General procedure for the microwave-assisted Suzuki cross-coupling reactions

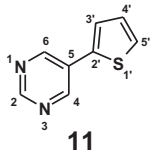
A solution of K_2CO_3 (346 mg, 2.5 mmol) in 4 mL H_2O was added to a mixture of bromo-substituted pyrimidine (**1**, **4a** or **5b**) (0.5 mmol), 2-thienylboronic acid (77 mg, 0.6 mmol), and $Pd(PPh_3)_4$ (29 mg, 5 mol %) in 3 mL THF. The resulting mixture was irradiated in a microwave apparatus at 150 °C (250 W) for 15 min. After that solvent was distilled off in vacuo, and the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired cross-coupling products (**8a**, **10** and **11**).



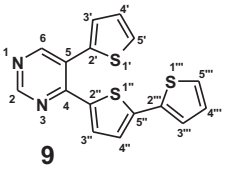
*4.5.1. 4,5-Dithiophen-2-yl-pyrimidine (**8a**).* It was obtained from compound **4a**. Yield (see Table 2, entry 1), beige powder; mp 100–103 °C. δ_H (500 MHz, $CDCl_3$) 6.94 (dd, 1H, H-4″, *J*=5.0, 3.9 Hz), 7.06 (dd, 1H, H-3″, *J*=3.9, 1.1 Hz), 7.14 (dd, 1H, H-3′, *J*=3.5, 1.3 Hz), 7.18 (dd, 1H, H-4′, J_1=5.1, 3.5 Hz), 7.46 (dd, 1H, H-5″, *J*=5.0, 1.1 Hz), 7.52 (dd, 1H, H-5′, *J*=5.1, 1.3 Hz), 8.64 (s, 1H, H-6), 9.11 (s, 1H, H-2); δ_C (126 MHz, $CDCl_3$) 124.14 (C-5), 127.74 (C-5′), 127.88 (C-4′), 128.11 (C-4″), 128.47 (C-3′), 130.84 and 130.86 (C-5″, C-3″), 136.28 (C-2′), 141.06 (C-2″), 157.55 (C-4), 157.79 (C-2), 159.07 (C-6); GC t_R 22.92 min; MS *m*/*z* (rel intensity) 244 (M^+, 100); Anal. Calcd for $C_{12}H_8N_2S_2$ (244.34): C, 58.99; H, 3.30; N, 11.46; S, 26.25. Found: C, 58.94; H, 3.39; N, 11.53; S, 26.14.



*4.5.2. 4-[2,2′]-Bithiophenyl-5-yl-pyrimidine (**10**).*[7] It has been obtained from compound **5b**. Yield (see Table 2, entries 2 and 3), bright yellow powder; mp 118–121 °C (lit.[7] 113–115 °C). δ_H (500 MHz, $CDCl_3$) 7.07 (dd, 1H, H-4″, *J*=5.1, 3.6 Hz), 7.23 (d, 1H, H-4′, *J*=3.9 Hz), 7.30 (dd, 1H, H-5″, *J*=5.1, 1.1 Hz), 7.31 (dd, 1H, H-3″, *J*=3.6, 1.1 Hz), 7.55 (dd, 1H, H-5, *J*=5.4, 1.4 Hz), 7.68 (d, 1H, H-3′, *J*=3.9 Hz), 8.67 (d, 1H, H-6, *J*=5.4 Hz), 9.12 (d, 1H, H-2, *J*=1.4 Hz); δ_C (126 MHz, $CDCl_3$) 114.82 (C-5), 124.71 (C-4′), 124.92 (C-3″), 125.74 (C-5″), 128.15 (C-4″), 128.43 (C-3′), 136.72 (C-2″), 140.03 (C-2′), 142.37 (C-5′), 157.03 (C-6), 158.52 (C-4), 159.08 (C-2); GC t_R 24.90 min; MS *m*/*z* (rel intensity) 244 (M^+, 100); Anal. Calcd for $C_{12}H_8N_2S_2$ (244.34): C, 58.99; H, 3.30; N, 11.46; S, 26.25. Found: C, 59.04; H, 3.27; N, 11.57; S, 26.12.



*4.5.3. 5-Thiophen-2-yl-pyrimidine (**11**).*[8c] It has been obtained from compound **1**. Yield (45 mg, 55%), pale yellow powder; mp 77–78 °C (lit.[8c] 77.2–78.0 °C). δ_H (400 MHz, $CDCl_3$) 7.18 (dd, 1H, H-4′, *J*=5.0, 3.6 Hz), 7.44 (dd, 1H, H-3′, *J*=3.6, 1.1 Hz), 7.47 (dd, 1H, H-5′, *J*=5.0, 1.1 Hz), 8.98 (s, 2H, H-4 and H-6), 9.13 (s, 1H, H-2); GC t_R 16.04 min; MS *m*/*z* (rel intensity) 162 (M^+, 100); Anal. Calcd for $C_8H_6N_2S$ (162.21): C, 59.24; H, 3.73; N, 17.27; S, 19.77. Found: C, 59.18; H, 3.63; N, 17.55; S, 19.64.

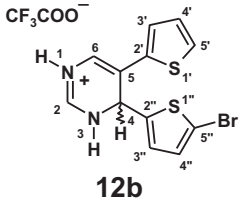


4.6. Synthesis of 4-[2,2′]-Bithiophenyl-5-yl-5-thiophen-2-yl-pyrimidine (9)

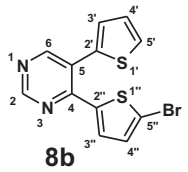
A solution of K_2CO_3 (691 mg, 5.0 mmol) in 4 mL H_2O was added to a mixture of 5-bromo-4-(5-bromothiophen-2-yl)-pyrimidine (**4b**) (160 mg, 0.5 mmol), 2-thienylboronic acid (154 mg, 1.2 mmol) and $Pd(PPh_3)_4$ (58 mg, 10 mol %) in 3 mL THF. The resulting mixture was irradiated in a microwave apparatus at 150 °C (250 W) for 15 min. After that solvent was distilled off in vacuo, and the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired cross-coupling products **9**. Compound **9** was obtained as a bright yellow powder; yield (163 mg, 59%); mp 120–122 °C. δ_H (500 MHz, $CDCl_3$) 6.87 (d, 1H, H-3″, *J*=4.0 Hz), 6.99 (d, 1H, H-4″, *J*=4.0 Hz), 7.03 (dd, 1H, H-4‴, *J*=5.1, 3.7 Hz), 7.16 (dd, 1H, H-3′, *J*=3.5, 1.2 Hz), 7.19 (dd, 1H, H-4′, *J*=5.1, 3.5 Hz), 7.25 (dd, 1H, H-3‴, *J*=3.7, 1.2 Hz), 7.26 (dd, 1H, H-5‴, *J*=5.1, 1.2 Hz), 7.53 (d, 1H, H-5′, *J*=5.1, 1.2 Hz), 8.61 (s, 1H, H-6), 9.09 (s, 1H, H-2); δ_C (126 MHz, $CDCl_3$) 123.91 (C-5), 124.58 (C-4″), 124.87 (C-3‴), 125.66 (C-5‴), 127.80 (C-5′), 127.97 (C-4′), 128.08 (C-4‴), 128.45 (C-3′), 131.78 (C-3″), 136.28 (C-2′), 136.71 (C-2‴), 139.50 (C-2″), 142.53 (C-5″), 157.19 (C-4), 157.84 (C-2), 159.07 (C-6); GC t_R 29.99 min; MS *m*/*z* (rel intensity) 326 (M^+, 100); Anal. Calcd for $C_{16}H_{10}N_2S_3$ (326.46): C, 58.87; H, 3.09; N, 8.58; S, 29.46. Found: C, 59.01; H, 3.23; N, 8.41; S, 29.35.

4.7. General procedure for the synthesis of S_N^H-products—4-(5-X-thiophen-2-yl)-5-thiophen-2-yl-pyrimidines (8a,b)

Thiophene (**2a**) or 2-bromothiophene (**2b**) (2 mmol) was added to a solution of 5-thiophen-2-yl-pyrimidine (**11**) (81 mg, 0.5 mmol) in CF_3COOH (2 mL). The resulting solution was stirred at room temperature for 24 h. After removal of the solvent under reduced pressure the residue was analyzed by GC–MS (and ^1H NMR for **12b**), and then residue was added to 3 mL of aqueous 33% KOH solution. After that a solution of $K_3Fe(CN)_6$ (329 mg, 1.0 mmol) in 2 mL of water was added. The resulting mixture was stirred for 2 h. After all starting material was consumed, the reaction mixture was poured into $CHCl_3$ (10 mL), washed with water, extracted with $CHCl_3$ (2×5 mL), dried by anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography and the desired compounds (**8a** or **8b**) were obtained in the corresponding yields (see Table 2, entries 1 and 2).



*4.7.1. 4-(5-Bromothiophen-2-yl)-5-(thiophen-2-yl)-3,4-dihydropyridin-1-ium (**12b**).* It's obtained as the reaction mixture (brown oil). δ_H (400 MHz, CD_3CN) 6.13 (s, 1H, H-4), 6.95 (s, 1H, H-6), 6.98 (dd, 1H, H-4′, *J*=5.0, 3.8 Hz) 7.04–7.07 (m, 3H, H-3′, H-3″, H-4″), 7.35 (dd, 1H, H-5′ *J*=5.0, 0.9 Hz), 8.08 (s, 1H, H-2), 11.3 (br s, 1H, NH); GC t_R 28.26 min; MS *m*/*z* (rel intensity) 324 (M^+-CF_3COOH, 100) for ^{79}Br, 326 (M^+-CF_3COOH, 100) for ^{81}Br.



*4.7.2. 4-(5-Bromothiophen-2-yl)-5-thiophen-2-yl-pyrimidine (**8b**).* Yield (see Table 3, entry 2), yellow crystal powder; mp 174–177 °C. δ_H (500 MHz, $CDCl_3$) 6.80 (d, 1H, H-3″, *J*=4.1 Hz), 6.89 (d, 1H, H-4″, *J*=4.1 Hz), 7.13 (dd, 1H, H-3′, *J*=3.5, 1.0 Hz), 7.18 (dd, 1H, H-4′, *J*=5.1, 3.5 Hz), 7.54 (dd, 1H, H-5′, *J*=5.1, 1.0 Hz), 8.62 (s, 1H, H-6), 9.07 (s, 1H, H-2); δ_C (126 MHz, $CDCl_3$) 119.29 (C-5″), 123.75 (C-5), 128.02 (2C, C-4′, C-5′), 128.62 (C-3′), 131.10 (C-4″), 131.15 (C-3″), 135.67 (C-2′), 142.60 (C-2″), 156.50 (C-4), 157.83 (C-2), 159.28 (C-6); GC t_R 25.29 min; MS *m*/*z* (rel intensity) 321 (M^+, 100) for ^{79}Br, 323 (M^+, 100) for ^{81}Br; Anal. Calcd for $C_{12}H_7BrN_2S_2$ (323.23): C, 44.59; H, 2.18; N, 8.67; S, 19.84. Found: C, 44.44; H, 2.39; N, 8.53; S, 19.92.

Acknowledgements

This work was supported by the Ural Division of the Russian Academy of Sciences (Program of Support of Young Scientists and Post-Graduates No. 11-3-NP-627; Grants 12-P-3-1014, 12-T-3-1025 and 12-T-3-1031), the State Program for Supporting of Leading Scientific Schools of the Russian Federation (grant NSh 5505.2012.3) and the Russian Foundation for Basic Research (grant No. 10-03-96078-r_ural_a). The authors would like to thank Ms. Rashida K. Novikova for obtaining of the single-crystal X-ray diffraction data.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.095. These data include MOL files and InChiKeys of the most important compounds described in this article.

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