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CONCISE SYNTHESIS OF TPCA-1 AND RELATED THIOPHENE-CARBOXAMIDES BY CROSS COUPLING

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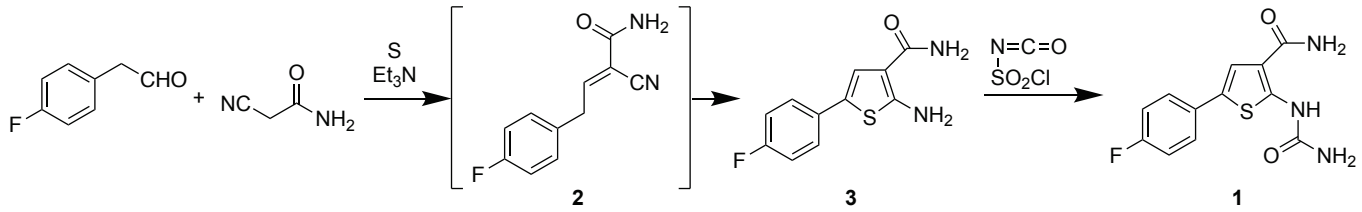
Abstract – A synthesis of 5-substituted 2-[(aminocarbonyl)amino]-3-thiophene-carboxamides is described. The coupling reaction of 2-ureidothiophene-3-carboxamide and various aryl compounds allows the concise approach of promising candidates for IKK-2 inhibitor, such as TPCA-1.

Protein kinases are regulators of a broad range of cellular processes. The enzymes responsible for the ubiquitination of phosphorylated IκB are constitutively active and the phosphorylation of IκB is a critical regulatory step in IκB degradation and subsequent NF-κB activation.[1] This phosphorylation is catalyzed by IκB kinase (IKK) complex which consists of two enzymatically active kinases, IKK-1 and IKK-2 and a regulatory subunit.[2] The physiological studies of the two kinases suggest that IKK-2, rather than IKK-1, plays a critical role in the NF-κB-regulated production of proinflammatory molecules and therefore the inhibitors of IKK and its related kinase are promising therapeutic agents for the treatment of inflammatory diseases and cancer.[3] Various IKK-2 inhibitors have been known so far, in particular, 2-[(aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide (**1**), so-called TPCA-1, is a pivotal inhibitor of IKK-2 which has a pIC_{50} of 7.7±0.2 on the isolated kinase and has 22-fold selectivity over IKK-1 and >550-fold selectivity over other kinases and enzymes.[4] Moreover, it has been shown that



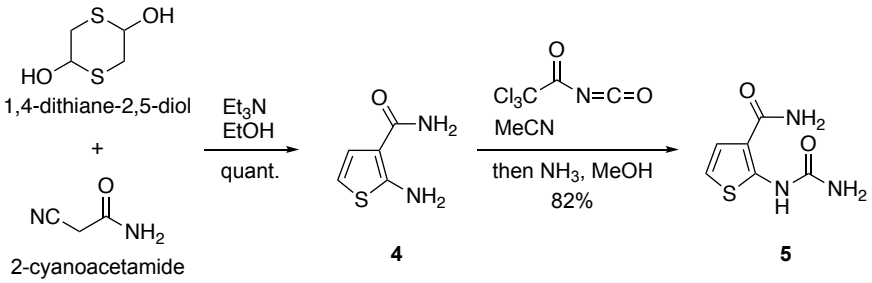
Scheme 1. Standard preparation of TPCA-1 (**1**)

Dedicated with respect to Dr. Kaoru Fuji on the occasion of his 80th birthday

the substituent at 4' position of phenyl group has highly spatial flexibility and the biological evaluation of various 4-substituted phenylthiophene derivatives have been examined so far.[5] The significant efforts of pharmacological studies involving **1** has been demonstrated; however, the synthetic studies concerning **1** and 4-substituted phenylthiophenes are limited. The standard preparation of **1** is the traditional Gewald synthesis which contains the base-catalyzed Knoevenagel condensation of a ketone with a β-ketonitrile **2**, followed by cyclization to a 2-aminothiophene **3** by sulfur (Scheme 1).[6]

On the other hand, a comprehensive synthesis of 4-substituted phenylthiophenes through Pd-catalyzed coupling reaction without protective group are much attractive. Over the past decades, much attention has been given to the direct cross coupling of π-conjugated units due to the importance of green chemistry and atom economy.[7] The cross-coupling reaction of thiophenes with aryl derivatives provides an efficient method for the synthesis of a wide variety of arylthiophenes. Recently efficient procedures for palladium-mediated coupling of heterocycles were demonstrated by Miura,[8] Mori,[9] Fagnou,[10] Lemaire,[11] and Lautens,[12] and other chemists.[13-15] Here we will describe concise synthesis of **1** and 4-substituted phenylthiophene derivatives by palladium catalyst.

Compound **4**, 2-aminothiophene-3-carboxamide, was easily prepared by known method.[16] The modified Gewald reaction of 1,4-dithiane-2,5-diol and 2-cyanoacetamide with base quantitatively afforded **4**, which was treated with trichloroacetyl isocyanate and subsequent ammonia to generate 2-ureidothiophene-3-carboxamide (**5**) in 82% yield (Scheme 2).

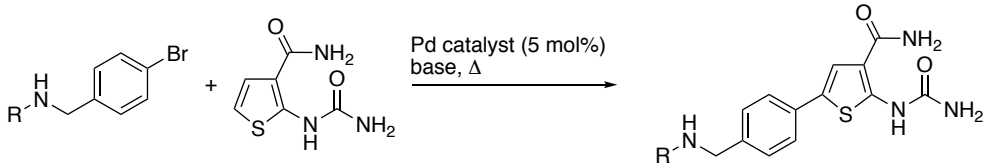


Scheme 2. Preparation of 2-ureidothiophene-3-carboxamide (**5**)

Our initial efforts focused on the direct cross coupling of **5** and aryl halides. Various direct arylation of the functionalized thiophenes have been reported and the regioselectivities of the arylation have been discussed so far. However, the preparation of TPCA-1 and 4-substituted phenylthiophene derivatives by direct arylation has not been demonstrated and the reaction of thiophene containing electron-withdrawing group is much challenging. We selected 4-bromobenzylamine derivatives as an aryl halide for preliminary attempt (Table 1). When *tert*-butyl carbamate **6a** was treated with **5** in the presence of $Pd(OAc)_2$ and AcOK in DMF at 150 °C, the coupled product was not produced at all (entry 1). The

reaction using DMA as a solvent was also fruitless (entry 2) but a trace of desired **7a** was detected in case of NMP as solvent (entry 3). Encouraged by this result, various conditions, such as palladium catalysts, ligands, bases, were examined; however, all attempts were unsuccessful (entries 3-7). Since the *tert*-butyl carbamate group may not tolerate heating condition, benzyl carbamate **6b** was next employed. Although NMP was not suitable solvent in this case (entry 8), it was found that the reaction of **5** and **6b** using $Pd(OAc)_2$ and AcOK in DMF led to small improvement of the yield of **7b** (entry 9). The reaction using DMA in place of DMF turned out to afford desired product **7b** in 7% yield (entry 10). As far as we know, it is the first example for direct coupling of 2-ureidothiophene-3-carboxamide and aryl bromide. Notably, the installation of substituent proceeded only at the C-5 position of thiophene and 4-substituted phenyl-thiophene was not observed. Other many efforts to improve the reaction yield, containing microwave-promoted reaction, were also attempted, but no coupling product was observed.

Table 1. Direct coupling of **5** and **6a/6b**



R = Boc **6a**
R = Cbz **6b**

5

R = Boc **7a**
R = Cbz **7b**

Entry	**6**	Catalyst	Ligand	Base	°C	Solvent	results
1	**6a**	$Pd(OAc)_2$	-	AcOK	150	DMF	ND
2	**6a**	$Pd(OAc)_2$	-	AcOK	150	DMA	ND
3	**6a**	$Pd(OAc)_2$	-	AcOK	150	NMP	trace
4	**6a**	$Pd(OAc)_2$	JohnPhos	Cs_2CO_3	150	DMF	ND
5	**6a**	$Pd_2(dba)_3$	-	AcOK	110	NMP	ND
6	**6a**	$PdCl(C_3H_5)(dppb)$	-	AcOK	130	DMA	ND
7	**6a**	$PdCl_2$	PCy_3	Ag_2CO_3	150	DMF	trace
8	**6b**	$Pd(OAc)_2$	-	AcOK	150	NMP	ND
9	**6b**	$Pd(OAc)_2$	-	AcOK	150	DMF	2%
10	**6b**	$Pd(OAc)_2$	-	AcOK	150	DMA	7%

Recent mechanism studies for Pd-catalyzed direct arylation of thiophenes suggest three pathways, S_EAr mechanism, Mizoroki-Heck mechanism, and CMD mechanism. Thiophene **5** contains electrophilic substituents at C-2 and C-3, and S_EAr and CMD mechanisms are much preferable. Our DFT calculations (B3LYP/6-31G*) suggested that the HOMO resides at C-5 position in thiophene but does not extend the

thiophene ring (Figure 1). It is reasonable that arylation proceeds at the electron-rich C-5 and the direct coupling is less effective for compound **5** as a substrate under this condition.[10,17]

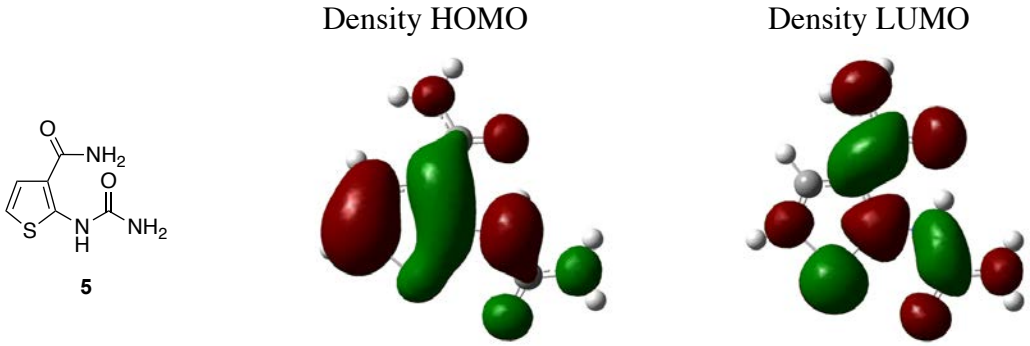
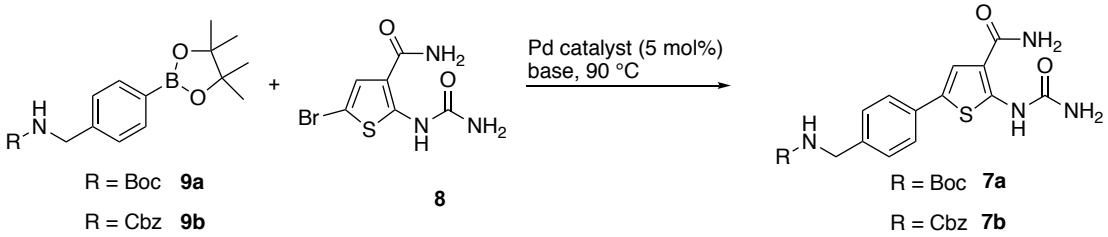


Figure 1. HOMO and LUMO densities of **5**

We next explored the arylation of **8** by Suzuki-Miyaura coupling (Table 2).[18] Bromination of **5** easily proceeded with NBS in THF to afford 5-bromo compound **8** in 71% yield. Suzuki-Miyaura reactions of **8** and pinacol arylboronates **9a**, **9b** were performed at 90 °C in the presence of palladium catalyst and various base. We first examined the reaction of **9b** using Pd(dppf)Cl_2 and NaOH in aqueous dioxane. The reaction slowly proceeded to give **7b** in 2% yield (entry 1). Using Na_2CO_3 as a base in aqueous DME, the yield was slightly improved (entry 2). On the other hand, Pd(PPh_3)$_4$ was suitable for the coupling reaction of **8** and **9b** (entry 3). It was turned out that the reaction with Pd(PPh_3)$_4$ and Na_2CO_3 in aqueous DME afforded **9b** in 36% yield (entry 5). To our delight, the reaction of **8** and **9b** of using Cs_2CO_3 in aqueous dioxane at 75 °C provided desired **7b** in 46% yield (entry 7). This condition was also effective for the coupling of **8** and **9a** to provide **7a** in 48% yield (entry 9). Furthermore, it was found that heating is required for coupling (entries 8 and 9).

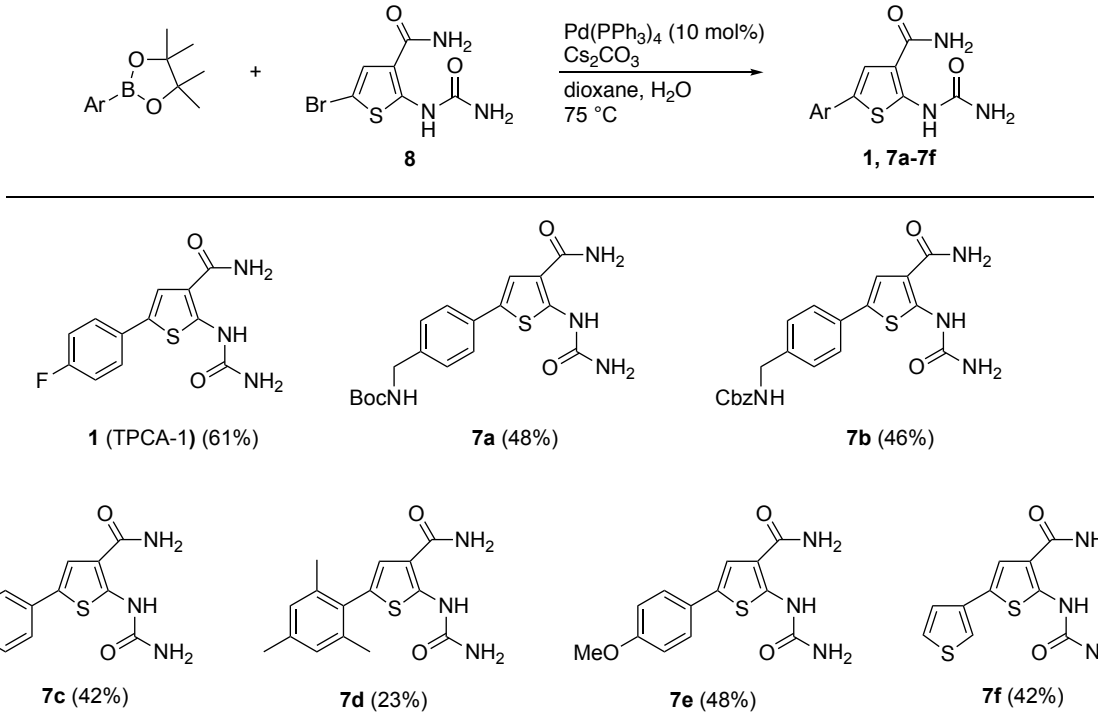
A variety of substituted aryl compounds were investigated to explore the generality of this protocol (Scheme 3). The reaction of simple pinacol phenylboronate and **8** afforded coupling product **7c** in 42% yield. Notably, bulky 2,4,6-trimethylphenylboronate also reacts with **8** to give the desired product **7d** in 23%. It is noteworthy that 4-fluoro-substrate provided TPCA-1 (**1**) in 61% yield and 4-methoxyphenyl derivative (**7e**) and 4-thiophenyl derivative (**7f**) were also obtained in acceptable yields. It is important to note that this approach avoids any protecting group manipulation.

Table 2. Suzuki-Miyaura coupling of **8** and **9a**/**9b**



Entry	**9**	Catalyst	Base	Solvent	results
1	**9b**	$Pd(dppf)Cl_2$	NaOH	dioxane-H_2O	2%
2	**9b**	$Pd(dppf)Cl_2$	Na_2CO_3	DME-H_2O	11%
3	**9b**	$Pd(PPh_3)_4$	AcOK	EtOH-PhMe	16%
4	**9b**	$Pd(PPh_3)_4$	K_2CO_3	dioxane-H_2O	8%
5	**9b**	$Pd(PPh_3)_4$	Na_2CO_3	DME-H_2O	36%
6 [*1]	**9b**	$Pd(PPh_3)_4$	Na_2CO_3	DME-H_2O	23%
7 [*2]	**9b**	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane-H_2O	46%
8 [*3]	**9a**	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane-H_2O	ND[*4]
9 [*2]	**9a**	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane-H_2O	48%

*[1] JohnPhos (8 mol%) was used as a ligand. *[2] The reaction was performed at 75 °C. *[3] The reaction was performed at rt. *[4] Compound **8** was recovered in 19% yield.



Scheme 3. Synthesis of substituted arylthiophenes

In conclusion, we have developed a concise formation of **1** and 4-substituted phenylthiophenes (**7a**-**7f**) by coupling reaction. The present method would be useful for the simple access to promising candidates for IKK-2 inhibitor. The biological properties of resulting products (**1** and **7a**-**7f**) are currently under investigation, collaborating with biologists.

EXPERIMENTAL

The reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N*,*N*-Dimethylformamide (DMF), and triethylamine (NEt_3) were distilled from CaH_2. Column chromatography was performed using silica gel (particle size 40-50 μm (flash)) or silica gel amine (SiO_2-amine, particle size 100 μm). Optical rotations were recorded on digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were measured using $CDCl_3$, or CD_3OD as solvent, and chemical shifts are reported as δ values in ppm based on internal $CHCl_3$ (7.26 ppm, ^{1}H; 77.0 ppm, ^{13}C), CD_3OD (3.31 ppm, ^{1}H; 49.0 ppm, ^{13}C). Mass (MS) and high resolution mass (HRMS) spectra were taken in EI, ESI or FAB mode.

2-Aminothiophene-3-carboxamide (4): To a solution of 2,5-dihydroxy-1,4-dithiane (5.00 g, 32.8 mmol) in EtOH (164 mL) were added 2-cyanoacetamide (2.76 g, 32.8 mmol) and triethylamine (9.11 mL, 65.7 mmol) and the mixture was stirred at 68 °C for 12 h. The reaction mixture was concentrated and extracted with AcOEt (30 mL x 3). The organic extracts were washed with brine (30 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO_2 120 g, hexane:AcOEt = 1:1) to afford compound **4** (4.87 g, 34.3 mmol, quant) as yellow powder; mp 138-139 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 6.71 (d, *J* = 7.6 Hz, 1H), 6.24 (d, *J* = 7.6 Hz, 1H), 6.17 (s, br, 2H), 5.36 (s, br, 2H); ^{13}C NMR (100 MHz $CDCl_3$) δ 167.6, 162.1, 123.3, 107.8, 107.4; FT-IR(neat) 3304, 1635, 1569, 1518, 1472, 1410, 1348, 771, 680, 482, 411 cm^{-1}; MS (EI) *m/z* 97, 125, 142 (100), (M^+); HRMS (EI) calcd for $C_5H_6N_2OS$ (M^+) 142.0201, found 142.0202.

1-(3-Carbamoylthiophen-2-yl)urea (5): To a solution of 2-aminothiophene-3-carboxamide (855 mg, 6.01 mmol) in MeCN (60 mL) was added dropwise trichloroacetyl isocyanate (0.75 mL, 6.61 mmol) dropwise at 0 °C and the mixture was stirred at rt for 3.5 h. To the mixture was added ammonia (2.0 M in MeOH, 20 mL) at 0 °C, and the reaction mixture was stirred at rt for 15 h and concentrated. Purification by chromatography (SiO_2-amine 95 g, $CHCl_3$: MeOH = 10 : 1) gave compound **5** (914 mg, 4.94 mmol, 82%) as white powder; mp 199-200 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (d, *J* = 5.6 Hz, 1H), 6.69 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 166.0, 151.0, 123.5, 115.6, 113.5; FT-IR (neat)

3336, 2536, 2422, 1679, 1496, 944, 823, 771, 687, 624 cm^{-1}; MS (FAB) *m/z* 154 (100), 186 (M^+); HRMS (FAB) calcd for $C_6H_7N_3O_2S$ (M^+) 185.0259, found 185.0258.

Direct coupling of 5 and 6b to 7b; **benzyl 4-(4-carbamoyl-5-ureidothiophen-2-yl)benzylcarbamate (7b):** To a solution of 1-(3-carbamoylthiophen-2-yl)urea **6b** (50 mg, 0.156 mmol) in DMA were added benzyl (4-bromobenzyl)carbamate **5** (43.4 mg, 0.234 mmol) and AcOK (30.6 mg, 0.312 mmol) and the mixture was degassed. To the mixture was added palladium acetate (1.8 mg, 0.00781 mmol) and the mixture was stirred at 150 °C for 22 h. To the reaction mixture was added H_2O (4.5 mL) and the mixture was extracted with hexane:AcOEt = 4:1 (10 mL x 5). The organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), dried and concentrated. The residue was purified by (SiO_2-amine 4 g, $CHCl_3$: MeOH = 40:1) to afford compound **7b** (4.3 mg, 0.01 mmol, 7%) as a white solid: mp 173-174 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 6.8 Hz, 2H), 7.50 (s, 1H), 7.34 (d, *J* = 5.2 Hz, 5H), 7.27 (d, *J* = 6.8 Hz, 2H), 5.10 (s, 2H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.8, 159.1, 157.1, 150.4, 139.5, 138.4, 134.5, 132.9, 129.5, 129.0, 128.9, 128.8, 126.0, 119.3, 1144 cm^{-1}; FT-IR (neat) 3339, 2926, 2466, 1681, 1522, 1448, 1344, 1256, 1148, 1038, 771; MS (FAB) *m/z* 91 (100), 425 (M^+); HRMS (FAB) calcd for $C_{21}H_{20}N4O_4S$ $(M)^+$ 424.1205, found 424.1196.

1-(5-Bromo-3-carbamoylthiophen-2-yl)urea (8): To a solution of 1-(3-carbamoylthiophen-2-yl)urea (140 mg, 0.756 mmol) in THF (9 mL) was added NBS (149 mg, 0.832 mmol) and the mixture was stirred at 0 °C for 1 h under shielding light. The reaction mixture was stirred at rt for 15 h, and concentrated. Purification by chromatography (20 g, $CHCl_3$: MeOH = 10:1) gave compound **8** (140.9 mg, 0.534 mmol, 71%) as pink powder; mp 221-222 °C (decomposed); ^1H NMR (400 MHz, CD_3OD) δ 7.24 (s, 1H), ^{13}C NMR (100 MHz, CD_3OD) δ 168.6, 157.1, 151.5, 125.9, 113.4, 103.2; FT-IR (neat) 3352, 3193, 1702, 1546, 1511, 1420, 1328, 1275, 1220, 771, 694 cm^{-1}; MS (FAB) *m/z* 91 (100), 263 [$(M+H)^+$], 265 [$(M+H+2)^+$]; HRMS (FAB) calcd for $C_6H_6{}^{79}BrN_3O_2S$ [$(M+H)^+$] 263.9438, found 263.9440, calcd for $C_6H_6{}^{81}BrN_3O_2S$ [$(M+H+2)^+$] 265.9410, found 265.9416.

Suzuki-Miyaura coupling of 8 and 9a to 7a; *tert*-butyl 4-(4-carbamoyl-5-ureidothiophen-2-yl)benzylcarbamate (7a): To a mixture of 1-(5-bromo-3-carbamoylthiophen-2-yl)urea **8** (53.3 mg, 0.202 mmol) in 1,4-dioxane-H_2O (7:1) were added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxabororan-2-yl)benzylcarbamate **9a** (100.9 mg, 0.303 mmol) and Cs_2CO_3 (263.1 mg, 0.807 mmol) and the mixture was degassed. To the mixture was added tetrakis(triphenylphosphino)palladium (23.3 mg, 0.0202 mmol) and the mixture was stirred at 75 °C for 18 h and concentrated. Purification of chromatography (SiO_2-amine 20 g, $CHCl_3$: MeOH =30:1) gave compound **7a** (37.9 mg, 0.0972 mmol, 48%) as a white solid; mp 188-189 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.40 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.12 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.8, 157.1, 150.4, 139.8, 134.4, 133.0, 128.8, 126.0, 119.2, 115.6, 114.4, 80.2, 44.7, 28.8; FT-IR (neat) 3342, 2976, 2451, 1670, 1523,

1429, 1344, 1257, 1162, 1038, 772 cm^{-1}; MS (FAB) *m/z* 57 (100), 391 (M^+); HRMS (FAB) calcd for $C_{18}H_{22}N_4O_4S$ (M^+) 390.1372, found 390.1367.

5-Phenyl-2-ureidothiophene-3-carboxamide (7c): ^1H NMR (400 MHz, CD_3OD) δ 7.57-7.51 (m, 3H), 7.37-7.32 (m, 2H), 7.24-7.21 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.8, 157.1, 150.5, 135.6, 133.2, 130.0, 128.0, 125.9, 119.4, 114.4; FT-IR (neat) 3336, 2422, 1604, 1521, 1457, 1339, 1222, 770, 686 cm^{-1}; MS (FAB) *m/z* 154 (100), 261 (M^+); HRMS (FAB) calcd for $C_{12}H_{11}N_3O_2S$ $(M)^+$ 261.0572, found 261.0523.

5-Mesityl-2-ureidothiophene-3-carboxamide (7d): ^1H NMR (400 MHz, CD_3OD) δ 6.81 (s, 2H), 6.77 (s, 1H), 2.18 (s, 3H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.0, 157.3, 151.1, 139.5, 139.1, 135.3, 131.3, 129.1, 122.5, 113.4, 21.2, 20.9; FT-IR (neat) 3249, 2587, 2422, 1608, 1509, 1418, 1328, 855, 770, 694 cm^{-1}; MS (ESI) *m/z* 326 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{15}H_{17}N_3NaO_2S$ [$(M+Na)^+$] 326.0940, found 326.0985.

5-(4-Methoxyphenyl)-2-ureidothiophene-3-carboxamide (7e): ^1H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.36 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.8, 160.5, 157.2, 149.8, 133.4, 128.3, 127.3, 118.0, 115.4, 114.3, 55.8; FT-IR (neat) 3338, 2550, 1685, 1610, 1522, 1447, 1346, 1248, 1026, 485 cm^{-1}; MS (FAB) *m/z* 93 (100), 291 (M^+); HRMS (FAB) calcd for $C_{13}H_{13}N_3O_3S$ $(M)^+$ 291.0678, found 291.0677.

5-Ureido-[2,3'-bithiophene]-4-carboxamide (7f): ^1H NMR (400 MHz, CD_3OD) δ 7.35 (dd, *J* = 4.8 Hz, 2.8 Hz 1H), 7.29-7.28 (m, 2H), 7.22 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.7, 157.1, 149.8, 136.7, 128.9, 127.5, 126.4, 119.3, 113.8; FT-IR (neat) 3338, 2918, 2852, 2133, 2016, 1607, 1534, 1461, 1219, 1079, 770, 693 cm^{-1}; MS (ESI) *m/z* 290 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{10}H_9N_3NaO_2S_2$ [$(M+Na)^+$] 290.0034, found 290.0037.

5-(4-Fluorophenyl)-2-ureidothiophene-3-carboxamide (1): ^1H NMR (400 MHz, CD_3OD) δ 7.49-7.44 (m, 2H), 7.37 (s, 1H), 7.01 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.7, 162.2, 157.1, 150.5, 132.1, 127.9, 127.8, 119.5, 116.9, 114.4; FT-IR (neat) 3337, 2422, 1695, 1524, 1340, 1230, 818, 768, 697, 527 cm^{-1}; MS (ESI) *m/z* 302 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{12}H_{10}FN_3NaO_2S$ [$(M+Na)^+$] 302.0375, found 302.0392.

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SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra of compounds **4**, **5**, **8**, **7a**-**7f**, and **1** and the summary of DFT calculation of **5** are available.

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