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

Norihiko Kawasaki, Hayato Fukuda, and Jun Ishihara*

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan: E-mail: jishi@nagasaki-u.ac.jp

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. 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. 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. 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\textsubscript{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. Moreover, it has been shown that

![Scheme 1. Standard preparation of TPCA-1 (1)](image-url)

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.\textsuperscript{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 $\beta$-ketonitrile 2, followed by cyclization to a 2-aminothiophene 3 by sulfur (Scheme 1).\textsuperscript{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 $\pi$-conjugated units due to the importance of green chemistry and atom economy.\textsuperscript{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,\textsuperscript{8} Mori,\textsuperscript{9} Fagnou,\textsuperscript{10} Lemaire,\textsuperscript{11} and Lautens,\textsuperscript{12} and other chemists.\textsuperscript{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.\textsuperscript{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)](image)

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).
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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>°C</th>
<th>Solvent</th>
<th>results</th>
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<tr>
<td>1</td>
<td>6a</td>
<td>-</td>
<td>AcOK</td>
<td>150</td>
<td>DMF</td>
<td>ND</td>
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<tr>
<td>2</td>
<td>6a</td>
<td>-</td>
<td>AcOK</td>
<td>150</td>
<td>DMA</td>
<td>ND</td>
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<tr>
<td>3</td>
<td>6a</td>
<td>-</td>
<td>AcOK</td>
<td>150</td>
<td>NMP</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>6a</td>
<td>JohnPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>150</td>
<td>DMF</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
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<td>-</td>
<td>AcOK</td>
<td>110</td>
<td>NMP</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>6a</td>
<td>PdCl(C$_3$H$_5$)(dppb)</td>
<td>-</td>
<td>AcOK</td>
<td>130</td>
<td>DMA</td>
</tr>
<tr>
<td>7</td>
<td>6a</td>
<td>PdCl$_2$</td>
<td>PCy$_3$</td>
<td>Ag$_2$CO$_3$</td>
<td>150</td>
<td>DMF</td>
</tr>
<tr>
<td>8</td>
<td>6b</td>
<td>-</td>
<td>AcOK</td>
<td>150</td>
<td>NMP</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>6b</td>
<td>-</td>
<td>AcOK</td>
<td>150</td>
<td>DMF</td>
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<tr>
<td>10</td>
<td>6b</td>
<td>-</td>
<td>AcOK</td>
<td>150</td>
<td>DMA</td>
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Recent mechanism studies for Pd-catalyzed direct arylation of thiophenes suggest three pathways, $S\tau$Ar mechanism, Mizoroki-Heck mechanism, and CMD mechanism. Thiophene 5 contains electrophilic substituents at C-2 and C-3, and $S\tau$Ar 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

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)Cl₂ and NaOH in aqueous dioxane. The reaction slowly proceeded to give 7b in 2% yield (entry 1). Using Na₂CO₃ as a base in aqueous DME, the yield was slightly improved (entry 2). On the other hand, Pd(PPh₃)₄ was suitable for the coupling reaction of 8 and 9b (entry 3). It was turned out that the reaction with Pd(PPh₃)₄ and Na₂CO₃ in aqueous DME afforded 9b in 36% yield (entry 5). To our delight, the reaction of 8 and 9b of using Cs₂CO₃ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>9</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9b</td>
<td>Pd(dppf)Cl₂</td>
<td>NaOH</td>
<td>dioxane-H₂O</td>
<td>2%</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>Pd(dppf)Cl₂</td>
<td>Na₂CO₃</td>
<td>DME-H₂O</td>
<td>11%</td>
</tr>
<tr>
<td>3</td>
<td>9b</td>
<td>Pd(PPh₃)₄</td>
<td>AcOK</td>
<td>EtOH-PhMe</td>
<td>16%</td>
</tr>
<tr>
<td>4</td>
<td>9b</td>
<td>Pd(PPh₃)₄</td>
<td>K₂CO₃</td>
<td>dioxane-H₂O</td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td>9b</td>
<td>Pd(PPh₃)₄</td>
<td>Na₂CO₃</td>
<td>DME-H₂O</td>
<td>36%</td>
</tr>
<tr>
<td>6 *₁</td>
<td>9b</td>
<td>Pd(PPh₃)₄</td>
<td>Na₂CO₃</td>
<td>DME-H₂O</td>
<td>23%</td>
</tr>
<tr>
<td>7 *₂</td>
<td>9b</td>
<td>Pd(PPh₃)₄</td>
<td>Cs₂CO₃</td>
<td>dioxane-H₂O</td>
<td>46%</td>
</tr>
<tr>
<td>8 *₃</td>
<td>9a</td>
<td>Pd(PPh₃)₄</td>
<td>Cs₂CO₃</td>
<td>dioxane-H₂O</td>
<td>ND *₄</td>
</tr>
<tr>
<td>9 *₂</td>
<td>9a</td>
<td>Pd(PPh₃)₄</td>
<td>Cs₂CO₃</td>
<td>dioxane-H₂O</td>
<td>48%</td>
</tr>
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</table>

*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 MgSO₄ or Na₂SO₄ 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 (NEt₃) were distilled from CaH₂. Column chromatography was performed using silica gel (particle size 40-50 μm (flash)) or silica gel amine (SiO₂-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. ¹H NMR (300 and 400 MHz) and ¹³C NMR (75 and 100 MHz) spectra were measured using CDCl₃, or CD₃OD as solvent, and chemical shifts are reported as δ values in ppm based on internal CHCl₃ (7.26 ppm, ¹H; 77.0 ppm, ¹³C), CD₃OD (3.31 ppm, ¹H; 49.0 ppm, ¹³C). 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 (SiO₂ 120 g, hexane:AcOEt = 1:1) to afford compound 4 (4.87 g, 34.3 mmol, quant) as yellow powder; mp 138-139 °C; ¹H NMR (400 MHz CDCl₃) 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); ¹³C NMR (100 MHz CDCl₃) 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 C₅H₆N₂OS (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 (SiO₂-amine 95 g, CHCl₃; MeOH = 10 : 1) gave compound 5 (914 mg, 4.94 mmol, 82 %) as white powder; mp 199-200 °C; ¹H NMR (400 MHz, CD₃OD) δ 7.16 (d, J = 5.6 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 166.0, 151.0, 123.5, 115.6, 113.5; FT-IR (neat)
3336, 2536, 2422, 1679, 944, 823, 771, 687, 624 cm\(^{-1}\); MS (FAB) \(m/z\) 154 (100), 186 (M\(^+\)); HRMS (FAB) calcd for C\(_6\)H\(_7\)N\(_3\)O\(_2\)S (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\(_2\)O (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 ℃; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 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); 13C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 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\(_{20}\)N\(_4\)O\(_4\)S (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 6b (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, 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); \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.24 (s, 1H), 13C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 168.6, 157.1, 151.5, 125.9, 113.4, 103.2; FT-IR (neat) 3352, 3193, 1702, 1546, 1511, 1420, 1328, 1275, 1200, 771, 694 cm\(^{-1}\); MS (FAB) \(m/z\) 91 (100), 263 [(M+H)\(^+\)], 265 [(M+H+2)+]; HRMS (FAB) calcd for C\(_6\)H\(_6\)\(_7\)\(_9\)BrN\(_3\)O\(_2\)S [(M+H)\(^+\)] 263.9438, found 263.9440, calcd for C\(_6\)H\(_6\)\(_8\)\(_1\)BrN\(_3\)O\(_2\)S [(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\(_2\)O (7:1) were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate 9a (100.9 mg, 0.303 mmol) and Cs\(_2\)CO\(_3\) (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; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 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); \(^1\)C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 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 C₁₈H₂₂N₄O₄S (M⁺) 390.1372, found 390.1367.

5-Phenyl-2-ureidothiophene-3-carboxamide (7c): ¹H NMR (400 MHz, CD₃OD) δ 7.57-7.51 (m, 3H), 7.37-7.32 (m, 2H), 7.24-7.21 (m, 1H); ¹³C NMR (100 MHz, CD₃OD) 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 C₁₂H₁₁N₃O₂S (M⁺) 261.0572, found 261.0523.

5-Mesityl-2-ureidothiophene-3-carboxamide (7d): ¹H NMR (400 MHz, CD₃OD) δ 6.81 (s, 2H), 6.77 (s, 1H), 2.18 (s, 3H), 2.04 (s, 6H); ¹³C NMR (100 MHz, CD₃OD) 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 C₁₅H₁₇N₃NaO₂S [(M+Na)⁺] 326.0940, found 326.0985.

5-(4-Methoxyphenyl)-2-ureidothiophene-3-carboxamide (7e): ¹H NMR (400 MHz, CD₃OD) 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); ¹³C NMR (100 MHz, CD₃OD) 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 C₁₃H₁₃N₃O₃S (M⁺) 291.0678, found 291.0677.

5-Ureido-[2,3'-bithiophene]-4-carboxamide (7f): ¹H NMR (400 MHz, CD₃OD) 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); ¹³C NMR (100 MHz, CD₃OD) 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 C₁₀H₉N₃NaO₂S₂ [(M+Na)⁺] 290.0034, found 290.0037.

5-(4-Fluorophenyl)-2-ureidothiophene-3-carboxamide (1): ¹H NMR (400 MHz, CD₃OD) δ 7.49-7.44 (m, 2H), 7.37 (s, 1H), 7.01 (t, J = 8.8 Hz, 2H); ¹³C NMR (100 MHz, CD₃OD) 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 C₁₂H₁₀FN₃NaO₂S [(M+Na)⁺] 302.0375, found 302.0392.

ACKNOWLEDGEMENTS

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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.

REFERENCES AND NOTES


