DOI: 10.1002/ejoc.200600951

Palladium-Catalyzed Buchwald–Hartwig Coupling of Deactivated Aminothiophenes with Substituted Halopyridines

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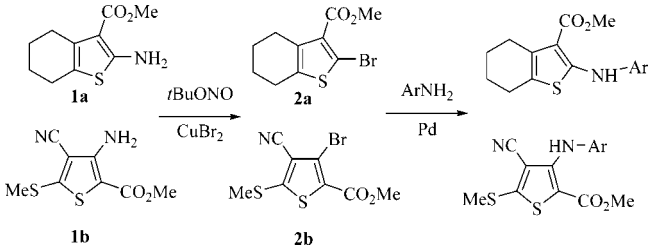
Keywords: Cross-coupling/ Nitrogen heterocycles / Sulfur heterocycles / Amines / Suzuki coupling

The palladium-catalyzed Buchwald–Hartwig coupling of several deactivated aminothiophenecarboxylates with differently substituted halopyridines has been performed for the first time by using $Pd(OAc)_2$, Xantphos as the ligand, and Cs_2CO_3 as the base. When 2,6-dihalopyridines were used, the proportion of diaminated product increases with the reactivity of the halopyridines (iodo > bromo > chloro). A bromo monoaminated pyridine derivative, obtained by Buchwald–Hartwig coupling, was further used in the Suzuki coupling of aryl boronic acids bearing electron-withdrawing or electron-donating groups. These latter compounds are very interesting as they possess diheteroarylamine and heteroaryl–aryl skeletons including pyridine and thiophene moieties.

Introduction

There are only a few reports on palladium-catalyzed amination of halothiophenes, and most of them deal with the amination of non- or monosubstituted halothiophenes.[1] Recently, we have described the synthesis of diarylamines in the thiophene series by the Buchwald–Hartwig coupling of polysubstituted bromothiophenes **2a** and **2b** with anilines.[2] We have also synthesized some diheteroarylamines and some polycyclic compounds by reacting the polysubstituted bromothiophenes with aminopyridines and aminoquinolines.[3] Bromothiophenes **2a** and **2b** were obtained from corresponding aminothiophenes **1a** and **1b**, respectively,[4] by a substitutive deamination (Scheme 1),[5] and of interest would be the direct use of the latter compounds in the Buchwald–Hartwig reaction as the "amino partner".



Scheme 1.

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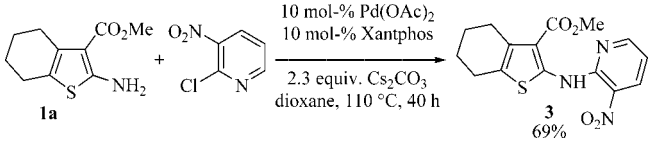
We only found one publication studying *N*-arylation of one aminothiophene.[6] However, we were not able to reproduce these results and our several attempts to couple compounds **1a** and **1b** with aryl bromides failed. We suppose that it was due to the deactivation of the aminothiophenes by electron-withdrawing groups in the *ortho* position. Indeed, some studies have shown that C–N bond forming reductive elimination was faster from complexes with more electron-donating amido groups and less electron-donating aryl groups.[7] So, we thought that the coupling of aminothiophenes with electron-poor heteroaryl halides would overcome this lack of reactivity.

In 1996, Buchwald et al described the first example of palladium-catalyzed amination of haloheteroaromatic substrates.[8] They succeeded in coupling 2-, 3-, and 4-bromopyridines with anilines and primary aliphatic amines. A few years later, the same group reported the use of chloropyridines.[9] The group of Maes and Dommisse published several papers studying the reactivity of dihalopyridines in the cross-coupling reaction with aminopyridines, aminopyrimidines, or aminopyrazines.[10] As a continuation of our previous work on Buchwald–Hartwig coupling, we decided to study the reactivity of 2- and 3-aminothiophenecarboxylates in the amination of halopyridines.

Results and Discussion

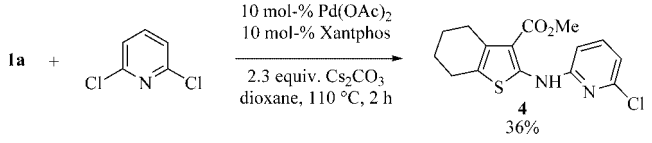
Buchwald has demonstrated in his first study on palladium-catalyzed amination of bromopyridines that activated substrates are not required and that relatively nonnucleophilic amines such as primary amines or anilines are efficiently arylated.[8] Unfortunately, our first attempt to couple aminothiophene **1a** with 2-bromopyridine failed. However, the use of 2-chloro-3-nitropyridine led to the forma-

tion of **3** in 69% yield (Scheme 2). Despite the fact that 2-chloropyridines are less reactive than their bromo counterparts, the presence of the very electron-withdrawing NO_2 group allows the reaction to proceed.



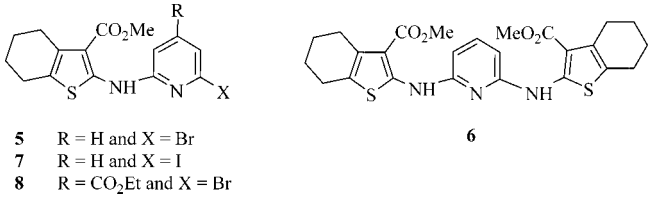
Scheme 2.

Coupling of aminothiophene **1a** (1.4 equiv.) with 2,6-dichloropyridine (1 equiv.) led to the exclusive formation of monoaminated product **4** in 36% yield (Scheme 3). The more electron-rich nature of intermediate **4** could explain the monoamination, as the presence of the introduced amino group may prevent a second oxidative addition. This behavior has already been observed by Maes in his work on 2,3-, 2,5-, and 2,6-dichloropyridines.[10a]



Scheme 3.

The same type of coupling of **1a** with 2,6-dibromopyridine gave monoaminated product **5** (54%) and diaminated product **6** (19%) (Figure 1). As Buchwald had described the diamination of 2,6-dibromopyridine by aniline in good yield,[8] we tried to increase the proportion of **6** by working with 2.4 equiv. of aminothiophene; however, the results were unexpected as compound **6** was not obtained. Moreover, the yield of **5** decreased to only 19% which is certainly due to the poisoning effect of excess aminothiophene.



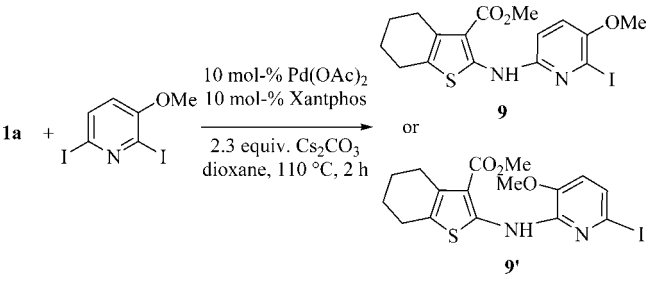
5 R = H and X = Br
7 R = H and X = I
8 R = CO_2Et and X = Br

6

Figure 1. Structures of compounds **5**–**8**.

Under the same conditions, the use of 2,6-diiodopyridine provided 48% of corresponding monoaminated product **7** and 28% of diaminated **6** after a 1 h reaction time. Better yields were not obtained by prolonged heating. Coupling of **1a** with 4-carbethoxy-2,6-dibromopyridine gave only monoaminated product **8** in 43% yield (Figure 1).

The coupling of **1a** with 3-methoxy-2,6-diiodopyridine could lead to compounds **9** and **9′**. (Scheme 4) We supposed that product **9** may be favored as the electron-donating effect of the methoxy group in 3-methoxy-2,6-diiodopyridine was lower in the 6-position than in the 2-position. Moreover, the steric hindrance is lower in **9**. Indeed, after reaction, we only obtained compound **9** (34%). This structure has been confirmed by a NOESY experiment which showed correlations between NH and 3-H on one hand and between 4-H and the methoxy group on the other hand.



Scheme 4.

Coupling of 3-aminothiophene **1b** with 2,6-dichloro- and 2,6-dibromopyridine afforded only monoaminated products **10** and **11** in 13% and 74% yield, respectively (Table 1). Reaction of 2-aminothiophene-3-carboxylate **1c** with 2,6-dibromopyridine gave monoaminated product **12** in 73% yield and diaminated product **13** in 22% yield. The same reaction performed with 2,6-diiodopyridine gave diaminated pyridine **13** as the major product in 51% yield and monoaminated product **14** in 28% yield (Table 1). 3-Aminothiophene-2-carboxylate **1d** gave monoaminated product **15** in 46% yield and diaminated product **16** in 32% yield, whereas 3-aminothiophene-2-carboxylate **1e** only gave monoaminated product **17** in 60% yield.

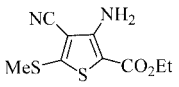
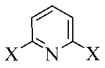
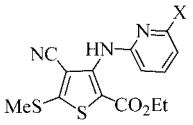
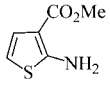
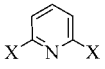
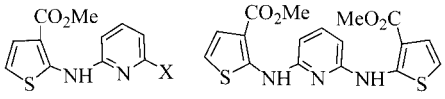
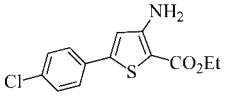
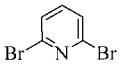
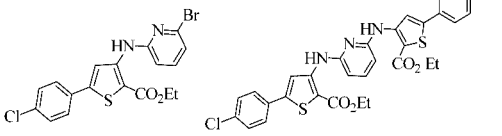
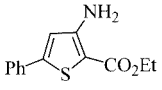
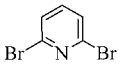
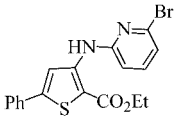
The obtained monoaminated halopyridines are also interesting as we can functionalize the 6-position with an aryl group by Suzuki coupling. For example, coupling of **5** with 4-methoxyphenylboronic acid or with 3-acetylphenylboronic acid under standard conditions allowed the formation of **18** and **19** in 43 and 61% yield, respectively (Scheme 5).

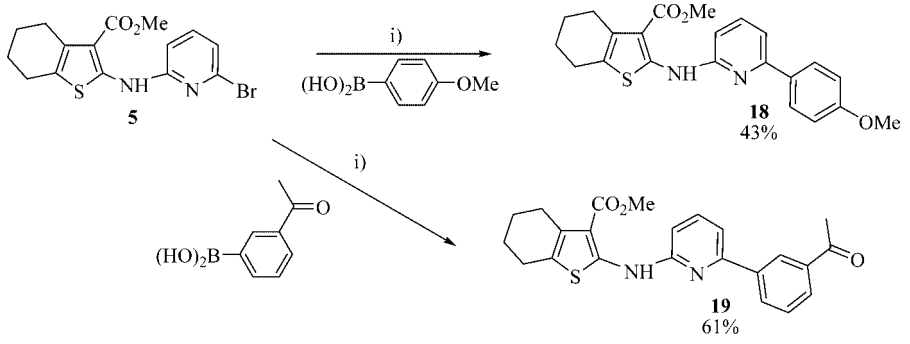
This approach is useful to access intermediates which may have antimicrobial activity like the 2-aminophenyl-3-cyano-4,6-diarylpyridines reported by Abdel-Aziz et al.[11]

Conclusions

In summary, we have shown for the first time that deactivated heterocyclic amines, 2-aminothiophene-3-carboxylates **1a** and **1c**, and 3-aminothiophene-2-carboxylates **1b**, **1d**, and **1e** can be N-arylated by halopyridines. We have observed (as expected) that the yields were higher when electron-withdrawing groups are present in the halopyridines. When 2,6-dihalopyridines were used, the proportion of the diaminated product increased with the reactivity of the halogen (I > Br > Cl). Compound **5** was arylated by the Suzuki coupling of arylboronic acids bearing either an electron-withdrawing (COMe) or an electron-donating group (OMe) to yield very interesting compounds with diheteroarylamine and heteroaryl–aryl skeletons.

Table 1. Palladium-catalyzed C–N cross-couplings of aminothiophenes with dihalopyridines.

Aminothiophene	Halopyridine	Results
 **1b**		 X = Cl **10** (13%) X = Br **11** (74%)
 **1c**	 X = Br X = I	 **12** (73%) + **13** (22%) **14** (28%) + **13** (51%)
 **1d**		 **15** (46%) + **16** (32%)
 **1e**		 **17** (60%)



i) 3 mol-% $Pd(OAc)_2$,15 mol-% PPh_3, 2M Na_2CO_3 aq. , DME, 80 °C, 20 h, argon

Scheme 5.

Experimental Section

General: $Pd(OAc)_2$, Xantphos, and Cs_2CO_3 were purchased from Aldrich. Melting points were determined with a Stuart SMP3 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with an AC Bruker 250 MHz spectrometer. The IR spectra were recorded with a Perkin–Elmer Spectrum BX. Elemental analyses were determined with a Thermofinnigan FlashEA 1112 elemental analyzer.

General Procedure for C–N Cross Coupling with Halopyridines: In a dry Schlenk tube, the halopyridine (0.5 mmol) was dissolved in dry dioxane (3 mL) under an argon atmosphere and $Pd(OAc)_2$ (10 mol-%), Xantphos (10 mol-%), and Cs_2CO_3 (2.3 equiv.) were added and stirred at 70 °C. After 5 min, the aminothiophene derivative (1.4 equiv.) was added under an argon atmosphere, and the reaction mixture was heated to 110 °C. The reaction was followed by TLC until its completion. After cooling to room temperature, the reaction mixture was diluted with diethyl ether and filtered. The oily solid obtained was then purified by column chromatography.

Methyl 2-(3-Nitropyridin-2-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (3): Column chromatography (CH_2Cl_2/cyclohexane, 1:9 to 1:1) gave compound **3** as a purple solid (115 mg, 69%). M.p. 208–210 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.80–1.83 (m, 4 H, CH_2), 2.68 (br. s, 2 H, CH_2), 2.83 (br. s, 2 H, CH_2), 3.97 (s, 3 H, CH_3), 6.93–6.98 (dd, J = 4.5 and 8.2 Hz, 1 H, ArH),

8.58–8.63 (m, 2 H, ArH), 13.27 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.9 (CH_2), 23.0 (CH_2), 24.3 (CH_2), 26.4 (CH_2), 51.4 (CH_3), 112.0 (C), 114.6 (CH), 127.2 (C), 129.2 (C), 131.6 (C), 135.4 (CH), 145.7 (C), 146.9 (C), 153.2 (CH), 165.8 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3080 (NH), 1674 (C=O), 1603 and 1505 (NO_2) cm^{-1}. $C_{15}H_{15}N_3O_4S$ (333.36): calcd. C 54.04, H 4.54, N 12.60, S 9.62; found C 54.04, H 4.62, N 12.38, S 9.47.

Methyl 2-(6-Chloropyridin-2-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4): Column chromatography (CH_2Cl_2/cyclohexane, 2:8 to 3:7) gave compound **4** as an off-white solid (58 mg, 36%). M.p. 166–168 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.77–1.81 (m, 4 H, CH_2), 2.64–2.67 (br. s, 2 H, CH_2), 2.75–2.78 (br. s, 2 H, CH_2), 3.86 (s, 3 H, CH_3) 6.71 (d, J = 7.9 Hz, 1 H, ArH), 6.83 (d, J = 7.9 Hz, 1 H, ArH), 7.50 (dd, J = 7.9 and 7.9 Hz, 1 H, ArH), 11.19 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.9 (CH_2), 23.1 (CH_2), 24.4 (CH_2), 26.5 (CH_2), 51.1 (CH_3), 108.3 (C), 109.1 (CH), 115.1 (CH), 124.3 (C), 130.5 (C), 139.6 (CH), 148.7 (C), 151.3 (C), 151.5 (C), 167.7 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3049 (NH), 1661 (C=O) cm^{-1}.

Methyl 2-(6-Bromopyridin-2-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5): Column chromatography (CH_2Cl_2/cyclohexane, 2:8 to 3:7) gave compound **5** as an off-white solid (99 mg, 54%). M.p. 158–160 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79–1.80 (m, 4 H, CH_2), 2.67 (br. s, 2 H, CH_2), 2.76 (br. s, 2 H, CH_2), 3.86 (s, 3 H, CH_3), 6.74 (d, J = 7.9 Hz, 1 H, ArH), 6.98 (d, J = 7.9 Hz, 1 H, ArH), 7.40 (dd, J = 7.9 and 7.9 Hz, 1 H, ArH), 11.18 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.9 (CH_2), 23.1 (CH_2), 24.4 (CH_2), 26.5 (CH_2), 51.0 (CH_3), 108.3 (C), 109.4 (CH), 118.9 (CH), 124.3 (C), 130.5 (C), 138.9 (C), 139.3 (CH), 151.2 (C), 151.4 (C), 167.7 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3198 (NH), 1663 (C=O) cm^{-1}. $C_{15}H_{15}BrN_2O_2S$ (367.26): calcd. C 49.06, H 4.12, N 7.63, S 8.73; found C 48.75, H 4.16, N 7.53, S 8.39.

Methyl 2-{6-[3-(Methoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino]pyridin-2-ylamino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (6): From thiophene **1a** and 2,6-dibromopyridine column chromatography (CH_2Cl_2/cyclohexane 3:7 to 6:4) gave compound **6** as an off-white solid (20 mg, 19%) or from thiophene **1a** and 2,6-diiodopyridine (CH_2Cl_2/cyclohexane, 5:5 to 7:3; 28%). M.p. 208–210 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80–1.81 (m, 8 H, CH_2), 2.63 (br. s, 4 H, CH_2), 2.77 (br. s, 4 H, CH_2), 3.87 (s, 6 H, CH_3), 6.56 (d, J = 7.9 Hz, 2 H, ArH), 7.52 (dd, J = 7.9 and 7.9 Hz, 1 H, ArH), 10.80 (s, 2 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.9 (2 CH_2), 23.2 (2 CH_2), 24.5 (2 CH_2), 26.6 (2 CH_2), 51.0 (2 CH_3), 102.8 (2 CH), 108.0 (2 C), 122.1 (2 C), 131.2 (2 C), 139.3 (CH), 151.2 (2 C), 152.5 (2 C), 167.1 (2 CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3163 (NH), 1661 (C=O) cm^{-1}.

Methyl 2-(6-Iodopyridin-2-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7): Column chromatography (CH_2Cl_2/cyclohexane, 1:1) gave compound **7** as a beige solid (100 mg, 48%). M.p. 221–223 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79–1.80 (m, 4 H, CH_2), 2.67 (br. s, 2 H, CH_2), 2.76 (br. s, 2 H, CH_2), 3.85 (s, 3 H, CH_3), 6.74 (d, J = 7.9 Hz, 1 H, ArH), 7.13–7.27 (m, 2 H, ArH), 11.14 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.0 (CH_2), 23.2 (CH_2), 24.4 (CH_2), 26.5 (CH_2), 51.1 (CH_3), 108.3 (C), 110.0 (CH), 113.5 (C), 124.2 (C), 126.1 (CH), 130.4 (C), 138.6 (CH), 150.9 (C), 151.2 (C), 167.7 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3163 (NH), 1661 (C=O) cm^{-1}.

Methyl 2-(6-Bromo-4-ethoxycarbonylpyridin-2-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (8): Column chromatography (CH_2Cl_2/cyclohexane, 1:1) gave compound **9** as a yellow solid (93 mg, 43%). M.p. 151–153 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.1 Hz, 3 H), 1.79–1.81 (m, 4 H, CH_2), 2.67 (br. s, 2 H, CH_2), 2.77 (br. s, 2 H, CH_2), 3.88 (s, 3 H, CH_3), 4.40 (q, J = 7.1 Hz, 2 H), 7.34 (s, 1 H, ArH), 7.49 (s, 1 H, ArH), 11.37 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.2 (CH_3), 22.9 (CH_2), 23.1 (CH_2), 24.4 (CH_2), 26.4 (CH_2), 51.2 (OCH_3), 62.1 (CO_2CH_2), 108.9 (C), 110.0 (CH), 117.9 (CH), 124.9 (C), 130.7 (C), 139.5 (C), 141.2 (C), 150.7 (C), 151.7(C), 163.7 (CO_2R), 167.7 (CO_2R) ppm. IR (KBr): $\tilde{\nu}$ = 2925 (NH), 1727 (C=O), 1659 (C=O) cm^{-1}. $C_{18}H_{19}BrN_2O_4S$ (439.32): calcd. C 49.21, H 4.36, N 6.38, S 7.30; found C 49.4, H 4.32, N 6.26, S 7.25.

Methyl 2-(6-Iodo-5-methoxypyridin-2-ylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (9): Column chromatography (CH_2Cl_2/cyclohexane, 1:1 to 1:0) gave compound **8** as a brown solid (72 mg, 34%). M.p. 160–162 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.78–1.80 (m, 4 H, CH_2), 2.64 (br. s, 2 H, CH_2), 2.77 (br. s, 2 H, CH_2), 3.85 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 6.73 (d, J = 7.9 Hz, 1 H, ArH), 7.06 (d, J = 7.9 Hz, 1 H, ArH), 11.04 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.9 (CH_2), 23.0 (CH_2), 24.3 (CH_2), 26.3 (CH_2), 50.8 (CH_3), 57.2 (CH_3), 105.7 (C), 107.1 (C), 110.1 (CH), 121.2 (CH), 122.7 (C), 130.2 (C), 145.4 (C), 149.6 (C), 152.2 (C), 167.6 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3205 (NH), 1649 (C=O) cm^{-1}. $C_{16}H_{17}IN_2O_3S$ (444.29): calcd. C 43.25, H 3.86, N 6.31, S 7.22; found C 43.66, H 4.03, N 6.14, S 7.16.

Ethyl 3-(6-Chloropyridin-2-ylamino)-4-cyano-5-(methylthio)thiophene-2-carboxylate (10): Column chromatography (CH_2Cl_2/cyclohexane, 1:1 to 8:2) gave compound **10** as a yellow pale solid (23 mg, 13%). M.p. 141–143 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 3 H), 2.69 (s, 3 H, SCH_3), 4.33 (q, J = 7.1 Hz, 2 H), 6.76 (d, J = 7.9 Hz, 1 H, ArH), 6.96 (dd, J = 8.0 and 0.5 Hz, 1 H, ArH), 7.56 (dd, J = 8.0 and 7.9 Hz, 1 H, ArH), 9.01 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.3 (CH_3), 17.7 (CH_3), 61.4 (CH_2), 103.7 (C), 108.2 (C), 110.4 (CH), 112.7 (C), 118.1 (CH), 140.2 (CH), 146.7 (C), 149.5 (C), 152.4 (C), 159.1(C), 162.6 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3340 (NH), 2221 (CN), 1671 (C=O) cm^{-1}. $C_{14}H_{12}ClN_3O_2S_2$ (353.85): C 47.52, H 3.42, N 11.88, S 18.12; found: C 47.16, H 3.82, N 11.50, S 20.95.

Ethyl 3-(6-Bromopyridin-2-ylamino)-4-cyano-5-(methylthio)thiophene-2-carboxylate (11): Column chromatography (CH_2Cl_2/cyclohexane, 1:1 to 8:2) gave compound **11** as a yellow pale solid (148 mg, 74%). M.p. 156–158 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 (t, J = 7.1 Hz, 3 H), 2.71 (s, 3 H, SCH_3), 4.34 (q, J = 7.1 Hz, 2 H), 6.79 (d, J = 7.9 Hz, 1 H, ArH), 7.13 (d, J = 7.9 Hz, 1 H, ArH), 7.45 (dd, J = 7.9 and 7.9 Hz, 1 H, ArH), 9.12 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.3 (CH_3), 17.7 (CH_3), 61.4 (CH_2), 104.0 (C), 108.2 (C), 110.7 (CH), 112.7 (C), 122.0 (CH), 139.8 (C), 139.9 (CH), 146.6 (C), 152.4 (C), 159.0 (C), 162.6 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3288 (NH), 2222 (CN), 1683 (C=O) cm^{-1}. $C_{14}H_{12}BrN_3O_2S_2$ (398.30): calcd. C 42.22, H 3.04, N 10.55, S 16.10; found C 42.28, H 3.20, N 10.10, S 15.65.

Methyl 2-(6-Bromopyridin-2-ylamino)thiophene-3-carboxylate (12): Column chromatography (CH_2Cl_2/cyclohexane, 1:1 to 3:2) gave compound **12** as a yellow pale solid (115 mg, 73%). M.p. 133–135 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, OCH_3), 6.63 (d, J = 6.0 Hz, 1 H, ArH), 6.79 (d, J = 7.9 Hz, 1 H, ArH), 7.03 (d, J = 7.9 Hz, 1 H, ArH), 7.21 (d, J = 6.0 Hz, 1 H, ArH), 7.44 (dd, J = 7.9 and 7.9 Hz, 1 H, ArH), 10.82 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.4 (CH_3), 109.3 (CH), 109.4 (C), 113.9 (CH), 119.4 (CH), 123.7 (CH), 138.9 (C), 139.6 (CH), 151.1 (C), 152.1 (C), 166.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3216 (NH), 1671 (C=O) cm^{-1}.

Methyl 2-{6-[3-(Methoxycarbonyl)thiophen-2-ylamino]pyridin-2-ylamino}thiophene-3-carboxylate (13): From thiophene **1c** and 2,6-dibromopyridine column chromatography (CH_2Cl_2/cyclohexane,

3:2 to 3:1) gave compound **13** as a yellow pale solid (30 mg, 22%) or from thiophene **1c** and 2,6-diiodopyridine (CH_2Cl_2/cyclohexane, 1:1 to 3:1; 70 mg, 51%). M.p. 172–174 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.91 (s, 6 H, 2 OC*H*$_3$), 6.54 (d, *J* = 5.8 Hz, 2 H, ArH), 6.62 (dd, *J* = 2.0 and 7.0 Hz, 2 H, ArH), 7.21 (dd, *J* = 2.3 and 5.8 Hz, 2 H, ArH), 7.60 (dd, *J* = 7.9 and 7.9 Hz, 1 H, ArH), 10.59 (s, 2 H, NH) ppm.^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.4 (2 CH_3), 103.0 (2 CH), 109.1 (2 C), 111.5 (2 CH), 124.3 (2 CH), 139.7 (CH), 150.9 (2 C), 153.5 (2 C), 166.4 (2 C) ppm. IR (KBr): 3257 (NH), 1670 (C=O) cm^{-1}.

Methyl 2-(6-Iodopyridin-2-ylamino)thiophene-3-carboxylate (14): Column chromatography (CH_2Cl_2/cyclohexane, 1:3 to 1:1) gave compound **14** as a pink pale solid (51 mg, 28%). M.p. 146–148 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OC*H*$_3$), 6.62 (d, *J* = 6.0 Hz, 1 H, ArH), 6.79 (d, *J* = 7.5 Hz, 1 H, ArH), 6.94 (dd, *J* = 7.8 and 7.8 Hz, 1 H, ArH), 7.20 (d, *J* = 6.0 Hz, 1 H, ArH), 7.60 (d, *J* = 7.8 Hz, 1 H, ArH), 10.77 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.5 (CH_3), 109.4 (C), 109.7 (CH), 113.5 (C), 113.9 (CH), 123.7 (CH), 126.5 (CH), 138.8 (CH), 150.6 (C), 152.0 (C), 166.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3225 (NH), 1670 (C=O) cm^{-1}.

Ethyl 3-(6-Bromopyridin-2-ylamino)-5-(4-chlorophenyl)thiophene-2-carboxylate (15): Column chromatography (CH_2Cl_2/cyclohexane, 1:3 to 2:3) gave compound **15** as a yellow solid (100 mg, 46%). M.p. 169–171 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.3 Hz, 3 H), 4.37 (q, *J* = 7.3 Hz, 2 H), 6.70 (d, *J* = 8.3 Hz, 1 H, ArH), 7.01 (d, *J* = 7.5 Hz, 1 H, ArH), 7.37–7.42 (m, 3 H, ArH), 7.64 (d, *J* = 8.3 Hz, 2 H, ArH), 8.60 (s, 1 H, ArH), 9.87 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.5 (CH_3), 60.9 (CH_2), 105.8 (C), 109.8 (CH), 117.8 (CH), 119.3 (CH), 127.3 (CH), 129.3 (CH), 132.1 (C), 134.9 (C), 139.7 (CH), 139.8 (C), 147.6 (C), 147.7 (C), 153.2 (C), 165.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3293 (NH), 1655 (C=O) cm^{-1}.

Ethyl 3-{6-[5-(4-Chlorophenyl)-2-ethoxycarbonyl]thiophen-3-ylamino}pyridin-3-ylamino-5-(4-chlorophenyl)thiophene-2-carboxylate (16): Column chromatography (CH_2Cl_2/cyclohexane, 2:3 to 1:1) gave compound **16** as a yellow solid (71 mg, 32%). M.p. 193–195 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.3 Hz, 6 H, 2 C*H*$_3$), 4.39 (q, *J* = 7.3 Hz, 4 H, 2 C*H*$_2$), 6.37 (d, *J* = 8.0 Hz, 2 H, ArH), 6.99 (d, *J* = 8.5 Hz, 4 H, ArH), 7.14 (dd, *J* = 1.8 and 6.8 Hz, 4 H, ArH), 7.49 (dd, *J* = 8.0 and 8.0 Hz, 1 H, ArH), 8.34 (s, 2 H, ArH), 9.64 (s, 2 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.5 (2 CH_3), 60.7 (2 CH_2), 103.6 (2 CH), 104.9 (2 C), 117.8 (2 CH), 126.4 (4 CH), 128.6 (4 CH), 131.3 (2 C), 134.4 (2 C), 139.6 (CH), 147.3 (2 C), 148.2 (2 C), 152.3 (2 C), 164.8 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 3283 (NH), 1665 (C=O) cm^{-1}.

Ethyl 3-(6-Bromopyridin-2-ylamino)-5-(phenyl)thiophene-2-carboxylate (17): Column chromatography (CH_2Cl_2/cyclohexane, 1:3 to 3:1) gave compound **17** as a yellow solid (120 mg, 60%). M.p. 146–148 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.3 Hz, 3 H), 4.36 (q, *J* = 7.3 Hz, 2 H), 6.68 (d, *J* = 7.5 Hz, 1 H, ArH), 6.99 (d, *J* = 7.5 Hz, 1 H, ArH), 7.35–7.46 (m, 4 H, ArH), 7.71 (d, *J* = 8.3 Hz, 2 H, ArH), 8.60 (s, 1 H, ArH), 9.88 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.5 (CH_3), 60.7 (CH_2), 105.6 (C), 109.7 (CH), 117.5 (CH), 119.2 (CH), 126.1 (2 CH), 128.9 (CH), 129.0 (2 CH), 133.6 (C), 139.6 (CH), 139.8 (C), 147.6 (C), 149.2 (C), 153.3 (C), 165.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3307 (NH), 1655 (C=O) cm^{-1}.

Methyl 2-[6-(4-Methoxyphenyl)pyridin-2-ylamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (18): From compound **5** (138 mg, 0.38 mmol) and 4-methoxyphenylboronic acid column chromatography (CH_2Cl_2/cyclohexane, 1:3) gave compound **18** as a yellow solid (65 mg, 43%). M.p. 157–159 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80–1.82 (m, 4 H, CH_2), 2.69–2.79 (m, 4 H, CH_2), 3.87 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 6.73 (d, *J* = 7.5 Hz, 1 H, ArH), 7.05 (d, *J* = 7.5 Hz, 2 H, ArH), 7.22–7.26 (m, 1 H, ArH), 7.61 (dd, *J* = 7.5 and 7.5 Hz, 1 H, ArH), 8.14 (d, *J* = 7.5 Hz, 2 H, ArH), 11.15 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.0 (CH_2), 23.2 (CH_2), 24.5 (CH_2), 26.6 (CH_2), 50.9 (CH_3), 55.3 (CH_3), 107.2 (C), 109.2 (CH), 111.6 (CH), 114.0 (2 CH), 123.1 (C), 128.5 (2 CH), 130.4 (C), 131.8 (C), 138.1 (CH), 151.4 (C), 152.0 (C), 155.4 (C), 160.4 (C), 167.7 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3271 (NH), 1648 (C=O) cm^{-1}. $C_{22}H_{22}N_2O_3S$ (394.49): calcd. C 66.98, H 5.62, N 7.10, S 8.13; found C 66.86, H 5.55, N 7.17, S 7.78.

Methyl 2-[6-(3-Acetophenyl)pyridin-2-ylamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (19): From compound **5** (70 mg, 0.19 mmol) and 3-acethylphenylboronic acid column chromatography (CH_2Cl_2/cyclohexane, 1:4 to 1:1) gave compound **19** as a yellow solid (46 mg, 61%). M.p. 153–155 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.81–1.83 (m, 4 H, CH_2), 2.66–2.80 (m, 7 H, 2 CH_2 and CO*C*H$_3$), 3.96 (s, 3 H, OCH_3), 6.84 (d, *J* = 7.5 Hz, 1 H, ArH), 7.38 (d, *J* = 7.5 Hz, 1 H, ArH), 7.58–7.73 (m, 2 H, ArH), 8.06 (d, *J* = 7.5 Hz, 1 H, ArH), 8.31 (d, *J* = 7.5 Hz, 1 H, ArH), 8.98 (s, 1 H, ArH), 11.22 (s, 1 H, NH) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 23.0 (CH_2), 23.1 (CH_2), 24.3 (CH_2), 26.5 (CH_2), 26.9 (CO*C*H$_3$), 51.0 (CH_3), 107.6 (C), 110.6 (CH), 112.2 (CH), 123.1 (C), 127.8 (CH), 128.4 (CH), 128.9 (CH), 130.6 (C), 131.1 (CH), 137.5 (C), 138.3 (CH), 139.1 (C), 151.4 (C), 151.5 (C), 154.1 (C), 167.7 (C), 198.2 (*C*OCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3265 (NH), 1687 (C=O), 1662 (C=O) cm^{-1}. $C_{23}H_{22}N_2O_3S$ (406.50): calcd. C 67.96, H 5.46, N 6.89, S 7.89; found C 67.74, H 5.55, N 6.57, S 7.25.

Acknowledgments

Financial support from the SRI of UPV-M is gratefully acknowledged. We also thank Egide (France) / Grices (Portugal) for support through the Pessoa program.

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Received: October 31, 2006
Published Online: February 14, 2007

