Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 975–981

TETRAHEDRON

Synthesis of diarylamines in the benzo[*b*]thiophene series bearing electron donating or withdrawing groups by Buchwald–Hartwig C–N coupling

Isabel C. F. R. Ferreira,[a] Maria-João R. P. Queiroz[a,*] and Gilbert Kirsch[b]

[a]*Departamento de Química, Universidade do Minho, 4710-057 Braga, Portugal*
[b]*Laboratoire d'Ingénierie Moleculaire et Biochimie Pharmacologique, Université de Metz, Faculté des Sciences, Ile du Saulcy, 57045 Metz, France*

Received 19 September 2002; revised 6 November 2002; accepted 17 December 2002

Abstract—Diarylamines in the benzo[*b*]thiophene series bearing electron donating or withdrawing groups, were prepared by Buchwald–Hartwig C–N coupling in moderate to high yields. The conditions used were $Pd(OAc)_2$ (3 mol%), BINAP as ligand (4 mol%) and Cs_2CO_3 as base (1.4 equiv.), in toluene at 100°C, being 6-bromo or amino benzo[*b*]thiophenes coupled, respectively, with substituted anilines or phenylbromides. The 6-aminobenzo[*b*]thiophene derivatives were also prepared by palladium catalyzed C–N coupling of the corresponding 6-bromo compounds with benzophenone imine, followed by acidic hydrolysis of the imino derivatives. When 4-nitrobromobenzene and 4-bromobenzonitrile were used as coupling components, triarylamines were also isolated in small amounts. The presence of a fluorine atom on the phenylbromide highly increases the diarylamine yields.

1. Introduction

The palladium catalyzed amination of aryl halides has become an important method for the synthesis of arylamines found in pharmaceuticals,[1,2] materials with important electronic properties[3–5] and ligands for transition metals.[6]

During the past six years extensive research devoted to the development of palladium catalyzed carbon–nitrogen bond formation has led to efficient systems that offer considerable advantages over the classical methods (i.e. non-activated substrates can be used, and neither highly polar solvents nor severe reaction conditions are required).[7,8] The combination Pd/racemic BINAP is an excellent catalyst system for the coupling of primary amines with arylbromides.[9,10] Although a general protocol had been developed for the palladium catalyzed cross coupling of primary and secondary amines with aryl bromides using sodium *tert*-butoxide (*t*-BuONa),[9] this base presented problems with a number of common functional groups such as esters, aldehydes, enolizable ketones, nitriles and nitro groups. The scope of this method was further expanded by the use of caesium carbonate (Cs_2CO_3),[10] allowing the coupling of aryl bromides which were incompatible with *t*-BuONa. With this methodology it is also possible to synthesize primary arylamines from aryl bromides using benzophenone imine as an ammonia surrogate.[11]

Here we report the synthesis of diarylamines in the benzo[*b*]thiophene series bearing electron donating or withdrawing groups, by palladium catalyzed amination of aryl halides using $Pd(OAc)_2$, racemic BINAP as ligand and Cs_2CO_3 as base. The benzo[*b*]thiophenes are important heterocycles either as biological active molecules or as electronic or luminescent components used in organic materials.[12] In some cases triarylamines were also obtained as by-products in a small amount. The triarylamine moiety is also known by its important electronic properties, particularly for electron luminescent devices.[13]

The 6-aminobenzo[*b*]thiophenes coupling components were also prepared by C–N cross coupling of the corresponding bromo compounds with benzophenone imine followed by acidic hydrolysis of the imino derivatives.

2. Results and discussion

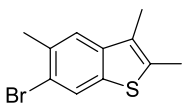
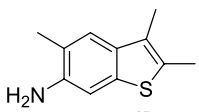
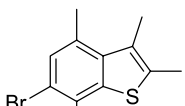
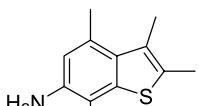
The regioselectively obtained 6-bromobenzo[*b*]thiophenes **1**[14] were coupled using two different catalytic systems, with benzophenone imine to give after hydrolysis of the imino derivatives, the corresponding 6-aminobenzo[*b*]thiophenes **2** (Table 1). As far as our knowledge this is the first time that aminobenzo[*b*]thiophenes were prepared using this methodology. Amine **2a** have already been prepared by us from

Keywords: Buchwald–Hartwig coupling; palladium; amination; diarylamines; benzo[*b*]thiophenes.

* Corresponding author. Tel.: +351-253604378; fax: +351-253678983; e-mail: mjrpq@quimica.uminho.pt

0040–4020/03/$ - see front matter
PII: S0040-4020(02)01656-3

Table 1. Synthesis and overall yields of 6-aminobenzo[*b*]thiophenes **2**

Bromo compound	Amine	Catalytic system	Time (h)	Yield (%)
 **1a**	 **2a**[15]	a	22	60
		b	16	50
 **1b**	 **2b**	a	20	50
		b	26	71

1.2 equiv. of $HN{=}C(Ph)_2$, dry toluene 100°C, Ar.
a—$Pd(OAc)_2$ (3 mol%), *rac*.BINAP (4 mol%), Cs_2CO_3 (1.4 equiv.).[11a]
b—$Pd_2(dba)_3$ (0.25 mol%), BINAP (0.75 mol%), CH_3ONa (1.4 equiv.).[11c]
The imino derivatives were hydrolyzed with HCl 2.0 M in THF at rt.

deprotection of the corresponding acetamide which was obtained by Beckmann rearrangement of the precursor oxime.[15]

Benzo[*b*]thiophenes **1** and **2** were coupled with anilines or phenylbromides bearing methoxy groups or different electron withdrawing groups to give diarylamines **4**–**8** in moderate to high yields using the same conditions (Table 2). Diarylamine **4a** has already been prepared by us in the same yield using *t*-BuONa as base.[15]

In the synthesis of diarylamines **5a** and **6a**, the corresponding triarylamines **5b** and **6b** were also isolated as by-products (Table 2). Increasing the amount of the aminobenzo[*b*]thiophene **2b** (1 to 1.2 equiv.) and decreasing the heating time (17 to 5 h), the diarylamine **6a** yield increased (40 to 51%) with the decrease of triarylamine **6b** yield (5 to 2%).

Despite we had previously concluded that for the synthesis of methoxylated diarylacetamides in this series by Goldberg coupling,[16] the amido group should be in the benzo[*b*]thiophene moiety, in this work the amino group may be in both systems to afford diarylamines in good yields.

Table 2. Synthesis of diarylamines **4**–**8**

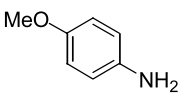
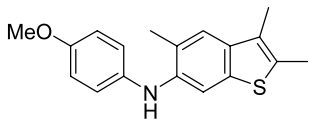
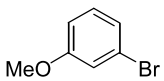
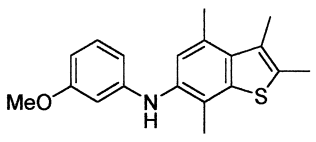
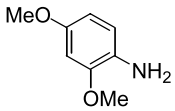
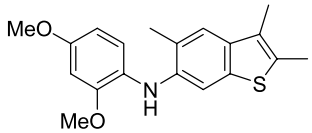
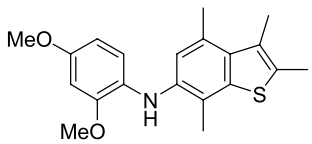
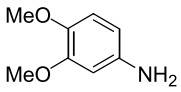
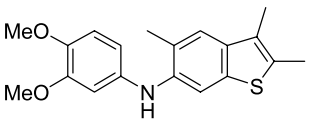
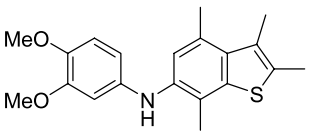
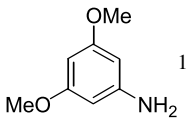
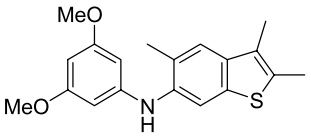
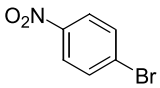
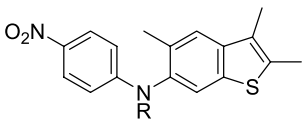
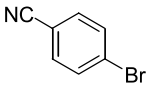
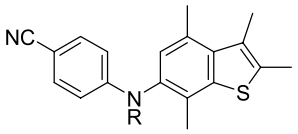
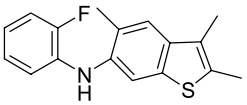
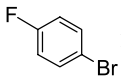
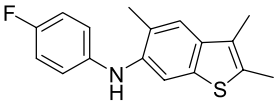
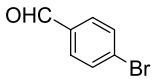
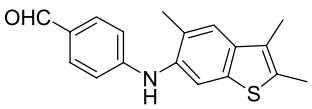
Aniline or Aryl bromide	Benzo[*b*]thiophene	Heating time (h)	Products and yields
	**1a**	21	 **4a**,[15] 60%
	**2b**	7	 **4b**, 50%
	**1a**	16	 **4c**, 71%
	1b	5	 **4d**, 55%

Table 2 (*continued*)

Aniline or Aryl bromide	Benzo[*b*]thiophene	Heating time (h)	Products and yields
	**1a**	17	 **4e,** 70%
	1b	17	 **4f**, 52%
 1.3 equiv.	**1a**	17	 **4g**, 80%
	**2a**	17	 **5a** R = H, 40% **5b** R = 4-$NO_2C_6H_4$, 12%
	**2b** 1.2 equiv.	5	 **6a** R = H, 51% **6b** R = 4-CNC_6H_4, 2%
 1.1 equiv.	**2a**	21	 **7a**, quantitative yield
 1.1 equiv.	**2a**	20	 **7b**, 90%
	**2a**	24	 **8**, 30%

Reaction conditions: $Pd(OAc)_2$ (3 mol%), *rac*.BINAP (4 mol%), Cs_2CO_3 (1.4 equiv.), dry toluene, 100°C, Ar. Control experiments were performed without catalyst and no diarylamines were formed.

3. Conclusion

With this work several diarylamines in the benzo[*b*]thiophene series bearing electron donating groups (1 or 2 OMe in different positions) or withdrawing groups (CN, NO_2, CHO and F) were prepared either from bromo or aminobenzo-[*b*]thiophenes. The use of Cs_2CO_3 proved to be general either in the synthesis of these compounds or in the synthesis of the primary benzo[*b*]thiophene amines, with no need of changing the catalytic system as some authors have claimed.[10a]

The diarylamines obtained can be very useful for several

applications (biological or in materials with electronic or luminescent properties) based also on the benzo[*b*]thiophene moiety properties and on the variety of substituents introduced. They can be cyclized to substituted thienocarbazoles, bioisosteres of natural anti-tumoral DNA intercalating compounds (methylated pyridocarbazoles), being the fluorodiarylamines, obtained in high yields, specially interesting for this purpose. The presence of a fluorine atom, useful for increasing the solubility of the molecules, is very important for biological applications.

4. Experimental

4.1. Materials and methods

Melting points (°C) were determined in a Gallenkamp apparatus and are uncorrected. IR spectra were recorded as nujol mulls on a Perkin–Elmer 1600-FTIR spectrophotometer and wavenumbers are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Plus (300 and 75,4 MHz respectively). $^1H-^1H$ spin–spin decoupling and DEPT θ 45° were used. Chemical shifts are given in ppm and coupling constants in Hz. The mass spectra were obtained by electronic impact in the mass spectrometry external service of the University of Vigo (Spain). Elemental analysis was performed on a LECO CHNS 932 elemental analyzer.

The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230–400 mesh. Preparative Layer Chromatography (PLC) was performed in 20×20 cm plates Macherey-Nagel, Layer 2 mm SIL G-200 UV_{254}. Petroleum ether refers to the boiling range 40–60°C. Ether refers to diethylether. When solvent gradient was used, the increase of polarity was made gradually from petroleum ether to mixtures of ether/petroleum ether increasing 10% of ether until the isolation of the product.

4.2. General procedure for the synthesis of 6-amino-benzo[*b*]thiophenes 2a, b by C–N coupling of compounds 1a or 1b with benzophenone imine and hydrolysis of the corresponding imino derivatives

Coupling with benzophenone imine: A dry Schlenk tube was charged, under Ar, with dry toluene (3–5 ml), the 6-bromo benzo[*b*]thiophenes **1a** or **1b** (0.500 g), benzophenone imine, the catalytic system (a) or (b) and the mixture was heated at 100°C for several hours (Table 1). After cooling, water and ether were added and the phases were separated. The aqueous phase was extracted with more ether and the organic extracts were collected, dried ($MgSO_4$) and filtered. Removal of the solvent gave the corresponding imine derivative as a yellow solid after some washes with MeOH to remove the excess of benzophenone imine and traces of toluene.

Hydrolysis of the imino derivatives:[11] To the imino derivative (~0.650 mol), THF (15 ml) and HCl 2 M (3 ml) were added and the mixture was stirred at room temperature for 15 min. HCl 0.5 M (10 ml) and hexane/ethyl acetate 2:1 (10 ml) were added. A precipitate came off and filtration gave a white solid. This solid was stirred with 20 ml of NaOH 30% and $CHCl_3$ was added. The phases were separated, the aqueous phase was extracted with $CHCl_3$ and the organic phases gave, after drying ($MgSO_4$), filtration and removal of the solvent the corresponding amines **2**.

4.2.1. 6-Amino-2,3,5-trimethylbenzo[*b*]thiophene (2a).[15] From bromo compound **1a** (1.96 mmol), using catalytic system (a) the corresponding imino derivative was obtained as a yellow solid (0.700 g, quantitative yield), mp 123–125. IR: 1663, 1611, 1592, 1571, 1488, 1461, 1445, 1377, 1314, 1287, 1246, 1229, 993, 958, 912, 866, 811, 784, 696. ^1H NMR: ($CDCl_3$) 2.23 (3H, s, Me), 2.34 (3H, s, Me), 2.40 (3H, s, Me), 6.78 (1H, s, H-7), 7.11–7.18 (2H, m, Ar-H), 7.22–7.29 (2H, m, Ar-H), 7.31 (1H, s, H-4), 7.41–7.53 (4H, m, Ar-H), 7.80–7.84 (2H, m, Ar-H). ^{13}C NMR: ($CDCl_3$) 11.36 (CH_3), 13.66 (CH_3), 18.75 (CH_3), 111.82, 121.85, 125.90 (C), 126.34 (C), 127.96, 128.12, 128.57, 128.86, 129.28, 130.54, 131.51 (C), 135.68 (C), 136.30 (C), 137.27 (C), 139.61 (C), 146.97 (C), 167.35 (C). MS *m/z*: 356 (25, M^++1), 355 (100, M^+), 298 (30), 278 (60) 263 (12) 86 (38) 84 (57). HRMS $C_{24}H_{21}NS$: calcd M^+ 355.139472; found M^+ 355.138947. This solid was submitted to hydrolysis following the general procedure and amine **2a** was obtained as a white solid (0.230 g, overall yield 60%), mp 96–98 [lit.,[15] 96–98]. ^1H NMR: ($CDCl_3$) 2.20 (3H, s, Me), 2.30 (3H, s, Me), 2.41 (3H, s, Me), 3.60 (2H, s, 2×N–H), 7.04 (1H, s, H-7), 7.26 (1H, s, H-7).

Using catalytic system (b) the overall yield for amine **2a** was 50%.

4.2.2. 6-Amino-2,3,4,7-tetramethylbenzo[*b*]thiophene (2b). From bromo compound **1b** (1.85 mmol) using catalytic system (b) the corresponding imino derivative was obtained as a yellow solid (0.690 g, quantitative yield) mp 145–147. IR: 1667, 1610, 1462, 1377, 1316, 1275, 1239, 1123, 1074, 956, 917, 867, 856, 787, 773, 750. ^1H NMR: ($CDCl_3$) 2.24 (3H, s, Me), 2.41 (3H, s, Me), 2.42 (3H, s, Me), 2.51 (3H, s, Me), 6.29 (1H, s, H-5) 7.05–7.14 (2H, m, Ar-H), 7.18–7.26 (2H, m, Ar-H), 7.35–7.50 (4H, m, Ar-H), 7.75–7.82 (2H, m, Ar-H). MS *m/z*: 370 (30, M^++1), 369 (100, M^+), 292 (40), 277 (20). HRMS $C_{25}H_{23}NS$: calcd M^+ 369.155122; found M^+ 369.153329. This solid was submitted to hydrolysis following the general procedure and amine **2b** was obtained as a white solid (0.270 g, overall yield 71%), mp 118–120. IR: 3407, 3328, 1615, 1593, 1573, 1484, 1461, 1377, 1328, 1264. ^1H NMR: ($CDCl_3$) 2.27 (3H, s, Me), 2.40 (3H, s, Me), 2.44 (3H, s, Me), 2.65 (3H, s, Me), 3.55 (2H, s, 2×N–H), 6.50 (1H, s, H-5). ^{13}C NMR: ($CDCl_3$) δ 13.83 (CH_3), 14.65 (CH_3), 15.20 (CH_3), 21.26 (CH_3), 112.03 (C), 117.03 (CH), 128.66 (C), 128.97 (C), 131.05 (C), 131.97 (C), 139.50 (C), 140.73 (C). Anal. Calcd for $C_{12}H_{15}NS$: C 70.20, H 7.36, N 6.82, S 15.61; found: C 70.16, H 7.26, N 6.75, S 15.58.

Using catalytic system (a) the amine **2b** was obtained in 50% overall yield.

4.3. General procedure for the synthesis of diarylamines bearing electron donating or withdrawing groups 4–8

A dry Schlenk tube was charged, under Ar, with dry toluene

(3–5 ml), the aniline or arylhalide, the benzo[*b*]thiophenes **1** or **2**, the catalytic system and the mixture was heated at 100°C for several hours (Table 2). The reaction was followed by TLC and stopped when no increase of the product seemed to occur. After cooling water and ether were added. The phases were separated, the aqueous phase was extracted with more ether and the organic phases collected, dried ($MgSO_4$) and filtered. Removal of the solvent gave an oil, after removal of traces of toluene with MeOH, which was submitted to column chromatography to give the product. In some cases triarylamines were also isolated as by-products.

4.3.1. 6-(4-Methoxyphenyl)amino-2,3,5-trimethylbenzo-[*b*]thiophene (4a).[15] From arylhalide **1a** (0.150 g, 0.590 mmol), 4-methoxyaniline (0.0720 g, 0.590 mmol) and using solvent gradient from neat petroleum ether to 10% ether/petroleum ether in the column chromatography compound **4a** was obtained as a white solid (0.105 g, 60%). Crystallization from ether/petroleum ether gave colorless crystals, mp 130–132 [lit.,[15] 130–132]. The spectroscopic properties were identical to those already described by us.

4.3.2. 6-(3-Methoxyphenyl)amino-2,3,4,7-tetramethyl-benzo[*b*]thiophene (4b). From amine **2b** (0.250 g, 1.20 mmol), 3-methoxybromobenzene (0.227 g, 1.20 mmol) and using solvent gradient from neat petroleum ether to 10% ether/petroleum ether in the column chromatography, compound **4b** was obtained as a white solid (0.189 g, 50%). Crystallization from ether/petroleum ether gave colorless crystals mp 162–164. IR: 3352 (N–H). ^{1}H NMR: ($CDCl_3$) 2.35 (3H, s, Me), 2.46 (3H, s, Me), 2.50 (3H, s, Me), 2.69 (3H, s, Me), 3.75 (3H, s, OMe), 5.42 (1H, s, N–H), 6.31–6.42 (3H, m, H-2′, 4′ and 6′), 6.99 (1H, s, H-5), 7.11 (1H, t, J=8 Hz, H-5′). ^{13}C NMR: ($CDCl_3$) 14.01 (CH_3), 15.18 (CH_3), 15.47 (CH_3), 21.32 (CH_3), 55.11 (OCH_3), 101.05, 104.31, 108.08, 122.40 (C), 123.63, 129.14 (C), 129.94, 131.07 (C), 131.79 (C), 134.74 (C), 135.75 (C), 140.33 (C), 147.37 (C), 160.73 (C). Anal. Calcd for $C_{19}H_{21}NOS$: C 73.28, H 6.80, N 4.50, S 10.29; found: C 73.04, H 6.62, N 4.58, S 10.25.

4.3.3. 6-(2,4-Dimethoxyphenyl)amino-2,3,5-trimethyl-benzo[*b*]thiophene (4c). From arylhalide **1a** (0.250 g, 0.980 mmol), 2,4-dimethoxyaniline (0.150 g, 0.980 mmol) and using solvent gradient from neat petroleum ether to 10% ether/petroleum ether in the column chromatography, compound **4c** was obtained as a white solid (0.227 g, 71%). Crystallization from ether/petroleum ether gave colorless crystals, mp 130–132. IR: 3387 (N–H). ^{1}H NMR: ($CDCl_3$) 2.26 (3H, s, Me), 2.39 (3H, s, Me), 2.43 (3H, s, Me), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 5.55 (1H, s, NH), 6.46 (1H, dd, J=8.7 and 3 Hz, H-5′), 6.57 (1H, d, J=3 Hz, H-3′), 7.05 (1H, d, J=8.7 Hz, H-6′), 7.38 (1H, s, H-7), 7.47 (1H, s, H-4). ^{13}C NMR: ($CDCl_3$) 11.37 (CH_3), 13.63 (CH_3), 18.34 (CH_3), 55.66 (2×OCH_3), 99.41, 103.77, 109.29, 118.24, 122.53, 124.92 (C), 126.31 (C), 126.90 (C), 130.57 (C), 135.41 (C), 136.66 (C), 139.62 (C), 150.44 (C), 154.53 (C). MS *m*/*z*: 328 (20, M^++1), 327 (100, M^+), 312 (40), 297 (20). HRMS $C_{19}H_{21}NO_2S$: calcd M^+ 327.129301; found M^+ 327.128560.

4.3.4. 6-(2,4-Dimethoxyphenyl)amino-2,3,4,7-tetramethyl-benzo[*b*]thiophene (4d). From arylhalide **1b** (0.160 g, 0.590 mmol), 2,4-dimethoxyaniline (0.0910 g, 0.590 mmol) and using solvent gradient from neat petroleum ether to 10% ether/petroleum ether in the column chromatography, compound **4d** was obtained as a white solid (0.111 g, 55%). Crystallization from ether/petroleum ether gave colorless crystals, mp 103–105. IR: 3407 (N–H). ^{1}H NMR: ($CDCl_3$) 2.35 (3H, s, Me), 2.45 (3H, s, Me), 2.48 (3H, s, Me), 2.67 (3H, s, Me), 3.79 (3H, s, OMe), 3.90 (3H, s, OMe), 5.50 (1H, s, NH), 6.37 (1H, dd, J=8.7 and 3 Hz, H-5′), 6.55 (1H, d, J=3 Hz, H-3′), 6.75 (1H, d, J=8.7 Hz, H-6′), 6.93 (1H, s, H-5). ^{13}C NMR: ($CDCl_3$) 13.97 (CH_3), 15.19 (CH_3), 15.32 (CH_3), 21.39 (CH_3), 55.63 (OCH_3), 55.72 (OCH_3), 99.32, 103.74, 115.17, 120.38 (C), 121.49, 128.88 (C), 129.07 (C), 130.82 (C), 130.88 (C), 134.61 (C), 136.40 (C), 140.45 (C), 149.19 (C), 153.54 (C). MS *m*/*z*: 342 (25, M^++1) 341 (100, M^+), 326 (23, M^+−15), 311 (19), 164 (95), 151 (20), 111 (64), 69 (38). Anal. Calcd for $C_{20}H_{23}NO_2S$: C 70.35, H 6.79, N 4.10, S 9.39; found: C 70.12, H 7.16, N 4.12, S 9.05.

4.3.5. 6-(3,4-Dimethoxyphenyl)amino-2,3,5-trimethyl-benzo[*b*]thiophene (4e). From arylhalide **1a** (0.150 g, 0.590 mmol), 3,4-dimethoxyaniline (0.0900 g, 0.590 mmol) and using solvent gradient from neat petroleum ether to 10% ether/petroleum ether in the column chromatography, compound **4e** was obtained as a white solid (0.135 g, 70%). Crystallization from ether/petroleum ether gave colorless crystals, mp 140–142. IR: 3380 (N–H). ^{1}H NMR: ([D_6]DMSO) 2.19 (3H, s, Me), 2.29 (3H, s, Me), 2.36 (3H, s, Me), 3.68 (6H, s, 2×OMe), 6.47 (1H, dd, J=8.4 and 2.4 Hz, H-6′), 6.65 (1H, d, J=2.4 Hz, H-2′), 6.83 (1H, d, J=8.4 Hz, H-5′), 7.08 (1H, s, H-7), 7.39 (2H, s, H-4 and N–H). ^{13}C NMR: ([D_6]DMSO) 11.21 (CH_3), 13.40 (CH_3), 18.47 (CH_3), 55.33 (OCH_3), 56.11 (OCH_3), 104.00, 109.45, 109.51, 113.28, 122.74, 125.52 (C), 126.24 (C), 129.97 (C), 134.88 (C), 135.84 (C), 138.53 (C), 140.26 (C), 142.91 (C), 149.55 (C). MS *m*/*z*: 328 (22, M^++1), 327 (100, M^+), 312 (62, M^+−15), 313 (14). Anal. Calcd for $C_{19}H_{21}NO_2S$: C 69.69, H 6.46, N 4.28, S 9.79; found: C 69.77, H 6.76, N 4.42, S 9.78.

4.3.6. 6-(3,4-Dimethoxyphenyl)amino-2,3,4,7-tetra-methylbenzo[*b*]thiophene (4f). From arylhalide **1b** (0.200 g, 0.740 mmol), 3,4-dimethoxyaniline (0.114 g, 0.740 mmol) and using solvent gradient from neat petroleum ether to 10% ether/petroleum ether in the column chromatography, compound **4f** was obtained as a white solid (0.132 g, 52%). Crystallization from ether/petroleum ether gave colorless crystals, mp 178–180. IR: 3358 (N–H). ^{1}H NMR: ([D_6]DMSO) 2.21 (3H, s, Me), 2.37 (3H, s, Me), 2.41 (3H, s, Me), 2.58 (3H, s, Me), 3.65 (3H, s, OMe), 3.66 (3H, s, OMe), 6.30 (1H, dd, J=8.6 and 2.5 Hz, H-6′), 6.53 (1H, d, J=2.5 Hz, H-2′), 6.77 (1H, d, J=8.6 Hz, H-5′), 6.87 (1H, s, H-5), 7.24 (1H, s, N–H). ^{13}C NMR: ([D_6]DMSO) 13.67 (CH_3), 14.91 (CH_3), 15.56 (CH_3), 21.02 (CH_3), 55.25 (OCH_3), 56.21 (OCH_3), 102.26, 107.34, 113.52, 118.77 (C), 120.63, 129.02 (C), 129.67 (C), 130.41 (C), 133.46 (C), 137.15 (C), 139.81 (C), 139.92 (C), 142.12 (C), 149.55 (C). MS *m*/*z*: 342 (24, M^++1), 341 (100, M^+), 326 (53, M^+−15). Anal. Calcd for $C_{20}H_{23}NO_2S$: C 70.35, H 6.79, N 4.10, S 9.39; found: C 69.95, H 6.73, N 4.10, S 9.02.

4.3.7. 6-(3,5-Dimethoxyphenyl)amino-2,3,5-trimethyl-benzo[*b*]thiophene (4g). From arylhalide **1a** (0.150 g,

0.590 mmol), 3,5-dimethoxyaniline (0.117 g, 0.760 mmol) and using solvent gradient from petroleum ether to 30% ether/petroleum ether in the column chromatography, compound **4g** was obtained as a white solid (0.155 g, 80%). Crystallization from ether/petroleum ether gave colorless crystals, mp 112–114. IR: 3385 (N–H). ^{1}H NMR: ($CDCl_3$) 2.28 (3H, s, Me), 2.37 (3H, s, Me), 2.46 (3H, s, Me), 3.75 (6H, s, 2×OMe), 5.40 (1H, s, N–H), 6.03–6.08 (3H, m, H-2′, 4′ and 6′), 7.42 (1H, s, H-7), 7.62 (1H, s, H-4). ^{13}C NMR: ($CDCl_3$) 11.37 (CH_3), 13.73 (CH_3), 18.42 (CH_3), 55.23 (2×OCH_3), 92.03, 94.75, 114.54, 122.70, 126.37 (C), 127.51 (C), 132.26 (C), 136.40 (C), 137.14 (C), 137.32 (C), 147.00 (C), 161.65 (C). MS *m/z*: 328 (25, M^++1), 327 (100, M^+). Anal. Calcd for $C_{19}H_{21}NO_2S$: C 69.69, H 6.46, N 4.28, S 9.79; found: C 69.43, H 6.59, N 4.36, S 9.48.

4.3.8. 6-(4-Nitrophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (5a) and 6-bis(4-nitrodiphenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (5b). From amine **2a** (0.170 g, 0.880 mmol) and 4-bromonitrobenzene (0.179 g, 0.880 mmol) and using solvent gradient from neat petroleum ether to 50% ether/petroleum ether in the column chromatography, compound **5a** was obtained as an orange solid (0.111 g, 40%). Crystallization from ether/petroleum ether gave orange crystals, mp 216–218. IR: 3354 (N–H). ^{1}H NMR: ($CDCl_3$) 2.31 (3H, s, Me), 2.35 (3H, s, Me), 2.50 (3H, s, Me), 6.08 (1H, s, N–H), 6.68 (2H, d, *J*=9.3 Hz, H-2′ and 6′), 7.50 (1H, s, H-7), 7.63 (1H, s, H-4), 8.09 (2H, d, *J*=9.3 Hz, H-3′ and 5′). ^{13}C NMR: ($CDCl_3$) 11.41 (CH_3), 13.88 (CH_3), 18.35 (CH_3), 112.74, 118.75, 123.15, 126.35, 126.56 (C), 130.10 (C), 133.73 (C), 134.57 (C), 136.40 (C), 139.13 (C), 139.79 (C), 151.85 (C). MS *m/z*: 313 (22, M^++1), 312 (100, M^+), 266 (15, M^+−46), 251 (20). HRMS $C_{17}H_{16}N_2O_2S$: calcd M^+ 312.093250; found 312.093531. It was also isolated a less polar product as a yellow solid which showed to be triarylamine **5b** (0.0460 g, 12%), mp 118–120. IR: 1596, 1580, 1493, 1462, 1377, 1339, 1299, 1280, 1178, 1150, 1109, 873, 843, 750, 739, 722, 699, 685, 514, 507. ^{1}H NMR: ($CDCl_3$) 2.14 (3H, s, Me), 2.33 (3H, s, Me), 2.52 (3H, s, Me), 7.11 (4H, d, *J*=9.3 Hz, H-2′, 2″, 6′ and 6″), 7.54 (1H, s, H-7 or 4), 7.56 (1H, s, H-4 or 7), 8.14 (4H, d, *J*=9.3 Hz, H-3′, 3″, 5′ and 5″). ^{13}C NMR: ($CDCl_3$) 11.41 (CH_3), 13.99 (CH_3), 18.51 (CH_3), 120.63, 122.95, 124.26, 125.57, 126.68 (C), 132.01 (C), 136.44 (C), 137.29 (C), 138.64 (C), 141.36 (C), 142.23 (C), 151.25 (C). MS *m/z*: 434 (27, M^++1), 433 (100, M^+). Anal. Calcd for $C_{23}H_{19}N_3O_4S$: C 63.73, H 4.42, N 9.69, S 7.40; found: C 63.40, H 4.89, N 9.34, S 7.97.

4.3.9. 6-(4-Cyanophenyl)amino-2,3,4,7-tetramethylbenzo[*b*]thiophene (6a) and 6-bis(4-cyanodiphenyl)amino-2,3,4,7-tetramethylbenzo[*b*]thiophene (6b). From amine **2b** (0.110 g, 0.530 mmol) and 4-bromobenzonitrile (0.0810 g, 0.440 mmol), heating for 5 h, and using solvent gradient from neat petroleum ether to 50% ether/petroleum ether in the column chromatography, compound **6a** was obtained as a white solid (0.0700 g, 51%). Crystallization from ether/petroleum ether gave colorless crystals, mp 230–232. IR: 3307 (N–H), 2216 (C≡N). ^{1}H NMR: ($CDCl_3$) 2.32 (3H, s, Me), 2.48 (3H, s, Me), 2.52 (3H, s, Me), 2.71 (3H, s, Me), 5.83 (1H, s, N–H), 6.65 (2H, d, *J*=9 Hz, H-2′ and 6′), 6.93 (1H, s, H-5), 7.43 (2H, d, *J*=9 Hz H-3′ and 5′). ^{13}C NMR: ($CDCl_3$) 14.12 (CH_3), 15.19 (CH_3), 15.53 (CH_3), 21.30 (CH_3), 100.06 (C≡N), 113.63, 120.21 (C), 124.85 (C), 125.25, 129.27 (C), 131.63 (C), 132.04 (C), 133.33 (C), 133.72, 137.36 (C), 140.34 (C), 150.17 (C). MS *m/z*: 307 (22, M^++1), 306 (100, M^+). HRMS $C_{19}H_{18}N_2S$: calcd M^+ 306.119071; found 306.118117. It was also isolated a less polar product as a white solid which showed to be triarylamine **6b** (3.00 mg, 2%), mp 283–285. IR: 2221 (C≡N). ^{1}H NMR: ($CDCl_3$) 2.12 (3H, s, Me), 2.50 (3H, s, Me), 2.53 (3H, s, Me), 2.70 (3H, s, Me), 6.79 (1H, s, H-5), 7.06 (4H, d, *J*=9 Hz, H-2′, 2″, 6′ and 6″), 7.51 (4H, d, *J*=9 Hz, H-3′, 3″, 5′ and 5″). ^{13}C NMR: ($CDCl_3$) 14.21 (CH_3), 15.17 (CH_3), 15.78 (CH_3), 21.31 (CH_3), 104.87 (C≡N), 119.09 (C), 121.04, 127.27 (C), 127.82, 129.43 (C), 133.03 (C), 133.50, 134.70 (C), 136.73 (C), 138.70 (C), 140.87 (C), 149.65 (C). MS *m/z*: 408 (30, M^++1), 407 (100, M^+). HRMS $C_{26}H_{21}N_3S$: calcd M^+ 407.145620; found 407.146061.

4.3.10. 6-(2-Fluorophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (7a). From amine **2a** (0.150 g, 0.785 mmol) and 2-bromofluorobenzene (0.1 ml, 0.915 mmol), compound **7a** was obtained as a brown solid (0.220 g, quantitative yield). Crystallization from ether/petroleum ether gave colorless crystals, mp 119–121. IR: 3383 (N–H). ^{1}H NMR: ($CDCl_3$) 2.29 (3H, s, Me), 2.40 (3H, s, Me), 2.48 (3H, s, Me), 5.60 (1H, s, N–H), 6.75–6.85 (1H, m, Ar-H), 6.94–7.02 (2H, m, Ar-H), 7.06–7.15 (1H, m, Ar-H), 7.45 (1H, s, H-7), 7.62 (1H, s, H-4). ^{13}C NMR: ($CDCl_3$) 11.38 (CH_3), 13.73 (CH_3), 18.29 (CH_3), 114.03 (CH), 115.18 (d, *J*=19 Hz, CH), 116.16 (d, *J*=2.3 Hz, CH), 119.33 (d, *J*=7.2 Hz, CH), 122.80 (CH), 124.34 (d, *J*=3.5 Hz, CH), 126.41 (C), 127.61 (C), 132.38 (C), 133.32 (d, *J*=11.2 Hz, C(F)*C*N), 136.42 (C), 136.48 (C), 137.48 (C), 152.44 (d, *J*=239.9 Hz, CF). MS *m/z*: 286 (20, M^++1), 285 (100, M^+), 284 (16, M^+−1), 270 (16, M^+−15). Anal. Calcd for $C_{17}H_{16}FNS$: C 71.55, H 5.65, N 4.91, S 11.23; found: C 71.34, H 6.00, N 5.01, S 10.98.

4.3.11. 6-(4-Fluorophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (7b). From amine **2a** (0.150 g, 0.785 mmol) and 4-bromofluorobenzene (0.12 ml, 0.942 mmol), compound **7b** was obtained as a light brown solid (0.200 g, 90%). Crystallization from ether/petroleum ether gave beige crystals, mp 159–160. IR: 3382 (N–H). ^{1}H NMR: ([D_6]DMSO) 2.21 (3H, s, Me), 2.28 (3H, s, Me), 2.38 (3H, s, Me), 6.84–6.90 (2H, m, Ar-H), 6.99–7.05 (2H, m, Ar-H), 7.37 (1H, s, N–H), 7.44 (1H, s, H-7 or H-4), 7.45 (1H, s, H-4 or H-7). ^{13}C NMR: ([D_6]DMSO) 11.15 (CH_3), 13.40 (CH_3), 18.37 (CH_3), 111.78 (CH), 115.58 (d, *J*=22.2 Hz, 2×CH), 117.79 (d, *J*=7.5 Hz, 2×CH), 122.84 (CH), 126.24 (C), 126.91 (C), 130.82 (C), 135.71 (C), 135.91 (C), 139.00 (C), 141.72 (d, *J*=1.96 Hz, C), 155.93 (d, *J*=234.6 Hz, CF). Anal. Calcd for $C_{17}H_{16}FNS$: C 71.55, H 5.65, N 4.91, S 11.23; found: C 71.55, H 5.80, N 5.00, S 11.25.

4.3.12. 6-(4-Formylphenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (8). From amine **2a** (0.0900 g, 0.470 mmol) and 4-bromobenzaldehyde (0.0870 g, 0.470 mmol) and after PLC 70% ether/petroleum ether (several elutions), compound **8** was obtained as a yellow solid (0.0410 g, 30%). Crystallization from ether/petroleum ether gave yellow crystals, mp 191–193. IR: 3321 (N–H), 1662 (C=O). ^{1}H NMR: ($CDCl_3$) 2.30 (3H, s, Me), 2.36 (3H, s,

Me), 2.49 (3H, s, Me), 5.94 (1H, s, N–H), 6.79 (2H, d, J=9 Hz, H-2′ and 6′), 7.49 (1H, s, H-7), 7.66 (1H, s, H-4), 7.72 (2H, d, J=9 Hz, H-3′ and 5′), 9.78 (1H, s, CHO). ^{13}C NMR: ($CDCl_3$) 11.39 (CH_3), 13.84 (CH_3), 18.37 (CH_3), 113.59, 118.14, 123.01, 126.52 (C), 127.81 (C), 129.80 (C), 132.22, 134.06 (C), 134.36 (C), 136.33 (C), 139.30 (C), 151.55 (C), 190.33 (C=O). MS *m/z*: 296 (20, M^++1), 295 (100, M^+), 280 (15, M^+−15). HRMS $C_{18}H_{17}NOS$: calcd M^+ 295.103086; found 295.103345.

Acknowledgements

Thanks are due to Foundation for the Science and Technology-IBQF-Univ. Minho (Portugal) for financial support, to the Research Incitement Programme of the Calouste Gulbenkian Foundation (Portugal) and to Escola Superior Agrária-Instituto Politécnico de Bragança for supporting in part Isabel C. F. R. Ferreira's PhD.

References

1. Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028–1030.
2. Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1505–1510.
3. (a) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213–214. (b) Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 4960–4966. (c) Zhang, X.-X.; Sadighi, J. P.; Mackewitz, T. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7606–7607.
4. (a) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527–7539. (b) Goodson, F. E.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 1700–1703. (c) Hauck, S. I.; Lakshmi, K. V.; Hartwig, J. F. *Org. Lett.* **1999**, *1*, 2057–2060.
5. (a) Bellmann, E.; Shaheen, S. E.; Thayumanavan, S.; Barlow, S.; Grubs, R. H.; Marder, S. R.; Kippelen, B.; Peyghambarian, N. *Chem. Mater.* **1998**, *10*, 1668–1676. (b) Thayumanavan, S.; Barlow, S.; Marder, S. R. *Chem. Mater.* **1997**, *9*, 3231–3235. (c) Kanbara, T.; Miyazaki, Y.; Hasegawa, K.; Yamamoto, T. *J. Polym. Sci. Part A: Polym. Chem.* **2000**, *38*, 4194–4199.
6. Greco, G. E.; Popa, A. I.; Schrock, R. R. *Organometallics*, **1998**, *17*, 5591–5593.
7. (a) Hartwig, J. F. *Synlett.* **1997**, 329–340. (b) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067.
8. (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
9. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
10. (a) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
11. (a) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367–6370. (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828. (c) Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repic, O.; Blacklock, T. J. *J. Org. Chem.* **2000**, *65*, 2612–2614.
12. (a) Campaigne, E. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp 863–934. (b) Ronald, K. R.; Jefery, B. P. *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 679–729.
13. Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327–5333.
14. Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *J. Heterocycl. Chem.* **2001**, *38*, 749–754.
15. Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2002**, *58*(39), 7943–7949.
16. Peixoto, F. M. C.; Queiroz, M.-J. R. P.; Kirsch, G. *J. Chem. Res. (S)* **1998**, 172–173, *J. Chem. Res. (M)*, 0801–0812.