

Synthesis and antimicrobial activity studies of *ortho*-chlorodiarylamines and heteroaromatic tetracyclic systems in the benzo[*b*]thiophene series

Maria-João R. P. Queiroz,^{a,*} Isabel C. F. R. Ferreira,^b Yannick De Gaetano,^{a,c} Gilbert Kirsch,^c Ricardo C. Calhelha^b and Leticia M. Estevinho^b

^aDepartamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

^bEscola Superior Agrária—Instituto Politécnico de Bragança, Campus de Sta Apolónia, 5301-855 Bragança, Portugal

^cLaboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Faculté des Sciences, Université de Metz, 1, bd Arago Metz Technopole, 57078 Metz Cedex 3, France

Received 10 March 2006; revised 19 June 2006; accepted 20 June 2006

Available online 14 July 2006

Abstract—*ortho*-Chlorodiarylamines in the 2,3,7-trimethylbenzo[*b*]thiophene series were prepared in high yields (70–85%) by C–N palladium-catalyzed cross-coupling using P(*t*-Bu)₃ as ligand and NaOt-Bu as base. A palladium-assisted C–C intramolecular cyclization of the coupling products gave thienocarbazoles and the dechlorinated diarylamines. Studies of antimicrobial activity of the compounds obtained, against representative species of bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus cereus* and *Bacillus subtilis*) and fungi (*Candida albicans*), were performed. We have also included in the biological assays some pyridine derivatives previously prepared by us, and it was possible to establish some structure–activity relationships (SARs).

© 2006 Elsevier Ltd. All rights reserved.

1. Introduction

In recent years we have been interested in palladium-catalyzed C–N cross-couplings in the benzo[*b*]thiophene series.^{1,2} We reported some general conditions to obtain diarylamines functionalizing the benzene ring of the benzo[*b*]thiophene system with arenes bearing electron-donating or -withdrawing groups.^{1b} The antimicrobial activity of diarylamines derivatives of 2,3,5-trimethylbenzo[*b*]thiophene was already studied by us.³

For the synthesis of *ortho*-bromodiarylamines in the benzo[*b*]thiophene series we have established different conditions for the functionalization of the benzene or the thiophene ring. The latter diarylamines were obtained in moderate to good yields and gave the corresponding tetracyclic thienocarbazoles and indo-

lobenzo[*b*]thiophenes using a palladium-assisted intramolecular cyclization.^{1c}

Bedford and Cazin described the synthesis of *ortho*-chlorodiphenylamines in high yields by C–N palladium-catalyzed cross-coupling of halobenzenes with *ortho*-chloroanilines using P(*t*-Bu)₃ as ligand and NaOt-Bu as base.⁴

In this work, we describe the synthesis of *ortho*-chlorodiaryamine derivatives of 2,3,7-trimethylbenzo[*b*]thiophene in high yields, using Bedford's conditions and the palladium-assisted C–C intramolecular cyclization to thienocarbazoles. Using the same type of reactions we have already reported the synthesis of an *ortho*-chlorodiheteroaryamine from 3-bromo-2-chloropyridine and 6-amino-2,3,7-trimethylbenzo[*b*]thiophene and its cyclization to the first thieno- δ -carboline.⁵ The latter compound has already shown antiproliferative activity upon photoactivation, in leukaemia and in solid tumour cell lines.⁶

Herein we report studies of the antimicrobial activity of the compounds prepared including also the pyridine

Keywords: Benzothiophenes; *ortho*-Chlorodiarylamines; Palladium; Thienocarbazoles; Thienocarboline; Antimicrobial activity.

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

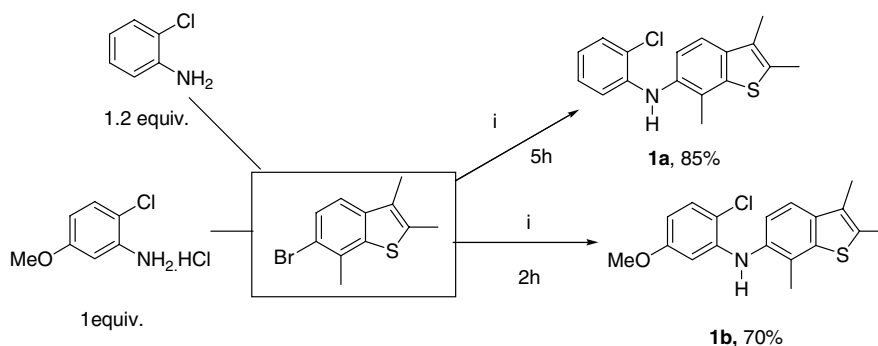
derivatives previously prepared by us, in order to establish some structure–activity relationships (SARs).

2. Results and discussion

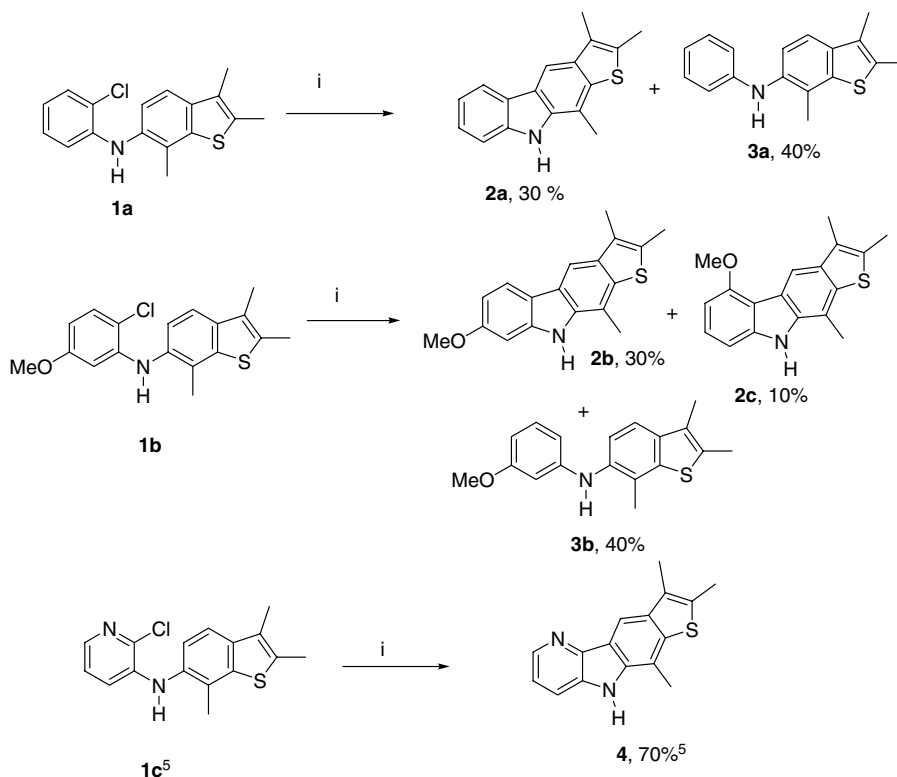
2.1. Synthesis

The *ortho*-chlorodiarylamines **1a** and **1b** were prepared in high yields, by palladium-catalyzed C–N cross-coupling⁷ of the 6-bromo-2,3,7-trimethylbenzo[*b*]thiophene⁸ with *ortho*-chloroanilines, using Bedford's conditions⁴ (Scheme 1).

The diarylamines **1a** and **1b** were cyclized to the corresponding thienocarbazoles using a palladium-assisted C–C intramolecular cyclization (Scheme 2) applying the Maes conditions⁹ that had been used in the cyclization of 3-chloro-2-(4-pyridinylamino)pyridine, needing in our case a bigger amount of Pd(OAc)₂. This reaction can be seen as an intramolecular C–H activation by a Pd(II) complex, resulting of oxidative addition of compounds **1** to Pd(0), presumably by an electrophilic displacement mechanism, to give a six-membered pallacycle which subsequently yields the thienocarbazoles **2** by reductive elimination, as suggested for the synthesis of carbazoles from *ortho*-chlorodiphenylamines.⁴



Scheme 1. Synthesis of *ortho*-chlorodiarylamines in the 2,3,7-trimethylbenzo[*b*]thiophene series. Reagents and condition: (i) Pd(OAc)₂ (5 mol%), P(*t*-Bu)₃ (7 mol%), NaOt-Bu (5 equiv), dry toluene, 105 °C, Ar.



Scheme 2. Intramolecular cyclization to thienocarbazoles **2** and thienocarboline **4**. Reagents and condition: (i) Pd(OAc)₂ (40 mol%), P(*t*-Bu)₃ (30 mol%), K₃PO₄ (10 equiv), dry dioxane, 120 °C, 20 h, Ar.

In the synthesis of thienocarbazoles **2**, the dechlorinated diarylamines **3a** and **3b** were obtained as major products and the starting *ortho*-chlorodiarylamines were also isolated. In the cyclization of **1b**, two thienocarbazoles **2b** and **2c** were formed (Scheme 2). The latter can be the result of the electrophilic attack of Pd(OAc)₂ on the aromatic rings of **3b** with extrusion of Pd(0).^{1a}

As already reported by us the cyclization of the *ortho*-chlorodiaryllamine **1c** gave the thienocarboline **4** in high yield by the same method (Scheme 2).⁵

2.2. In vitro antimicrobial activity evaluation

An evaluation of the antibacterial activity using two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram-positive bacteria (*Bacillus subtilis* and *Bacillus cereus*) and the antifungal activity using *Candida albicans* as a representative species of fungi was assessed for compounds **1a–c**, **2a,b**, **3b** and **4**. The minimal inhibitory concentration (MIC in µg/mL) was determined using an adaptation of agar streak dilution method based on radial diffusion.^{10,11} In the same conditions different concentrated solutions of ampicillin (antibacterial) and cycloheximide (antifungal) were used as standards. The MIC was considered to be the lowest concentration of the tested compound which inhibits growth of bacteria or fungi on the plate. The diameters of the inhibition zones corresponding to the MICs are presented in Table 1. The compounds tested are not active against *Pseudomonas aeruginosa* starting from DMSO solutions of 1000 µg/mL of each compound.

From the analysis of Table 1 it is possible to establish some SARs. The only active compound against *E. coli* in the concentrations tested is the *ortho*-chlorodiaryllamine **1b** (MIC 12.5 µg/mL), the methoxy group being the responsible for the activity. Against Gram + bacteria the MICs for **1b** are much lower than those for **1a**. Comparing **1b** with **1c** (the pyridine derivative) the latter shows to be more active against *B. cereus* (MIC 3.13 µg/mL) but less active against *B. subtilis*. Against *C. albicans* **1b** and **1c** present the same MIC (25 µg/mL) which is lower than the MIC obtained for **1a** (50 µg/mL).

Comparing **1b** with the corresponding dechlorinated diaryllamine **3b**, the MICs for the latter are much more

lower for *B. cereus* and for *C. albicans* (0.05 µg/mL) and even lower than those for ampicillin and cycloheximide.

Among the cyclized products **2a** and **2b**, the methoxylated thienocarbazole **2b** presents the lower MICs. The thieno- δ -carboline **4** presents better results than the corresponding thienocarbazole **2a** for *B. cereus* and *C. albicans* and the same MIC for *B. subtilis* which is lower than the MIC for ampicillin.

3. Conclusion

ortho-Chlorodiarylamines in the 2,3,7-trimethylbenzo[b]thiophene series were prepared in high yields by palladium-catalyzed C–N cross-coupling. A palladium-assisted C–C intramolecular cyclization gave the corresponding thienocarbazoles in low to moderate yields, and the dechlorinated diarylamines as major products. Studies of antimicrobial activity were performed using the synthesized compounds and including a thieno- δ -carboline and its *ortho*-chlorodiaryllamine precursor, previously prepared by us. Some structure–activity relationships were established and the importance of the methoxylated compounds is pointed out (very low MICs). The thienocarboline showed lower MICs for *B. cereus* and for *C. albicans* than the corresponding thienocarbazole but for *B. subtilis* both present the same MIC.

4. Experimental

4.1. Materials and methods

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The ¹H NMR spectra were measured on a Varian Unity Plus at 300 MHz. Spin–spin decoupling was used to assign the signals. The ¹³C NMR spectra were measured in the same instrument at 75.4 MHz (using DEPT θ 45°).

Elemental analyses were determined on a LECO CHNS 932 elemental analyser. Mass spectra (EI) and HRMS were made by the mass spectrometry service of University of Vigo-Spain.

Table 1. Antimicrobial activity of compounds **1a–c**, **2a,b**, **3b** and **4**

Compounds	MIC in µg/mL (zone of inhibition in mm)			
	<i>E. coli</i> CECT 101	<i>B. cereus</i> CECT148	<i>B. subtilis</i> CECT498	<i>C. albicans</i> CECT 1394
1a	Not active ^a	25 (8)	50 (6)	50 (11)
1b	12.5 (6)	6.25 (8)	6.25 (5)	25 (5)
1c	Not active ^a	3.13 (7)	25 (7)	25 (8)
3b	Not active ^a	0.05 (9)	6.25 (12)	0.05 (9)
2a	Not active ^a	25 (15)	3.13 (8)	100 (10)
2b	Not active ^a	0.5 (9)	0.05 (13)	0.05 (10)
4	Not active ^a	6.25 (15)	3.13 (10)	25 (8)
Ampicillin	6.25 (15)	3.13 (13)	12.5 (10)	—
Cycloheximide	—	—	—	12.5 (5)

CECT-Spanish type culture collection of Valencia University.

^a Not active starting from 1000 µg/mL.

Column chromatography was performed on Macherey–Nagel silica gel 230–400 mesh. Petroleum ether refers to the boiling range 40–60 °C. Ether refers to diethyl ether. When solvent gradient was used, the increase of polarity was done gradually from neat petroleum ether to mixtures of ether/petroleum ether increasing 10% of ether until the isolation of the product. Preparative layer chromatography (PLC) was performed in 20 × 20 cm² plates Macherey–Nagel silica plates layer 2 mm SIL G-200 UV₂₅₄. P(*t*-Bu)₃ was purchased from Strem as an hexane solution.

For the in vitro antimicrobial activity, suspensions of the microorganism were prepared to contain approximately 10⁸ cfu/mL and the plates were inoculated. A stock solution of the synthesized compound (1000 µg/mL) in DMSO was prepared and graded dilutions of the tested compounds were incorporated in a cavity (depth 3 mm, diameter 4 mm) made in the center of the petridish (nutrient agar for antibacterial activity and Sabouraud vs dextrose agar medium for antifungal activity). The plates were incubated at 37 °C (for bacteria) and at 30 °C (for fungi) for 24 h in duplicate. Positive control using only inoculation and negative control using only DMSO in the cavity were carried out.

4.2. General procedure for the synthesis of *ortho*-chlorodiarylamines **1a** and **1b**

In a dry *Schlenk* tube it was poured under Ar with stirring, dry toluene (3–5 mL) 6-bromo-2,3,7-trimethylbenzo[*b*]thiophene, Pd(OAc)₂ (5 mol %), P(*t*-Bu)₃ (7 mol %), NaOt-Bu (5 equiv) and the amine (2-chloroaniline or 2-chloro-*m*-anisidine hydrochloride). The mixture was heated under Ar for some hours at 105 °C (following by TLC). After cooling, water and ether were added and the phases were separated. The organic phase was dried (MgSO₄), filtered and removal of the solvent under reduced pressure gave an oil (residues of toluene were removed with methanol) which was submitted to column chromatography using 10% ether/petroleum ether as eluent, to give the *ortho*-chlorodiarylamines.

4.2.1. 6-(2-Chlorophenyl)amino-2,3,7-trimethylbenzo[*b*]thiophene (1a). From 6-bromo-2,3,7-benzo[*b*]thiophene (150 mg, 0.590 mmol) and 2-chloroaniline (81.0 mg, 0.640 mmol) and heating for 5 h compound **1a** was obtained as a colourless solid (152 mg, 85%). Crystallization from ether/petroleum ether gave colourless crystals, mp 124–126 °C. ¹H NMR (CDCl₃): 2.31 (3H, s, CH₃), 2.41 (3H, s, CH₃), 2.51 (3H, s, CH₃), 5.97 (1H, s, N–H), 6.63 (1H, dd, *J* = 8.1 and 1.5 Hz, H-6'), 6.72 (1H, td, *J* = 8.1 and 1.5 Hz, H-4'), 7.03 (1H, td, *J* = 8.1 and 1.5 Hz, H-5'), 7.27 (1H, d *J* = 8.4 Hz, ArH), 7.35 (1H, dd, *J* = 8.1 and 1.5 Hz, H-3'), 7.45 (1H, d, *J* = 8.4 Hz, ArH) ppm. ¹³C NMR (CDCl₃): 11.48 (CH₃), 13.86 (CH₃), 15.96 (CH₃), 113.70 (CH), 118.69 (CH), 119.38 (CH), 119.59 (C), 122.57 (CH), 126.80 (C), 127.48 (CH), 127.73 (C), 129.34 (CH), 133.27 (C), 134.24 (C), 138.42 (C), 139.75 (C), 142.58 (C) ppm. Anal. Calcd for C₁₇H₁₆ClNS: C, 67.65; H, 5.34; N, 4.64; S, 10.62. Found: C, 67.46; H, 5.52; N, 4.78; S, 10.63.

4.2.2. 6-(2-Chloro-5-methoxyphenyl)amino-2,3,7-trimethylbenzo[*b*]thiophene (1b). From 6-bromo-2,3,7-benzo[*b*]thiophene (150 mg, 0.590 mmol) and 2-chloro-*m*-anisidine hydrochloride (115 mg, 0.590 mmol) and heating for 2 h, compound **1b** was isolated as a colourless solid (135 mg, 70%). Crystallization from ether/petroleum ether gave colourless crystals, mp 152–154 °C. ¹H NMR (CDCl₃): 2.32 (3H, s, ArCH₃), 2.42 (3H, s, ArCH₃), 2.52 (3H, s, ArCH₃), 3.65 (3H, s, OCH₃), 5.95 (1H, br s, N–H), 6.20 (1H, d, *J* = 3 Hz, H-6'), 6.29 (1H, dd, *J* = 8.7 and 3 Hz, H-4'), 7.24 (1H, d, *J* = 8.7 Hz, H-3'), 7.28 (1H, d, *J* = 8.4 Hz, ArH), 7.45 (1H, d, *J* = 8.4 Hz, ArH) ppm. ¹³C NMR: 11.45 (CH₃), 13.84 (CH₃), 15.95 (CH₃), 55.32 (OCH₃), 99.77 (CH), 103.97 (CH), 111.58 (C), 119.42 (CH), 122.75 (CH), 126.95 (C), 127.73 (C), 129.59 (CH), 133.35 (C), 134.03 (C), 138.55 (C), 139.78 (C), 143.45 (C), 159.35 (C) ppm. MS *m/z* (%): 334 (8), 333 (M⁺ ³⁷Cl, 38), 332 (22) 331 (M⁺ ³⁵Cl, 100). Anal. Calcd for C₁₈H₁₈ClNOS: C, 65.15; H, 5.47; N, 4.22; S, 9.66. Found: C, 64.97; H, 5.58; N, 4.33; S, 9.65.

4.3. General procedure for the synthesis of thienocarbazoles **2**

In a dry *Schlenk* tube it was poured under Ar with stirring, dry dioxane (6–8 mL), Pd(OAc)₂ (40 mol %), P(*t*-Bu)₃ (30 mol %), the *ortho*-chlorodiarylamines **1a** or **1b** and finely ground K₃PO₄ (10 equiv). The mixture was heated under Ar for 20 h at 120 °C. After cooling ethyl acetate was added and the mixture was filtered. Removal of solvents gave an oil which was submitted to PLC (several elutions) to give thienocarbazoles **2** and the diarylamines **3**. The starting materials were also isolated as the less polar products.

4.3.1. 2,3,10-Trimethyl-9H-thieno[2,3-*b*]carbazole (2a) and 6-(phenyl)amino-2,3,7-trimethylbenzo[*b*]thiophene (3a). From compound **1a** (70.0 mg, 0.233 mmol) and PLC (25% ether/petroleum ether), diarylamine **3a** was isolated as a white solid (25.0 mg, 40%), mp 133–135 °C. ¹H NMR (CDCl₃): 2.29 (3H, s, CH₃), 2.41 (3H, s, CH₃), 2.49 (3H, s, CH₃), 5.48 (1H, s, NH), 6.79–6.86 (3H, m, ArH), 7.18–7.29 (3H, m, ArH), 7.41 (1H, d, *J* = 8.4 Hz, ArH). ¹³C NMR (CDCl₃): 11.45 (CH₃), 13.80 (CH₃), 15.97 (CH₃), 115.41 (2 × CH), 119.21 (CH), 119.24 (CH), 120.51 (CH), 124.50 (C), 127.69 (C), 129.23 (2 × CH), 132.34 (C), 135.80 (C), 137.34 (C), 139.90 (C), 145.78 (C) ppm. Anal. Calcd for C₁₇H₁₇NS: C, 76.36; H, 6.41; N, 5.24; S, 11.99. Found: C, 76.56; H, 6.23; N, 4.89; S, 11.72. Thienocarbazole **2a** was obtained as a white solid (18.5 mg, 30%), mp 210–211 °C. ¹H NMR (CDCl₃): 2.42 (3H, s, CH₃), 2.54 (3H, s, CH₃), 2.70 (3H, s, CH₃), 7.23–7.29 (1H, m, Ar–H), 7.40–7.46 (2H, m, Ar–H), 7.86 (1H, s, NH), 8.11–8.16 (2H, m, Ar–H) ppm. ¹³C NMR (CDCl₃): 11.80 (CH₃), 14.01 (CH₃), 15.17 (CH₃), 109.69 (CH), 110.51 (CH), 111.59 (C), 119.23 (CH), 120.24 (CH), 122.24 (C), 124.20 (C), 125.70 (CH), 127.46 (C), 130.19 (C), 135.16 (C), 136.61 (C), 136.87 (C), 140.33 (C) ppm. MS *m/z* (%): 267 (M⁺+2, 6), 266 (M⁺+1, 20), 265 (M⁺, 100), 250 (19); calcd for C₁₇H₁₅NS: 265.0925. Found M⁺: 265.0917.

4.3.2. 7-Methoxy-2,3,10-trimethyl-9H-thieno[2,3-*b*]carbazole (2b), 5-methoxy-2,3,10-trimethyl-9H-thieno[2,3-*b*]carbazole (2c) and 6-(3-methoxyphenyl)amino-2,3,7-trimethylbenzo[*b*]thiophene (3b). From compound **1b** (50.0 mg, 0.151 mmol) and PLC (35% ether/petroleum ether), diarylamine **3b** was isolated as a white solid (18.0 mg, 40%), mp 103–105 °C. ^1H NMR (CDCl_3): 2.30 (3H, s, Ar-CH₃), 2.41 (3H, s, Ar-CH₃), 2.50 (3H, s, Ar-CH₃), 3.75 (3H, s, OCH₃), 5.48 (1H, br s, NH), 6.34–6.42 (3H, m, ArH), 7.12 (1H, t, $J = 8$ Hz, H-5'), 7.28 (1H, d, $J = 8.4$ Hz, ArH), 7.41 (1H, d, $J = 8.4$ Hz, ArH). ^{13}C NMR (CDCl_3): 11.44 (CH₃), 13.80 (CH₃), 15.97 (CH₃), 55.12 (OCH₃), 101.06 (CH), 104.44 (CH), 108.10 (CH), 119.22 (CH), 121.07 (CH), 124.96 (C), 127.69 (C), 129.98 (CH), 132.51 (C), 135.51 (C), 137.55 (C), 139.80 (C), 147.35 (C), 160.77 (C). MS m/z (%): 299 ($\text{M}^+ + 2$, 7), 298 ($\text{M}^+ + 1$, 21), 297 (M^+ , 100). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NOS}$: C, 72.69; H, 6.44; N, 4.71; S, 10.78. Found: C, 72.49; H, 6.38; N, 4.89; S, 10.54.

Thienocarbazole **2c** was isolated as a white solid (4.50 mg, 10%), mp 214–216 °C. ^1H NMR (CDCl_3): 2.44 (3H, s, ArCH₃), 2.54 (3H, s, ArCH₃), 2.69 (3H, s, ArCH₃), 4.15 (3H, s, OCH₃), 6.72 (1H, d, $J = 7.9$ Hz, ArH), 7.07 (1H, d, $J = 7.9$ Hz, ArH), 7.36 (1H, t, $J = 7.9$ Hz, H-7), 7.89 (1H, s, NH), 8.35 (1H, s, H-4). MS m/z (%): 297 ($\text{M}^+ + 2$, 10), 296 ($\text{M}^+ + 1$, 16), 295 (M^+ , 70). HRMS $\text{C}_{18}\text{H}_{17}\text{NOS}$: calcd M^+ 295.1031; found 295.1034.

Thienocarbazole **2b** was isolated as the most polar product, as a white solid (13.5 mg, 30%), mp 190–192 °C. ^1H NMR (CDCl_3): 2.41 (3H, s, ArCH₃), 2.53 (3H, s, ArCH₃), 2.66 (3H, s, ArCH₃), 3.93 (3H, s, OCH₃), 6.86 (1H, dd, $J = 8.6$ and 2.1 Hz, H-6), 6.96 (1H, d, $J = 2.1$ Hz, H-8), 7.79 (1H, br s, NH), 7.98–8.01 (2H, d overlapped with a s, H-4 and H-5). ^{13}C NMR (CDCl_3): 11.82 (CH₃), 14.01 (CH₃), 15.14 (CH₃), 55.63 (OCH₃), 95.03 (CH), 107.53 (CH), 108.91 (CH), 111.42 (C), 114.48 (C), 118.04 (C), 120.95 (CH), 122.42 (C), 127.46 (C), 130.10 (C), 135.22 (C), 136.70 (C), 141.65 (C), 159.00 (C). MS m/z (%): 297 ($\text{M}^+ + 2$, 7), 296 ($\text{M}^+ + 1$, 22), 295 (M^+ , 100). HRMS $\text{C}_{18}\text{H}_{17}\text{NOS}$: calcd M^+ 295.1031; found 295.1035.

Acknowledgments

The authors thank the Foundation for the Science and Technology (Portugal) for financial support to Centro de Química—Univ. Minho, CIMO-ESA-IPBragança. Programme Sócrates-Erasmus (Univ. Metz → Univ. Minho) for financial support of Yannick De Gaetano in Portugal.

References and notes

- (a) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2002**, *58*, 7943–7947; (b) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 975–981; (c) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 3737–3743.
- Queiroz, M.-J. R. P.; Begouin, A.; Ferreira, I. C. F. R.; Kirsch, G.; Calhelha, R. C.; Barbosa, S.; Estevinho, L. M. *Eur. J. Org. Chem.* **2004**, 3679–3685.
- Ferreira, I. C. F. R.; Calhelha, R. C.; Estevinho, L. M.; Queiroz, M.-J. R. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5831–5833.
- Bedford, R.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310–2311, and cited references.
- Queiroz, M.-J. R. P.; Castanheira, E. M. S.; Pinto, A. M. R.; Ferreira, I. C. F. R.; Begouin, A.; Kirsch, G. *J. Photochem. Photobiol. A: Chem.* **2006**, *181*, 290–296.
- Viola, G.; Salvador, A.; Vedaldi, D.; Fortunato, E.; Darsò, S.; Basso, G.; Queiroz, M.-J. R. P. *J. Photochem. Photobiol. B: Biol.* **2006**, *82*, 105–116.
- For reviews on palladium-catalyzed C–N cross-couplings see (a) Hartwig, J. F. *Synlett* **1997**, 329–340; (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146; (c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209.
- (a) Cagniant, P.; Faller, P.; Cagniant, D. *Bull. Soc. Chim. France* **1966**, 3055–3065; (b) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *J. Heterocycl. Chem.* **2001**, *38*, 749–754.
- Jonckers, T. H. M.; Maes, B. U. W.; Lemièrre, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Domisse, R. A. *Synlett* **2003**, 615–618.
- Hawkey, P. M.; Lewis, D. A. *Medical Bacteriology—A Practical Approach*; Oxford University Press: UK, 1994, pp 181–194.
- Rameshkumar, N.; Ashokkumar, M.; Subramanian, E. H.; Ilavarasan, R.; Sridhar, S. K. *Eur. J. Med. Chem.* **2003**, *38*, 1001–1004.