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Palladium-catalyzed amination and cyclization to heteroannellated indoles and carbazoles

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Abstract—New *ortho*-bromodiarylamines in the benzo[*b*]thiophene series were prepared by palladium-catalyzed amination, either in the benzene or in the thiophene ring. These were submitted to palladium-catalyzed cyclization, under different required conditions, to give several differently substituted thieno[3,2-*c*] or [2,3-*b*]carbazoles and indolo[3,2-*b*]benzo[*b*]thiophenes. This constitutes a novel synthetic route to both tetracyclic systems. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Heteroannellated indole and carbazole alkaloids constitute an important class of natural compounds due to their biological activities mostly based on their special affinity toward DNA.[1] Therefore, these compounds play a crucial role as potential leads for the discovery of antitumor active drugs using bioisosteric replacements.[2] The use of classical isosteres as benzene, thiophene and pyridine resulted in analogues with biological activity retention among different series of pharmacological agents with changes in selectivity, toxicity and metabolic stability. However there are many examples where this methodology has resulted in the preparation of molecules with marked increases in potency as well as efficacy.[3] With this in mind, recently we have studied several convergent ring B routes for the synthesis of methylated thienocarbazoles, bioisosteres of pyridocarbazoles (ellipticines and olivacines), from precursors obtained either by C–C[4] or C–N[5] palladium or copper catalyzed cross couplings followed by intramolecular cyclizations. In particular, using the Sakamoto's palladium-catalyzed cyclization conditions, described for the convergent ring B synthesis of carbazoles and carbolines from *ortho*-bromodiarylamine precursors,[6] we were not able to obtain the corresponding thienocarbazole from an *ortho*-bromodiarylamine. Under the same conditions this was possible from the *ortho*-bromodiarylacetamide occurring cyclization with *N*-deprotection.[5] In the same work another method based on the palladium electrophilic attack on both aromatic rings of *ortho*-unhalogenated diarylamines and on the reoxidation of Pd(0) formed by $Cu(OAc)_2$, allowed also the synthesis of a ring A methoxylated thienocarbazole.[5]

Herein we describe the synthesis of several differently substituted thieno[3,2-*c*] and [2,3-*b*]carbazoles and indolo[3,2-*b*]benzo[*b*]thiophenes via *ortho*-bromodiarylamines. The latter were obtained by palladium-catalyzed amination[5,7] performed on both rings of the benzo[*b*]thiophene moiety and were submitted to palladium-catalyzed intramolecular cyclization under Sakamoto's[6] or Jeffery's[8] conditions as required. The tetracyclic compounds prepared may have biological activity or/and may be used as biomarkers due to their fluorescence already studied by us[9] and possible DNA intercalation which is in study. The presence of methoxy groups in this type of compounds showed to be important for biological activity, the 9-methoxyellipticine[10] being much more active than the ellipticine itself. The *ortho*-bromodiarylamines obtained may be interesting either for biological or for electroluminescent devices, in this latter case not only by their own properties but also by allowing polymerization to polyarylamines, using the same type of palladium-catalyzed amination.[11]

2. Results and discussion

2.1. Synthesis of *ortho*-bromodiarylamines and intramolecular cyclization to thienocarbazoles

6-Bromo and 6-amino 2,3,5-trimethylbenzo[*b*]thiophenes **1**[4] and **2a**[5,7] were coupled respectively with *ortho*-bromo anilines **3** or 1,2,4-tribromobenzene under Buchwald–Hartwig palladium-catalyzed amination[12] conditions to

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give *ortho*-bromodiarylamines **4** which were submitted to intramolecular cyclization under Jeffery's conditions[8] (Scheme 1). Aniline **3a** was prepared by bromination of *p*-anisidine using tetrabutylammoniumtribromide (Bu_4NBr_3) following the literature procedure for the synthesis of **3b**.[13]

The yields of **4a–d** were in the range of 30–35% in the best case, after choosing the right base. During the synthesis of **4a** and **4b**, *ortho*-dehalogenation to the corresponding diarylamines **5a** and **5b** also occurred (10–15%).

The methoxylated *ortho*-bromodiarylamines **4a** and **4b** were obtained using *t*-BuONa as the base, while for the synthesis of **4d**, Cs_2CO_3 was the most effective base.

We had previously reported the preparation of the diarylamine **4c**, but the cyclization under Sakamoto's conditions ($Pd(OAc)_2$, Na_2CO_3 in DMF) didn't afford the corresponding thienocarbazole.[5] These conditions were also not effective when applied to the new substituted *ortho*-bromodiarylamines **4a**, **4b** and **4d** obtained in the present work. The use of Jeffery's conditions with tetrabutylammonium bromide (Bu_4NBr),[8] allowed the cyclization of **4a–c** to afford the thienocarbazoles **6a–c** in moderate to quantitative yields (Scheme 1). Some dehalogenation occurred in the synthesis of thienocarbazole **6b** depending on the temperature. In the synthesis of **6c** no dehalogenation occurred and the unreacted diarylamine was recovered.

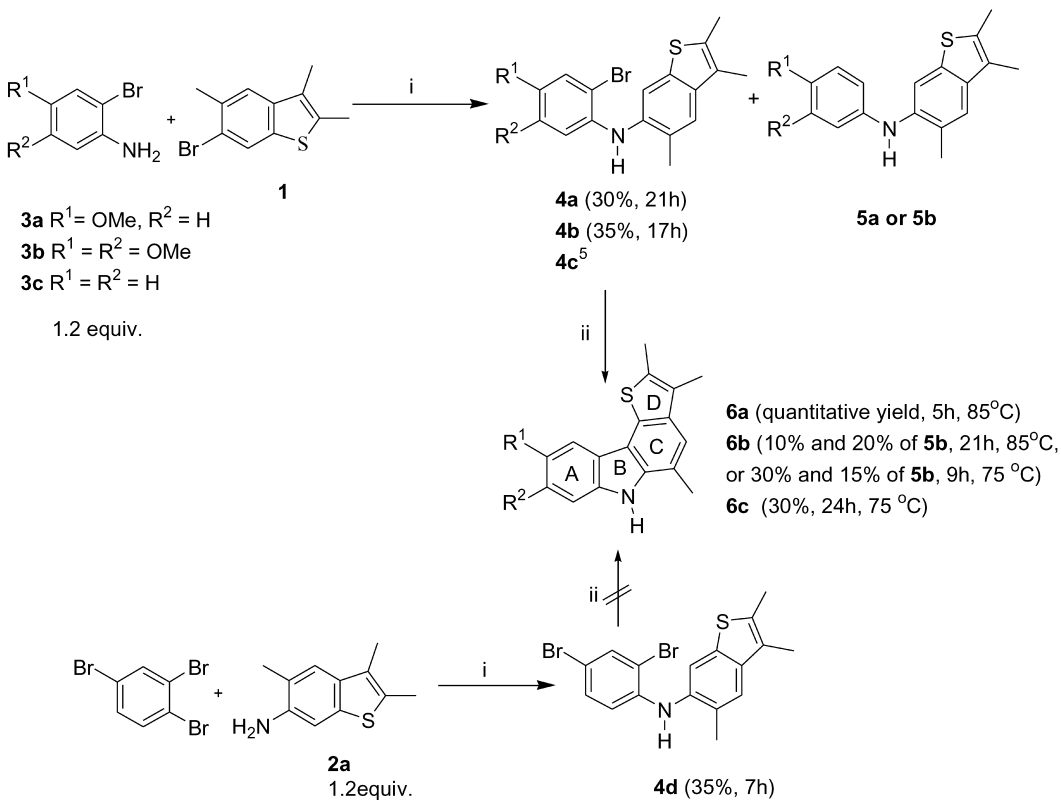
When applied to *ortho*-bromodiarylamine **4d**, the same conditions didn't afford the corresponding thienocarbazole (Scheme 1). This is in agreement with other authors who had already observed that these conditions were not effective for substrates having electron withdrawing groups.[8b]

Following the same methodology the linear thieno[2,3-*b*]-carbazole **6d** was obtained from the *ortho*-bromodiarylamine **4e**, which was prepared from the coupling of 2-bromo-iodobenzene with 6-amino-2,3,4,7-tetramethylbenzo[*b*]thiophene **2b**[7] (Scheme 2). No dehalogenation was observed either in the coupling or in the cyclization reaction. In the synthesis of **6d** higher amounts of catalyst and Bu_4NBr were needed together with longer time and higher temperature, the additions being made after 24 h of heating at 85°C. The reaction was heated for more 24 h at 95°C in the new conditions, as shown in Scheme 2.

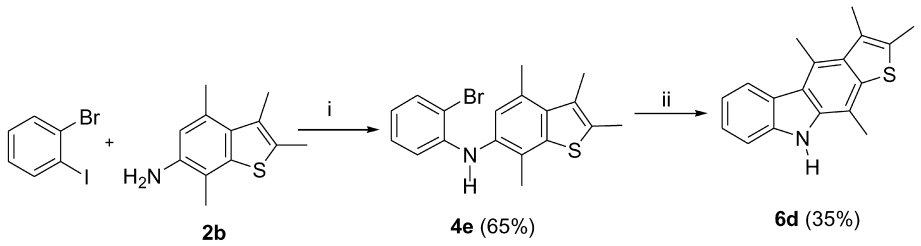
The cyclization of *ortho*-bromodiarylamines **4** in the presence of Bu_4NBr may be due to the coordination and thereby solvation of the palladium intermediates by the bromide ions present in the reaction mixture. Once the 'locked' palladium catalyst is released from the substrates, the catalytic cycle continues smoothly as claimed by others.[8b]

2.2. Synthesis of *ortho*-bromodiarylamines and intramolecular cyclization to indolobenzo[*b*]thiophenes

3-Bromobenzo[*b*]thiophene was coupled with *ortho*-bromoanilines **3a–c** to give the corresponding *ortho*-bromodiarylamines **7a–c** (30–40%) (Scheme 3). The use of *t*-BuONa as the base and higher amounts of $Pd(OAc)_2$ and



Scheme 1. Synthesis of *o*-bromodiarylamines **4** and intramolecular cyclization to thienocarbazoles **6**. (i) $Pd(OAc)_2$(3 mol%), BINAP(4 mol%). *t*-BuONa or Cs_2CO_3 (1.4 equiv.) toluene 90°C or 100°C, under Ar; (ii) $Pd(OAc)_2$ (50 mol%), K_2CO_3(2.5 equiv.), Bu_4NBr(Stoichi.), DMF 75 or 85°C, under Ar.



Scheme 2. Synthesis of *o*-bromodiarylamine **4e** and intramolecular cyclization to thienocarbazoles **6d**. (i) $Pd(OAc)_2$(3 mol%), BINAP(4 mol%). *t*-BuONa (1.4 equiv.) toluene 22 h, 100°C, under Ar; (ii) $Pd(OAc)_2$ (50+50 mol%), k_2CO_3(2.5 equiv.), Bu_4NBr (Stoichi.+0.5 equiv.), DMF 24 h, 85°C,+24 h, 95°C under Ar.

BINAP were necessary for the coupling in these cases. The diarylamines **7** were cyclized to the corresponding indolobenzo[*b*]thiophenes **8** in good to high yields, under Sakamoto's conditions and without the need of Bu_4NBr (Scheme 3). This is due to the fact that the cyclization in this case is toward a more reactive heterocyclic ring instead of a benzene ring.

Unexpectedly when 1.2 equiv. of 2-bromoaniline were used in the coupling reaction, it was possible to obtain compound **8c** directly in 20% yield together with diarylamine **7c** in 16% yield. Attempts to obtain also the methoxylated compounds **8a** and **8b** in a one pot procedure using the latter conditions, were not successful. Indolobenzo[*b*]thiophene **8c** had already been prepared by other authors using a different method.[14]

3. Conclusion

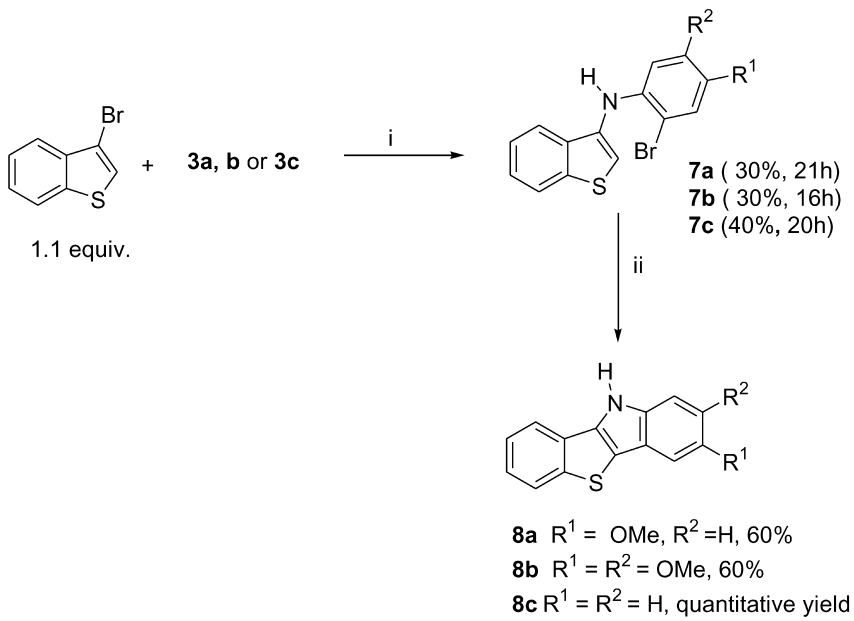
A novel synthetic route to thienocarbazoles and indolobenzo[*b*]thiophenes is presented via *ortho*-bromodiarylamines obtained by palladium-catalyzed amination on both rings of the benzo[*b*]thiophene moiety. The palladium-catalyzed intramolecular cyclization to thienocarbazoles was successful when tetrabutylammonium bromide was used, following Jeffery's conditions, while the indolobenzo[*b*]thiophenes were obtained simply by the application of the Sakamoto's conditions.

Both tetracyclic heteroaromatic systems being bioisosteres of natural anti-tumor pyridocarbazoles can act as DNA-binding agents which may be used as medical or relevant probes or drugs due to their fluorescence properties. The presence of methoxy groups in the molecules can be very important for the biological activity of this type of compounds as observed for 9-methoxyellipticine. The *ortho*-bromodiarylamines could also find application either in biology or in materials science due not only to their properties of diarylamine moiety but also by allowing polymerization to polyarylamines.

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



Scheme 3. Synthesis of *o*-bromodiarylamines **7** and intramolecular cyclization to indolobenzo[*b*]thiophenes **8**. (i) $Pd(OAc)_2$(5 mol%), BINAP(7.5 mol%). *t*-BuONa (1.4 equiv.) toluene 100°C, under Ar; (ii) $Pd(OAc)_2$ (10 mol%), Na_2CO_3(1.4 equiv.), reflux DMF.

(300 and 75.4 MHz, respectively). ^{1}H–^{1}H spin–spin decoupling and DEPT θ 45° were used. Chemical shifts are given in ppm and coupling constants in Hz. The mass spectra (EI) and the HRMS were obtained from the mass spectrometry external service of the University of Vigo (Spain). Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

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^2 Plate 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 neat petroleum ether to mixtures of ether/petroleum ether increasing 10% of ether until the isolation of the product.

Compounds **1** and **2** were prepared by methods already described by us.[4,5,7] Compound **3b** was prepared as already described by others.[13] Compound **4c** was already prepared by us from compound **1** or **2a**.[5]

4.1.1. 2-Bromo-4-methoxyaniline (3a). To a solution of *p*-anisidine (1.0 g, 8.1 mmol) in CH_2Cl_2 (27 ml) and MeOH (13 ml) was added Bu_4NBr_3 (3.6 g, 7.5 mmol) and the mixture was stirred at r.t. for 2 h. Ether (15 ml) and sat. Na_2SO_3 solution (30 ml) were added and the phases were separated. The organic phase was washed with water (20 ml), dried ($MgSO_4$) and filtered. Removal of the solvent gave an oil which was submitted to column chromatography using solvent gradient from neat petroleum ether to 50% ether/petroleum ether to give compound **3a** (0.69 g, 42%) as a purple oil. ^{1}H NMR: ($CDCl_3$) 3.69 (2H, s, 2×NH), 3.73 (3H, s, OMe), 6.72–6.74 (2H, m, 2×Ar-H), 7.01 (1H, broad s, Ar-H). ^{13}C NMR: ($CDCl_3$) 55.85 (OCH_3), 109.56 (C), 114.97, 116.60, 117.39, 137.81 (C), 152.60 (C). MS: 203 (97, M$^+$ ^{81}Br), 201 (100, M$^+$ ^{79}Br), 188 (90, M$^+$ ^{81}Br−15), 186 (92, M$^+$ ^{79}Br−15). HRMS C_7H_8BrNO: calcd M$^+$ ^{79}Br 201.98228; found 201.98365.

As a less polar product, 2,6-dibromo-4-methoxyaniline was also isolated as white crystals (0.45 g, 20%), mp 81–83. ^{1}H NMR: ($CDCl_3$) 3.73 (3H, s, OMe), 4.20 (2H, s, 2×N–H), 7.03 (2H, s, H-3 e 5). MS: 283 (39, M$^+$ ^{81}Br, ^{81}Br) 281 (79, M$^+$ ^{79}Br, ^{81}Br), 279 (41, M$^+$ ^{79}Br, ^{79}Br), 268 (47, 283−15), 266 (100, 281−15), 264 (50, 279−15). Anal. Calcd for $C_7H_7Br_2NO$: C 29.93, H 2.51, N 4.99; found: C 30.10, H 2.62, N 4.98.

4.2. General procedure for the synthesis of *ortho*-bromodiarylamines precursors of thienocarbazoles

A dry Schlenk tube was charged, under Ar, with dry toluene (3–5 ml), the aniline or aryl halide, the benzo[*b*]thiophene **1** or **2**, $Pd(OAc)_2$ (3 mol%), racemic BINAP (4 mol%), t-BuONa or Cs_2CO_3 as base (1.4 equiv.), and the mixture was heated at 90°C or 100°C respectively, for several hours (Scheme 1 or 2). The reaction was followed by TLC. After cooling water and ether were added. The phases were separated, the aqueous phase was extracted with more ether and the organic phase was 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 and in some cases the correponding dehalogenated diarylamine.

4.2.1. 6-(2-Bromo-4-methoxyphenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (4a). From 6-bromobenzo[*b*]thiophene **1** (0.49 g, 1.9 mmol), 2-bromo-4-methoxyaniline **3a** (0.46 g, 2.3 mmol) and using petroleum ether in the column chromatography, compound **4a** was obtained as a white solid (0.22 g, 30%). Crystalization from ether/petroleum ether gave colourless crystals, mp 120–122. IR: 3413 (N–H). ^{1}H NMR: ($CDCl_3$) 2.29 (3H, s, Me), 2.40 (3H, s, Me), 2.47 (3H, s, Me), 3.80 (3H, s, OMe), 5.61 (1H, s, N–H), 6.81 (1H, dd, *J*=9 and 3 Hz, H-5′), 6.98 (1H, d, *J*=9 Hz, H-6′), 7.18 (1H, d, *J*=3 Hz, H-3′), 7.44 (2H, s, H-4 and 7). ^{13}C NMR: ($CDCl_3$) 11.35 (CH_3), 13.67 (CH_3), 18.29 (CH_3), 55.83 (OCH_3), 112.05, 113.71 (C), 114.45, 118.02, 118.93, 122.73, 126.29 (C), 126.35 (C), 131.69 (C), 135.83 (C), 136.57 (C), 136.68 (C) 138.26 (C), 153.92 (C). MS: 377 (100, M$^+$ ^{81}Br), 375 (97, M$^+$ ^{79}Br), 362 (28, M$^+$ ^{81}Br−15), 360 (26, M$^+$ ^{79}Br−15), 298 (21, M$^+$−80), 281 (28). HRMS $C_{18}H_{18}BrNOS$: calcd M$^+$ ^{79}Br 375.02925; found 375.02964.

As a slightly more polar product the corresponding dehalogenated amine **5a** was also isolated (82 mg, 15%) with identical properties to a sample prepared by us from other starting materials.[7]

4.2.2. 6-(2-Bromo-4,5-dimethoxyphenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (4b). From 6-bromobenzo[*b*]thiophene **1** (0.40 g, 1.6 mmol), 2-bromo-4,5-dimethoxyaniline **3b**[13] (0.44 g, 1.9 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 (0.22 g, 35%). Crystallization from ether/petroleum ether gave colourless crystals, mp 125–127. IR: 3377 (N–H). ^{1}H NMR: ($CDCl_3$) 2.29 (3H, s, Me), 2.40 (3H, s, Me), 2.46 (3H, s, Me), 3.72 (3H, s, OMe), 3.87 (3H, s, OMe), 5.59 (1H, s, N–H), 6.61 (1H, s, H-6′), 7.07 (1H, s, H-3′), 7.44 (1H, s, H-4 or 7), 7.47 (1H, s, H-7 or 4). ^{13}C NMR: ($CDCl_3$) 11.36 (CH_3), 13.69 (CH_3), 18.35 (CH_3), 55.99 (OCH_3), 56.56 (OCH_3), 102.32, 102.42 (C), 112.54, 115.83, 122.80, 126.40 (C), 126.67 (C), 131.95 (C), 135.99 (C), 136.53 (C), 136.89 (C), 137.98 (C), 143.53 (C), 149.17 (C). MS: 407 (100, M$^+$ ^{81}Br), 405 (98, M$^+$ ^{79}Br), 392 (35, M$^+$ ^{81}Br−15), 390 (33, M$^+$ ^{79}Br−15). HRMS $C_{19}H_{20}BrNO_2S$: calcd M$^+$ ^{79}Br 405.03981; found 405.04168.

As a slightly more polar product the corresponding dehalogenated amine **5b** was also isolated (50 mg, 10%) with identical properties to a sample prepared by us from other starting materials.[7]

4.2.3. 6-(2,4-Dibromophenyl)amino-2,3,5-trimethylbenzo[*b*]thiophene (4d). From 6-aminobenzo[*b*]thiophene **2a** (0.15 g, 0.78 mmol), 1,2,4-tribromobenzene (0.21 g, 0.65 mmol) and using petroleum ether in the column chromatography, compound **4d** was obtained as a white solid (0.10 g, 35%). Crystallization from petroleum ether gave colourless crystals, mp 156–158. IR: 3408 (N–H). ^{1}H NMR: ($CDCl_3$) 2.29 (3H, s, Me), 2.33 (3H, s, Me), 2.47 (3H,

s, Me), 5.44 (1H, s, N–H), 6.64 (1H, dd, *J*=9 and 3 Hz, H-5′), 7.05 (1H, d, *J*=3 Hz, H-3′), 7.38 (1H, d, *J*=9 Hz, H-6′), 7.44 (1H, s, H-7), 7.55 (1H, s, H-4). ^{13}C NMR: ($CDCl_3$) 11.39 (CH_3), 13.79 (CH_3), 18.36 (CH_3), 112.84 (C), 115.79, 115.91, 119.83, 122.99, 125.17 (C), 126.45 (C), 128.52 (C), 133.24 (C), 133.74, 135.77 (C), 136.44 (C), 138.37 (C), 145.82 (C). MS: 427 (57, M^+ ^{81}Br, ^{81}Br), 425 (100, M^+ ^{79}Br, ^{81}Br), 423 (53, M^+ ^{79}Br, ^{79}Br). Anal. Calcd for $C_{17}H_{15}Br_2NS$: C 48.02, H 3.56, N 3.29, S 7.54; found: C 48.27, H 3.79, N 3.30, S 7.29.

4.2.4. 6-(2-Bromophenyl)amino-2,3,4,7-tetramethylbenzo[*b*]thiophene (4e). From 6-aminobenzo[*b*]thiophene **2b** (0.15 g, 0.73 mmol), 2-bromo-iodobenzene (0.21 g, 0.73 mmol) and using neat petroleum ether to 10% ether/petroleum ether in the column chromatography purification, compound **4e** was obtained as a white solid (0.17 g, 65%). Crystallization from ether/petroleum ether gave colourless crystals, mp 148–150. IR: 3384 (N–H). ^{1}H NMR: ($CDCl_3$) 2.34 (3H, s, Me), 2.47 (3H, s, Me), 2.52 (3H, s, Me), 2.71 (3H, s, Me), 5.91 (1H, s, N–H), 6.59–6.67 (2H, m, H-4′ and 6′), 6.97 (1H, s, H-5), 7.07 (1H, td, *J*=7.8 and 1.5 Hz, H-5′), 7.50 (1H, dd, *J*=7.8 and 1.5 Hz, H-3′). ^{13}C NMR: ($CDCl_3$) 14.09 (CH_3), 15.20 (CH_3), 15.49 (CH_3), 21.30 (CH_3), 110.08 (C), 113.93, 119.12, 124.26 (C), 125.11, 128.15, 129.20 (C), 131.31 (C), 132.53, 132.57 (C), 133.65 (C), 136.64 (C), 140.29 (C), 143.64 (C). Anal. Calcd for $C_{18}H_{18}BrNS$: C 60.00, H 5.04, N 3.89, S 8.90; found: C 60.23, H 5.03, N 3.95, S 8.90.

4.3. General procedure for the intramolecular cyclization of *ortho*-bromodiarylamines 4 to thieno-[3,2-*c*]carbazoles 6a–c

A dry Schlenk tube was charged, under Ar, with dry DMF (3–4 ml), the *ortho*-bromodiarylamine **4**, $Pd(OAc)_2$ (50 mol%), K_2CO_3 as base (2.5 equiv.), Bu_4NBr (stoich.) and the mixture was heated at 75°C or 85°C for several hours (Scheme 1). The reaction was followed by TLC. After cooling $CHCl_3$ was added. The phases were separated, the aqueous phase was extracted with more $CHCl_3$ and the organic phase was dried ($MgSO_4$) and filtered. Removal of the solvent gave an oil, which was submitted to PLC (50% ether/petroleum ether) unless stated, to give the product and in some cases the corresponding dehalogenated diarylamine.

4.3.1. 9-Methoxy-2,3,5-trimethyl-6*H*-thieno-[3,2-*c*]carbazole (6a). From *ortho*-bromodiarylamine **4a** (0.11 g, 0.29 mmol) and heating for 5 h at 85°C, following the general procedure, the thienocarbazole **6a** was obtained as a white solid (86 mg, quantitative yield), which after crystalization from ether/petroleum ether gave colourless crystals, with identical properties to a sample prepared by other method.[5]

4.3.2. 8,9-Dimethoxy-2,3,5-trimethyl-6*H*-thieno-[3,2-*c*]carbazole (6b). From *ortho*-bromodiarylamine **4b** (0.13 g, 0.32 mmol) and heating for 9 h at 75°C, following the general procedure, the thienocarbazole **6b** was obtained as a white solid (30 mg, 30%), after PLC (50% ether/petroleum ether). Crystallization from ether/petroleum ether gave colourless crystals, mp 210–212. IR: 3438 (N–H). ^{1}H NMR: ($CDCl_3$) 2.39 (3H, s, Me), 2.58 (3H, s, Me), 2.64 (3H, s, Me), 3.98 (3H, s, OMe), 4.09 (3H, s, OMe), 7.03 (1H, s, H-7), 7.37 (1H, s, H-10), 7.57 (1H, s, H-4), 8.01 (1H, s, N–H). ^{13}C NMR: ($CDCl_3$) 11.77 (CH_3), 13.74 (CH_3), 17.13 (CH_3), 55.16 (OCH_3), 56.56 (OCH_3), 94.45, 103.61, 115.11 (C), 116.35 (C), 117.14 (C), 118.04, 127.07 (C), 127.48 (C), 129.22 (C), 133.73 (C), 134.82 (C), 136.23 (C), 144.72 (C), 148.84 (C). MS: *m*/*z* 325 (100, M^+). HRMS $C_{19}H_{19}NO_2S$: calcd M^+ 325.11365; found 325.11520.

The corresponding dehalogenated diarylamine **5b** was also isolated as a more polar product (16 mg, 15%) with identical properties to a sample prepared by other method.[7]

4.3.3. 2,3,5-Trimethyl-6*H*-thieno-[3,2-*c*]carbazole (6c).[5] From *ortho*-bromodiarylamine **4c** (85 mg, 0.25 mmol) the thienocarbazole **6c** was obtained as a white solid after PLC (19 mg, 30%). Crystallization from ether/petroleum ether gave colourless crystals, with identical properties to a sample prepared by other method.[5]

4.3.4. 2,3,4,7-Tetramethyl-9*H*-thieno-[2,3-*b*]carbazole (6d). From *ortho*-bromodiarylamine **4e** (0.12 g, 0.33 mmol), following the general procedure described above but increasing the amounts of the catalyst and of Bu_4NBr and the temperature after 24 h (like shown in Scheme 2) and heating for more 24 h, the thienocarbazole **6d** was obtained after column chromatography using petroleum ether to 30% ether/petroleum ether as a white solid (33 mg, 35%). Crystallization from ether/petroleum ether gave colourless crystals, mp 232–234. IR: 3414 (N–H). ^{1}H NMR: ($CDCl_3$+DMSO-d_6) 2.28 (3H, s, Me), 2.42 (3H, s, Me), 2.45 (3H, s, Me), 3.05 (3H, s, Me), 6.98 (1H, t, *J*=8 Hz, ArH), 7.18 (1H, t, *J*=8 Hz, ArH), 7.29 (1H, d, *J*=8 Hz, H-8), 8.05 (1H, d, *J*=8 Hz, H-5) 9.80 (1H, s, N–H). ^{13}C NMR: ($CDCl_3$+DMSO-d_6) 13.87 (CH_3), 14.63 (CH_3), 16.04 (CH_3), 16.60 (CH_3), 108.46 (C), 110.03, 117.84, 120.99 (C), 122.36, 124.05 (C), 124.25, 124.86 (C), 128.14 (C), 128.62 (C), 131.90 (C), 136.04 (C), 136.65 (C), 140.67 (C). Anal. Calcd for $C_{18}H_{17}NS$: C 77.38, H 6.13, N 5.01, S 11.47; found: C 77.52, H 6.09, N 5.03, S 11.52.

4.4. General procedure for the synthesis of *ortho*-bromodiarylamines 7 precursors of indolobenzo[*b*]-thiophenes

A dry Schlenk tube was charged, under Ar, with dry toluene (3–5 ml), 3-bromobenzo[*b*]thiophene (1.1 equiv.), the *ortho*-bromoaniline **3**, $Pd(OAc)_2$ (5 mol%), racemic BINAP (7.5 mol%) and *t*-BuONa (1.4 equiv.) as base and the mixture was heated at 100°C for several hours (Scheme 3). The reaction was followed by TLC. After cooling water and ether were added. The organic phase was separated, dried ($MgSO_4$) and solvent removed to give an oil which was submitted to chromatographic purification using solvent gradient from petroleum ether to 30% ether/petroleum ether to give the product and starting materials.

4.4.1. 3-(2-Bromo-4-methoxyphenyl)aminobenzo[*b*]thiophene (7a). From 2-bromo-4-methoxyaniline **3a** (0.50 g, 2.5 mmol), compound **7a** was obtained as a rosed solid after chromatographic purification (0.24 g, 30%). Crystallization from ether/petroleum ether gave rosed crystals, mp 85–87.

IR: 3395 (N–H). ^{1}H NMR: ($CDCl_3$) 3.79 (3H, s, OMe), 6.00 (1H, broad s, N–H), 6.79 (1H, dd, J=9 and 2.7 Hz, H-5′), 6.95 (1H, s, H-2), 7.05 (1H, d, J=9 Hz, H-6′), 7.16 (1H, d, J=2.7 Hz, H-3′), 7.38–7.42 (2H, m, 2×ArH), 7.66–7.69 (1H, m, ArH), 7.83–7.87 (1H, m, ArH). ^{13}C NMR: ($CDCl_3$) 55.88 (OCH_3), 109.39, 112.02 (C), 114.57, 117.44, 117.91, 120.62, 123.20, 124.01, 124.95, 134.45 (C), 135.16 (C), 135.99 (C), 138.89 (C), 153.63 (C). MS: 335 (100, M^+ ^{81}Br), 333 (96, M^+ ^{79}Br), 320 (42, M^+ ^{81}Br−15), 318 (42, M^+ ^{79}Br−15), 254 (25, M^+−80), 239 (23), 223 (25), 210 (32). HRMS $C_{15}H_{12}BrNOS$ calcd M^+ ^{79}Br 333.98565; found 333.98695.

4.4.2. 3-(2-Bromo-3,4-dimethoxyphenyl)aminobenzo-[*b*]thiophene (7b). From 2-bromo-4,5-dimethoxyaniline **3b**[13] (0.50 g, 2.2 mmol), heating for 16 h and following the general procedure, compound **7b** was obtained as a rosed solid after chromatographic purification (0.23 g, 30%). Crystallization from ether/petroleum ether gave rosed crystals, mp 100–102. IR: 3413 (N–H). ^{1}H NMR: ($CDCl_3$) 3.71 (3H, s, OMe), 3.87 (3H, s, OMe), 5.99 (1H, s, N–H), 6.76 (1H, s, H-6′), 6.97 (1H, s, H-2), 7.06 (1H, s, H-3′), 7.39–7.43 (2H, m, 2×ArH), 7.68–7.73 (1H, m, ArH), 7.84–7.88 (1H, m, ArH). ^{13}C NMR: ($CDCl_3$) 56.03 (OCH_3), 56.59 (OCH_3), 100.99 (C), 101.41, 109.19, 115.78, 120.66, 123.21, 124.05, 125.07, 134.40 (C), 135.12 (C), 135.99 (C), 138.89 (C), 143.38 (C), 149.26 (C). Anal. Calcd for $C_{16}H_{14}BrNO_2S$: C 52.76, H 3.87, N 3.85, S 8.80; found: C 52.70, H 4.16, N 3.97, S 8.86.

4.4.3. 3-(2-Bromophenyl)aminobenzo[*b*]thiophene (7c). From 2-bromoaniline **3c** (0.50 g, 2.9 mmol), compound **7c** was obtained as an oil after chromatographic purification (0.35 g, 40%). ^{1}H NMR: ($CDCl_3$) 6.30 (1H, s, N–H), 6.65–6.75 (1H, m, ArH), 6.98 (1H, dd, J=8.1 and 1.5 Hz, H-6′), 7.10–7.17 (1H, m, ArH),7.18 (1H, s, H-2) 7.36–7.43 (2H, m, 2×ArH), 7.55 (1H, dd, J=8.1 and 1.5 Hz, H-3′), 7.64–7.67 (1H, m, ArH), 7.85–7.89 (1H, m, ArH). ^{13}C NMR: ($CDCl_3$) 110.45 (C), 113.63, 114.78, 120.12, 120.90, 123.15, 124.11, 124.97, 128.31, 132.62, 133.51 (C), 134.84 (C), 138.74 (C), 142.37 (C). MS: 305 (70, M^+ ^{81}Br), 303 (69, M^+ ^{79}Br), 224 (75), 223 (100). HRMS $C_{14}H_{10}BrNS$: calcd M^+ ^{81}Br 305.97425; found 305.97304.

4.5. General procedure for the intramolecular cyclisation of *ortho*-bromodiarylamines 7 to indolo-[3,2-*b*]benzo[*b*]thiophenes 8

ortho-Bromodiarylamines **7**, $Pd(OAc)_2$ (10%) and Na_2CO_3 (1.4 equiv.) were refluxed in dry DMF (4–5 ml), for 2 h. The reaction was followed by TLC. After cooling, $CHCl_3$ was added. The organic phase was separated, dried ($MgSO_4$), filtered and the solvent removed to give the product which was submitted to crystallization using ether/petroleum ether.

4.5.1. 9-Methoxy-6*H*-indolo[3,2-*b*]benzo[*b*]thiophene (8a). From *ortho*-bromodiarylamine **7a** (70 mg, 0.21 mmol) compound **8a** was obtained as colourless crystals (32 mg, 60%), mp 212–213.5. IR: 3420 (N–H). ^{1}H NMR: ($CDCl_3$) 3.93 (3H, s, OMe), 6.98 (1H, dd, J=9 and 2.4 Hz, H-8), 7.23 (1H, d, J=2.4 Hz, H-10), 7.33–7.46 (3H, m, 3×ArH), 7.82–7.92 (2H, m, 2×ArH), 8.46 (1H, s, N–H). ^{13}C NMR: ($CDCl_3$) 55.88 (OCH_3), 101.16, 112.91, 113.36, 116.18 (C), 119.36, 122.78 (C), 124.13, 124.25, 124.41, 126.74 (C), 135.47 (C), 137.60 (C), 142.76 (C), 154.32 (C). MS: 253 (100, M^+), 238 (20, M^+−15), 210 (48). Anal. Calcd for $C_{15}H_{11}NOS$: C 71.42, H 4.38, N 5.53, S 12.66; found: C 71.09, H 4.31, N 5.55, S 12.30.

4.5.2. 8,9-Dimethoxy-6*H*-indolo[3,2-*b*]benzo[*b*]thiophene (8b). From *ortho*-diarylamine **7b** (0.10 g, 0.28 mmol) compound **8b** was obtained as a beje solid (46 mg, 60%), mp 120–122. IR: 3406 (N–H). ^{1}H NMR: ($CDCl_3$ +([D_6]DMSO) 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 6.91 (1H, s, H-7), 7.03 (1H, s, H-10), 7.10–7.16 (1H, m, H-3 or 4), 7.21–7.27 (1H, m, H-4 or 3), 7.70 (1H, broad d, J=8 Hz, H-2 or 5), 7.79 (1H, broad d, J=8 Hz, H-5 or 2), 10.60 (1H, s, N–H). ^{13}C NMR: ([D_6]DMSO) 55.79 (OCH_3), 55.92 (OCH_3), 95.44, 100.39, 114.45 (C), 114.74 (C), 119.03, 122.78, 123.67, 123.73, 126.99 (C), 134.99 (C), 136.13 (C), 141.55 (C), 144.22 (C), 147.01 (C). MS: 283 (100, M^+), 268 (35, M^+−15). Anal. Calcd for $C_{16}H_{13}NO_2S$ calcd C 67.82, H 4.62, N 4.94, S 11.31; found: C 67.44, H 4.94, N 4.95, S 10.88.

4.5.3. 6*H*-Indolo[3,2-*b*]benzo[*b*]thiophene (8c). From *ortho*-bromodiarylamine **7c** (80 mg, 0.26 mmol) compound **8c** was obtained as a white solid (58 mg, quantitative yield). Crystallization from ether/petroleum ether gave colourless crystals, mp 251–253 (lit[14] 250–252). ^{1}H NMR: ($CDCl_3$) 7.22–7.50 (4H, m, H-3,4, 8 and 9), 7.55 (1H, broad d, J=8 Hz, ArH), 7.79(1H, broad d, J=8 Hz, ArH), 7.88 (1H, broad d, J=8 Hz, ArH), 7.92 (1H, broad d, J=8 Hz, ArH), 8.60 (1H, s, N–H). ^{13}C NMR: ($CDCl_3$) 112.15, 116.59 (C), 119.33, 119.36, 120.22, 122.50 (C), 123.34, 124.14, 124.25, 124.43, 126.63 (C), 136.82 (C), 140.54 (C), 142.87 (C). MS: 223 (100, M^+), 121 (11). HRMS $C_{14}H_9NS$: calcd M^+ 223.045571; found 223.045592.

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