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. Therefore, these compounds play a crucial role as potential leads for the discovery of antitumor active drugs using bioisosteric replacements. 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. 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 or C–N 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-bromodiarylamines, 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. 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.

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 performed on both rings of the benzo[b]thiophene moiety and were submitted to palladium-catalyzed intramolecular cyclization under Sakamoto’s or Jeffery’s 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 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-methoxylepticine being much more active than the ellipticine itself. The ortho-bromodiarylamines obtained may be interesting either for biological or for electro-luminescent devices, in this latter case not only by their own properties but also by allowing polymerization to polarylamines, using the same type of palladium-catalyzed amination.

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 14 and 2a were coupled respectively with ortho-bromoanilines 3 or 1,2,4-tribromobenzene under Buchwald–Hartwig palladium-catalyzed amination conditions to...
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\(_4\)NBr\(_3\)) 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\(_2\)CO\(_3\) 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\(_2\)CO\(_3\) 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\(_4\)NBr),\(^8\) 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\(_4\)NBr 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\(_4\)NBr 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-bromonilines 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
BINAP were necessary for the coupling in these cases. The diarylamines 7 were cyclized to the corresponding indolo[71x562]b[76x562]benzo[71x562]b[76x562]thiophenes 8 in good to high yields, under Sakamoto’s conditions and without the need of Bu4NBr (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 indolo[70x353]benzo[75x353]b[70x353]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 13C NMR spectra were recorded on a Varian Unity Plus.

Scheme 2. Synthesis of o-bromodiarylamines 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%), k2CO3(2.5 equiv.), Bu4NBr (Stoichi.+0.5 equiv.), DMF 24 h, 85°C,+24 h, 95°C under Ar.

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%), Na2CO3(1.4 equiv.), reflux DMF.
(300 and 75.4 MHz, respectively). 1H–1H spin–spin decoupling and DEPT 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 cm² 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.

A dry Schlenk tube was charged, under Ar, with dry toluene (3–5 ml), the aniline or aryl halide, the benzothiophene or 1H-NMR: (CDCl 3) 2.29 (3H, s, Me), 2.47 (3H, s, Me), 2.33 (3H, s, Me), 2.47 (3H, s, Me), 3.80 (3H, s, OMe), 5.61 (1H, s, N–H), 6.81 (1H, d, J = 9 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). 13C NMR: (CDCl 3) 113.35 (CH 3), 13.67 (CH 2), 18.29 (CH 2), 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 + 81Br), 375 (97, M + 81Br), 362 (28, M + 81Br–15), 360 (26, M + 79Br–15), 298 (21, M + 78–80), 281 (28). HRMS C 19H 18BrNO: calcd M + 78Br 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.

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 4 NB r (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.

1H NMR: (CDCl 3) 3.69 (2H, s, 2H), 6.72–6.74 (2H, m, 2H), 7.41 (1H, d, J = 9 Hz, H-5), 7.44 (2H, s, H-4 and 7). 13C NMR: (CDCl 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), 143.53 (C), 149.17 (C). MS: 377 (100, M + 81Br), 375 (97, M + 81Br), 362 (28, M + 81Br–15), 360 (26, M + 79Br–15), 298 (21, M + 78–80), 281 (28). HRMS C 19H 18BrNO: calcd M + 78Br 375.02925; found 375.02964.

4.1.2. 2-(2-Bromo-4-methoxyphenyl)amino-2,3,5-trimethylbenzo[b]thiophene (4a). From 6-bromobenzothiophene 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%). Crystallization from ether/petroleum ether gave colourless crystals, mp 120–122. IR: 3377 (N–H), 3151 (CH 3), 1175 (C–O), 1504 (C=C), 1543 (C=C). MS: 407 (100, M + 79Br), 405 (98, M + 78Br), 392 (35, M + 78Br–15), 390 (33, M + 78Br–15). HRMS C 19H 18BrNO: calcd M + 78Br 375.03981; found 405.04168.

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

A dry Schlenk tube was charged, under Ar, with dry toluene (3–5 ml), the aniline or aryl halide, the benzothiophene or 1H-NMR: (CDCl 3) 2.29 (3H, s, Me), 2.33 (3H, s, Me), 2.47 (3H, s, Me). 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 corresponding dehalogenated diarylamine.
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’). 13C NMR: (CDCl3) 11.39 (CH3), 13.79 (CH3), 18.36 (CH2), 112.84 (C), 115.79, 119.51, 118.72, 122.97, 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 (75, M+), 353, 325, 191, 148, 146, 138, 136, 128, 118, 116, 83, 79, 77, 75. 1H NMR: (CDCl3) 2.39 (3H, s, Me), 2.58 (3H, s, Me), 2.64 (3H, s, Me), 2.38 (3H, s, Me), 2.98 (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). 13C NMR: (CDCl3) 11.77 (CH3), 13.74 (CH3), 17.13 (CH3), 55.16 (OCH3), 56.56 (OCH3), 94.45, 103.61, 115.11 (C), 116.35 (C), 117.14 (C), 118.04, 127.07 (C), 127.48 (C), 129.22, 133.73 (C), 134.82 (C), 136.23 (C), 144.72 (C), 148.84 (C). MS: m/e 325 (100, M+). HRMS C19H19NO3: calc 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.5

4.3. 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-bromobenz[b]thiophene (1.1 equiv.), the ortho-bromodiarylane, Pd(OAc)2 (5 mol%), racemic BINAP (1.4 equiv.), 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 (MgSO4) 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 30% ether/petroleum ether to give the product and starting materials.

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-bromobenz[b]thiophene (1.1 equiv.), the ortho-bromodiarylane, 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 (MgSO4) 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-(Bromo-4-methoxyphenyl)aminobenz[b]thiophene (7a). From 2-bromo-4-methoxyaniline 3a (0.50 g, 2.5 mmol), compound 7a was obtained as a white solid after chromatographic purification (0.24 g, 30%). Crystallization from ether/petroleum ether gave rose crystals, mp 85–87.

IR: 3395 (N–H). 1H NMR: (CDCl3) 3.93 (3H, s, OMe), 6.98 (1H, dd, 8 Hz, ArH), 7.31–7.36 (2H, m, ArH), 7.68–7.73 (1H, m, ArH), 8.21–8.26 (2H, m, ArH). Anal. Calcld for C16H13NO2S: 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. 6H-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 (lit14 250–252). 1H NMR: (CDCl3) 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). 13C NMR: (CDCl3) 112.15, 115.69 (C), 119.03, 119.36, 120.22, 122.50 (C), 123.34, 124.11, 124.97, 128.31, 132.62, 133.51 (C), 134.84 (C), 138.74 (C), 142.37 (C). MS: 305 (70, M+81Br), 303 (69, M+81Br 5.2), 224 (75), 223 (100). HRMS C14H10BrNS: calcd M+ 223.045571; found 223.04592.

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