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Tandem palladium-catalyzed borylation and Suzuki coupling (BSC) to thienocarbazole precursors

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Abstract—Substituted 2-methyl-2'-nitro diaryl compounds in the benzo[*b*]thiophene series were prepared by palladium-catalyzed, two-step, one-pot borylation/Suzuki coupling (BSC) reaction in good to high yields. The borylation reaction was performed on methylated 6-bromobenzo[*b*]thiophenes using pinacolborane and was followed by in situ Suzuki coupling with substituted (CF₃, OMe) 2-bromonitrobenzenes. The compounds obtained were cyclized to the corresponding ring A substituted thienocarbazoles which can have biological activity or/and be used as biomarkers due to their fluorescence properties and possible DNA intercalation. © 2003 Elsevier Science Ltd. All rights reserved.

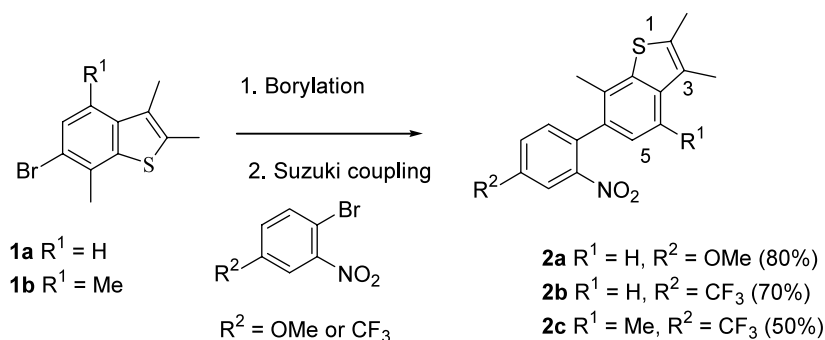
1. Introduction

The synthesis of heteroannellated carbazoles continues to attract a lot of interest due to the expected biological activity of these products. Thienocarbazoles, bioisosteres of the natural anti-tumor pyridocarbazoles (ellipticine and olivacine), are interesting targets not only for biological activity but also to be used as biomarkers due to their fluorescence properties¹ and possible DNA intercalation. We have already developed several convergent ring B routes for the synthesis of methylated thienocarbazoles by intramolecular

cyclization of precursors obtained either by C–C² or C–N³ palladium or copper-catalyzed cross couplings.

In the C–C cross coupling route we have described the synthesis of nitro precursors of ring A unsubstituted thienocarbazoles from bromobenzo[*b*]thiophenes by a one-pot, three-step reaction (bromine–lithium exchange, boron transmetalation and Suzuki coupling) in moderate yields.²

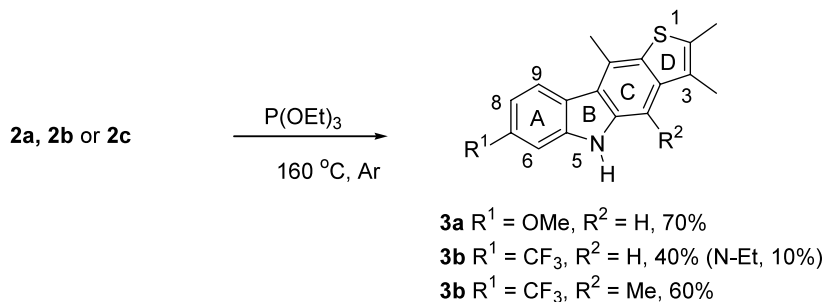
We report here an improved synthesis of nitro precursors of ring A substituted (CF₃, OMe) thienocarbazoles



Scheme 1. Reagents and conditions: (1) pinacolborane, Pd(OAc)₂, 2-(dicyclohexylphosphino)biphenyl, Et₃N, dioxane 1 h, 80°C; (2) 2-bromonitrobenzene, H₂O, Ba(OH)₂·8H₂O, 1 h, 100°C (see Ref. 5).

Keywords: palladium; borylation; Suzuki coupling; 2-methyl-2'-nitro biaryls; benzo[*b*]thiophenes.

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Scheme 2. Reductive cyclization to thienocarbazoles **3** (see Ref. 7).

by palladium-catalyzed, two-step, one-pot borylation/Suzuki coupling (BSC) reaction⁴ in good to high yields (50–80%). To our knowledge it is the first time that this methodology is applied to the synthesis of 2-methyl-2'-nitro biaryls.

2. Results and discussion

Tri- or tetramethylated 6-bromobenzo[*b*]thiophenes **1a** or **1b** were boronated using pinacolborane and this was followed by in situ Suzuki coupling with substituted (CF_3 , OMe) 2-bromonitrobenzenes (Scheme 1). The nature of the substituents *ortho* to the bromine atoms on both aromatic rings, methyl as EDG on the component to be boronated and nitro as EWG on the coupling component, proved to be suitable for this reaction and in agreement with the rules postulated by others.⁴

The yield obtained in the synthesis of compound **2c** is probably due to the lower reactivity of compound **1b** as we have already noticed in C–N coupling reactions.⁶

The nitro compounds **2** were then cyclized to the corresponding new linear thienocarbazoles **3** in moderate to good yields, using triethylphosphite as shown in Scheme 2.

In the synthesis of **3a** and **3b** only vestiges of the N–Et compounds were observed in the ¹H NMR of the crude mixtures. The N–Et derivative of **3b** was isolated in 10% yield, lowering the yield of the N–H compound.

3. Conclusion

We have applied the BSC reaction to the synthesis of new 2-methyl-2'-nitro biaryl precursors of tetracyclic heteroaromatic systems which can have biological activity and/or can be used as biomarkers. This reaction proved to be compatible either with additional electron donating (OMe) or withdrawing (CF_3) groups which are known by their importance in the solubility of the molecules and in biological activities.

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- (a) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268–9271; (b) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2002**, *67*, 1199–1207.
- Typical procedure for the BSC reaction:** A dry Schlenk tube was charged under Ar with the 6-bromobenzo[*b*]thiophene **1a** or **1b** (1 mmol) in dioxane (2–3 mL), Et_3N (4 equiv.), $\text{Pd}(\text{OAc})_2$ (5 mol%), 2-(dicyclohexylphosphino)biphenyl (20 mol%) and pinacolborane (3 equiv.) and the mixture was heated at 80°C for 1 h. After cooling, water (2–3 mL), the substituted 2-bromonitrobenzene (0.7 equiv.) and $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (3 equiv.) were added, and the solution was heated at 100°C for 90 min. After cooling, water and CH_2Cl_2 were added. The phases were separated, the aqueous phase was extracted with more CH_2Cl_2 and the organic phase was dried (MgSO_4) and filtered. Removal of the solvent gave a brown solid which was submitted to column chromatography using solvent gradient from neat petrol to 10% ether/petrol to give compounds **2** as solids which were recrystallized from ether/petrol.
2a isolated yield: 80%; yellow crystals, mp 186–188°C; found: C, 66.12; H, 5.49; N, 4.31; S, 9.98%, calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{S}$: C, 66.04; H, 5.23; N, 4.28; S, 9.79%; δ_{H} (300 MHz, CDCl_3) 2.27 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.94 (s, 3H, OCH₃), 7.13 (d, 1H, 5-H, *J* 8 Hz), 7.18 (dd, 1H, 5'-H, *J* 8 and 3 Hz), 7.28 (d, 1H, 6'-H, *J* 8 Hz), 7.46 (d, 1H, 4-H, *J* 8 Hz), 7.52 (d, 1H, 3'-H, *J* 3 Hz); δ_{C} (75.4 MHz, CDCl_3) 11.49 (CH_3), 13.87 (CH_3), 18.06 (CH_3), 55.90 (OCH₃), 108.66 (CH), 118.61 (CH), 118.91 (CH), 125.37 (CH), 127.84 (C), 128.51 (C), 129.28 (C), 131.82 (C), 133.49 (CH), 135.00 (C), 138.92 (C), 140.52 (C), 149.87 (C), 159.02 (C).

2b isolated yield: 70%; orange crystals, mp 162–164°C; found: C, 59.18; H, 4.01; N, 3.77; S, 9.04%, calcd for C₁₈H₁₄F₃NO₂S: C, 59.17; H, 3.86; N, 3.83; S, 8.77%; δ_{H} (300 MHz, CDCl₃) 2.29 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 7.12 (d, 1H, 5-H, *J* 8 Hz), 7.51 (d, 1H, 4-H, *J* 8 Hz), 7.57 (d, 1H, 6'-H, *J* 8 Hz), 7.90 (dd, 1H, 5'-H, *J* 8 and 2 Hz) 8.26 (d, 1H, 3'-H, *J* 2 Hz).

2c isolated yield: 50%; yellow crystals, mp 203–205°C; found: C, 60.01; H, 4.51; N, 3.78; S, 8.36%, calcd for C₁₉H₁₆F₃NO₂S: C, 60.15; H, 4.25; N, 3.69; S, 8.45%; δ_{H} (300 MHz, CDCl₃) 2.23 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 2.74 (s, 3H, CH₃), 6.82 (s, 1H, 5-H), 7.55 (d, 1H, 6'-H, *J* 8 Hz), 7.89 (broad d, 1H, 5'-H, *J* 8 Hz), 8.25 (broad s, 1H, 3'-H).

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7. **Typical procedure for reductive cyclization:** A dry Schlenk tube was charged under Ar with compound **2a–c** (0.4 mmol) and triethyl phosphite (1.5 mL) and the mixture was heated at 160°C for 3 h 30. The excess of triethyl phosphite was removed after a work-up with water, extractions with chloroform and evaporation on the oil vacuum pump. The oil obtained was submitted to crystallization from petrol to give compound **3**.

3a isolated yield: 70%; colourless crystals, mp 220–222°C; found 295.10339, calcd for C₁₈H₁₇NOS 295.10307; δ_{H} (300 MHz, CDCl₃) 2.34 (s, 3H, CH₃), 2.55 (s, 3H, CH₃), 2.98 (s, 3H, CH₃), 3.92 (s, 3H, OCH₃), 6.85–6.90 (m, 2H, 6 and 8-H), 7.37 (s, 1H, 4-H), 7.90 (broad s, 1H, N-H), 8.08 (d, 1H, 9-H, *J* 9 Hz); δ_{C} (75.4 MHz, CDCl₃) 11.81 (CH₃), 14.20 (CH₃), 18.63 (CH₃), 55.58 (OCH₃), 94.51 (CH), 99.18 (CH), 107.33 (CH), 117.45 (C), 120.11 (C), 123.04 (CH), 124.63 (C), 127.13 (C), 130.99 (C), 133.15 (C), 138.69 (C), 138.84 (C), 141.98 (C), 158.46 (C).

3b isolated yield: 40%; colourless crystals, mp 248–250°C; found: C, 64.81; H, 4.36; N, 4.22; S, 9.56%, calcd for C₁₈H₁₄F₃NOS: C, 64.85; H, 4.23; N, 4.20; S, 9.62%; δ_{H} (300 MHz, CDCl₃) 2.36 (s, 3H, CH₃), 2.57 (s, 3H, CH₃), 3.04 (s, 3H, CH₃), 7.47 (s, 1H, 4-H) 7.51 (dd, 1H, 8-H, *J* 8 and 1 Hz) 7.68 (d, 1H, 6-H, *J* 1 Hz), 8.15 (broad s, 1H, N-H), 8.29 (d, 1H, 9-H, *J* 8 Hz).

3c isolated yield: 60%; colourless crystals, mp 251–253°C; found: C, 65.66; H, 4.74; N, 4.06; S, 9.13%, calcd for C₁₉H₁₆F₃NS: C, 65.69; H, 4.64; N, 4.03; S, 9.23%; δ_{H} (300 MHz, CDCl₃) 2.54 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 2.93 (s, 3H, CH₃), 3.02 (s, 3H, CH₃), 7.49 (broad d, 1H, 8-H, *J* 8 Hz) 7.72 (broad s, 1H, 6-H), 8.10 (broad s, 1H, N-H), 8.29 (d, 1H, 9-H, *J* 8 Hz).