Synthesis and intramolecular cyclization of novel β,β-bis-(benzo[*b*]thienyl)dehydroalanine derivatives

Ana S. Abreu, Natália O. Silva, Paula M. T. Ferreira and Maria-João R. P. Queiroz*

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

Abstract

The methyl ester of *tert*-butyloxycarbonyl-β,β-dibromodehydroalanine was obtained in a one pot procedure from bis-(*N*-*tert*-butyloxycarbonyl)dehydroalanine. The former was reacted with several boronic benzo[*b*]thiophene acids under Suzuki cross coupling conditions, to give new β,β-bis-(benzo[*b*]thienyl)dehydroalanines in high yields. These compounds were cyclized to pyrrole derivatives by treatment with $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMF.

Keywords: β,β-dibromodehydroalanine, β,β-bis-(benzo[*b*]thienyl)dehydroalanine; Suzuki cross coupling, pyrrole derivatives.

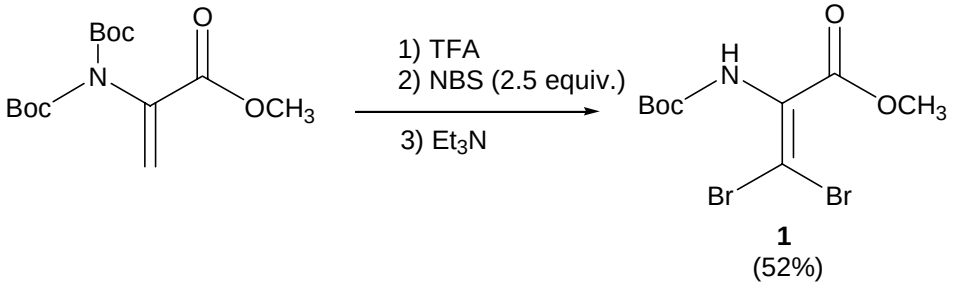
1. Introduction

Unsaturated amino acids constitute an important class of target compounds. When inserted into peptides they confer resistance to enzymatic degradation and induce conformational constrains which leads to changes in the secondary structure of peptides. Dehydroamino acids are also found in a family of polycyclic peptide antibiotics known as lantibiotics and have served as intermediates in the synthesis of non-proteinogenic amino acids.[1,2] The benzo[*b*]thiophenes are important heterocycles either as biological active molecules or as sensors due to their luminescent properties.[3] Here we describe the synthesis of new β,β-disubstituted dehydroamino acid derivatives using Suzuki cross coupling from β,β-dibromodehydroalanine and several boronic benzo[*b*]thiophene acids.

* Email: mjrpq@quimica.uminho.pt, Fax: +351-253678983

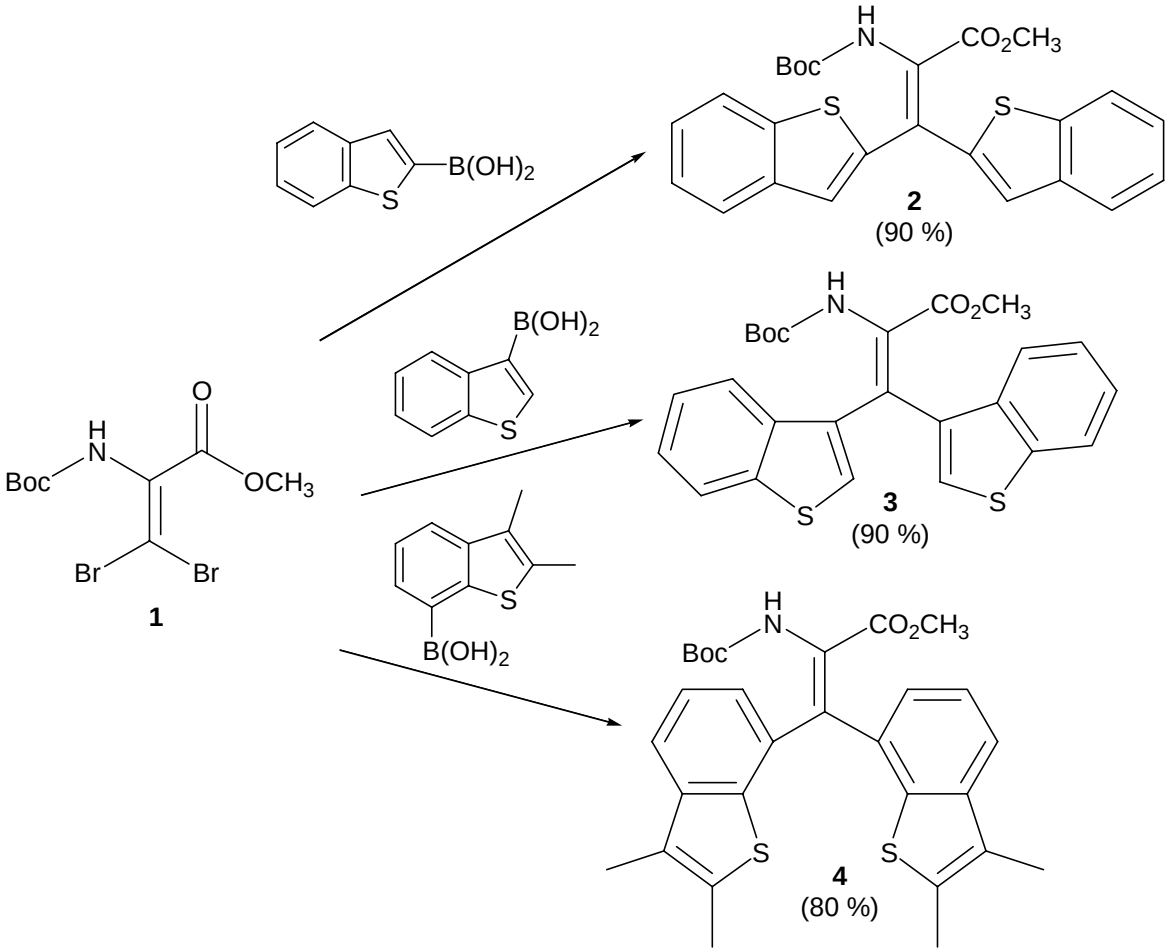
2. Results and discussion

The synthesis of *N*-acetyl-β,β-dichloro-α,β-dehydroalanine methyl ester was reported by Kolar *et al*.[4] in 54% yield, treating the corresponding β-clorodehydroalanine derivative with chlorine and Dabco.
In this work the methyl ester of *tert*-butyloxycarbonyl-β,β-dibromodehydroalanine was obtained in good yield in a one pot procedure. The methyl ester of bis-(*N*-*tert*-butyloxycarbonyl)dehydroalanine was reacted, in dichloromethane, with TFA followed by NBS (2.5 equiv.) and subsequent treatment with triethylamine (Scheme 1).[5]



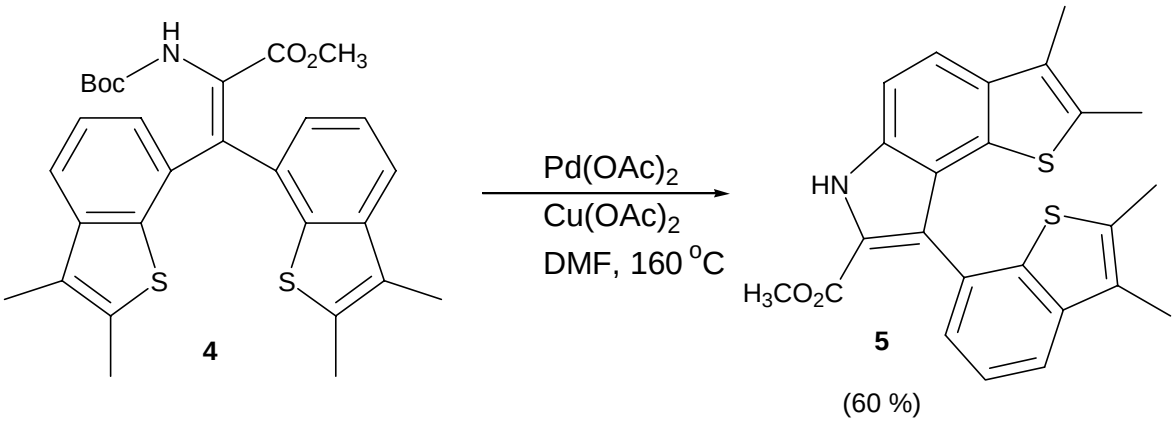
Scheme 1.

Compound 1 was then reacted with several boronic benzo[*b*]thiophene acids (5 equiv.) using $PdCl_2(PPh_3)_2$ as catalyst and Na_2CO_3 as base in DME/H_2O (10/1) at 90 ^oC, to give β,β-bis-(benzo[*b*]thienyl)dehydroalanines in high yields (Scheme 2).[6]



Scheme 2.

Compound **4** was treated with $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMF at 160 ^{o}C giving a 2,3-disubstituted thienoindole **5** in good yield (Scheme 3).[7] Using the same conditions compounds **2** and **3** were cyclized to the corresponding pyrrole derivatives in moderate yield (~30%). These compounds resulted from an intramolecular cyclization with *N*-deprotection, involving the α-NH and one of the benzo[*b*]thiophene carbon atoms.



Scheme 3.

Using the β,β-dibromodehydroalanine derivative we were able to synthesize novel β,β-disubstituted dehydroamino acids linked to either the benzene or the thiophene ring of the benzo[*b*]thiophene moiety. These compounds were *N*-deprotected and cyclized to benzo[*b*]thienylpyrroles in a one procedure. Both types of compounds can be biologically active, can be used in peptidomimetics and/or can be used as biomarkers due to their fluorescence proprieties.

3. Acknowledgements

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4. References

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5. To a solution of Boc-ΔAla(*N*-Boc)-OMe (5.00 mmol) in dichloromethane (0.1 mol dm^{-3}), TFA (1 mL) was added with strong stirring at room temperature. After 2 hours, NBS (12.5 mmol; 2.22 g) was added and it was left stirring overnight. The mixture was then treated with triethylamine (18.8 mmol), left stirring for 30 min. and then washed with water, $NaHCO_3$ (1 mol dm^{-3}) and brine (2 × 30 mL each), dried over $MgSO_4$, filtered and evaporated at reduced pressure to give an oil. Column chromatography on silica using 30% diethyl ether / petroleum ether 40-60 °C gave compound **1** (52 %) as colourless crystals, m.p. 81.4-82.5 °C, $C_9H_{13}NO_4Br_2$ found (calc.): C

30.19 (30.11); H 3.88 (3.65); N 4.05 (3.90). δ_H (300 MHz,$CDCl_3$): 1.47 (9H, s, CH_3 Boc), 3.89 (3H, s, OCH_3), 6.37 (1H, s, NH). δ_C (75.4 MHz, $CDCl_3$): 27.98, 52.98, 68.91, 82.63, 132.71, 150.89, 162.53.

6. To a solution of compound **1** (0.100 mmol; 36.0 mg) in DME/H_2O (10:1; 2.20 mL), 7-boronic-2,3-dimethylbenzo[*b*]thiophene acid (0.500 mmol; 103 mg), Na_2CO_3 (0.400 mmol; 42.4 mg), $PdCl_2(PPh_3)_2$ (20 mol%; 14.0 mg) were added and the mixture was heated for 1 hour at 90 ^oC. The DME was removed under reduced pressure and the residue was dissolved in 15 mL of ethyl acetate. The organic layer was then washed with water and brine (2 × 5 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography on silica (230-400mesh) using 30% diethyl ether / petroleum ether 40-60 ^oC, gave compound **4** (80 %) as yellow crystals, m.p. 191.4-193.4 ºC, $C_{29}H_{31}NS_2O_4$ found (calc.): C 66.82 (66.77); H 6.25 (5.99); N 2.70 (2.68); S 11.90 (12.29). δ_H (300 MHz,$CDCl_3$): 1.45 (9H, s, CH_3 Boc), 2.23 (3H, s, Ar-CH_3), 2.30 (3H, s, Ar-CH_3), 2.31 (3H, s, Ar-CH_3), 2.44 (3H, s, Ar-CH_3), 3.44 (3H, s, OCH_3), 6.01 (1H, s, NH), 7.14-7.36 (4H, m, ArH), 7.52 (1H, dd, *J* 7.5 and 1.5 Hz, ArH), 7.58 (1H, d, *J* 7.5 Hz, ArH). δ_C (75.4 MHz, $CDCl_3$): 11.40, 11.49, 13.62, 13.69, 28.10, 52.13, 81.19, 121.04, 121.50, 123.56, 124.19, 124.80, 125.78, 126.55, 126.88, 128.20, 129.88, 132.79, 134.36, 134.69, 137.88, 138.17, 141.49, 141.73, 152.63, 165.96.
7. To a solution of compound **4** (0.228 mmol; 119 mg) in dry DMF (2.30 mL), $Pd(OAc)_2$ (50 mol%; 25.6 mg), $Cu(OAc)_2.H_2O$ (0.68 mmol; 136.6 mg) were added and the mixture was heated at 160 ^oC, for 1 h 30 min. Ethyl acetate (50 mL) was then added and the organic layer washed with water and brine (2 × 25 cm^3 each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography on silica using 70% dichloromethane/petroleum ether 40-60 ^oC, gave compound **5** (60 %) as light yellow crystals m.p. 292.5-294.3 ºC. $C_{24}H_{21}NS_2O_2$ HRMS M^+ found (calc.): 419.0999 (419.10137). (300 MHz) δ_H (300 MHz,$CDCl_3$): 2.29 (3H, s, Ar-CH_3), 2.30 (3H, s, Ar-CH_3), 2.38 (3H, s, Ar-CH_3), 2.39 (3H, s, Ar-CH_3), 3.69 (3H, s, OCH_3), 7.35 (1H, dd, *J* 7.5 and 1 Hz, ArH), 7.45 (1H, d, *J* 8.7 Hz, ArH), 7.52 (1H, t, *J* 7.5 Hz, ArH), 7.59 (1H, d, *J* 8.7 Hz, ArH), 7.73 (1H, dd, *J* 7.5 and 1 Hz, ArH), 9.20 (1H, s, NH). δ_C (75.4 MHz, $CDCl_3$): 11.62, 11.68, 13.42, 13.81, 51.86, 109.07, 120.15, 120.66, 122.06, 122.80, 123.99, 125.32, 126.94, 127.16, 128.24, 128.33, 130.96, 133.09, 134.09, 135.57, 139.93, 141.04, 162.02.