Synthesis of new β-amidodehydroaminobutyric acid derivatives and of new tyrosine derivatives using copper catalyzed C-N and C-O coupling reactions

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Abstract. Several β-amidodehydroaminobutyric acid derivatives were prepared from N,C-diprotected β-bromodehydroaminobutyric acids and amides by a copper catalyzed C-N coupling reaction. The best reaction conditions include the use of a catalytic amount of CuI, *N,N'*-dimethylethylenediamine as ligand and K_2CO_3 as base in toluene at 110 ºC. The stereochemistry of the products was determined using NOE difference experiments and the results obtained are in agreement with an *E*-stereochemistry. Thus, the stereochemistry is maintained in the case of the *E*-isomers of β-bromodehydroaminobutyric acid dervatives, but when the *Z*-isomers were used as substrates the reaction proceeds with inversion of configuration. The use of β-bromodehydrodipeptides as substrates was also tested. It was found that the reaction outcome depend on the stereochemistry of the β-bromodehydrodipeptide and on the nature of the first amino acid residue. The products isolated were the β-amidodehydrodipeptide derivatives and/or the corresponding dihydropyrazines.
The same catalytic system (CuI/*N,N'*-dimethylethylene diamine) was used in the C-O coupling reactions between a tyrosine derivative and aryl bromides. The new *O*-aryltyrosine derivatives were isolated in moderate to good yields. The photophysical properties of two of these compounds were studied in four solvents of different polarity. The results show that these compounds after deprotection can used as fluorescence markers.

Keywords: Copper - *N,N'*-dimethylethylene diamine - cross-couplings - dehydroamino acid derivatives - fluorescent amino acids.

Introduction

Copper-catalyzed coupling reactions between aryl halides and nucleophiles constitute an important method for the formation of C-N and C-O bonds. The traditional copper assisted Ullmann reactions require harsh conditions namely high temperatures and the use of stoichiometric amounts of copper, can only be applied to activated aryl halides and give moderate yields (Beletskaya and Cheprakov 2004). However, in the last few years the use of bidentate ligands allowed this type of reaction to be performed at much lower temperatures and in the presence of copper as catalyst (Bao et al. 2005; Ma and Cai 2008; Chen et al. 2008; Monnier and Taillefer 2009). Among these chelating ligands the 1,2-diamines are used in the efficient coupling of several types of substrates having a free N-H or O-H. Most of the research work developed so far in this area involves aromatic substrates nevertheless there are several reports on the use of vinyl halides as reagents. Thus, Shen *et al.* (2000; 2002) developed a copper (I) carboxylate-catalyzed coupling of vinyl iodides and amides using cesium carbonate as base in NMP or DMSO at 90 ºC. Buchwald (Jiang et al. 2003; Martin et al. 2007) described an efficient protocol for the copper-catalyzed coupling of amides and carbamates with vinyl halides using *N*,*N*'-dimethylethylenediamine (DMED) as ligand and potassium or cesium carbonate as base. The authors were able to prepare in good yields an array of enamides from cyclic and acyclic primary amides and cyclic secondary amides with differently substituted vinyl bromides and iodides. Although Buchwald *et al.* stated that *N*,*N*-dimethylglycine was much less effective than *N*,*N*'-dimethylethylenediamine as ligand, Pan *et al.* (2004) reported the CuI catalyzed coupling reaction of vinyl halides with amides using *N*,*N*-dimethylglycine as ligand, cesium carbonate as base in dioxane. Furthermore the authors attributed Buchwald results with *N*,*N*-dimethylglycine to the use of toluene as solvent.

On the basis of our previous work on the synthesis of non-proteinogenic amino acids using palladium catalyzed C-C and C-N coupling reactions (Abreu et al. 2003; Ferreira et al. 2009) we have decided to apply copper catalyzed C-N and C-O couplings to the synthesis of new amino acid derivatives. Thus, several methyl esters of β-amidodehydroamino acids were prepared in good to high yields from β-bromodehydroaminobutyric acid derivatives and several amides using CuI as catalyst and of *N*,*N*'-dimethyl ethylenediamine as ligand. The same catalytic system was tested in the C-O coupling (Ma and Cai 2003; Xia and Taillefer 2008) of a tyrosine derivative and aryl halides to give new *O*-aryltyrosines. The photophysical properties of two of the new amino acids prepared having a pyrenyl and a biphenyl moiety were evaluated in four solvents of different polarity.

Materials and methods

Melting points (°C) were determined in a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus at 300 and 75.4 MHz, respectively or on a Bruker Avance II^{+} at 400 and 100.6 MHz, respectively. Heteronuclear correlations (^{1}H-^{13}C, HMQC and HMBC) were also preformed. Chemical shifts are given in ppm and coupling constants in Hz. MS and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain; elemental analysis was performed on a LECO CHNS 932 elemental analyser. The optical rotation was determined in a ACTIVITY-AA-1000 polarimeter.

The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230-400 mesh. Petroleum ether refers to the boiling range 40-60 °C. When solvent gradient was used, the increase of polarity was made from neat petroleum ether to mixtures of diethyl ether/petroleum ether, increasing 10% of diethyl ether each time until the isolation of the product. All compounds were pure by NMR.

Spectroscopic measurements: All the solutions were prepared using spectroscopic grade solvents. Absorption spectra were recorded in a Jasco V-630 UV-Vis spectrophotometer. Fluorescence measurements were performed using a HORIBA Jobin Yvon Fluoromax-4 spectrofluorimeter, equipped with a monochromator in both excitation and emission and a temperature controlled cuvette holder. Fluorescence spectra were corrected for the instrumental response of the system.

For fluorescence quantum yield determination, the solutions were previously bubbled for 40 minutes with ultrapure nitrogen. The fluorescence quantum yields (Φ_s) were determined using the standard method (equation 1) (Demas and Crosby 1971; Fery-Forgues and Lavabre 1999). 9,10-diphenylanthracene in ethanol [Φ_r = 0.95 (Morris et al. 1976)] and naphthalene in cyclohexane [Φ_r = 0.23 (Berlman 1971)] were used as references.

$$\Phi_s = \frac{A_r F_s n_s^2}{A_s F_r n_r^2} \Phi_r \quad (1)$$

where A is the absorbance at the excitation wavelength, F the integrated emission area and n the refraction index of the solvents used. Subscripts refer to the reference (r) or sample (s) compound.

Synthesis of compounds ***Z*-1** (Silva et al. 2002), ***E*-1** (Silva et al. 2002), ***Z*-3** (Ferreira et al. 2010b) and ***E*-3** (Ferreira et al. 2010b). The synthesis of these compounds was described elsewhere.

General procedure for the synthesis of β-amidodehydroamino acid derivatives

An over-dried Schelenk tube was charged with CuI (5.0 mol%), the β-bromodehydroaminobutyric acid

derivative, the amide (1.5 eq), K_2CO_3 (2 eq.) and *N*,*N*'-dimethylethylenediamine (20 mol%) followed by the addition of dry toluene (1 mL). The tube was sealed, and the reaction mixture was stirred at 110 ºC for 5 h. After the system had cooled to room temperature, the solvent was evaporated. The reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water and brine (2 x 30 mL each). After drying over $MgSO_4$ the extract was taken to dryness at reduced pressure. Crystallization with ethyl acetate/petroleum ether afforded the corresponding β-amidodehydroamino acid derivative.

Synthesis of (*E*)-methyl 3-benzamido-2-(*tert*-butoxycarbonylamino)but-2-enoate, ***E*-2a**

The general procedure described above was followed with compound ***Z*-1** (1 mmol, 294 mg) as substrate to give compound ***E*-2a** (229 mg, 69%) as a white solid. M.p. 128.0 – 129.0 ºC (from ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): 1.45 (s, 9 H, CH_3 Boc), 2.62 (s, 3 H, γCH_3), 3.77 (s, 3 H, OCH_3), 5.54 (br s, 1 H, αNH), 7.48-7.56 (m, 3 H, ArH), 7.97 (d, *J* = 7.2 Hz , 2 H, ArH), 12.36 (br s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 16.82 (γCH_3), 28.24 [C(*C*H_3)$_3$], 52.06 (OCH_3), 80.37 [O*C*(CH$_3$)$_3$], 105.53 (C), 127.63 (CH), 128.83 (CH), 132.38 (CH), 134.13 (C), 154.72 (C), 154.78 (C=O), 165.70 (C=O), 168.46 (C=O) ppm. $C_{17}H_{22}N_2O_5$ (334.37): calcd. C 61.07, H 6.63, N 8.38; found C 60.78, H 6.911, N 8.354.
The general procedure described above was followed with compound ***E*-1** (0.25 mmol, 73.5 mg) as substrate to give compound ***E*-2a** (55 mg, 64%).

Synthesis of (*E*)-methyl 3-(4-bromobenzamido)-2-(*tert*-butoxycarbonylamino)but-2-enoate, ***E*-2b**

The general procedure described above was followed with compound ***Z*-1** (0.5 mmol, 147 mg) as substrate and CuI (10 mol%) to give compound ***E*-2b** (165 mg, 80%) as a white solid. M.p. 141.0 – 142.0 ºC (from ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): 1.48 (s, 9 H, CH_3 Boc), 2.59 (s, 3 H, γCH_3), 3.80 (s, 3 H, OCH_3), 5.54 (br s, 1 H, αNH), 7.63 (d, *J* = 8.4 Hz , 2 H, ArH), 7.83 (d, *J* = 8.4 Hz , 2 H, ArH), 12.39 (br s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): 16.77 (γCH_3), 28.22 [C(*C*H_3)$_3$], 52.16 (OCH_3), 80.46 [O*C*(CH$_3$)$_3$], 105.81 (C), 127.36 (C), 129.18 (CH), 132.10 (CH), 132.98 (C), 154.46 (C=O), 154.71 (C), 164.70 (C=O), 168.54 (C=O) ppm. $C_{17}H_{21}BrN_2O_5$ (413.26): calcd. C 49.41, H 5.12, N 6.78; found C 49.31, H 5.195, N 6.774.
The general procedure described above was followed with compound ***E*-1** (0.5 mmol, 147 mg) as substrate to give compound ***E*-2b**. Column chromatography using diethyl ether/petroleum ether (1:1) gave compound ***E*-2b** (157 mg, 76%).

Synthesis of (*E*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(4-methoxybenzamido)but-2-enoate, ***E*-2c**

The general procedure described above was followed with compound ***Z*-1** (0.25 mmol, 73 mg) as substrate and CuI (10 mol%) to give compound ***E*-2c** (53 mg, 58%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.49 (s, 9 H, CH_3 Boc), 2.61 (s, 3 H, γCH_3), 3.80 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.49 (br s, 1 H, αNH), 6.98 (d, *J* = 8.8 Hz , 2 H, ArH), 7.95 (d, *J* = 8.8 Hz , 2 H, ArH), 12.32 (br s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 16.80 (γCH_3), 28.26 [C(*C*H_3)$_3$], 52.02 (OCH_3), 55.45 (OCH_3), 80.34 [O*C*(CH$_3$)$_3$], 104.97 (C), 114.07 (CH), 126.47 (C), 129.69 (CH), 154.87 (C=O), 155.18 (C), 162.96 (C), 165.22 (C=O), 168.58 (C=O) ppm. HRMS (ESI): calcd. for $C_{18}H_{24}N_2NaO_6$ 387.15321; found 387.15282.
The general procedure described above was followed with compound ***E*-1** (0.25 mmol, 73 mg) to give compound ***E*-2c** (61 mg, 67%).

Synthesis of (*E*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(4-nitrobenzamido)but-2-enoate, ***E*-2d**

The general procedure described above was followed with compound ***Z*-1** (0.25 mmol, 73 mg) as substrate to give compound ***E*-2d** (22 mg, 23%) as a white solid. M.p. 179.0 – 184.0 ºC (from ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): 1.49 (s, 9 H, CH_3 Boc), 2.61 (s, 3 H, γCH_3), 3.82 (s, 3 H, OCH_3), 5.56 (br s, 1 H, αNH), 8.13 (d, *J* = 8.8 Hz , 2 H, ArH), 8.35 (d, *J* = 8.8 Hz , 2 H, ArH), 12.55 (br s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 16.75 (γCH_3), 28.22 [C(*C*H_3)$_3$], 52.32 (OCH_3), 80.66 [O*C*(CH$_3$)$_3$], 106.73 (C), 124.02 (CH), 128.78 (CH), 139.61 (C), 150.03 (C), 153.85 (C), 154.59 (C=O), 163.50 (C=O), 168.59 (C=O) ppm. HRMS (micrOTOF): calcd. for $C_{17}H_{21}N_3NaO_7$ 402.12772; found 402.12717.
The general procedure described above was followed with compound ***E*-1** (0.25 mmol, 73 mg) to give compound ***E*-2d** (34 mg, 36%).

Synthesis of (*E*)-methyl 3-acetamido-2-(*tert*-butoxycarbonylamino)but-2-enoate, ***E*-2e**

The general procedure described above was followed with compound ***Z*-1** (0.5 mmol, 147 mg) as substrate, CuI (10 mol%) and DMED (30 mol%) for 12h to give compound ***E*-2e**. Column chromatography using diethyl ether/petroleum ether ((2:1) gave compound ***E*-2e** (97 mg, 71%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9 H, CH_3 Boc), 2.15 (s, 3 H, CH_3), 2.46 (s, 3 H, γCH_3), 3.76 (s, 3 H, OCH_3), 5.44 (br s, 1 H, αNH), 11.42 (br s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): 16.55 (γCH_3), 25.53 (CH_3), 28.22 [C(*C*H_3)$_3$], 51.91 (OCH_3), 80.36 [O*C*(CH$_3$)$_3$], 104.71 (C), 154.36 (C), 154.79 (C=O), 168.19 (C=O), 169.19 (C=O) ppm. HRMS (micrOTOF): calcd. for $C_{12}H_{20}N_2NaO_5$ 295.12699; found 295.12644.

Synthesis of (*E*)-methyl 2,3-bis(benzamido)but-2-enoate, ***E*-2f**

The general procedure described above was followed with compound ***E*-3** (0.25 mmol, 75 mg) as substrate giving compound **4** (31 mg, 58%) and compound ***E*-2f** (30 mg, 37%). Compound ***E*-2f** was obtained as a white solid, m.p. 98.0-99.0ºC (from ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): 2.64 (s, 3 H, γCH_3), 3.79 (s, 3 H, OCH_3), 7.11 (br s, 1 H, αNH), 7.44-7.61 (m, 6 H, ArH), 7.90 (m, 2 H, ArH), 8.01 (d, *J* = 7.6 Hz , 2 H, ArH), 12.47 (br s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 17.12 (γCH_3), 52.26 (OCH_3), 104.96 (C), 127.28 (CH), 127.70 (CH), 128.77 (CH), 128.89 (CH), 132.04 (CH), 132.49 (CH), 133.99 (C), 134.09 (C), 154.73 (C), 165.74 (C=O), 167.01 (C=O), 167.96 (C=O) ppm. HRMS (micrOTOF): calcd. for $C_{19}H_{18}N_2NaO_4$ 361.11643; found 361.11588.
The general procedure described above was followed with compound ***Z*-3** (0.5 mmol, 149 mg) to give after column chromatography using diethyl ether/petroleum ether compound **4** (40 mg, 37%) together with Bz-ΔAbu-OMe **5** (Ferreira et al. 2008).

Synthesis of methyl 3,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrazine-2-carboxylate, **9**

The general procedure described above was followed with compound ***E*-6** (0.25 mmol, 88 mg) as substrate giving compound **9** (21 mg, 30%) together with Boc-Gly-ΔAbu-OMe (22 mg, 32%). Compound **9** was obtained as a white solid. M.p. 105.0-106.0ºC (from ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): 1.44 (s, 9 H, CH_3 Boc), 2.60 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 4.41 (br s, 2 H, CH_2), 5.22 (br s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): 11.84 (CH_3), 28.23 [C(*C*H_3)$_3$], 37.74 (CH_2), 51.92 (OCH_3), 80.20 [O*C*(CH$_3$)$_3$], 127.30 (C), 155.42 (C=O), 156.76 (C), 159.24 (C=O), 162.46 (C=O) ppm. HRMS (ESI): calcd. for $C_{12}H_{18}N_2NaO_5$ 293.11079; found 293.11091.
The general procedure described above was followed with compound ***Z*-6** (0.5 mmol, 176.0 mg) to give after column chromatography using diethyl ether/petroleum ether compound **9** (90 mg, 63%).

Synthesis of *E*-methyl 7-isopropyl-3,11,11-trimethyl-1,6,9-trioxo-1-phenyl-10-oxa-2,5,8-triazadodec-3-ene-4-carboxylate, ***E*-8** and of methyl 5-isopropyl-3,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrazine-2-carboxylate, **10**

The general procedure described above was followed with compound ***E*-7** (0.16 mmol, 62 mg) as substrate giving compound ***E*-8** (14 mg, 21%) and compound **10** (14.5 mg, 29%). Compound ***E*-8** was obtained as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.99-1.06 (m, 6 H, CH_3), 1.47 (s, 9 H, CH_3 Boc), 2.22-2.26 (m, 1 H, CH), 2.55 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 3.98-4.02 (m, 1 H, CH), 7.01 (br s, 1 H, NH), 7.44-7.52 (m, 2 H, ArH), 7.54-7.58 (m, 1 H, ArH), 7.96-7.99 (m, 2 H, ArH), 12.40 (br s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 16.91 (CH_3), 19.30 (CH_3), 19.35 (CH_3), 28.29 [C(*C*H_3)$_3$], 30.31 (CH), 51.04 (OCH_3), 60.36 (CH), 80.20 [O*C*(CH$_3$)$_3$], 104.50 (C), 127.67 (CH), 128.86 (CH), 132.47 (CH), 134.05 (C), 154.69 (C), 155.99 (C=O), 155.68 (C=O), 167.82 (C=O), 171.73 (C=O) ppm. HRMS (M+H): calcd. for $C_{22}H_{32}N_3O_5$ 434.22856; found 434.22855. Compound **10** was obtained as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): 0.88-0-92 (m, 6 H, CH_3), 1.41 (s, 9 H, CH_3 Boc), 2.09-2.20 (m, 1 H, CH), 2.59 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 4.68-4.73 (m, 1 H, CH), 5.26 (br s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): 11.94 (CH_3), 17.87 (CH_3), 18.72 (CH_3), 28.22 (CH_3 Boc), 32.81 (CH), 51.92 (OCH_3), 54.02 (CH), 79.84 [C(*C*H_3)$_3$], 127.17 (C), 155.33 (C=O), 156.21 (C), 162.10 (C=O), 162.63 (C=O) ppm. HRMS (ESI): calcd. for $C_{15}H_{24}NaN_2O_5$ 335.15774; found 335.15763.
The general procedure described above was followed with compound ***Z*-7** (0.28 mmol, 110 mg) to give after column chromatography using diethyl ether/petroleum ether compound **10** (75 mg, 80%).

General Procedure for the synthesis of *O*-aryltyrosine derivatives

An over-dried Schelenk tube was charged with CuI (15 mol%), *N*,*N*'-dimethylethylenediamine (50 mol%), aryl halide (1 equiv.), Boc-L-Tyr-OMe (1.5 equiv.), Cs_2CO_3 (1.5 eq.) and followed by the addition of dry toluene (1 mL). The tube was sealed, and the reaction mixture was stirred at 100ºC. After the system had cooled to room temperature, the solvent was evaporated. The reaction mixture was dissolved in ethyl acetate (50 mL) and washed with $KHSO_4$ (1 M), $NaHCO_3$ (1 M) and brine (30 mL each). After drying over $MgSO_4$ the extract was taken to dryness at reduced pressure. The residue was submitted to column chromatography using a solvent gradient from neat petroleum ether to mixtures of ether/petroleum ether, increasing 10% of ether each time until the isolation of the product.

Synthesis of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(pyren-1-yl)-tyrosine, **11**
The general procedure described above was followed with 1-bromopyrene (0.2 mmol, 56 mg) and Boc-Tyr-OMe (0.3 mmol, 89 mg) for 24h to afford compound **11** (35 mg, 35%) as a white solid. M.p. 64.0 – 65.0 ºC (from ethyl acetate/petroleum ether). $[\alpha]_D$ = -24.5 (c=0.1, CH_3OH) ^{1}H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9 H, CH_3 Boc), 3.02-3.16 (m, 2 H, βCH_2), 3.74 (s, 3 H, OCH_3), 4.61 (q, *J* = 7.2 Hz, 1 H, αCH), 5.05 (d, *J* = 7.2 Hz, 1 H, NH), 6.98-7.00 (m, 2 H, ArH), 7.11 (d, *J* = 8.0 Hz, 2 H, ArH), 7.62 (d, *J* = 8.0 Hz, 1 H, ArH), 8.00-8.20 (m, 7 H, ArH), 8.35 (d, *J* = 9.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 28.29 [C(*C*H_3)$_3$], 37.66 (βCH_2), 52.23 (OCH_3), 54.47 (αCH), 79.95 [O*C*(CH$_3$)$_3$], 117.12 (CH), 117.97 (CH), 119.95 (CH), 121.06 (CH), 122.94 (C), 124.73 (C), 124.83 (CH), 125.01 (CH), 125.46 (CH), 125.99 (C), 126.29 (CH), 126.37 (CH), 127.10 (CH), 127.52 (CH), 127.77 (C), 130.48 (C), 130.68 (CH), 131.35 (C), 150.15 (C-O), 155.05 (C=O), 157.80

(C-O), 172.30 (C=O) ppm. $C_{31}H_{31}NO_5$ (497.58): calcd. C 74.83, H 6.28, N 2.81; found C 74.94, H 6.001, N 2.838.

Synthesis of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(4-nitrophenyl)-tyrosine, **12**

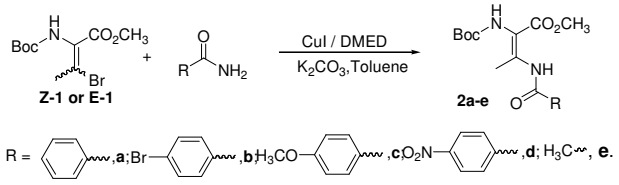
The general procedure described above was followed with 1-bromo-4-nitrobenzene (0.2 mmol, 40.4 mg) and Boc-Tyr-OMe (0.3 mmol, 89 mg) as substrate for 24h to afford compound **12** (48 mg, 58%) as an oil. $[\alpha]_D$ = +29.1 (c=0.1, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9 H, CH_3 Boc), 3.00-3.06 (m, 1 H, βCH_2), 3.15-3.20 (m, 1 H, βCH_2), 3.75 (s, 3 H, OCH_3), 4.61 (q, *J* = 7.0 Hz, 1 H, αCH), 5.05 (d, *J* = 7.0 Hz, 1 H, NH), 6.99-7.03 (m, 4 H, ArH), 7.20 (d, *J* = 8.4 Hz, 2 H, ArH), 8.20 (d, *J* = 9.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 28.28 [C(CH_3)$_3$], 37.95 (βCH_2), 52.33 (OCH_3), 54.42 (αCH), 80.06 [O*C*(CH_3)$_3$], 117.09 (CH), 120.52 (CH), 125.92 (CH), 131.17 (CH), 133.42 (C), 142.67 (C), 153.73 (C-O), 155.00 (C=O), 163.27 (C-O), 172.15 (C=O) ppm. HRMS (micrOTOF): calcd. for $C_{21}H_{24}N_2NaO_7$ 439.14812; found 439.14757.

Synthesis of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(biphenyl-4-yl)-tyrosine, **13**

The general procedure described above was followed with 1-bromobiphenyl (0.2 mmol, 47 mg) and Boc-Tyr-OMe (0.3 mmol, 89 mg) as substrate for 24h to afford compound **13** (30 mg, 34%) as an oil. . $[\alpha]_D$ = + 34.1 (c=0.1, CH_3OH).^{1}H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9 H, CH_3 Boc), 3.01-3.06 (m, 1 H, βCH_2), 3.10-3.15 (m, 1 H, βCH_2), 3.74 (s, 3 H, OCH_3), 4.60 (dd, *J* = 6.8 Hz and *J* = 6.0 Hz, 1 H, αCH), 5.02 (d, *J* = 6.8 Hz, 1 H, NH), 6.99 (d, *J* = 8.4 Hz, 2 H, ArH), 7.07 (d, 2 H, *J* = 8.4 Hz, ArH), 7.12 (d, *J* = 8.8 Hz, 1 H, ArH), 7.32-7.36 (m, 1 H, ArH), 7.42-7.46 (m, 2 H, ArH), 7.54-7.59 (m, 4 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 28.29 [C(CH_3)$_3$], 37.72 (βCH_2), 52.23 (OCH_3), 54.46 (αCH), 79.96 [O*C*(CH_3)$_3$], 118.97 (CH), 119.05 (CH), 126.88 (CH), 127.03 (CH), 128.41 (CH), 128.76 (CH), 130.64 (CH), 130.97 (C), 136.34 (C), 125.99 (C), 126.29 (CH), 126.37 (CH), 127.10 (CH), 127.52 (CH), 127.77 (C), 140.50 (C), 155.04 (C=O), 156.23 (C-O), 156.72 (C-O), 172.29 (C=O) ppm. HRMS (micrOTOF): calcd. for $C_{27}H_{29}NNaO_5$ 470.19434; found 470.19510.

Results and Discussion

In this work the copper catalyzed vinylation of primary amides with β-halo-β-substituted dehydroamino acids was investigated. Considering the variety of conditions proposed for the reaction between amides and vinyl halides we have decided to screen the copper catalyzed amidation of β-bromodehydroamino acids under several reaction conditions using the *Z*-isomer of the methyl ester of *N*-*tert*-butoxycarbonyl-β-bromodehydroaminobutyric acid ***Z*-1** (Silva et al. 2002) and benzamide as substrates (Scheme 1). The conditions proposed by Pan *et al.* (2004) namely CuI (10 mol%), *N*,*N*-dimethylglycine (20 mmol%), Cs_2CO_3 (2 equiv.) in dioxane at 80 ºC failed to give the β-benzamidodehydroaminobutyric acid derivative **2a**. By changing the solvent for toluene or the base for K_2CO_3 the only compounds isolated were the reactants together with the debrominated dehydroaminobutyric acid derivative. Using Buchwald conditions (Jiang et al. 2003; Martin et al. 2007), CuI (5 mol%), DMED (20 mol%), K_2CO_3 (2 equiv.) in toluene at 110 ºC, it was possible to isolate the methyl ester of the β-amidodehydroaminobutyric acid **2a** in 69% yield. Changing the base for Cs_2CO_3 or the solvent for DMF failed to give the product. In view of these results Buchwald *et al.* conditions were applied to the synthesis of several β-amidodehydroaminobutyric acid derivatives (**2a-e**) (Scheme 1, Table 1) from the ***Z*-1** and ***E*-1** (Silva et al. 2002) and aryl or alkyl primary amides. Compounds ***Z*-1** and ***E*-1** were obtained from a threonine derivative by a sequential dehydration reaction followed by halogenation developed in our laboratories.(Ferreira et al. 2007).



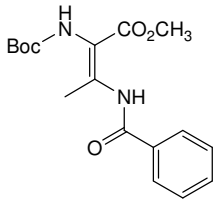
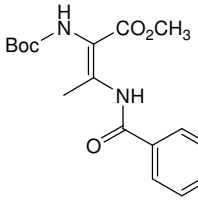
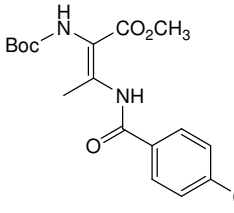
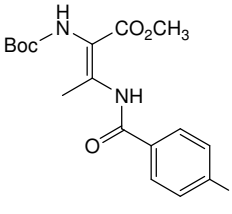
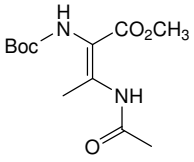
Scheme 1. Synthesis of β-amidodehydroaminobutyric acid derivatives **2a-e** from the *E*- or *Z*-isomers of the methyl ester of *N*-*tert*-butoxycarbonyl-β-bromodehydroaminobutyric acid and several amides.

The β-amidodehydroaminobutyric acid derivatives were obtained in moderate to good yields (58-80%) except when 4-nitrobenzamide was used (23% and 36% yield) (Table 1). The results show a similar reactivity of both *Z*- and *E*-isomers of the β-bromodehydroaminobutyric acid derivative **1** and of aryl and alkylamides.

The stereochemistry of the β-amidodehydroaminobutyric acid derivatives was determined by NOE difference experiments by irradiating the α-NH and OCH_3 protons and observing NOE enhancements in the γ-CH_3 protons and in the β-amide protons, respectively. This is in agreement with an *E*-stereochemistry. Although it is reported that the copper catalyzed coupling between vinyl halides and amides proceed with maintenance of the geometry of the C-C double bond in the case of the tetrasubstituted vinyl halides ***Z*-1** and ***E*-1** it was found that the stereochemistry is maintained in the case of the *E*-isomer but when the *Z*-isomer was used as substrate the coupling products have an *E*-stereochemistry. This can be attributed to the steric hindrance of the *Z*-β-amidodehydroaminobutyric acid derivatives.

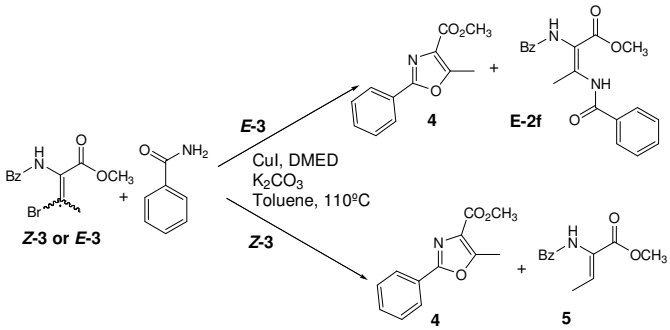
The use of a β-iododehydroaminobutyric acid derivative was also tested and it was found that the reaction between the *Z*-isomer of the methyl ester of *N*-*tert*-butoxycarbonyl-β-iododehydroaminobutyric acid and benzamide gave the coupled product, ***E*-2a** in 46% yield together with a considerable amount of the dehalogenated dehydroaminobutyric acid derivative. The only products isolated from the reaction of the methyl ester of *N*-(*tert*-butoxycarbonyl)-β-bromodehydrophenylalanine and benzamide were the reactants together with the debrominated dehydrophenylalanine. Thus, the nature of the halogen and of the group linked to the β-carbon atom are important issues to be taken into consideration in this type of reactions involving dehydroamino acid derivatives.

Table 1. Results obtained in synthesis of β-amidodehydroaminobutyric acid derivatives.

Substrate	Product	Yield (%)
***Z*-1**	 ***E*-2a**	69
***E*-1**	***E*-2a**	64
***Z*-1**	 ***E*-2b**	80[a]
***E*-1**	***E*-2b**	76
***Z*-1**	 ***E*-2c**	58[a]
***E*-1**	***E*-2c**	67
***Z*-1**	 ***E*-2d**	23[b]
***E*-1**	***E*-2d**	36[b]
***Z*-1**	 ***E*-2e**	71[a]

[a] 10 mol% of CuI. [b] It was isolated Boc-ΔAbu-OMe.

To evaluate the influence of other *N*-protecting groups namely acyl protecting groups, the methyl esters of *N*-benzoyl-β-bromodehydroaminobutyric acid (***Z*-3** and ***E*-3**) (Ferreira et al. 2010b) were reacted with benzamide (Scheme 2).



Scheme 2. Reaction between the *E*- and *Z*-isomers of the methyl ester of *N*-benzoyl-β-bromodehydroaminobutyric acid and benzamide.

The coupled product ***E*-2f** [(*E*)-methyl 2,3-bis(benzamido)but-2-enoate] was isolated in 38 % yield together with the trisubstituted oxazole **4** (Ferreira et al. 2008) (58 % yield) using ***E*-3** as substrate. When ***Z*-3** was reacted with benzamide the only products isolated were the corresponding oxazole **4** (Ferreira et al. 2008) (37 % yield) together with the methyl ester of *N*-benzoyldehydroaminobutyric acid (**5**). These results were expected since recently it was developed in our laboratories a new method for the synthesis of oxazoles from *N*-acyl-β-bromodehydroaminobutyric acid derivatives by treatment with base. The mechanism proposed for this reaction involves the attack of the carbonyl oxygen on the β-carbon atom of the dehydroaminobutyric acid with loss of the halogen anion. As the reaction medium in the C-N cross-coupling is basic the cyclization to give the oxazole can also occur affecting the reaction outcome (Ferreira et al. 2010a). The ^{1}H NMR spectra in $CDCl_3$ of compounds ***E*-2a-f** clearly show the presence of two broad singlets, one between 11.42 and 12.55 ppm and the other between 5.34 and 7.11 ppm, originated from the β- and α-NH, respectively (Table 2).

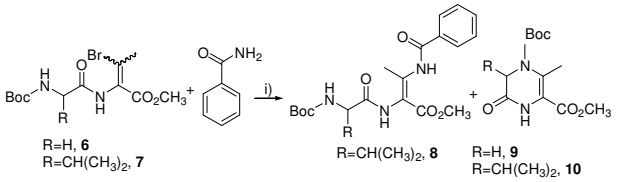
Table 2. Chemical shifts in $CDCl_3$ of the NH protons in compounds ***E*-2a-f**.

Compound	α-NH / ppm	β-NH / ppm
***E*-2a**	5.34	12.36
***E*-2b**	5.54	12.39
***E*-2c**	5.49	12.32
***E*-2d**	5.56	12.55
***E*-2e**	5.44	11.42
***E*-2f**	7.11	12.47

The high chemical shifts of the β-NH amide proton are due to the conjugation with the α,β-unsaturated carbonyl system of the dehydroamino acid. As expected higher values are observed for compounds ***E*-2a-d** and

***E*-2f** with aromatic groups linked to the amide function and the lowest value is observed for compound ***E*-2e** with a methyl group linked to the amide. When comparing the chemical shifts of the α-NH of compounds ***E*-2a-e** with that of compounds ***E*-1** (6.00 ppm) (Silva et al. 2002) and ***Z*-1** (6.23 ppm) (Silva et al. 2002) it is possible to observe an upfield effect probably because of the shielding of the β-NH. The same effect was also found by comparing the chemical shift of the α-NH of compound ***E*-2f** with those of the α-NH of compounds ***E*-3** (8.04 ppm) (Ferreira et al. 2010b).

This reaction was also tested using β-bromodehydroaminobutyric acid dipeptides [***Z*-6** (Ferreira et al. 2007), ***E*-6** (Ferreira et al. 2007), ***Z*-7** (Ferreira et al. 2010b) and ***E*-7** (Ferreira et al. 2010b)] and benzamide as coupling components (Scheme 3, Table 3).

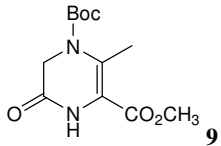
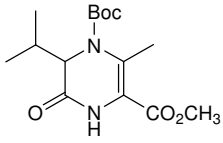
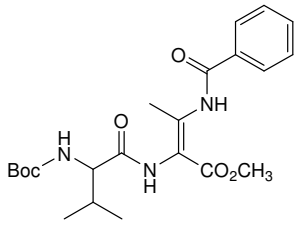


i) CuI (5 mol%), DMED (20 mol%), K_2CO_3 (2 eq.), toluene, 110 ºC.

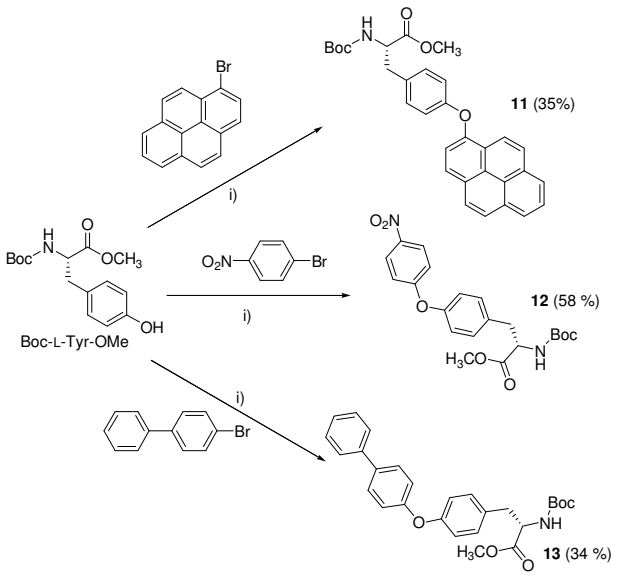
Scheme 3. Reaction between the *E*- and *Z*-isomers of the methyl ester of *N*-(*tert*-butoxycarbonyl)-β-bromodehydroaminobutyric acid dipeptides and benzamide.

It was found that the products obtained in C-N coupling reactions between dipeptides having a β-bromodehydroaminobutyric acid residue as the second amino acid and benzamide depend on the stereochemistry of the dehydrodipeptide and on the nature of the first amino acid. Thus, the formation of the β-benzamidodehydrodipeptide ***E*-8** was only observed with the *E*-isomer of compound **7**. The intermolecular C-N coupling product ***E*-8**, was isolated together with similar amounts of the pyrazine derivative **10**. The pyrazine derivative was the only product obtained from the reaction of ***Z*-6** and ***E*-6** with benzamide. The dihydropyrazines **9** and **10** result from the intramolecular C-N coupling between the α-NH of the first amino acid and the vinyl halide moiety of the dehydroamino acid residue.

Table 3. Coupling products obtained from the reaction of β-bromodehydroaminobutyric acid dipeptides and benzamide.

Reagent	Products
***Z*-6**	 **9** (63 %)
***E*-6**	**9** (30 %) + Boc-Gly-ΔAbu-OMe (32 %)
***Z*-7**	 **10** (80 %)
***E*-7**	 ***E*-8** (21 %) + **10** (29%)

In order to test the versatility of the catalytic system (CuI / *N,N'*-dimethylethylene diamine) used in the C-N couplings between dehydroaminobutyric acid derivatives and amides it was decided prepare O-aryltyrosines using C-O coupling reactions between tyrosine derivatives and aryl bromides, namely 1-bromopyrene, 1-bromo-4-nitrobenzene and 4-bromobiphenyl (Scheme 4). The coupling products **11**, **12** and **13** were obtained in moderate yields (34 – 58%).



i) CuI (15 mol%), *N*,*N*-dimethylethylene diamine (50 mol%), Cs_2CO_3 (1.5 equiv.), toluene, 100 ºC.

Scheme 4. Synthesis of new *O*-aryltyrosine derivatives obtained by reacting a the methyl ester of *N*-*tert*-butoxycarbonyl-L-tyrosine with aryl bromides.

In order to increase the reaction yields Pan *et al.* (2004) conditions [CuI as catalyst, *N*,*N*-dimethylglycine as ligand, Cs_2CO_3 as base in dioxane at 80 ºC] were used in the coupling between the methyl ester of *N*-*tert*-butoxycarbonyl tyrosine and 4-bromobiphenyl. Compound **12** was isolated in 32% yield which indicates that in the case of C-O couplings between aryl halides and tyrosine derivatives it is possible to use both catalytic systems with similar results.

Since compounds **11** and **13** have a pyrenyl and a biphenyl moiety respectively, it was decided to study their photophysical properties. Thus the absorption and fluorescence properties of these compounds were studied in four solvents of different polarity (cyclohexane, ethyl acetate, acetonitrile and ethanol). The normalized absorption and fluorescence spectra of compounds **11** and **13** are presented in figure 1. The maximum absorption (λ_{abs}) and emission wavelengths (λ_{em}), molar absorption coefficients (ε) and fluorescence quantum yields (Φ_F) for these compounds are presented in table 4.

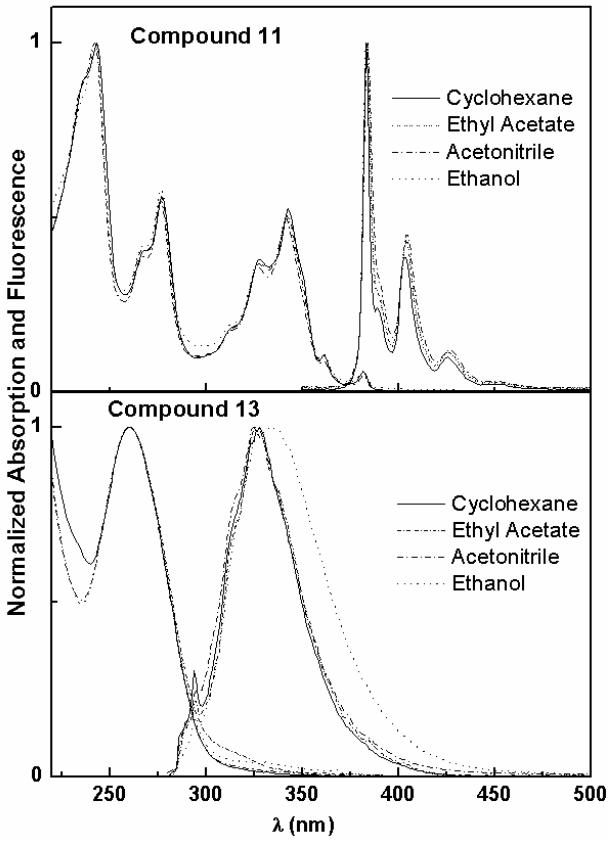


Figure 1. Normalized absorption and emission spectra of compounds **11** (λ_{ex} 345 nm) and **13** (λ_{ex} 270 nm) in four solvents of different polarity.

Compounds **11** and **13** displayed low influence of the solvent on the absorption and emission spectra. The two compounds present absorption spectra with high molar absorption coefficients (ε >2.1x10^4 M^{-1}cm^{-1}) at the lowest energy maximum in all solvents studied (Table 4).

The high ε values observed can indicate a predominance of π-π* character in these compounds (Creed 1984; Albinsson et al. 1989; Lippert et al. 2004). Compound **11** exhibits absorption and emission spectra that resemble those of pyrene (Kalyanasundaram and Thomas 1977; Winnik 1993) with well-defined vibrational structure (Figure 1), and presents high fluorescence quantum yields in all solvents studied (Table 4) [Φ_F = 0.58 for pyrene in cyclohexane (Hissler et al. 1999)]. The fluorescence spectrum of biphenyl is structured whereas the absorption spectrum is broad and structureless which is characteristic of a chromophore that is non-planar in the ground state and more planar in its first excited singlet state. Unlike biphenyl compound **13** presents a non-structured fluorescence emission in all solvents (Figure 1) and moderate fluorescence quantum yields similar to those observed for biphenyl (Table 4) [Φ_F = 0.18 for biphenyl in cyclohexane (Valeur 2001; Lim and Li 1970; Bridges et al. 1965)]. In ethanol can be detected a band enlargement together with a bathochromic shift. This behavior points to an intramolecular charge transfer (ICT) character of the excited state.

Table 4. Maximum absorption (λ_{abs}) and emission wavelengths (λ_{em}), molar extinction coefficients (ε) and fluorescence quantum yields (Φ_F) for compounds **11** (λ_{ex} 345 nm) and **13** (λ_{ex} 270 nm).

Solvent	λ_{abs} (nm) ($\varepsilon/10^4$ $M^{-1}cm^{-1}$)		λ_{em}(nm)		Φ_F [a]	
	11	**13**	**11**	**13**	**11**	**13**
Cyclohexane	382 (0.28), 361 (0.50), 343 (2.50), 328 (1.81), 317 (0.94,sh), 277 (2.67), 269 (1.93), 243 (4.76), 238 (4.30,sh)	260 (2.33)	383, 389, 404, 426	328	0.56	0.15
Ethyl acetate	382 (0.30), 361 (0.54), 342 (2.65), 328 (1.92), 317 (1.03,sh), 277 (2.95), 268 (2.16)	260 (2.55)	384, 389 (sh), 404, 427	325	0.38	0.15
Acetonitrile	382 (0.26), 361 (0.49), 342 (2.80), 327 (2.02), 317 (1.07,sh), 277 (3.08), 267 (2.19), 242 (5.65), 237 (5.07,sh)	260 (2.36)	384, 389 (sh), 405, 427	326	0.37	0.20
Ethanol	382 (0.28), 361 (0.49), 342 (2.30), 327 (1.69), 316 (0.92,sh), 277 (2.64), 268 (1.92), 242 (4.55), 236 (3.85,sh)	260 (2.19)	383, 390 (sh), 404, 425	335	0.40	0.18

[a] relative to 9,10-diphenylanthracene in ethanol (Φ = 0.95 at 25ºC) (Morris et al. 1976) for **11**; relative to naphthalene in cyclohexane (Φ = 0.23) (Berlman 1971) for **13**. Error about 10%. Ethyl Acetate *cut-off*: 260 nm. [**11**] and [**13**] = $1x10^{-6}$ M to measure the fluorescence quantum yields. [**11**] and [**13**] = $2x10^{-5}$ M to determine the molar extinction coefficients.

In solution tyrosine presents a maximum of fluorescence emission between 303 and 305 nm as a non-structured band (Lakowicz 1999; Eftink 2000). The introduction of a biphenyl or a pyrenyl moiety in tyrosine, results in a new amino acid derivative with emission bands located at lower energy and with higher fluorescent quantum yields [Φ_F = 0.14 for tyrosine in water (Lakowicz 1999)]. The results obtained indicate that after deprotection these compounds could be used as fluorescent markers. Compound **11** can be use as a fluorescent probe in peptides and proteins since this compound can be excited without simultaneous excitation of other aromatic amino acids (tyrosine, tryptophan and phenylalanine) that absorb light at λ < 300 nm (Lakowicz 1999; Eftink 2000).

Conclusions

Copper catalyzed C-N and C-O coupling reactions were applied to the synthesis of non-proteinogenic amino acids namely β-amidodehydroaminobutyric acid derivatives and *O*-aryltyrosine derivatives. When β-bromodehydroaminobutyric acid derivatives and primary amides were used as substrates it was found that Buchwald conditions (Jiang et al. 2003; Martin et al. 2007) namely CuI (5 mol%), DMED (20 mol%), K_2CO_3 (2 equiv.) in toluene at 110 ºC gave the best results. This reaction was also applied to dipeptides having a dehydroaminobutyric acid as the second residue. The products obtained were the β-amidodehydrodipeptides and/or the corresponding tetrahydropyrazine derivatives. The latter is the result of an intramolecular C-N coupling between the α-NH of the first amino acid and the vinyl halide moiety of the dehydroamino acid residue. In the case of dipeptides the reaction outcome depends on the stereochemistry of the β-halodehydrodipeptide and of the nature of the first amino acid. The stereochemistry of the β-amidodehydroaminobutyric acid derivatives was determined by NOE difference experiments. Although it is reported that this type of coupling reactions occurs maintaining the stereochemistry of the vinyl halide in the case of the *Z*-isomers of the β-halodehydroaminobutyric acid derivatives the reaction proceed with inversion of the configuration affording only the *E*-isomers. The C-O couplings between a tyrosine derivative and aryl halides were less sensitive to reaction conditions affording the *O*-aryltyrosines in moderate yields.

The photophysical properties of the *O*-pyrenyltyrosine and the *O*-biphenyltyrosine derivatives were studied in four solvents of different polarity. The results indicate that after deprotection these compounds can be used as fluorescent markers. The *O*-pyrenyltyrosine derivative can be particularly useful as a fluorescent marker for peptides and proteins since it can be excited without simultaneous excitation of other aromatic amino acids.

Acknowledgments

This work was financed by FEDER through "Programa Operacional Factores de Competitividade" – COMPETE and by FCT – "Fundação para a Ciência e Tecnologia" through

project “Projecto Estratégico - UI 686 - 2011-2012” Ref: PEst-C/QUI/UI0686/2011. The NMR spectrometer is part of the National NMR Network (RNRMN) and was purchased in the framework of the National Programme for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and Fundação para a Ciência e a Tecnologia (FCT) and is supported with funds from FCT. G.P. acknowledges FCT for a PhD grant SFRH/BD/38766/2007. H.V. acknowledges FCT for a PhD grant SFRH/BD/7265/2010.

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